EPA-UNEPSA SCIENTIFIC ACTIVITY (2018-2020)

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UNION OF NATIONAL EUROPEAN PAEDIATRIC SOCIETIES AND ASSOCIATIONS (EPA-UNEPSA)

EPA-UNEPSA SCIENTIFIC ACTIVITY (2018-20)

A collection of articles dedicated to child health promotion and care published by EPA-UNEPSA during the period 2018-20.

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INTRODUCTION

The European Paediatric Association, the Union of National Paediatric Societies and Associations (EPA-UNEPSA) complies with the strategy of building bridges between and among medical and non-medical experts. The aim of EPA-UNEPSA is to educate without being limited by boundaries, across country borders, while respecting national idiosyncrasies.

In recent years, EPA-UNEPSA has brought together 50 European national paediatric associations and societies, to develop a shared "learning across borders" process and to start the debate on different issues of child health care ranging from psychological to medical, legal and economic topics. Furthermore, EPA-UNEPSA expanded on planning, performing and publishing studies on child health care services in Europe. Finally yet importantly, EPA attracted not only paediatricians but also other experts in child health care, who were willing to be actively involved in projects aiming at improving child health care on a European level.

In 2019 EPA-UNEPSA has joined forces with the European Confederation of Primary Care Pediatricians (ECPCP). The two Scientific societies have entered into a strategic agreement and now work together with the aim *to advocate on behalf of European children and to urge the other European paediatric societies to also join forces with them to pursue the common goal of "European Paediatrics speaking with one voice"*

The ambitions and objectives of the European Paediatric Association are to improve the health of children and young people in Europe, and to advance the quality of health care services for children and their families in Europe.
The articles included in this e-book deal with a great variety of topics reflecting current discussions and controversies, idiosyncrasies and standards, gasp and bridges as well as challenges and achievements. With respect to the enormous benefit of a successful communication between professionals, we have chosen to make most of our previous publications available to as many pediatricians as possible.

EPA-UNEPSA has broaden its intellectual basis by creating a multidisciplinary society to avoid fragmentation of paediatrics, and to allow tackling the legal, economic and organisational challenges of child health care in Europe. Last but not least EPA-UNEPSA constantly works to put the children and young people into the centre of its activities.

Enjoy reading the articles and please do not hesitate to contact the EPA-UNEPSA Editorial Board by sending your questions and comments to the articles.

Massimo Pettoello-Mantovani
on behalf of the EPA-UNEPSA Board of Directors

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European Pediatricians: Speaking with One Voice to Advocate for Children and Their Health

Leyla Namazova-Baranova, MD, PhD[1], Angel Carrasco-Sanz, MD[2], Mehmet Vural, MD[1], Gottfried Huss, MD[2], Julije Mestrovic, MD[1], Shimon Barak, MD[2], Hilary Hoey, MD[1], Andreas Werner, MD[2], Mario Schuhmacher, MD[2], and Massimo Pettoello-Mantovani, MD, PhD[1]

In May of 2019 the European Paediatric Association, which is the Union of National European Paediatric Societies and Associations (EPA/UNEPSA), and the European Confederation of Primary Care Paediatricians (ECPCP) signed a key partnership memorandum of understanding, which marks an important step for European pediatricians toward the goal of speaking with 1 voice to advocate for children and their health. These 2 European pediatric societies together represent more than 200 000 European pediatricians working in primary, secondary, and tertiary pediatric care.

Despite frequent public statements regarding the importance of adequately supporting child healthcare, in reality pediatric care in Europe is traditionally not sufficiently prioritized by national authorities involved in the key decisional processes related to children's health. Consequently, the responsibility for children's primary care is frequently transferred to health care professionals other than pediatricians who have received limited pediatric training.[1] Key decisions regarding this important aspect of child health are based on changing political visions and policies of single nations and frequently are impacted by economic contingencies. This is despite the evidence that primary pediatric care provided by pediatricians achieves important public health goals, such as less hospitalization of children, higher vaccination rates, and reduced prescription of antibiotics.[2]

The EPA/UNEPSA, ECPCP, and the European Academy of Pediatrics, currently the 3 main European pediatric organizations, are characterized by several common features, objectives, and ambitions. However, their ability to effectively interact with national and international public health authorities and legislators has been traditionally limited by their inability to speak with 1 voice to advocate for children and their health. The agreement between the EPA/UNEPSA and ECPCP will pave the way for achieving a unification of all European pediatric forces actively engaged in protecting children's health and promoting their well-being.

EPA/UNEPSA	European Paediatric Association/Union of National European Paediatric Societies and Associations
ECPCP	European Confederation of Primary Care Paediatricians

Mission and Objectives of the EPA/UNEPSA

EPA/UNEPSA, the union of the major national European pediatric societies and associations, operates on a nonprofit basis. Founded more than 40 years ago with the purpose of building scientific bridges between Eastern and Western Europe, which were then separated by the Iron Curtain, the EPA/UNEPSA has become the largest European pediatric organization. The main objectives of EPA/UNEPSA are to promote child health and comprehensive pediatric care, and to encourage the scientific cooperation and interaction between the national European pediatric scientific organizations, as well as among European pediatricians working in primary, secondary, and tertiary care.

The EPA/UNEPSA is active in promoting and supporting scientific and editorial projects in the area of pediatric health care, working closely with the major international organizations, including the World Health Organization, the United Nations, and the Council of Europe. Since its foundation in 1976, the EPA/UNEPSA has encouraged the education of patients, families, and care givers by making available specialized knowledge to generalists. Throughout the years, it has worked to improve the quality of pediatric care in all European countries, including both member and nonmember states of the European Union, by promoting the importance of clinical research and its implementation into practice. As a pan-European pediatric association representing 50 different national groups and organizations, the EPA/UNEPSA embraces diversity and fosters the exchange of experiences and cooperation among all European pediatricians.

The Role of the ECPCP and Its Goals

The ECPCP represents more than 30 000 European pediatricians, members of 22 societies from 18 European countries, engaged in community pediatrics and primary childcare. The ECPCP regards infants, children, and adolescents as its

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Table. Joint activities and aims agreed between EPA/UNEPSA and ECPCP

- Create synergies wherever possible between both organizations and their members.
- Exchange and disseminate information on reciprocal activities and projects to their respective networks.
- Advertise the periodical conferences/meetings of the 2 organizations.
- Work to develop a periodical joint meeting/congress and share its scientific program.
- Develop joint educational activities/projects.
- Develop joint editorial activities/projects.
- Consult and share the texts of future recommendations, guidelines, and statements involving child health and care, before releasing any document, which could be in contrast with the principles of the 2 organizations.
- Pursue a common strategy leading to the development of a common unique organization including ECPCP, EPA/UNEPSA, as well as EAP and other major European associations.
- Develop an effective format to enable the existing European societies to more effectively and efficiently speak with 1 voice advocating for European children and adolescents, while being respectful of the reciprocal areas of interests, missions, and expertise of the participating organizations.

main subject of care, respecting their autonomy and involving parents, guardians, and/or custodians as integral part of the "unit of care." Their strong conviction is that pursuing this goal relies on the development and implementation of attainable and accessible primary healthcare services and facilities of the highest standards in all countries in accordance and fulfillment of the Alma Ata declaration,[3] the United Nations Convention on the right of Children, and the World Health Organization Charter.[4]

The ECPCP advocates for the role of pediatricians as deliverers of primary care in the community from postnatal health care to late adolescence. It has developed procedures and trained personnel to define and develop tools useful to optimize primary care services in the countries that have chosen pediatricians as primary caretakers. Pediatric primary care is in many situations delivered by professionals other than pediatricians; these individuals may lack adequate scientific knowledge, proper skills, and formal training, which are key elements required for the provision of adequate healthcare. Therefore, the ECPCP, with the strong support of its member societies, has chosen to broaden the activities of the organization and actively work and collaborate with organizations of other European and non-European countries lacking facilities and funding for primary care pediatrics, with the aim of ensuring that optimal levels of primary care will be also provided.

The EPA/UNEPSA and ECPCP Joining Forces to Advocate for European Children

The ECPCP and EPA/UNEPSA are convinced that a systematic and coordinated interaction of primary, secondary, and tertiary care specialist pediatricians is essential to the health and well-being of children. Both organizations recognize the importance of working closely and jointly designing and developing a common strategy that will enable European pediatrics to speak with an influential and authoritative voice on behalf of European children and adolescents.

The EPA/UNEPSA and ECPCP believe that a strong and united voice is needed to raise the awareness of national and international legislators about the importance of child and adolescent health for the future of the European continent.[5] A joint effort by the main European pediatric organizations will effectively promote the importance of the accessibility to the best care available for all children living in Europe, who should benefit from cutting-edge scientific research and discoveries that are protected by age-appropriate laws and regulations.[6]

Both the ECPCP and the EPA have agreed to work together in an egalitarian spirit to develop joint projects and activities and to accomplish common future goals (**Table**).

Conclusion

Having assessed the needs of their member pediatric societies, EPA/UNEPSA and ECPCP are actively collaborating to form a joint umbrella European pediatric organization with the goal of uniting the voices, actions, and visions of European pediatricians to protect and promote the health and well-being of children in Europe. ■

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References

1. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
2. Ehrich J, Tenore A, Del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
3. World Health Organization. Declaration of Alma-Ata. International Conference on Primary Health Care. Alma-Ata, USSR, 6-12 September, 1978. http://www.who.int/publications/almaata_declaration_en.pdf. Accessed May 15, 2019.
4. UNICEF. Child poverty in perspective: an overview of child well-being in rich countries. Innocenti Report Card. Vol 7. Florence, Italy: UNICEF Innocenti Research Centre. www.unicef.org/media/files/ChildPovertyReport.pdf. Accessed May 15, 2019.
5. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: a Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177(Suppl):S1-10.
6. Ehrich J, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-8.e2.

Looking at the Future, Learning from the Past: Current Activities and Upcoming Goals of the European Paediatric Association, the Union of National European Paediatric Societies and Associations

Massimo Pettoello-Mantovani, MD, PhD, Julije Mestrovic, MD, Mehmet Vural, MD, and Leyla Namazova-Baranova, MD, PhD

Presidents and delegates of the European pediatric societies and associations gathered in Istanbul, Turkey, in December 2019 to renew the Board of Directors of the European Paediatric Association (EPA), which is the Union of National European Paediatric Societies and Associations (EPA/UNEPSA)[1] (**Table I**; available at www.jpeds.com). Following a discussion among the delegates of the EPA/UNEPSA member organizations, the newly elected Board will engage proactively in leading the union of European pediatric organizations toward the challenges facing the discipline of pediatrics in the areas of research, education, knowledge transfer, and advocacy for children's health and well-being. Major efforts of the new Board will include projects for the improvement of healthcare systems in Europe[2] and the development of educational programs designed to form stronger advocates and skillful professionals able to best meet their patients' challenges and be confident in their leadership as experts in child and adolescent health. This commentary describes the current activities and perspectives of EPA/UNEPSA and its new board of directors.

Looking at the Future, Learning from the Past

Civil society and culture have progressively and substantially changed in Europe and globally; as a result, the discipline of pediatrics is facing profound transformations and needs constant innovation to meet the ever-increasing needs of the patients.[3] In fulfilling its responsibilities, the new EPA/UNEPSA Board will enjoy the encouragement and strong support showed by the member societies during the General Assembly. The Board members will work in an energetic, team atmosphere and in close collaboration with the member societies, which will allow them to succeed in achieving their objectives and to meet the challenges posed by a dynamic evolving world.[4,5]

EPA/UNEPSA can ground its activities on a solid international network of collaborations developed worldwide. This will assist EPA/UNEPSA in best serving the interests of the European children and in building new bridges between pediatricians in East and West, as well as in the North and South of Europe.[6] The activities of the Board will be characterized by working to balance the need to respect cultural and social diversities with the importance for European pediatricians to "speak with one voice" on behalf of children.[7] This goal will be pursued tirelessly, by seeking the collaboration and harmonization among the main European pediatric constituencies, in respect of their mission and statutory independency, and by acknowledging the distinct role of primary, secondary, and tertiary pediatric care.

Foundation and History of EPA/UNEPSA

EPA/UNEPSA is a pan-European scientific association that operates on a nonprofit basis, working closely with the major international organizations, including the World Health Organization, United Nations, European Medicines Agency, and the Council of Europe. Its main objective is to encourage scientific cooperation between not-for-profit national European pediatric organizations and between European pediatricians working in primary, secondary, and tertiary pediatric settings, to promote child health and well-being and to foster comprehensive pediatric care.[1]

EPA/UNEPSA was founded 45 years ago in the St Sophia Children's Hospital in Rotterdam by 18 European countries. It now represents 50 National European Pediatric Societies and Associations and their more than 150 000 member pediatricians working in Europe. Its General Assembly is composed of the presidents of the major national pediatric societies active in the nations of geographic Europe or culturally linked to the European continent. Currently more than three-quarters of all European countries are represented in EPA/UNEPSA (**Table II**; available at www.jpeds.com). In its role as the prominent European pediatric organization, EPA/UNEPSA has especially fostered education of healthcare professionals, families, caregivers, and patients. This important goal has been pursued throughout the years

EPA	European Paediatric Association
IPA	International Pediatric Association
KOL	Key opinion leader
UNEPSA	Union of National European Paediatric Societies and Associations

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by developing programs focused on transferring specialist knowledge to generalists and promoting public health information and prevention programs.[8,9]

A fundamental element of EPA/UNEPSA's role as a pan-European organization is to understand and embrace diversity[6] and to foster the exchange of experiences and cooperation among pediatricians in Europe, enabling its member societies and associations to exchange scientific information and share best practices, in the spirit of "learning across borders and languages."[9]

Its major milestones and activities include the biannual international meeting Europaediatrics, a formal collaboration with *The Journal of Pediatrics*, research studies and educational courses, and the collaboration with the International Pediatric Association (IPA).

The Biannual International Meeting Europaediatrics

Periodical meetings of the presidents of the national European pediatric societies focus on the most urgent issues of pediatric healthcare.[10] This biannual flagship event has become an important tradition of bringing together pediatricians and child health professionals from Europe and throughout the world. The objective of Europaediatrics is health promotion and prevention of disease and disability through primary, secondary, and tertiary prevention and where prevention is not possible to provide up-to-date, evidence-based information on treatment. Optimization of health and well-being of children and their families and promotion of children's rights to health, equity, and social justice are among the key topics.[2] Scientific programs are developed in collaboration with the national European pediatric societies along with major subspecialty societies, the World Health Organization, and international societies across the world. Its workshops and scientific sessions are known for being of benefit to generalists as well as specialists in Europe and beyond.

Formal Collaboration with *The Journal of Pediatrics*

In 2012, EPA/UNEPSA established a formal affiliation with *The Journal of Pediatrics*. The affiliation and close collaboration with this journal are key factors in fulfilling the EPA/UNEPSA educational mission, as the society fully embraces the mission of *The Journal*,[11] contributing its efforts to improve the quality of the health and care of infants, children, and adolescents. Through a series of commentaries published monthly in the EPA section of *The Journal*, authors provide information on new technologies and debate current issues in public health, bringing attention to major health problems to a diverse audience of pediatric healthcare professionals. From the articles published in this section, the pediatric community around the world also can read about new EPA/UNEPSA initiatives and the progress of its ongoing, long-term projects. Important organizational changes are periodically announced, and members can follow the Society's current thinking on how to further improve European pediatrics and receive updates on the educational efforts of the society. EPA/UNEPSA believes in empowering general pediatricians with the best-available information on research in the field so that they can make informed decisions for individual patients, a vision that is shared with *The Journal*.[9,11]

Research Studies and Educational Courses

EPA/UNEPSA activities include the development of key opinion leader (KOL) working groups. KOLs involved in these activities typically are respected medical experts highly regarded in their field as a result of their innovative research, publications in high-impact research journals, and presentations at renowned conferences. The reports and articles developed by these working groups in collaboration with EPA/UNEPSA include concise information on the most important recommendations for clinical practice. Their studies and expert opinions address clinical topics of current importance for pediatricians.[12]

Pediatricians will be leaders in defining and creating a sound body of scientific and practical knowledge concerning child health.[13] To support this goal, EPA/UNEPSA has developed a program of KOL courses, which aim to transfer knowledge from different areas of specialty pediatrics to general pediatricians. The courses cover various areas of pediatrics, with special focus on prevention, as well as on diagnostic and therapeutic innovations in the management of child and adolescent health.[14]

Collaboration with IPA and Future Goals

EPA/UNEPSA leadership strongly feels that IPA is for all societies and is working actively to gather the major European pediatric organizations to join EPA/UNEPSA in working within IPA, with the aim of speaking with one voice to advocate for children's health and well-being.

In 2019, EPA/UNEPSA entered a seminal agreement with the European Confederation of Primary Care Pediatrician/Confédération Européenne de Pédiatrie Ambulatoire,[7] active in Europe for 30 years, representing 22 national European Societies and more than 30 000 primary care pediatricians. EPA/UNEPSA emphasizes the importance of a close collaboration between secondary and primary care pediatrics. In the future, combined programs developed with European Confederation of Primary Care Pediatrician/Confédération Européenne de Pédiatrie Ambulatoire are designed to include projects in the area of diseases prevention and health promotion.

Conclusions

The aim of EPA/UNEPSA is to promote children's rights to health, equity, and social justice. More than a quarter of a century has passed since the iron curtain between East and West Europe, and the importance of exploring similarities

and differences in current challenges and approaches to child health across Europe has not declined. EPA/UNEPSA, with the key contribution of its 50 member societies, has the potential to understand and address differences in pediatric policy and practice among different nations. After 45 years, EPA/UNEPSA is still an expanding and vital instrument in improving the knowledge of European pediatricians and for enhancing health services for all children and the cooperation among their caretakers in Europe, in a continuing effort to fulfill its role as the largest European pediatric association. ■

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References

1. European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA/UNEPSA). www.epa-unepsa.org. Accessed February 10, 2020.
2. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
3. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of Pediatric Workforce and Education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
4. Pettoello-Mantovani M, Pop TL, Mestrovic J, Ferrara P, Giardino I, Carrasco-Sanz A, et al. Fostering resilience in children: the essential role of healthcare professionals and families. J Pediatr 2019;205:298-9.e1.
5. Ferrara P, Guadagno C, Sbordone A, Amato M, Spina G, Perrone G, et al. Child abuse and neglect and its psycho-physical and social consequences: a review of the literature. Curr Pediatr Rev 2016;12:301-10.
6. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.
7. Namazova-Baranova L, Carrasco-Sanz A, Vural M, Huss G, Mestrovic J, Barak S, et al. European pediatricians: speaking with one voice to advocate for children and their health. J Pediatr 2019;211:227-8.
8. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270-1.e1.
9. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
10. Biasci P, Carrasco Sanz A, Pop TL, Pettoello-Mantovani M, D'Avino A, Nigri L. The state of children's health in Europe. J Pediatr 2019;209:260-1.e1.
11. The journal of pediatrics. www.jpeds.com. Accessed, February 10, 2020.
12. Albenzio M, Campanozzi A, D'Apolito M, Santillo A, Pettoello-Mantovani M, Sevi A. Differences in protein fraction from goat and cow milk and their role on cytokine production in children with cow's milk protein allergy. Small Ruminant Res 2012;105:202-5.
13. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, et al. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.
14. Ehrich J, Stengritt D, Jaeger D, Namazova-Baranova L, Pettoello-Mantovani M, Lenton S. The Dilemma of International Pediatric Congresses in Europe: Starting the Debate. J Pediatr 2015;166:504-506.e1.

Table I. 2020 EPA/UNEPSA organization chart

Board of Directors	
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Past-President:	Leyla Namazova-Baranova, MD, PhD, Full Professor of Pediatrics (Russia)
Vice-President:	Eli Somekh, MD, Full Professor of Pediatrics (Israel)
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Secretary General:	Julije Mestrovic, MD, Full Professor of Pediatrics (Croatia)
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Council Member:	Tudor Pop, MD, PhD, Full Professor of Pediatrics (Romania)
Council Member:	Angel Carrasco-Sanz, MD, President ECPCP (Spain)
Council Member and President of the biannual scientific Congress Europaediatrics 2020:	Aida Mujkic, MD, PhD, Full Professor of Pediatrics (Croatia)

Table II. European nations currently represented in EPA/UNEPSA through main national pediatric societies and associations

- Albania
- Armenia
- Austria
- Azerbaijan
- Belarus
- Belgium
- Bosnia/Herzegovina
- Bulgaria
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Estonia
- France
- Georgia
- Greece
- Hungary
- Iceland
- Ireland
- Israel
- Italy
- Kazakhstan
- Kyrgyz Republic
- Kosovo
- Latvia
- Lithuania
- Luxembourg
- Malta
- Moldova
- Monaco
- Montenegro
- North Macedonia
- Norway
- Poland
- Portugal
- Romania
- Russia
- Serbia
- Slovakia
- Slovenia
- Spain
- Sweden
- Turkey
- Ukraine
- Uzbekistan
- United Kingdom
- Vatican City

TÜRK PEDİATRİ ARŞİVİ
TURKISH ARCHIVES of PEDIATRICS

Review

Children facing natural, economic and public health crisis in Europe: The risks of a predictable unpredictability

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Abstract

This opening article for the volume dedicated to the diversity of paediatric healthcare systems in Europe, discusses the topic of children facing natural, economic, and public health crises in Europe. The natural and economic adversities and public health crises, which have repeatedly stormed the globe during the past twenty years, have often unveiled a low degree of self-sufficiency and a high degree of unpreparedness by European countries. It is always the case that the most vulnerable take the brunt, and these adverse events have shown their effects and a negative direct impact particularly on the population aged 0–18 years, with important implications for families and communities. The article discusses a rational approach to properly confront future public health emergencies and crises in general. The authors stress the concept that such approaches should be built on past negative experiences, in order to explore, identify, and make clear which are the priorities governing the disaster management activities at all levels in this population group. The authors conclude that safeguarding the health of children could be effectively accomplished by developing adequate, shared emergency management strategies. Improving pediatric preparedness approaches with the use of emergency measures and ongoing collaboration will facilitate a better and more efficient response, able to effectively care for the needs of children in actual crises.

Keywords: Children, crisis, disasters, emergency, preparedness

Introduction

The United Nations 2019 demographic report shows that the population living within the geographic and political borders of Europe, including Turkey, is about 975,000,000 people, or 12.5% of the world population (1). Children under the age of 18 years make up nearly 23%, or 225 million individuals (1). Given the significant number of children living in Europe, their unique needs should be taken into consideration by governments and legislators and more thoroughly integrated into healthcare planning at local and national levels, and systematically included in the recommendations elaborated by European political organisms, primarily the Council of Europe (2). However, the requirements of this important part of the European population seem not to have been taken into sufficient account by European authorities and local governments during the past 50 years (3, 4).

The natural and economic adversities and public health crises, which have repeatedly stormed the globe during the past twenty years, have often unveiled a low degree of self-sufficiency and a high degree of unpreparedness by European countries (5–7). It is always the case that the most vulnerable take the brunt, and these adverse

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events have shown their effects and a negative direct impact particularly on the population aged 0–18 years, with important implications for families and communities. A rational approach to properly confronting future public health emergencies and crises in general, should be to build on past negative experiences, in order to explore, identify, and make clear which are the priorities governing the disaster management activities at all levels in this population group.

Natural, economic disasters and public health emergencies

Natural, economic disasters and public health emergencies are interconnected phenomena (8). The effects of natural disasters and public health crises on economic instability has been the subject of decades-long research, engaging experts since the beginning of the last century. However, the interest, studies, and analysis of these phenomena seem to be confined to experts and professionals in the area of public health, economics, and disaster management because natural, economic, and public health emergencies appear to be views by governments and legislators as predictably unpredictable events.

Trauma is a global issue (9). Disasters and distressing natural events occur periodically around the world and need to be met with rescue and recovery interventions including adequate health approaches (9). The nature and effects of these disasters are progressively more complex because they are influenced by several factors including climate change, population movement, economic interdependence, and the general phenomenon of globalization (10). During the past 20 years (1998–2018), climate-related and geophysical disasters killed 1.3 million people, 320,000 of whom were children, and left a further 4.4 billion injured, homeless, displaced or in need of emergency assistance (10). The majority of fatalities were due to geophysical events; over 90% of all disasters were caused by floods, storms, droughts, heat waves, and other extreme weather events. Floods impacted the largest number of people, with more than two billion, and drought affected an additional 1.5 billion individuals (10). During the same period, earthquakes killed nearly 750,000 people, and storms, including tropical cyclones and hurricanes, killed 233,000 people. Single events can be devastating, as in the case of the earthquake in China in 2008 that killed almost 70,000 people and injured close to 375,000, with around 18,000 recorded as missing (11). The number of children affected by natural disasters attributed to climate change is estimated to be over 170 million per year, and the number of children seriously injured or dying each year from such disasters is high, as yet undetermined (12). Direct economic losses due to the sum of natural disasters are valued at US$ 2908 billion. Climate-related disasters, which caused US$ 2245 billion or 77% of the total economic loss, is responsible for economic distress and poverty worldwide, and at least 85% of the population who develop disease due to climate change are children (10, 13).

The impact of economic crises on child health is a consolidated notion (8). The recent 2008 economic crisis was severe, involving national economies at a global level. It equally affected public health services of nations presenting either a weak or a strong domestic growth, and raised strong concerns about the sustainability of public healthcare systems of European Nations, and ultimately about the health of European citizens (8). The worsening nutrition habits observed in disadvantaged families worldwide were caused by difficulties in food access and availability, mainly due to the escalating prices of foods (8, 14, 15). In 2009, alarming data were reported from Africa, where in sub-Saharan African countries was described a surplus of 30,000–50,000 infant deaths. In Europe, the unfortunate and improvident penalizing economic measures imposed by the European Union (EU) to some member countries, instead of providing relief, caused heavy damages to their national socio-economic systems and generated long-term negative effects on health systems throughout the Union (6, 8, 16). In Greece, perinatal, neonatal, and infant mortality all increased by 20% to over 30% from 2008 to 2010 (17). In particular, stillbirth rates increased from 3.31/1000 in 2008 to 4.28/1000 in 2009 and 4.36/1000 in 2010, showing a 32% increase over 2 years (18). Further data show that other areas of public health were also negatively impacted, as the prevalence of psychosocial problems have risen by 40%, conduct disorders by 28%, school leaves by 25%, bullying by 22%, suicide attempts 20%, illegal and additive substances have risen by 19%, and family conflicts by 51% (19, 20).

The recent pandemic caused by COVID-19, as in the two preceding instances of the emergence of coronavirus disease (SARS in 2002 and 2003, and Middle East respiratory syndrome in 2012 and 2020), has posed critical challenges for the public health, research, and medical communities (7, 21). During epidemic events, children can be disproportionately affected compared with older age groups, as in the case of pandemic influenza 1-H1N1 (22). Furthermore, although clinical manifestations in children could be less severe than in adult patients, as in the case of COVID-19, reports from areas involved by the pandemic show that children and adolescents are significantly hit by the psychological consequences related to the epidemic (23).

Table 1. Children's distinctive conditions and needs in emergencies

- Academic failure, post-traumatic stress disorder, depression, anxiety, bereavement, behavioural disorders, including delinquency and substance abuse (long-lasting effects)
- Higher susceptibility of children to chemical, biologic, radiologic, and nuclear accidents (need of special medications, doses, and delivery systems).
- Major vulnerability of younger children during adverse situations (inability to avoid or escape dangers, identify themselves, preserve self-estimate and make critical decisions)
- Need of secure attachment to adult figures as their base of security (care, shelter, transportation, and protection from predators).
- Children's need to continue relying on their schools, care providers, or other child congregate care environments, which must be prepared to ensure children's safety.
- Importance for children to be rapidly reunited with their legal guardians if separated from them during a disaster.
- Easy access to disaster shelters equipped with age-appropriate supplies such as diapers, cribs, baby formula, and food.

All these events have further warned governments worldwide about the importance of preparedness for adequate crisis management, regardless of its nature. This is particularly important for Europe, due to the difficulty of coordinating the efforts of 53 different countries, which have often shown irreconcilable cultural, political, and economic visions. The several threats posed to global health during recent years have particularly emphasized the importance for countries to accelerate the development of guidelines for short, medium, and long-term preparedness, to be applicable to different situations, and to enhance the ability to develop adequate strategies and target resources. Effective strategies should also guide states and their local authorities to better identify impediments, which at any level may delay timely distribution of funds, identify best practices and make recommendations to overcome these complications. Most importantly, effective strategies should include a competent communication system that is able to reach both local administrators and populations, in order to keep them informed as to program requirements and opportunities for assistance.

The importance of developing reliable and effective coordinated strategies

A nation's ability to prepare for, respond to, and recover from disaster, especially in regard to children, should not depend on a single level or agency of government, and cannot be tackled with fragmented approaches (24). An effective system for disaster management should depend on well-planned, coordinated, interactive strategies and reliable methodologies, based on a shared responsibility, centred on each team member doing what it does best and leveraging the expertise and strengths of others, and most importantly, it must be checked for its applicability. Capabilities, policies, and programs are currently fragmented and need clearly stated desired outcomes, priorities, and resources for children, across and among all levels of governments.

Children have distinctive needs in emergencies

The deficiency of clear priorities and sufficient resources for children and families, which is generally observed in Europe in times of emergencies, seems to be mainly related to the absence of comprehensive national strategies, inclusive of children's needs. Strategies designed for emergency events should provide platforms for developing adequate and short- and long-term objectives and capabilities, applicable at national and local levels, and able to more cohesively address gaps in disaster preparedness, response, and recovery for children. Children have unique vulnerabilities that must be addressed by specific emergency management activities and policies because they are not small adults (Table 1) (25).

Turning learning into action

Typically, children present unique needs in all types of emergencies and disasters, which can be anticipated. Therefore, in developing disaster management strategies, governments should place a specific and sustained focus on children in their daily and disaster response activities. The important first step to take should be the inclusion of children as a distinct group within population categories labeled 'at-risk,' 'vulnerable' or 'special needs,' rather than as part of larger categories. A further key step should be the creation of centralized and permanent authorities at a national level that are able to identify and fix gaps in disaster policies and programs for children and families. Their purpose would be to ensure appropriate support for the safety and security of children, including children with disabilities, before, during and after natural and health-related emergencies, including epidemics, earthquakes, tornadoes, fires, floods, hurricanes, and acts of terrorism. Authorities for children should provide effective recommendations for national-level guidance to families, schools, and childcare providers concerning personal precautions, possible access to medical treatments, and school closures. This would facilitate the develop-

Table 2. Factors influencing children's emotional reactions in emergencies

- Experiencing a direct impact or indirect involvement with an adverse event
- Have suffered a previous episode of emergency
- Fear for the loss of a loved one
- Fear for the loss of a family member, close friend, or pet
- Fear for the unknown
- Uncertainty of their own health
- Have suffered physical injury
- Sense of uncertainty transmitted by parents and/or caregivers
- Separation from parents, families and/or caregivers
- Availability of family resources
- Change of routine and life conditions
- Change of lifestyles
- Cultural background
- Level of education
- Interfamily relations
- Level of communication among family members
- Recurring exposure to media coverage of traumatic events and aftermath
- Community reaction, resilience ability to respond and recover to adversities

ment and implementation of distinct disaster planning for the population aged 0–18 years and the activation of dedicated tasks, as in the case of the children's health teams created in the United States of America, Middle East, and Europe in response to the 2009 1-H1N1 pandemic, which disproportionately affected children (26).

Caring for children after emergency is over

The amount of damage caused by a disaster can be overwhelming and affect children physically and mentally. Separation from school, family, and friends can create a great amount of stress and anxiety for children (Table 2). Once the initial disaster event is over, it can take a very long time for families and communities to return to a normal level of functionality. Helping in the return to pre-emergency conditions and standard lifestyle is the primary goal in children. However, communities are often at high risk for further adverse events or a prolonged condition of instability. Therefore, it will be important to assess whether the goal should be to achieve a new normality, with better infrastructure and acceptable stability, rather than to re-establish a pre-event normal status. The recovery of an impacted population, takes much longer than just rebuilding structures for living, working, studying or relaxing. Several studies have shown different long-term effects of adverse events on children, as in the case of mental health disorders including depression, that were found in a large pediatric community over more than 4 years after the 2008 earthquake in China, which killed almost 70,000 people and injured nearly 370,000 (11, 27).

Children's reactions are often influenced by the adults' behavior around them. The best support for children is provided when parents and caregivers reactions to adverse events are stable and they deal with emergencies with confidence. However, the impact of trauma associated with both the disaster itself, and prolonged or difficult recoveries, can last a very long time in children. Therefore, resilience, the personal attribute that help children to manage everything, from little disappointments to large life traumas, should be nurtured and implemented by public health programs in children and teenagers living in communities hit by adverse events (28). Resilient adults may initially protect themselves through the period of trauma and recovery, and transmit a sense of resilience to their children. However, if recovery takes a long time and stressful conditions are prolonged, it will be difficult for adults to remain the sole resilient defense and support for children. Fostering resilience must then be an integrated part of any strategic plan of recovery for children hit by natural, economic or health disasters (28).

Appropriate communication strategies are also key in the management of adversities in order to disseminate correct information coherent with the strategic plans adopted (29). Finally, people and children in particular can become increasingly distressed if they see repeated images of a disaster in the media, therefore limiting the amount of exposure to media coverage should be a good practice to be recommended and implemented.

Conclusions

Children are often overly impacted by natural disasters, global and national economic distress events, and health-related emergencies. Public health systems have been shown to often be unprepared in properly responding to these periodic adverse events, causing children to carry a significant health burden, because they are the most vulnerable members of the population. However, they remain generally underrepresented in preparedness planning and activities. In particular, Europe, seems to show a high degree of unpreparedness due to the characteristic diversity between the health systems of its 53 nations (30, 31). Supporting and improving synergies, and establishing effective collaborations between public health systems and pediatric communities are key factors in the effort of safeguarding the health of children, which can be accomplished by developing adequate, shared emergency management strategies. Improving pediatric preparedness approaches with the use of emergency measures and ongoing collaboration will facilitate a better and efficient response able to effectively care for the needs of children in actual crises.

The lack of cross-sector interactions and collaborative investment in public health systems and services is an impediment to developing a satisfactory pediatric emergency preparedness. Several local and community-based programs addressing preparedness are in effect in each European nation (3, 32). However, the scale of problems is too large to be handled solely on a local basis. High-functioning community-based models of children's preparedness are necessary, but are not replacements for government planning, initiatives, and large-scale funding. Although hoping for the best, the political gridlocks and economic constraints that frequently distress European countries, suggest that, currently in the area of programming children's preparedness for emergencies, we should be at least prepared to avoid the worst. Providing comprehensive recommendations to national authorities and actively advocating for children's health and their needs in adverse circumstances should become a priority for national pediatric societies and associations. Making children a priority will have important implications at all levels of government for training, equipment, supplies, and exercises, because priorities drive investment and resource allocation decisions.

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References

1. United Nations. World Population Prospects 2019. Data Booklet. Available at: http://www.europeanmigrationlaw.eu/documents/UN-WorldPopulationProspects2019-Databooklet.pdf. Accessed 09 April, 2020.
2. Council of Europe. Common standards and policies. Available at: https://www.coe.int/en/? Accessed 03 April, 2020.
3. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/ Union of National European Paediatric Societies and Associations". J Pediatr 2016; 177S: S1–10.
4. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of Pediatric Workforce and Education in 2012 in Europe: A Need for Unifying Concepts or Accepting Enjoyable Differences? J Pediatr 2015; 167: 471–6.e4.
5. European Environment Agency. Disasters in Europe: more frequent and causing more damage. Available at: https://www.eea.europa.eu/highlights/natural-hazards-and-technological-accidents Accessed 10 April, 2020.
6. Karanikolos M, Mladovsky P, Cylus J, et al. Financial crisis, austerity, and health in Europe. Lancet 2013; 381: 1323–31.
7. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. N Engl J Med 2020; 382: 1268–9.
8. Pettoello-Mantovani M, Namazova-Baranova L, Ehrich J. Integrating and rationalizing public healthcare services as a source of cost containment in times of economic crises. Ital J Pediatr 2016; 42: 18.
9. Schnyder U. Trauma is a global issue. Eur J Psychotraumatol 2013; 4: 10.3402/ejpt.v4i0.20419.
10. Centre for Research on the Epidemiology of Disasters - CRED. 2018 Review of Disaster Events. Supplementary Information. Brussels: UC Louvain. Available at: https://www.cred.be/2018-review-disaster-events. Accessed 12 April, 2020.
11. Cheng J, Liang Y, Fu L, Liu Z. Posttraumatic stress and depressive symptoms in children after the Wenchuan earthquake. Eur J Psychotraumatol 2018; 9: 1472992.
12. Codeanu TA, Celenza A, Jacobs I. Does disaster education of teenagers translate into better survival knowledge, knowledge of skills, and adaptive behavioral change? A systematic literature review. Prehosp Disaster Med 2014; 29: 629–42.
13. Pass Philipsborn R, Chan K. Climate change and global child health. Pediatrics 2018; 141: e20173774.
14. Pettoello Mantovani M, Guandalini S, Ecuba P, Corvino C, di Martino L. Lactose malabsorption in children with symptomatic Giardia lamblia infection: feasibility of yogurt supplementation. J Pediatr Gastroenterol Nutr 1989; 9: 295–300.
15. Albenzio M, Campanozzi A, D'Apolito M, Santillo A,

Mantovani MP, Sevi A. Differences in protein fraction from goat and cow milk and their role on cytokine production in children with cow's milk protein allergy. Small Ruminant Research 2012; 105: 202–5.
16. Pianese P, Salvia G, Campanozzi A, et al. Sterol profiling in red blood cell membranes and plasma of newborns receiving total parenteral nutrition. J Pediatr Gastroenterol Nutr 2008; 47: 645–51.
17. Rajmil L, Fernandez de Sanmamed MJ, Choonara I, et al. Impact of the 2008 economic and financial crisis on child health: a systematic review. Int J Environ Res Public Health 2014; 11: 6528–46.
18. Vlachadis N, Kornarou E. Increase in stillbirths in Greece is linked to the economic crisis. BMJ 2013; 346: f1061.
19. Anagnostopoulos DC, Soumaki E. The state of child and adolescent psychiatry in Greece during the international financial crisis: a brief report. Eur Child Adolesc Psychiatry 2013; 22: 131–4.
20. Ferrara P, Caporale O, Cutrona C, et al. Femicide and murdered women's children: which future for these children orphans of a living parent?. Ital J Pediatr 2015; 41: 68.
21. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14: 523–34.
22. Sachedina N, Donaldson LJ. Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. Lancet 2010; 376: 1846–52.
23. Jiao WY, Wang LN, Liu J, et al. Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic. J Pediatr 2020; 221: 264–6.e1.
24. Ehrich JH, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the Debate on Pediatric Subspecialties and Specialist Centers: Opportunities for Better Care or Risks of Care Fragmentation?. J Pediatr 2015; 167: 1177–8.e2.
25. More P. Children are not small adults. Lancet 1998; 352: 630.
26. Shahrour N. Lessons learned from the 2009-2010 H1N1 pandemic. Avicenna J Med 2012; 2: 38–9.
27. Dyregrov A, Yule W, Olff M. Children and natural disasters. Eur J Psychotraumatol 2018; 9: 1500823.
28. Pettoello-Mantovani M, Pop TL, Mestrovic J, et al. Fostering Resilience in Children: The Essential Role of Healthcare Professionals and Families. J Pediatr 2019; 205: 298–9.e1.
29. McIntosh ED, Janda J, Ehrich JH, Pettoello-Mantovani M, Somekh E. Vaccine Hesitancy and Refusal. J Pediatr 2016; 175: 248–9.e1.
30. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014; 165: 424–6.
31. Hojsak I, Fabiano V, Pop TL, et al. Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups. Acta Paediatr 2018; 107: 927–37.
32. Corsello G, Ferrara P, Chiamenti G, Nigri L, Campanozzi A, Pettoello-Mantovani M. The Child Health Care System in Italy. J Pediatr 2016; 177S: S116–26.

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REVIEW ARTICLE

Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups

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ABSTRACT

Aim: The use of probiotics has been covered by many guidelines, position papers and evidence-based recommendations, but few have referred to specific patient groups or clinical indications. This review summarises recommendations and scientifically credited guidelines on the use of probiotics for children with selected clinical conditions and provides practice points.

Methods: An expert panel was convened by the European Paediatric Association in June 2017 to define the relevant clinical questions for using probiotics in paediatric health care and review and summarise the guidelines, recommendations, position papers and high-quality evidence.

Results: The panel found that specific probiotic strains were effective in preventing antibiotic-associated and nosocomial diarrhoea, treating acute gastroenteritis and treating infantile colic in breastfed infants. However, special caution is indicated for premature infants, immunocompromised and critically ill patients and those with central venous catheters, cardiac valvular disease and short-gut syndrome. This review discusses the safety of using probiotics in selected groups of paediatric patients and the quality of the available products providing practice points based on proved findings.

Conclusion: Efficacy of probiotics is strain specific. Their benefits are currently scientifically proven for their use in selected clinical conditions in children and not recommended for certain patient groups.

INTRODUCTION

Knowledge on the role of gut microbiota in health and disease is developing rapidly, and the number of published scientific papers on the benefits of its modifications is increasing exponentially. It is, therefore, of no surprise that the medical community and the general public are asking for evidence-based answers on when and how to modify gut microbiota in order to improve health in general or to treat or prevent specific diseases.

Abbreviations
AAD, Antibiotic-associated diarrhoea; AGE, Acute gastroenteritis; EPA, European Paediatric Association; ESPGHAN, The European Society for Paediatric Gastroenterology, Hepatology and Nutrition; *LGG*, *Lactobacillus rhamnosus* GG; RCT, Randomised controlled trial; RTI, Respiratory tract infections; UNEPSA, Union of National European Paediatric Societies and Associations; URTI, Upper respiratory tract infections.

The ability to manipulate the composition and metabolic footprints of our gut microbiota has been well known for decades, namely through the use of probiotics, prebiotics

Key notes
- This European review summarises recommendations and scientifically credited guidelines on the use of probiotics for children with selected clinical conditions and provides practice points.
- An expert panel convened by the European Paediatric Association found that specific probiotic strains were effective in preventing antibiotic-associated and nosocomial diarrhoea, treating acute gastroenteritis and treating infantile colic in breastfed infants.
- However, special caution is indicated for certain groups, including premature infants, immunocompromised and critically ill patients.

and the combination of these two, known as synbiotics (1). Since 2014, the currently valid definition of probiotics, from the WHO and the International Scientific Association for Probiotics and Prebiotics, has been: 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' (2).

Discussions about how to use probiotics for various clinical indications have been advanced by many different guidelines, position papers and evidence-based recommendations. There has been a more limited number with regard to specific population groups and fewer on the roles of prebiotics and synbiotics. However, their use in vulnerable populations such as in infants and children, and in defined clinical conditions, should be more rigorously controlled. In addition, their use in clinical practice should follow evidence-based recommendations whenever they are available.

That is why the European Paediatric Association, the Union of the National European Paediatric Societies and Associations (EPA/UNEPSA), convened a panel of independent European experts to examine probiotic supplementation. The panel was chosen based on their scientific profile and publication history and all members were active participants in the work and activities of the Association.

The aim of this review was to summarise the scientifically credited guidelines and recommendations that were currently available on the use of probiotics in paediatric healthcare practice (3) and recommend points for use in clinical practice in selected clinical conditions. The panel decided not to include foods containing probiotics, prebiotics and synbiotics, because it is out of the scope of this paper. We also excluded the use of live bacteria to prevent necrotising enterocolitis in premature babies.

METHODS

The panel of experts organised by EPA/UNEPSA, who are the co-authors of the present review, met in person in June 2017. The aim of that meeting was to define the clinical questions of special relevance for the use of probiotics in paediatric health care, to propose the scope of the paper on the review and the outline what would be included, to discuss the research methods and to set the time limits. The document was further developed and discussed by email from June to October 2017, and the final recommendations for clinical practice, called practice points, were agreed on by all the panel members and finally approved during a teleconference in November 2017.

We searched the PubMed and Cochrane Library databases up to September 2017 for any relevant guidelines, recommendations and position papers covering the paediatric clinical indications that were selected and retrieved the most recent high-quality evidence. The searches were limited to documents published in English. If any of the guidelines were unavailable, outdated or inappropriate, and high-quality evidence existed, such as at least two prospective randomised placebo-controlled trials with the same outcome (4), the expert panel used those to formulate its recommendations for paediatric clinical practice.

Probiotics for preventing common infections

Description of the problem

Common acute infections in children are a significant burden for health care, especially for children attending day care centres, who have a two to three times higher chance of acquiring common infections than children who stay at home (5). Most common infections include upper respiratory tract infections (URTI) and acute gastroenteritis (AGE). They also make more outpatient doctor and emergency care visits and higher antibiotic use (6). All that presents a substantial economic burden for the family and the healthcare system in general, with an estimated cost of around 1.8 billion US Dollars per year in the United States (6).

Current preventive measures are of limited effectiveness, and therefore, an increasing number of randomised controlled trials (RCTs) have investigated the role of probiotics in the prevention of common infections in children.

Current recommendations

Currently, there are no recommendations from relevant authorities on the use of probiotics in the prevention of common infections in children attending day care centres.

There are systematic reviews which have evaluated the available literature, and the most recent one, which included a meta-analysis, was published in 2016 (7). That meta-analysis found that probiotics in general reduced the risk of a respiratory tract infection (RTI) by a relative risk (RR) of 0.89 and a 95% confidence interval (95% CI) of 0.82–0.96. However, this meta-analysis had several limitations: age groups were evaluated together and there was no strain-specific analysis. Therefore, it is difficult to extrapolate these results into clinical practice.

Summary of the latest evidence

With respect to the prevention of RTI in general, studies have found an overall positive effect in children beyond infancy (8–15). Most of the studies found reductions in URTIs, but questions remain unanswered about the strains to use and when to recommend them.

There were two probiotic strains examined in more than two well-designed RCTs, and they were *Lactobacillus rhamnosus* GG (LGG) and *Bifidobacterium (B). animalis* subsp. *lactis* (BB-12). LGG was examined in three studies (8,11,13) covering a total of 1375 children receiving doses from 10^8 to 10^9 CFU/day, and all the studies reported positive effects on lowering the incidence of RTIs (16). The other strain investigated in four RCTs (17–20) was *B. animalis* subsp. *lactis BB-12,* and in contrast to LGG, all the results were negative (16). There were no more probiotic strains, or their combinations, evaluated in more than two RCTs.

Most of the studies that investigated probiotic use to prevent URTIs also investigated the risk of acquiring gastrointestinal infections, but the evidence on preventing

gastrointestinal infections was even weaker (16). There were no meta-analyses that assessed the overall effect, and based on literature search, there were no two RCTs that investigated the same probiotic strain and yielded positive results (16). Moreover, both studies that investigated LGG found no effect (8,11) and the similar results were on *B. animalis* subsp. *lactis* (BB-12) (18,19). All these results should be interpreted with caution because most of them were performed in the winter period when the incidence of gastrointestinal infections was lower, and therefore, the valid argument could be that the sample size was not sufficiently powered to assess gastrointestinal risk (16).

Practice points

- If probiotics are considered for the prevention of URTIs in children attending day care centres during the winter months, only LGG should be considered. However, the evidence is limited and meta-analyses confirming its efficacy are lacking.
- There is no convincing evidence to recommend the use of probiotics for preventing gastrointestinal infections in day care centres.

Prevention of nosocomial infections

Description of the problem

Nosocomial or hospital-acquired or health care-associated infections develop during a hospital stay, and they are not present or incubating at admission (21). The incidence of nosocomial infections on paediatric wards is still high, even in developed countries, and ranges from 5% to 10% (22). Gastrointestinal and RTIs account for the most of them. Nosocomial infections have several negative impacts: they worsen outcome of the treatment, prolong hospital stays and increase hospital expenses (10). Current standard preventive measures, such as increased hygiene, have a positive effect and decrease infections spreading, but cannot successfully prevent all of them (23,24).

Current recommendations

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Working Group on Prebiotics and Probiotics recommends that if probiotics for preventing nosocomial diarrhoea are considered, LGG should be used at a dose of least 10^9 CFU/day, for the duration of hospital stay (25). There are no recommendations for preventing RTIs in children hospitalised on paediatric wards.

Summary of the latest evidence

The systematic review from the ESPGHAN Working Group on Prebiotics and Probiotics identified eight RCTs, out of which the majority (n = 3) investigated LGG (25). Analysis of the two RCTs, involving 823 subjects, showed that children provided with LGG during their hospital stay had a reduced risk of nosocomial diarrhoea from 13.9% to 5.2% (RR 0.35, 95% CI 0.19–0.65) (25). *L. reuteri* DSM 17938 was investigated by two RTCs at two different doses and both of them – 10^8 CFU/day (26) and 10^9 CFU/day (27) – were not effective (RR 1.11, 95% CI 0.68–1.81) (25).

There is only limited evidence on the role of probiotics in the prevention of nosocomial URTIs outside intensive care units, and this comprised two, albeit big, RCTs (16). One RCT investigated LGG given to 742 children at a dose of 10^9 CFU and found that it reduced the risk of URTI (25). The other study, performed at the same centre, used *B. animalis* subsp. *lactis* (BB-12) at the same dose and was not able to prove positive effect (28). In conclusion, although there is evidence that some probiotic strains could have been effective in preventing RTIs, the evidence is insufficient to recommend their routine use.

Practice points

- If the use of probiotics for the prevention of nosocomial diarrhoea is considered, only LGG can be recommended and the patient should receive least 10^9 CFU/day for the duration of the hospital stay.
- There is insufficient evidence to recommend probiotic use for the prevention of nosocomial respiratory tract infections.

Prevention of allergy

Description of the problem

Allergic diseases are one of the main health problems in children. The current prevalence varies between 5% and 10% and is still increasing (29). The World Allergy Organization reports that approximately one in five people suffers from some form of allergic disease, such as allergic rhinitis, asthma, conjunctivitis, eczema, food allergies, drug allergies and other severe allergic reactions (30). In the United States, allergies are the sixth leading cause of chronic illness, with an annual cost for health care of 18 billion US Dollars (31). Furthermore, in the last 25 years, admissions for food allergies have increased by 500%, and for anaphylaxis, they have increased by 615% (32,33). The increasing incidence and high burden of allergies on families and on the health system and society, in general, prompts the use of effective preventive strategies, including probiotics, especially for children at high risk of atopic diseases.

Current recommendations

The World Allergy Organization recommends the use of probiotics (i) in pregnant women who are carrying a child with a high risk of allergy, (ii) in breastfeeding women when the infant faces a high risk of allergy and (iii) in infants with atopic predisposition (34).

These recommendations do not address the role of specific strains or their combinations, the dose of probiotics that should be offered or the duration of the treatment. In contrast to The World Allergy Organization, other guidelines do not recommend the use of probiotics in the prevention of atopic diseases due to high variations in the evidence obtained (35–37).

Summary of the latest evidence

There have been numerous RCTs that have investigated the role of probiotics in preventing allergies, mainly atopic dermatitis and sensitisation. Unfortunately, the study protocols differed in respect to probiotic species and strains, in respect to doses and duration of treatment and, most importantly, in respect to the timing of the application, such as only during pregnancy (38,39), during pregnancy and maternal administration during breastfeeding (40–42), during pregnancy and in infants (43–54) and only in infants (55–58).

The most recent meta-analysis comprised 17 RCTs covering 4755 children and showed that the use of probiotics, in general, decreased the risk of atopic dermatitis (RR 0.78, 95% CI 0.69–0.89), especially if a combination of probiotics was used (RR 0.54, 95% CI 0.43–0.68) (59). However, no significant difference in terms of preventing asthma, wheezing or rhinoconjunctivitis was found (59). Other meta-analyses focused on the time when probiotics were administered (60). Pooled analysis showed that probiotics could reduce the risk of atopy most efficiently if administered prenatally to pregnant mother and postnatally to the child (RR 0.71, 95% CI 0.57–0.89) (60). That protocol was, as previously stated, used in the majority of studies. Furthermore, some of these studies followed children for longer periods of time (46–48,52,53). Follow-up studies revealed that, although risk for atopic dermatitis remained reduced over time, the risk for other allergic diseases, such as wheezing and allergic rhinoconjunctivitis, was increased in the probiotic group (47, S61). This provides additional complications for the decision to recommend probiotics. In conclusion, the evidence to recommend specific probiotic strains or combinations for the prevention of atopy is insufficient (35–37).

Practice points

- Based on the currently available evidence, probiotics cannot be recommended for the prevention of atopic diseases.

Probiotics for the prevention of antibiotic-associated diarrhoea

Description of the problem

Antibiotic-associated diarrhoea (AAD) is defined as diarrhoea that occurs in relation to an antibiotic treatment and is attributed to the drugs after the exclusion of other possible aetiologies (S62). AAD is common in children and may affect up to a third of patients treated with antibiotics, especially in the case of broad-spectrum anti-infective drugs (S63). Treatment with probiotics relies on the hypothesis that AAD is due to changes in gut microbiota caused by antibiotics. Younger or immunocompromised children, as well as hospitalised children, may benefit most from a reduction in AAD episodes (S62). In addition to preventing episodes of AAD, further benefits that could be achieved with the probiotics are a decreased duration of hospital stays, reduced medical costs and decreased rates of comorbidity (S62).

Current recommendations

The ESPGHAN Working Group on Prebiotics and Probiotics (S64) recommends the use of LGG or *Saccharomyces (S). boulardii* for the prevention of AAD. Similarly, a 2017 recommendation for Asia-Pacific region children supported the use of LGG or *S. boulardii* for the prevention of AAD (S65).

Summary of the latest evidence

A 2015 Cochrane review (S66) found that the incidence of AAD in the probiotic group was 8% (163/1992) compared to 19% (364/1906) in the control group (RR 0.46, 95% CI 0.35–0.61; $I^2 = 55\%$) based on a total number of 3898 participants. In the ESPGHAN Working Group for Prebiotics and Probiotics Clinical Guidelines (S64), the pooled results of all the available RCTs, namely five studies covering 445 children, showed that, compared with placebos or no treatment, LGG administration reduced the risk of AAD from 23% to 9.6% (RR 0.48, 95% CI 0.26–0.89) and that the number needed to treat was eight (95% CI 6–40), The administration of *S. boulardii* reduced the risk from 20.9% to 8.8% in six RCTs covering 1653 children (RR 0.43, 95% CI 0.30–0.60) and the number needed to treat was nine (95% CI 7–12). Furthermore, *S. boulardii* reduced the risk of diarrhoea associated with *Clostridium difficile* in two RCTs covering 579 children (RR 0.25, 95% CI 0.08–0.73).

Practice points

- In order to prevent AAD, LGG or *S. boulardii* should to be considered.
- *S. boulardii* should also to be considered to prevent *C. difficile*-associated diarrhoea.
- Other strains of probiotics, either single strains or in combination, are not currently recommended.
- No safety data on the use of probiotics for preventing AAD in severely ill children are available, and therefore, their use should be subjected to special scrutiny.

Probiotics for the treatment of acute gastroenteritis

Description of the problem

AGE is a very common disease in children. In Western industrialised countries, it accounts for millions of visits to primary care practices and to emergency department, as well as hospital admissions in developing countries. It still represents one of the major causes of deaths (S67). ESPGHAN has defined AGE as a decrease in consistency of stools – loose or liquid – and, or an increase in the frequency of evacuations, at least three in 24 hours, with or without fever or vomiting (S68). The mainstay of the treatment for AGE is rehydration using oral rehydrating solutions, while drugs are considered unnecessary in the majority of cases (S68). As an adjunct to oral rehydrating solution, administering probiotics could further diminish

the duration of the disease and the severity of the clinical symptoms. That is why it was investigated by several RCTs.

Current recommendations

The position paper by the ESPGHAN Working Group on Prebiotics and Probiotics (S68) summarised all the relevant evidence on the use of probiotics in the treatment of AGE, it recommended that only two live microorganisms, LGG and *S. boulardii*, should be considered in the treatment of AGE in children as an adjunct to oral rehydrating solution (S68). Recommendations for children in the Asia-Pacific region have also strongly supported the use of LGG and *S. boulardii* as adjunct treatments to oral rehydration therapy for gastroenteritis (S65).

Summary of the latest evidence

Combined data from 11 RCTs on 2,444 children (S69) showed that LGG significantly reduced the duration of diarrhoea compared with placebos or no treatment (mean difference −1.05 days, 95% CI −1.7 to −0.4). This was particularly valid for children treated in Europe, as shown in five RCTs involving 744 participants (mean difference −1.3 days, 95% CI −2.0 to −0.5) (S69).

In a review published in 2012, the use of *S. boulardii* at a daily dose of between 250 and 750 mg, compared with placebos or no intervention, significantly reduced both the duration of diarrhoea in 11 RCTs covering 306 subjects (mean difference −0.99 days, 95% CI −1.4 to −0.6) and the risk of diarrhoea on day three in nine RCTs covering 1,128 (RR 0.52, 95% CI 0.4–0.65) (S70). In hospitalised children, the use of *S. boulardii* also reduced the duration of hospitalisation in 449 subjects (mean difference −0.8 days, 95% CI −1.1 to −0.5) (S70).

Practice points

- When treating AGE in children, LGG and *S. boulardii* may be considered as an adjunct to the oral rehydration therapy.
- LGG should be administered for 5 to 7 days, at a dose of $\geq 10^{10}$ CFU/day, and *S. boulardii* should be administered for 5 to 7 days, at a dose of 250–750 mg/day. There are currently no recommendations for other strains or products containing single or multiple strains of probiotics.
- Probiotics should ideally be initiated early in the course of diarrhoea.

Treatment of functional pain disorders

Description of the problem

In respect to functional disorders associated with abdominal pain, probiotics have been investigated for treatment of irritable bowel syndrome and for functional abdominal pain not otherwise specified (S71). According to the last Rome IV criteria (S71), irritable bowel syndrome should be considered if abdominal pain occurs during at least 4 days per month and is associated with a change in frequency of defecation and/or a change in the appearance of stools. Functional abdominal pain is defined as a pain that appears at least four times per month and includes episodic or continuous abdominal pain that does not occur solely during physiologic events and which, after appropriate evaluation, cannot be fully explained by another medical condition (S71). Both conditions are very frequent and affect up to one-third of school-aged children (S72). Furthermore, due to mainly unexplained aetiology, there is no causal treatment. As one of the findings has been altered intestinal microbiota, probiotics were proposed as one of the treatment modalities (S73).

Current recommendations

This review did not find relevant guidelines for the use of probiotics in children with functional abdominal pain disorders.

Summary of the latest evidence

A 2017 meta-analysis showed that probiotics, in general, significantly reduced the frequency of abdominal pain compared to placebos, with a standardised mean difference of −0.55 (95% CI −0.98 to −0.12) (S74). Unfortunately, this meta-analysis did not perform strain-specific analysis. Moreover, the protocols differed in respect to primary outcomes, duration of interventions and type of functional abdominal pain disorders. As a result, clinically relevant recommendations cannot be provided. The only strain-specific meta-analysis evaluated the role of LGG for abdominal pain-related gastrointestinal disorders in children (S75). This meta-analysis included three RCTs and found that the use of LGG moderately decreased pain in the overall population with abdominal pain-related functional gastrointestinal disorders (RR 1.31, 95% CI 1.08–1.59) and in the irritable bowel syndrome subgroup (RR 1.70, 95% CI 1.27–2.27), but not for functional abdominal pain and dyspepsia. However, as this meta-analysis was from 2011, five RCTs were subsequently published, all involving *L. reuteri* DSM 17938 (S76–S80). Of those, three found more pronounced pain reductions in probiotic group (S77–S79). Interestingly, placebos were able to significantly reduce pain intensity as well (S79,S81,S82).

In conclusion, there is some evidence that probiotics could decrease the pain intensity in children with functional abdominal pain disorders and only two stains (LGG and *L. reuteri* DSM 17 938) were proven to be effective in more than two RCTs. However, it was difficult to interpret the results as they included different study protocols, durations of interventions, primary outcomes and type of pain.

Practice points

- Due to the limitations of the available evidence and lack of current guidelines, no recommendation can be provided on the use of probiotics for treating functional abdominal pain disorders.

Probiotics for the prevention and treatment of infantile colic

Description of the problem

Infantile colic is a common problem affecting 10% to 30% of healthy, thriving infants (S83). According to the Rome IV criteria, infantile colic may be diagnosed in an infant who is less than 5 months of age when their symptoms start and stop, they present with recurrent and prolonged periods of crying, fussing or irritability that occur without an obvious cause that cannot be prevented or resolved by caregivers, and in whom there is no evidence of failure to thrive, fever or illness (S84). The aetiology is still undefined, but intestinal dysbiosis has been hypothesised as a possible underlying condition, implying that probiotics could be useful in prevention and/or treatment.

Current recommendations

Currently, no statements and recommendations have been issued by the relevant European Societies and Institutions for the use of probiotics in infant colic. However, Latin-American Guidelines were published in 2015 (S85), and there are recommendations covering children in the Asia-Pacific region (S65), both supporting the use of the strain of *L. reuteri* DSM 17938 for the prevention and treatment of infantile colic.

Summary of the latest evidence

As far as prevention is concerned, although some promising results have been shown with *L. reuteri* DSM 17938, data are scarce (S86). The evidence is stronger for treatment. A review by Szajewska et al. identified four RCTs that showed that the use of *L. reuteri* DMS 17938 reduced crying times in breastfed infants with infantile colic (S87). In contrast, one RCT that recruited both breastfed and formula-fed infants did not confirm this effect (S88). A meta-analysis from 2014 included three RCTs and found that, compared with placebos, administration of *L. reuteri* DSM 17938 reduced crying times on day 21 by 43 minutes (mean difference −43 min/day, 95% CI −68 to −19), but mainly in exclusively or predominantly breastfed infants (mean difference −57 min/day, 95% CI −67 to −46) (S89). Other studied strains (LGG) and mixtures of probiotics did not have an effect (S87).

Practice points

- If the use of probiotic is considered, *L. reuteri* DSM 17938 is the only strain shown to be effective in treating infantile colic in breastfed infants.
- If administered, the dose of *L. reuteri* DSM 17938 should be at least 10^8 CFU/day, provided for 21–30 days.
- Limited evidence on the use of *L. reuteri* DSM 17938 in the prevention of infantile colic precludes specific recommendation.
- There is no evidence for other strains of probiotics or products containing probiotic mixtures.

Safety of probiotic use

Description of the problem

In the recent years, the use of probiotics has increased worldwide, and therefore, it is particularly important that the risks of probiotic treatments are discussed and acknowledged (S90). The most commonly used microbiota are species or strains of *Bifidobacterium*, of *Lactobacillus* and of *Saccharomyces*. The safety issues that are most commonly described in the literature for those three genera, in particular for the LGG (S91) and for *S. boulardii*, are more as a consequence of their frequent use and not a marker of their impaired safety (S92). There are also increased safety concerns on the use of probiotics if other species that belong to the same genera are pathogenic (*Streptococcus, Bacillus* and *Enterococcus*). As each probiotic strain is expected to have a specific clinical effect, the safety profile could possibly be different for each probiotic (S93). However, the safety issues have not been established for most of them and the data have only been generated as secondary outcomes. It is important to note that there are a lack of studies assessing the safety of probiotics as the primary study outcome (S94).

In general, the side effects of probiotic use could be systemic infections, deleterious metabolic activities, immune stimulation in susceptible populations, gastrointestinal symptoms and the transfer of genes coding for potentially dangerous bacterial features, such as antimicrobial resistance (S95). Other possible safety risks include metabolic effects, such as the production of D-lactate with lactic acidosis, deconjugation of bile salt, and short- and long-term immunomodulating effects. The latter are particularly relevant for neonatal use and the transfer of genetic material such as plasmids coding for antimicrobial resistance from probiotic bacteria to more pathogenic bacteria (S90,S91,S94,S95). Finally, there are also adverse effects limited to mild gastrointestinal symptoms, such as abdominal cramping, nausea, diarrhoea, flatulence and of taste alteration, but the studies described no difference compared to the placebo (S94).

Current recommendations

This review could not find relevant recommendations or guidelines related to the safety issues of probiotics. Most of the reported adverse effects were based on case reports or case series and further properly designed RCTs to assess this issue as a primary outcome should be undertaken.

In 2011, the US Agency for Healthcare Research and Quality published a report on the safety of probiotics, based on a systematic review of 622 RCTs (S94). There were four main conclusions to this report. The first referred to the Generally Recognised as Safe Status and said that the evidence that properly addressed the safety of probiotics was limited, but the majority of probiotic strains that were studied should be generally regarded as safe. Secondly, the report stated that there were no safety issues in specific populations and that the case reports suggested that the adverse effects were more frequent in patients with compromised health. Another key finding was that there was no

conclusive evidence that using a mixture of different probiotic strains had more adverse events than using one probiotic strain. The final finding was that the long-term effects of probiotic strains use were unknown (S94).

Summary of the latest evidence

Sepsis. The risk for fungaemia associated with *S. boulardii* is increased in critically ill patients, those in intensive care units, those using mechanical ventilation or fitted with central venous catheters, those treated with broad-spectrum antibiotics and those who are immunosuppressed or premature neonates (S92,S96,S97). Clinical practice guidelines do not recommend the use of *S. boulardii* in patients with *C. difficile* infections who are critically ill (S98). In children, sepsis with Lactobacillus strains has been reported in association with prematurity, short-gut syndrome, cardiac surgery, immunosuppression and cerebral palsy (S99–S104).

Various studies have shown that patients who are potentially at a major risk for septic dissemination are immunocompromised patients, including those in a debilitated state or with a malignancy, and premature infants. Minor risk factors are the presence of a central venous catheter, impaired intestinal barrier, short-gut syndrome, administration of probiotics by jejunostomy, concomitant administration of broad-spectrum antibiotics (probiotics resistance), high mucosal adhesion or the known pathogenicity of probiotic strains and cardiac valvular disease (S64,S90,S105).

Metabolic effects. The Probiotics in Pancreatitis Trial, a multicentre, double-blind, placebo-controlled clinical trial, demonstrated a higher mortality rate in adult patients with severe pancreatitis who were treated with multispecies probiotic preparation in most of the cases due to bowel ischaemia. These were *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum and Bifidobacterium lactis*. The study conclusion was that in patients with severe pancreatitis the probiotics should not be administered (S106, S107). However, this study has been seriously criticised in respect of a number of factors, including its design, choice of patients and outcome variables, and therefore, the final results should be treated with caution.

Effect on immune system development. There are no long-term studies to prove the immunological adverse reactions due to probiotic use in human subjects (S90,S91,S105). However, there are many RCTs where probiotics were given to patients to prevent allergic disease very early in life, including prenatally in pregnant women, and for a long period of time (S46–S48,S52,S53). Follow-ups of these studies revealed that, although the risk for atopic dermatitis remained reduced over time, the risk for other allergic diseases, namely wheezing and allergic rhinoconjunctivitis, was increased in the probiotic group (S47,S61). Those findings imply that probiotics could have a long-term effect on the immune system, but the exact mechanisms and the long-term outcomes are yet to be determined.

The transfer of antimicrobial resistance. The transfer of antimicrobial resistance has been demonstrated for *Lactobacillus,* which is naturally resistant to vancomycin (S90, S91). LGG has no plasmids that contain transferable or other antibiotic resistance (S91). *Lactobacillus reuteri* ATCC 55730 had a transferable resistance trait for tetracycline and lincomycin and therefore was replaced by a new strain, *L. reuteri* DSM 17938 (S108). The use of *Enterococcus faecium* SF68 strain in acute gastroenteritis was not recommended for children due to the possible transfer of vancomycin-resistant genes (S109).

Practice points

- The use of probiotics in children seems to be safe in general, even when provided in high doses.
- Probiotics should be used with caution in special situations, such as prematurity, immunocompromised patients, critically ill patients, those with central venous catheter, cardiac valvular disease and short-gut syndrome.
- Some probiotic strains are not recommended for use in children, such as Enterococcus *faecium* SF68, due to the possible transfer of vancomycin-resistance genes.
- In children with the *C. difficile* infection, *S. boulardii* is proven to be efficacious; however, due to the potential infectious spread, special caution is required in critically ill patients.

Quality of the commercial probiotic products

Description of the problem

Increased awareness and knowledge of the potential benefits of probiotics have resulted in the exponential growth in number of commercial products, making it one of the fastest growing global markets with the best forecast for further growth up to 2020 (S110). Probiotic products are coming onto the market in a wide range of different forms. For example, they are being added to foods or provided as supplements packed into capsules, pills, suspensions, powder sachets, sprays and granulates. However, because they are categorised as dietary, food supplements (S111), foods for specific health use (S112) or as natural health products (S113), probiotic products have to comply with significantly less stringent criteria than medicinal products or drugs. This raises doubts about their quality and that is why the ESPGHAN Working Group for Prebiotics and Probiotics performed a literature search and provided recommendations (S114). Based on their review of the literature, the authors concluded that the majority of studies reported on more than one labelling inconsistency in most of the tested products. The strains were frequently misidentified and misclassified, the products were occasionally contaminated with facultative or even obligatory pathogens, strains were not viable, and the number of colonies was diminished to the extent that precluded health benefit. Probiotic products licensed as drugs were also affected, although not to the same extent (S114).

Table 1 Summary of proposed practice points for every reported clinical indication

Clinical indication	Practice points
Prevention of common infections	• If probiotics are considered for prevention of upper respiratory tract infections in children attending day care centres during winter months, only LGG could be considered. However, evidence is limited and meta-analyses confirming its efficacy are lacking. • There is no convincing evidence to recommend the use of probiotic for the prevention of gastrointestinal infections in day care centres.
Prevention of nosocomial infections	• If the use of probiotic for prevention of nosocomial diarrhoea is considered, only LGG (at least 10^9 CFU/day, for the duration of hospital stay) can be recommended. • The evidence to recommend probiotic use in the prevention of nosocomial respiratory tract infections is insufficient.
Prevention of allergy	• Based on the currently available evidence, probiotics cannot be recommended for prevention of atopic diseases.
Prevention of antibiotic-associated diarrhoea	• In prevention of AAD, LGG or *S. boulardii* should be considered. • *S. boulardii* is also to be considered in the prevention of C difficile-associated diarrhoea. • Other strains of probiotics, single or in combination, are currently not recommended. • No safety data on the use of probiotics for prevention of AAD in severely ill children are available; thus, their use should be subjected to special scrutiny.
Treatment of acute gastroenteritis	• In the treatment of AGE in children, LGG and *S. boulardii* may be considered as an adjunct to the oral rehydration therapy. • LGG should be administered for 5–7 days, at dose $\geq 10^{10}$ CFU/day. • *S. boulardii* should be administered for 5–7 days, at dose 250–750 mg/day. • Other strains or products containing single or multiple strains of probiotics have currently no recommendation. • Probiotic should ideally be initiated early in the course of diarrhoea.
Treatment of functional abdominal pain disorders	• Due to limitations of the available evidence and lack of current guidelines, no recommendation can be provided on the use of probiotics in the treatment of functional abdominal pain disorders.
Probiotics for prevention and treatment of infantile colic	• If the use of probiotic is considered, *L. reuteri* DSM 17938 is the only strain shown to be effective in the treatment of infantile colic in breastfed infants. • If administered, the dose of *L. reuteri* DSM 17938 is to be at least 10^8 CFU/day, provided for 21–30 days. • Limited evidence on the use of *L. reuteri* DSM 17938 in the prevention of infantile colic precludes specific recommendation. • Other strains of probiotics or products containing probiotic mixtures have currently no evidence.
Safety of probiotic use	• The use of probiotics in children seems to be safe in general, even when provided in high doses. • Probiotics should be used with caution in special situations such as prematurity, immunocompromised patients, critically ill patients, central venous catheter, cardiac valvular disease and short-gut syndrome. • Some probiotic strains are not recommended to be used in children, such as Enterococcus faecium SF68, due to the possible transfer of vancomycin-resistance genes. • In children with *C. difficile* infection *S. boulardii* is proven to be efficacious, however due to potential infectious spread, a special caution is required in critically ill patients.
Quality of the commercial probiotic products	• To secure that the patient will receive a probiotic product that meets the required quality cannot be solved by the health practitioner, and therefore, this paper does not provide practice points on this issue.

AAD = antibiotic-associated diarrhoea; LGG = *Lactobacillus rhamnosus* GG.

Current recommendations

Due to the important quality issues listed above, and to establish the documented effect on health, the ESPGHAN Working Group recommended the following (S114): (i) a precise identification of the microorganisms to strain level; (ii) products prescribed for specific clinical indications and situations to be subjected to rigorous clinical trials; (iii) systematic quality controls by the respective authorities to confirm the viability- and strain-level identification of the active ingredients; (iv) adverse events, potentially related to probiotic products should be reported and a register of those events should be maintained by health authorities (S114).

Summary of the latest evidence

Since the publication of the ESPGHAN Position Paper (S114), one further paper provided a consumer's guide for the use of probiotics (S115). However, neither of them can solve the problem of quality issues and should be considered as calls for improvement of the regulatory control mechanisms.

Practice points

- The health practitioner cannot ensure, on his or her own, that the patient receives a probiotic product that meets the required quality. For that reason, this paper does not provide practice points on this issue. This issue needs to be resolved by the respected regulatory agencies, including the European Pharmacopoeia which proposed, in a paper published 2017, actions to harmonise quality standards for live biotherapeutic products used in human health care (S116).

CONCLUSION

Probiotics have been prescribed to children since birth with increased frequency, in order to either prevent or treat various clinical conditions. Therefore, the EPA-UNEPSA expert panel defined the clinical conditions that have special relevance for the use of probiotics in paediatric health care. Based on the current guidelines and recent high-quality evidence, they have provided instructions for their use in paediatric health care in Europe.

Positive instructions on the use of strictly defined strains are suggested for (i) the prevention of upper respiratory tract infections in children attending day care centres; (ii) the prevention of nosocomial diarrhoea; (iii) the prevention of antibiotic-associated diarrhoea; (iv) the treatment of acute gastroenteritis; and (v) the treatment of infantile colic in breastfed babies (Table 1).

Probiotics are not recommended for (i) the prevention of gastrointestinal infections in day care centres; (ii) the prevention of nosocomial respiratory tract infections; (iii) the prevention of atopic diseases; (iv) the prevention of infantile colic; and (v) the treatment of functional abdominal pain disorders (Table 1).

All the practice points, listed in Table 1, are based on the current literature. However, the knowledge of probiotics is developing and future studies may reveal positive effects for other clinical conditions and for other probiotic strains.

Although probiotics are generally regarded as safe, there are clinical conditions in which their use requires special caution, such as prematurity, immunocompromised patients, critically ill patients, those with a central venous catheter, cardiac valvular disease and short-gut syndrome.

Improved control mechanisms by the respective regulatory agencies are advocated to ensure that patients receive commercial probiotic products that meet the required quality.

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CONFLICTS OF INTEREST

Iva Hojsak has been a clinical investigator and, or, speaker for Biogaia, Chr Hansen, Biogaia, Medisadria, Nutricia, Pharmas. Olivier Goulet has been a clinical investigator and/or speaker for Fresenius Kabi, Danone and Biocodex. Fugen Cullu Çokuğraş has been a speaker for Abbott and Danone. Sanja Kolaček has been a clinical investigator and/or speaker for Abbott, Abbvie, Biogaia, Chr Hansen, Danone, MEDIS, Nestle, Nutricia and MSD. The other authors have no conflict of interest to declare.

References

1. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol* 2017; 14: 491–502.
2. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014; 11: 506–14.
3. Gerber-Grote A, Namazova-Baranova L, Hoey H, Pettoello-Mantovani M, Vural M, Mestrovic J, et al. European Paediatric Association, the Union of National European Paediatric Societies and Associations Turns 40 Years: What This European Platform Offers to Pediatricians. *J Pediatr* 2017; 186: 217–8.
4. Center for Drug Evaluation and Research; Center for Biologics Evaluation and Research. Guidance for industry: providing clinical evidence of effectiveness for human drug and biological products, 1998. Available at: http://www.fda.gov/downloads/Drugs%20/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf.
5. Silverstein M, Sales AE, Koepsell TD. Health care utilization and expenditures associated with child care attendance: a nationally representative sample. *Pediatrics* 2003; 111: 371–5.
6. Haskins R. Acute illness in day care: how much does it cost? *Bull N Y Acad Med* 1989; 65: 319–43.
7. Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, et al. Probiotics for prevention and treatment of respiratory tract infections in children: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2016; 95: e4509.
8. Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ* 2001; 322: 1327.
9. Lin JS, Chiu YH, Lin NT, Chu CH, Huang KC, Liao KW, et al. Different effects of probiotic species/strains on infections in preschool children: a double-blind, randomized, controlled study. *Vaccine* 2009; 27: 1073–9.
10. Hojsak I, Abdovic S, Szajewska H, Milosevic M, Krznaric Z, Kolacek S. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. *Pediatrics* 2010; 125: 1171–7.
11. Hojsak I, Snovak N, Abdovic S, Szajewska H, Misak Z, Kolacek S. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. *Clin Nutr* 2010; 29: 312–6.
12. Merenstein D, Murphy M, Fokar A, Hernandez RK, Park H, Nsouli H, et al. Use of a fermented dairy probiotic drink containing Lactobacillus casei (DN-114 001) to decrease the rate of illness in kids: the DRINK study. A patient-oriented, double-blind, cluster-randomized, placebo-controlled, clinical trial. *Eur J Clin Nutr* 2010; 64: 669–77.
13. Kumpu M, Kekkonen RA, Kautiainen H, Jarvenpaa S, Kristo A, Huovinen P, et al. Milk containing probiotic Lactobacillus rhamnosus GG and respiratory illness in children: a randomized, double-blind, placebo-controlled trial. *Eur J Clin Nutr* 2012; 66: 1020–3.
14. Leyer GJ, Li S, Mubasher ME, Reifer C, Ouwehand AC. Probiotic effects on cold and influenza-like symptom incidence and duration in children. *Pediatrics* 2009; 124: 172–9.
15. Gutierrez-Castrellon P, Lopez-Velazquez G, Diaz-Garcia L, Jimenez-Gutierrez C, Mancilla-Ramirez J, Estevez-Jimenez J, et al. Diarrhea in preschool children and Lactobacillus reuteri: a randomized controlled trial. *Pediatrics* 2014; 133: 904–9.
16. Hojsak I. Probiotics in Children – What is the Evidence? *Pediatr Gastroenterol Hepatol Nutr* 2017; 20: 139–46.
17. Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. *Pediatrics* 2005; 115: 5–9.

18. Merenstein DJ, Smith KH, Scriven M, Roberts RF, Sanders ME, Petterson S. The study to investigate the potential benefits of probiotics in yogurt, a patient-oriented, double-blind, cluster-randomised, placebo-controlled, clinical trial. *Eur J Clin Nutr* 2010; 64: 685–91.
19. Merenstein D, Gonzalez J, Young AG, Roberts RF, Sanders ME, Petterson S. Study to investigate the potential of probiotics in children attending school. *Eur J Clin Nutr* 2011; 65: 447–53.
20. Hojsak I, Mocic Pavic A, Kos T, Dumancic J, Kolacek S. Bifidobacterium animalis subsp. lactis in prevention of common infections in healthy children attending day care centers - Randomized, double blind, placebo-controlled study. *Clin Nutr* 2016; 35: 587–91.
21. World Health Organization DoCD, Surveillance and Response. *Prevention of hospital-acquired infections*. Geneva, Switzerland: World Health Organization, 2002. Publication WHO/ CDS/CSR/EPH/2002.12.
22. World Health Organisation/Patient Safety. *Report on the burden of endemic health care-associated infection worldwide*. Geneva, Switzerland: World Health Organization, 2011.
23. Posfay-Barbe KM, Zerr DM, Pittet D. Infection control in paediatrics. *Lancet Infect Dis* 2008; 8: 19–31.
24. Ejemot-Nwadiaro RI, Ehiri JE, Arikpo D, Meremikwu MM, Critchley JA. Hand washing promotion for preventing diarrhoea. *Cochrane Database Syst Rev* 2015; 9: CD004265.
25. Hojsak I, Szajewska H, Canani RB, Guarino A, Indrio F, Kolacek S, et al. Probiotics for the prevention of Nosocomial diarrhea in children. *J Pediatr Gastroenterol Nutr* 2018; 66: 3–9.
26. Wanke M, Szajewska H. Lack of an effect of Lactobacillus reuteri DSM 17938 in preventing nosocomial diarrhea in children: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2012; 161: 40–3.
27. Urbanska M, Gieruszczak-Bialek D, Szymanski H, Szajewska H. Effectiveness of *Lactobacillus reuteri* DSM 17938 for the prevention of Nosocomial diarrhea in children: a randomized, double-blind. placebo-controlled trial. *Pediatr Infect Dis J* 2016; 35: 142–5.
28. Hojsak I, Tokic Pivac V, Mocic Pavic A, Pasini AM, Kolacek S. Bifidobacterium animalis subsp. lactis fails to prevent common infections in hospitalized children: a randomized, double-blind, placebo-controlled study. *Am J Clin Nutr* 2015; 101: 680–4.
29. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn J, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J* 2013; 6: 21.
30. Pawankar R, Walkter Canonica G, Holgate ST, Lockey RF. World Health Organization. White Book on Allergy, 2011–2012. Executive Summary.
31. Centers for Disease Control and Prevention. Allergies, 2011. Available at: https://www.cdc.gov/healthcommunication/toolstemplates/entertainmented/tips/Allergies.html.
32. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007; 62: 91–6.
33. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992–2012. *J Allergy Clin Immunol* 2015; 135: 956–63.
34. Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, Agarwal A, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics. *World Allergy Organ J* 2015; 8: 4.
35. Schafer T, Bauer CP, Beyer K, Bufe A, Friedrichs F, Gieler U, et al. S3-Guideline on allergy prevention: 2014 update: guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Society for Pediatric and Adolescent Medicine (DGKJ). *Allergo J Int* 2014; 23: 186–99.
36. ASCIA Guidelines. Infant feeding and allergy prevention, 2016. Available at: https://www.allergy.org.au/patients/allergy-prevention/ascia-guidelines-for-infant-feeding-and-allergy-prevention.
37. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014; 69: 590–601.
38. Ou CY, Kuo HC, Wang L, Hsu TY, Chuang H, Liu CA, et al. Prenatal and postnatal probiotics reduces maternal but not childhood allergic diseases: a randomized, double-blind, placebo-controlled trial. *Clin Exp Allergy* 2012; 42: 1386–96.
39. Boyle RJ, Ismail IH, Kivivuori S, Licciardi PV, Robins-Browne RM, Mah LJ, et al. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy* 2011; 66: 509–16.
40. Huurre A, Laitinen K, Rautava S, Korkeamaki M, Isolauri E. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. *Clin Exp Allergy* 2008; 38: 1342–8.
41. Dotterud CK, Storro O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol* 2010; 163: 616–23.
42. Rautava S, Kainonen E, Salminen S, Isolauri E. Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. *J Allergy Clin Immunol* 2012; 130: 1355–60.
43. Abrahamsson TR, Jakobsson T, Bottcher MF, Fredrikson M, Jenmalm MC, Bjorksten B, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119: 1174–80.
44. Abrahamsson TR, Jakobsson T, Bjorksten B, Oldaeus G, Jenmalm MC. No effect of probiotics on respiratory allergies: a seven-year follow-up of a randomized controlled trial in infancy. *Pediatr Allergy Immunol* 2013; 24: 556–61.
45. Allen SJ, Jordan S, Storey M, Thornton CA, Gravenor MB, Garaiova I, et al. Probiotics in the prevention of eczema: a randomised controlled trial. *Arch Dis Child* 2014; 99: 1014–9.
46. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; 357: 1076–9.
47. Kalliomaki M, Salminen S, Poussa T, Isolauri E. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119: 1019–21.
48. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003; 361: 1869–71.
49. Kopp MV, Hennemuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus GG supplementation. *Pediatrics* 2008; 121: 850–6.
50. Kim JY, Kwon JH, Ahn SH, Lee SI, Han YS, Choi YO, et al. Effect of probiotic mix (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. *Pediatr Allergy Immunol* 2010; 21: 386–93.

51. Niers L, Martin R, Rijkers G, Sengers F, Timmerman H, van Uden N, et al. The effects of selected probiotic strains on the development of eczema (the PandA study). *Allergy* 2009; 64: 1349–58.
52. Wickens K, Black PN, Stanley TV, Mitchell E, Fitzharris P, Tannock GW, et al. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2008; 122: 788–94.
53. Wickens K, Black P, Stanley TV, Mitchell E, Barthow C, Fitzharris P, et al. A protective effect of *Lactobacillus rhamnosus* HN001 against eczema in the first 2 years of life persists to age 4 years. *Clin Exp Allergy* 2012; 42: 1071–9.
54. Wickens K, Stanley TV, Mitchell EA, Barthow C, Fitzharris P, Purdie G, et al. Early supplementation with Lactobacillus rhamnosus HN001 reduces eczema prevalence to 6 years: does it also reduce atopic sensitization? *Clin Exp Allergy* 2013; 43: 1048–57.
55. Soh SE, Aw M, Gerez I, Chong YS, Rauff M, Ng YP, et al. Probiotic supplementation in the first 6 months of life in at risk Asian infants–effects on eczema and atopic sensitization at the age of 1 year. *Clin Exp Allergy* 2009; 39: 571–8.
56. West CE, Hammarstrom ML, Hernell O. Probiotics during weaning reduce the incidence of eczema. *Pediatr Allergy Immunol* 2009; 20: 430–7.
57. Prescott SL, Wiltschut J, Taylor A, Westcott L, Jung W, Currie H, et al. Early markers of allergic disease in a primary prevention study using probiotics: 2.5-year follow-up phase. *Allergy* 2008; 63: 1481–90.
58. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007; 119: 184–91.
59. Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A, et al. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. *Allergy* 2015; 70: 1356–71.
60. Zhang GQ, Hu HJ, Liu CY, Zhang Q, Shakya S, Li ZY. Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2016; 95: 2562.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Supplementary References.

The Diversity of Pediatric Residency Programs across Europe: Admission Procedures, Curricula and Duration of Courses

Ruya Meric, MD[1], Roy Gavin Stone, MD[2], Vasile Valeriu Lupu, MD[3], Søren Lomholt, MD[4], Marija Slobođanac, MD[5], Balázs Andras Maár, MD[6], and Enrica Manca, MD[7]

The European Young Paediatricians Association[1] (EURYPA) is an independent pan-European scientific association created with the aim of supporting the educational efforts of the new generations of European pediatricians. The overall purpose is to improve the health of children through networking, educational initiatives, training, multicenter research projects, and sharing of opportunities among pediatric residents, trainees and young pediatricians.[2] The purpose of this commentary is to describe the activities of EURYPA and to discuss the issue of the diversity of pediatric residency programs across Europe, with the aim of contributing to the debate on how these programs should evolve in the context of the different European changing and often diverging healthcare systems.

The EURYPA Association: Foundation and Current Goals

EURYPA was founded in 2015 through the efforts of delegates belonging to the young pediatricians and residents sections of 11 major national European pediatric societies. Its activities developed in close collaboration with the European Paediatric Association (EPA), the Union of the National European Paediatric Societies and Associations (UNEPSA), with whom EURYPA shares common efforts to promote children's rights to health, equity, and social justice.[3,4]

The first formal meeting was held in October 2015 in Padua, Italy, promoted by the Italian Society of Pediatrics and the Turkish Pediatric Association, and the first congress celebrated in Istanbul in December 2015. EURYPA has held 6 international meetings throughout the years, in collaboration with several national European pediatric societies. The statute of the organization was instated in June, 2019, in Dublin, Ireland during the EURYPA congress organized in parallel to the 9th Europediatrics meeting, and the assembly elected the current board of directors (**Table I**; available at www.jpeds.com). Eligibility criteria for EURYPA membership include medical doctors in pediatric training and pediatricians within 5 years of completion of pediatric residency. To facilitate the further development of the membership, registrations are completed through a website or by mail.[1] There are no age restrictions on membership, which expires after 10 years of completion of residency.

Increasing Opportunities through Networking

Varying healthcare systems, diverse cultures, differing and often incompatible national economic strategies, and geographical issues are barriers to the development of a homogeneous pediatric training across Europe. Although achieving a uniform program is outside of the scope of EURYPA, efforts toward improvement are not.[5] Free movement within and across the European Schengen border-free zone and implementation of European working directives, have changed the workplace for better and contributed toward equal opportunity for pediatric trainees across Europe.[6] However, availing of this opportunity and embarking into different "healthcare ecosystems" is difficult without local knowledge opportunities and chances for networking and communication.[7] Among the goals of EURYPA is to help trainees to overcome these barriers.

To this purpose, EURYPA is working actively to create a platform for networking and communication among European residents and young pediatricians through symposiums, congresses, courses, and summer schools. EURYPA is also actively maintaining and expanding its networking among the member countries, through sessions hosted by national European pediatric societies (in Moscow in February 2020).

Through the EURYPA link program developed online, individual members will have a reference person in each member country who will act as a local focal point to gather and distribute information regarding the circulation from 1 EURYPA member state to another. This network of collegiality aims to provide a resource to implement the local knowledge needed to promote exchange of educational and scientific information,

EPA	European Paediatric Association
EURYPA	European Young Paediatricians' Association
UNEPSA	Union of the National European Paediatric Societies and Associations

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Table II. Length of education, type of admission procedure to residency, and work hours of residents in pediatrics in 8 European nations

Country	Years of medical school	Admission to residency by test	Admission to residency by interview	Years of residency course	Work hours/week
Croatia	6	No	Yes	5	40
Denmark	6	No	Yes	5	37
Hungary	6	None	–	5	40
Ireland	4-5	No	Yes	7	42
Italy	6	Yes	No	5	38
Romania	6	Yes	No	5	35
Russia	6	Yes	No	2	40
Turkey	6	Yes	No	4	40

international training programs, and imparting skills as well as work opportunities for young European pediatricians.

Diversity in Admission Procedures, Duration, and Pediatric Training Curricula of Residency Courses in Europe

Developing a comparable and assessable medical education systems is not an easy task in Europe. A previous study performed by EPA/UNEPSA in 2014 showed profound diversities among the EU28 postgraduate pediatric programs, which were attributable to a multiplicity of factors.[8] In 2019, the EURYPA working group on education, through its networking and information sharing platform, started a project aiming to explore the diversity among pediatric residency programs in Europe. The preliminary report, discussed during the annual EURYPA-EPA/UNEPSA joint conference in Istanbul, studied key diversity issues, including admission procedures, duration of courses, type of education and curricula, night shifts and salary, in 8 European EU (Ireland, Romania, Italy, Hungary, Denmark, Croatia), and other countries (Turkey, Russia).[9]

A major difference between countries shown by the EURYPA report is the variable duration of pediatric training. In each of the 8 countries studied, medical degrees are awarded after the completion of a 6-year degree program. However, the duration of pediatric postgraduate education is quite variable; in Ireland, a residency in pediatrics lasts 7 years; in Hungary, Denmark, Italy, Romania, and Croatia it is 5 years; in Turkey 4 years; and in Russia 2 years. Differences exists also in the admission procedures; Russia, Italy, Romania, and Turkey require various types of admission tests, whereas Denmark, Croatia, Ireland, and Hungary enroll the residents through different kinds of interview processes. Working hours per week, not including night shifts, show differences between the national systems studied between EU and non-EU countries, and also within EU countries (**Table II**).

A further diversity shown by the EURYPA preliminary report is the difference of pediatric curricula between the various countries, which in several cases leads the governments to issue different kind of professional titles, causing a substantial later confusion in describing and assigning competences to pediatricians. This inconsistent terminology is particularly confusing in reference to the organization of community and children's (nonhospital) first-contact services, because significant differences exist among the various pediatric healthcare systems in Europe, where the 3 existing main models of pediatric care are based on whether primary care general physicians, primary care pediatricians, or combinations of both are primarily responsible for children's care.[10] Existing differences between curricula may also reflect the absence of postgraduate education programs, including primary care pediatrics in some European nations.[11] The EURYPA report showed that in all 8 countries studied, residents in pediatrics receive training in secondary and tertiary care. However in Romania, Denmark, and Ireland there is very little or no training in primary care pediatrics (**Table III**; available at www.jpeds.com). Although the management of first-contact services is in fact a well-recognized social issue in Europe, it is subjected to frequent changes of political strategy and policies of the single nations, and often challenged by economic contingencies, as shown by the 2009 global crisis.[12]

Conclusions

The future of pediatric healthcare in Europe will be a serious challenge in the next years. It may be characterized not only by a shortage of pediatricians, as anticipated by several studies, but also by a shortage of well-trained newly accredited pediatricians.[13-15] EURYPA is fully engaged in studying and showing the contradictions and seemingly irreconcilable differences of the diverse European health systems, with the aim to raise the attention of legislators about the need of a unitary vision, leading to the development of effective and coherent pediatric training programs in Europe. ■

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References

1. European Young Pediatricians Association. www.eurypa.org. Accessed March 1, 2020.

2. Lupu A, Erfidan E, Ferreira-Magalhaes M, Lewis S, Lupu VV, Fitzgerald M, et al. The evolution of the European Young Pediatricians Association (EURYPA). J Pediatr 2019;207:267-8.e1.
3. European Paediatric Association/Union of National European Paediatric Societies and Associations. www.epa-unepsa.org. Accessed March 1, 2020.
4. Gerber-Grote A, Namazova-Baranova L, Hoey H, Pettoello-Mantovani M, Vural M, Mestrovic J, et al. European Paediatric Association, the Union of National European Paediatric Societies and Associations Turns 40 Years: what this European platform offers to pediatricians. J Pediatr 2017;186:217-8.e2.
5. Gray S, Raschetti R, Beşer ÖF, Elicin PU, Aversa S, Pamuk G, et al. European Young Pediatricians Association: laying the foundations for collaboration, integration, and networking among pediatricians of the future. J Pediatr 2016;171:324-5.e1.
6. European Union Commission. Schengen area. https://ec.europa.eu/home-affairs/what-we-do/policies/borders-and-visas/schengen_en. Accessed March 13, 2020.
7. DXC. Technology. Connected Healthcare Ecosystems. www.dxc.technology/au/offerings/146241-connected_healthcare_ecosystems. Accessed March 13, 2020.
8. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
9. European Young Pediatrician Association-EPA/UNEPSA joint Conference. Istanbul, 1-2 December 2019. Proceedings. Berlin, Germany: EPA/UNEPSA; 2019.
10. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of Pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
11. Ehrich JH, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-8.e2.
12. Pettoello-Mantovani M, Namazova-Baranova L, Ehrich J. Integrating and rationalizing public healthcare services as a source of cost containment in times of economic crises. Ital J Pediatr 2016;42:18.
13. Ehrich J, Pettoello-Mantovani M. Never-ending stories, the loop in pediatrics-how many pediatricians need to be trained in European countries to keep the pediatric workforce stable? J Pediatr 2018;196:332-3.e3.
14. Ehrich J, Fruth J, Jansen D, Gerber-Grote A, Pettoello-Mantovani M. How to calculate the risk of shortage and surplus of pediatric workforce? J Pediatr 2018;199:286-7.e2.
15. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Diversity of child health care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations. J Pediatr 2016;177S:S1-10.

Table I. 2020 EURYPA organizational chart: Board of directors

President	Ruya Meric, MD, Istanbul Medical Faculty-Cerrahpasa (Turkey)
Vice President	Roy Gavin Stone, MD, Children's Health Ireland at Crumlin (Ireland)
Secretary General	Vasile Valeriu Lupu, MD, "Grigore T. Popa" University of Medicine (Romania)
Assistant Secretary	Søren Lomholt, MD, Viborg Regional Hospital (Denmark)
Assistant Secretary	Marija Slobodanac, MD, Health Centre Đakovo (Croatia)
Treasurer	Balazs Andras Maar, MD, Heim Pál National Pediatric Institute (Hungary)
Assistant Treasurer	Enrica Manca, MD, University of Foggia (Italy)

Table III. Clinical work settings included in the training of pediatric residents in 8 European nations

Country	Primary care	Secondary care	Tertiary care
Croatia	•	•	•
Denmark	–	•	•
Hungary	•	•	•
Ireland	–	•	•
Italy	•	•	•
Romania	–	•	•
Russia	•	•	•
Turkey	•	•	•

The Diversity of Pediatric Residency Programs across Europe: Quality Assurance of Training, Night Shifts, and Wages

Ruya Meric, MD[1], Roy Gavin Stone, MD[2], Vasile Valeriu Lupu, MD[3], Søren Lomholt, MD[4], Marija Slobodanac, MD[5], Balázs Andras Maár, MD[6], and Enrica Manca, MD[7]

Debating the activities of the European Young Paediatricians Association[1] (EURYPA) and the issue of diversity of pediatric residency programs across Europe, we discussed the diversity in admission procedures, duration, and pediatric training curricula of residency courses in Europe.[2] We now discuss the issues of quality assurance of training, night shifts, and wages, which are of great importance for pediatric residents in Europe.

The Issue of Quality Assurance for Pediatric Postgraduate Education in Europe

Quality assurance (QA) and quality improvement (QI) methods[3] used to evaluate activities, review performances, and testing within normal educational requirements, are of key importance for the benefit of medical students and residents, doctors, and certainly for the health of people. However, a proper and dependable QA and QI for pediatric training, applicable to all European nations, seems to be currently a mirage, mainly owing to the profound diversity of healthcare systems and postgraduate pediatric training programs within and between EU and non-EU European countries.[4] Such diversity seems to be somehow irreconcilable, because the existing profound diversities of pediatric training among the 50 European countries[5] are traceable to a multiplicity of factors. They include the significant differences among the various pediatric healthcare systems, the organization of children's (nonhospital) first contact services, the variable importance given by some nations to community and primary care pediatrics, and the budget cuts to healthcare services, which are frequently used by governments to reduce national deficits.[6]

At least 4 types of mainstream healthcare systems coexist in Europe (Bismarck, Beveridge, Semashko, and free market).[7,8] A classification by the Organization for Economic Cooperation and Development showed that European countries variously adopt more than 25 different combinations of regulation, financing, and provision, based on whether healthcare is state based, societal based, private based, or a completely mix type, which may in part explain why different countries need different types of pediatric healthcare professionals.[9] Furthermore, 1 study emphasized that significant and consistent diversities exist also between pediatric training programs performed in each of the EU-27 countries.[4,10] The European Union of Medical Specialists (Union Européenne des Médecins Spécialistes), a private nongovernmental organization regulated by Belgian law, which represents the national associations of medical specialists defending their interests, has collaborated for many years with the European Union (EU) in developing European standards in postgraduate medical specialist training. However, its long-lasting task is still in progress, as a satisfactory and dependable QA and QI of postgraduate medical education is based on comparable educational goals among different healthcare systems.[11] In absence of these factors, to develop a credible QA and QI standardized analysis in higher education applicable to the European Nations seems to be currently unrealistic. The existing significant diversities among different healthcare systems, cultural views, and medical educational systems in Europe seem to represent a major obstacle to a proper and dependable QA and QI assessment.

Regulations of Night Shifts of Pediatric Residents in Europe

The majority of European states (47/50) belong to the Council of Europe (CE).[12] They maintain their sovereignty, but commit themselves through conventions and treaties. The CE is well-distinct from the 27-nation EU, although it is sometimes confused with it. Unlike the EU, the CE cannot make binding laws, although it does have the power to enforce select international agreements reached by European states on various topics and the member states adopt the CE directives, which are integrated in their national laws.[13]

In 2003, the CE issued a general directive, which regulates working hours, maximum hours of duty, rest time during working hours, and maximum weekly working hours for all

CE	Council of Europe
EU	European Union
EURYPA	European Young Paediatricians Association
QA	Quality assurance
QI	Quality improvement

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professions. The directive instructs the member states that the average working time for healthcare professionals, including residents, should not exceed 48 hours in a 7-day period and a daily rest of 11 consecutive hours per 24-hour period, a rest period for every 6 hours must be adopted by state rules or through collective agreements.[13] However, a broad flexibility exists in how the member states comply with the CE directive. For instance, some of the countries give the residents the next day off to rest after their duty hours, whereas others do not. EURYPA studied the compliance to the CE directive on night shifts, in 6 European EU (Ireland, Romania, Italy, Hungary, Denmark, and Croatia) and 2 non-EU (Turkey and Russia) countries. Residents in these countries have comparable working hours per week; however, the calculation does not include nightshifts.[2] The number of night shifts usually depends on the hospital that residents works in. The average number of hours per week per night shift and the number of night shifts per month performed by residents in pediatrics in the 8 countries studied, and whether they benefit of resting time after the night shifts, are shown in **Figure 1** (available at www.jpeds.com). Among the hardest part of being a resident are the night shifts. The long and restless working hours in a job with high expectations from the patients generate a burden that can negatively impact the quality of work. On-call requirements, crowded emergency departments, busy neonatal intensive care units, the unstable inpatients, undetermined treatment protocols, and challenging physical conditions may well contribute to "burnout." There are country-specific efforts being made to balance residents' working time and night shifts, although they seem to be unsuccessful.

The Broad Difference of Residents' Wages between European Countries

In Europe, there are 3 main models of pediatric healthcare, which are based on whether primary care general physicians, primary care pediatricians, or combinations of both are primarily responsible for care.[11,15] This important factor significantly contributes to the differences among the pediatric healthcare systems currently adopted and in constant evolution in the various countries, and influence the type of competences required of pediatricians. A major effort is currently undertaken by the European pediatric societies, aimed at developing a corpus of recommendations which could be adopted by the various countries in order to coherently remodel and update their pediatric healthcare systems, while respecting local needs.[15] European healthcare systems are therefore evolving and need changes, and so are the capabilities physicians need to best practice medicine and serve their patients' needs. Pediatric medical education in Europe is facing a period of transformation, and medical schools are beginning to innovate to prepare new physicians for the emerging needs of patients and their care.[16] These efforts suggest the importance to provide residents with new competencies, including social and economic acumen, data analytic skills, and broadened interpersonal relationship skills, including enhanced communication and leadership skills.[10,17]

Because residents serve as a reliable and skilled labor source for the hospitals in which they train, their work should be acknowledged through adequate salaries. The EURYPA report showed a significant diversity of residents' wage among the 8 countries studied.[10] European countries have different economic conditions and residents earn different amounts of money in different hospitals, even in the same city. In several cases, differences also exist between junior and senior residents.[14] **Figure 2** (available at www.jpeds.com) shows the average monthly salary of pediatric residents throughout the residency program, in each country. In the 8 selected countries, the annual average earning of medical residents is $22 900, and in the US the average earning of a medical resident is $61 200 annually.[10,18,19]

The data show that the highest wages are provided in Ireland and Italy.[20] In Ireland, pediatric residents are paid an incremental basic salary starting at approximately 1750 Euro/month, which increases up to 3100 euro/month at the end of training. In Denmark, wages are 3000 Euro/month throughout 5 years of the program. However, the cost of living in Denmark is about one-half the cost of living compared with Ireland and Italy. In Romania, although life is as expensive and the residency is as long as in Denmark, the salary is 3 times less. In Turkey, residents earn 1300 Euro/month during the 4 years of the program, which is consistent with the cheapest cost of living compared with the other countries studied. In Croatia and Hungary, where the cost of living is higher than in Turkey, residents' wages are one-third less. Finally, in Russia, where the cost of living is high and the duration of pediatric residency is 2 years long, no wages are provided, because residents receive their compensation in the form of a 200 euro/month scholarship.

Conclusions

Political strategic decisions in the area of pediatric health care and education in Europe seem to be often driven by the pressure to "deliver more for less." The process of reorganizing the residency programs in Europe is likely to be uneasy and complicated by the broad diversity of legislations between countries. However, there is light at the end of the tunnel. Differences in pediatric residency programs across Europe could be transformed by thoughtful planning, involving mutual collaboration, rather than by externally imposed directives. However, quick solutions and approaches, often broadly diverse and based on political and economic motivations, rather than driven by educational and public health rational choices, would be unsustainable in the long term.[21,22] ■

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References available at www.jpeds.com.

References

1. European Young Pediatricians Association. www.eurypa.org/. Accessed July 1, 2020.
2. Meric R, Gavin Stone R, Lupu VV, Lomholt S, Slobodanac M, Maár BA, et al. The diversity of pediatric residency programs across Europe: admission procedures, curricula and duration of courses. J Pediatr 2020;222:266-8.e1.
3. Karle H, Gordon D. Quality standards in medical education. Lancet 2007;370:1828.
4. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Diversity of child health care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations. J Pediatr 2016;177S:S1-10.
5. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
6. Pettoello-Mantovani M, Namazova-Baranova L, Ehrich J. Integrating and rationalizing public healthcare services as a source of cost containment in times of economic crises. Ital J Pediatr 2016;42:18.
7. Health Care Systems. Four basic models. www.pnhp.org/single_payer_resources/health_care_systems_four_basic_models.php. Accessed March 31, 2020.
8. Karjalainen S. European health care reform: analysis of current strategies. BMJ 1998;316:1468.
9. Böhm K, Schmid A, Götze R, Landwehr C, Rothgang H. Classifying OECD healthcare systems: a deductive approach. https://econpapers.repec.org/paper/zbwsfb597/165.htm. Accessed March 31, 2020.
10. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
11. Ehrich JH, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-8.e2.
12. Council of Europe. Common standards and policies. www.coe.int/en/. Accessed April 3, 2020.
13. The Council of Europe. 47 member states. www.coe.int/en/web/portal/47-members-states. Accessed March 31, 2020.
14. European Young Pediatrician Association-EPA/UNEPSA joint Conference; 2019. Istanbul, Turkey.
15. Ehrich J, Pettoello-Mantovani M. Never-Ending Stories, the Loop in Pediatrics-How Many Pediatricians Need to be Trained in European Countries to Keep the Pediatric Workforce Stable? J Pediatr 2018;196:332-3.e3.
16. Ehrich J, Fruth J, Jansen D, Gerber-Grote A, Pettoello-Mantovani M. How to calculate the Risk of shortage and surplus of pediatric workforce? J Pediatr 2018;199:286-7.e2.
17. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
18. Medscape. Medscape's residents salary and debt report 2019. www.medscape.com/. Accessed April 3, 2020.
19. Career Guide. Pay & salary. www.indeed.com/career-advice/pay-salary/how-much-do-surgical-residents-make. Accessed April 3, 2020.
20. Corsello G, Ferrara P, Chiamenti G, Nigri L, Campanozzi A, Pettoello-Mantovani M. The child health care system in Italy. J Pediatr 2016;177:S116-26.
21. Campbell C, Spencer SA. The implications of the Working Time Directive: how can paediatrics survive? Arch Dis Child 2007;92:573-5.
22. Gray S, Raschetti R, Beşer ÖF, Elicin PU, Aversa S, Pamuk G, et al. European Young Pediatricians Association: laying the foundations for collaboration, integration, and networking among pediatricians of the future. J Pediatr 2016;171:324-5.e1.

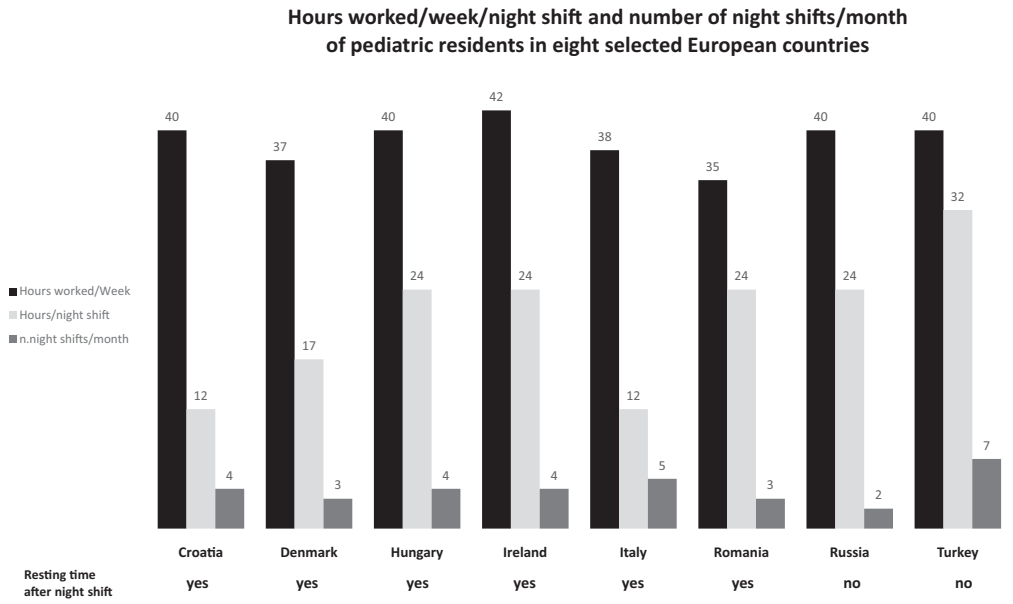
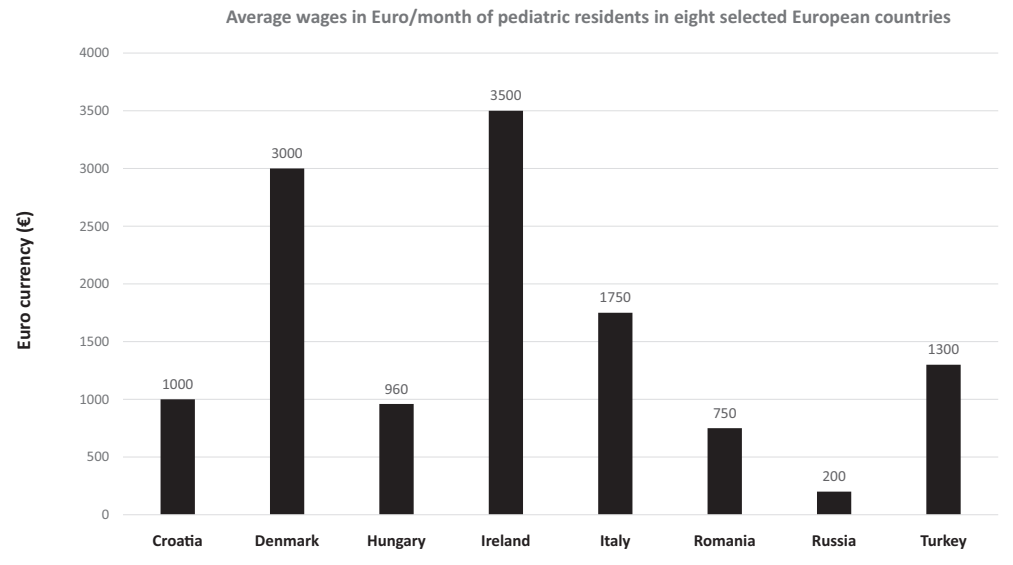


Figure 1. Number of hours worked/week, number of hours worked/night shift, resting time after night shifts and number of night shifts performed monthly by residents in pediatrics are shown for 8 selected European countries.



Cost of 1.0L water bottle	€0.60	€0.50	€0.25	€1.00	€1.00	€0.50	€0.70	€0.20
Duration of residency	5	5	5	7	5	5	2	4

Figure 2. Average monthly salary of pediatric residents in 8 European countries during their residency program. Duration of programs (in years) is shown for each country and the average cost of a 1 L of water bottle is reported as an arbitrary indicator of the local cost of living.

The *Hikikomori* Phenomenon of Social Withdrawal: An Emerging Condition Involving Youth's Mental Health and Social Participation

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The issue of social isolation and loneliness involving individuals during their developmental years has gathered increased attention from researchers, policy-makers, and the public, raising concerns about the negative effects of this condition on youth's well-being. In youngsters, the use of media devices, including social network platforms, video games, and interactive apps, continues to increase exponentially and the initial use of social network is about 10 years of age.[1,2] This is likely owing to the use of using these tools to build a social identity and develop new, unconventional forms of personal expression.

A new severe and prolonged form of social withdrawal, called *hikikomori* from a Japanese word indicating self-seclusion, was observed typically among adolescents and youth transitioning to adulthood, living in economically advanced countries.[3,4] The objective of this editorial is to raise awareness on the burden and risks faced by adolescents developing this emerging form of social withdrawal. The *hikikomori* phenomenon is part of the group of new morbidities causing children and adolescents to limit their activity owing to a chronic health condition with attendant psychological problems.[4] We further emphasize the importance of including new morbidities involving mental health and social participation in formal pediatric training, to enable new generations of pediatricians to identify and properly manage these disorders.[5]

Definition of the *Hikikomori* Disorder

The term *hikikomori* describes individuals who have withdrawn from their community.[3] The initial reports emphasized the close relation of the clinical manifestation with the local culture, as suggested by the name, which is a compound Japanese word made of 2 verbs indicating the attitude of an individual "to pull back" (*hiku*) and "to self-seclude" (*komoru*).[6] However, increasing reports from around the world provided a better understanding of this condition and suggested that *hikikomori* is a global health problem, which may exist as an independent primary diagnosis.[7,8]

The elemental attribute of *hikikomori* is the social isolation; the distinctive element is the sociospatial self-segregation of affected individuals, who are predominately adolescents and marginally young adults.[9] This form of physical isolation typically take place at home, where these persons spend most of the day avoiding exposure to any form of socialization (at school, sport centers, and similar socializing contexts) for days, weeks, or months.[10] *Hikikomori* seems to be more prevalent in males.[11,12]

The relative novelty of this clinical phenomenon accounts for the absence of a clear standardized definition.[13] Whether *hikikomori* is a symptom of other psychiatric disorders or the direct cause of co-occurring major mental health disorders is currently debated.[13] *Hikikomori* could be considered a new primary psychiatric disorder in future versions of the *Diagnostic and Statistical Manual of Mental Disorders*, despite the presence of some clinical overlap with other mental disorders.[3,14]

Published reports have clarified the pathologic features of *hikikomori*, and have built a consensus regarding its clinical characteristics, complications, and management.[13] Individuals with *hikikomori* present a severe social isolation characterized by a marked physical self-inflicted seclusion in their home. Typically, such isolation persist for a minimum of at least 6 months, being associated with major functional impairment or distress.[8] During the period of 3-6 months of self-isolation at home persons may be classified as presyndromic individuals.[8,13]

The characteristics and duration of isolation at home are key diagnostic factors. Individuals who break their status of isolation at home 4 or more times during a week cannot be classified as *hikikomori*. Persons may manifest different grades of disease, depending on whether the frequency of leaving home (mild, moderate, or severe *hikikomori*). The behavior of individuals who do not leave home more than 3 times a week is considered as marked social isolation.[8,13]

Epidemiology

The difficulty in establishing the epidemiology of *hikikomori* is the wide heterogeneity in the definitions of this disorder as

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well as the criteria adopted by various studies performed in different countries. For instance, while in Japan the duration of social withdrawal longer than 6 months is considered a distinctive diagnostic criteria, in other countries, including the Republic of Korea, Hong Kong, and some European countries, this time limit is decreased to 3 months.[15,16] Therefore, the lack of consensus on diagnostic criteria, together with various sociocultural features involving a variety of cross-cultural factors, may account for the variable prevalence rates reported by the studies performed in different geographic areas.[3]

The prevalence of *hikikomori* ranges from 0.87% to 1.2% in Japan, whereas in Hong Kong it is reported to be 1.9%, and 2.3% in Korea.[15,17-19] In Italy, *hikikomori* is estimated to involve about 1.2% of the population between 0 and 18 years of age, and in Spain, reports show that in groups of persons affected by social withdrawal, individuals diagnosed as *hikikomori* are 12.6%.[11,20,21] Similar data were observed in France.[22,23] In the US, 1 study described *hikikomori* as a cross-national phenomenon that can be assessed by a standardized assessment approach, which may assist the identification of *hikikomori* individuals in groups of persons with substantial psychosocial impairment and disability.[24]

Risk Factors and Therapeutic Strategies

Hikikomori coexists with a variety of psychiatric disorders, which are suggested to be preexisting risk conditions that give raise to this disorder.[6,12] For instance, it is not unusual for patients with psychotic disorders to retreat into a situation of physical withdrawal and persons with depression or affected by depressed mood may present symptoms that may evolve in the form of withdrawal-like outcomes.[12] Social anxiety disorder and other anxiety-related disorders may trigger *hikikomori*, and anxiety in social interactions is a prominent comorbid psychiatric disorder among persons with *hikikomori*.[25] Personality disorders, including avoidant, paranoid, dependent, schizoid, antisocial, borderline, narcissistic, and schizotypal, are reported to be risk factors for *hikikomori*. Severe physical fatigue and pain causing physical impairment when walking or moving may precipitate a *hikikomori*-like state.[12]

Therapeutic intervention for *hikikomori* is challenging. A multidimensional intervention is generally recommended in these patients, including a progressive approach centered on family support. It is unlikely that individuals with *hikikomori* will seek treatment spontaneously; therefore, in persons living with family members, the role of the family is of key importance. The initial approach, in close coordination with family members, is based on the first contact and assessment of the individual affected, followed by his or her direct support. These steps are followed by specific training interventions with intermediate-transient group activities (group therapy), and social participation trials.[26] The goal is the alleviation of loneliness and the development of favorable conditions that allow increased social interactions and sociability.[12]

Conclusions

The *hikikomori* phenomenon affects adolescents or young adults who resolve to isolate from the outside world, often owing to preexisting risk conditions. They remain cloistered and particularly secluded in their bedrooms for days, months, or even years on end. This pathologic disorder has been described as a new independent condition, which can be included among the group of new morbidities.[4] The members of the European Paediatric Association working group on social pediatrics, would like to further emphasize the role of pediatricians in providing increased attention to the prevention, early detection, and management of the various behavioral, developmental, and social functioning problems represented by new morbidities,[4] which are increasingly encountered in pediatric practice.[27,28] ■

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References

1. Ehrich JH, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-88.e2.
2. McDool E, Powell P, Rberts J, Taylor K. Social media use and children's wellbeing. The IZA Institute of Labor Economics. Bonn, Germany, http://ftp.iza.org/dp10412.pdf. Accessed May 24, 2020.
3. Pozza A, Coluccia A, Kato T, Gaetani M, Ferretti F. The 'Hikikomori' syndrome: worldwide prevalence and co-occurring major psychiatric disorders: a systematic review and metaanalysis protocol. BMJ Open 2019;9:e025213.
4. American Academy of Pediatrics. American Academy of Pediatrics the new morbidity revisited: a renewed commitment to the psychosocial aspects of pediatric care. Committee on Psychosocial Aspects of Child and Family Health. Pediatrics 2001;108:1227-30.
5. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
6. Kato TA, Kanba S, Teo AR. Hikikomori: multidimensional understanding, assessment, and future international perspectives. Psychiatr Clin Neurosci 2019;73:427-40.
7. Malagón-Amor Á Martín-López LM, Córcoles D, Gonzàlez A, Bellsolà M, Teo AR, et al. Family features of social withdrawal syndrome (hikikomori). Front Psychiatry 2020;11:138.
8. Kato TA, Kanba S, Teo AR. Hikikomori: experience in Japan and international relevance. World Psychiatr 2018;17:105-6.
9. Yong RK, Fujita K, Chau PY, Sasaki H. Characteristics of and gender difference factors of hikikomori among the working-age population: a cross-sectional population study in rural Japan. Nihon Koshu Eisei Zasshi 2020;67:237-46.
10. Teo AR, Gaw AC. Hikikomori, a Japanese culture-bound syndrome of social withdrawal? A Proposal for DSM-V. J Nerv Ment Dis 2010;198:444-9.
11. Malagón-Amor Á, Córcoles-Martínez D, Martín-López LM, Pérez-Solà V. Hikikomori in Spain: a descriptive study. Int J Soc Psychiatry 2015;61:475-83.
12. Kondo N, Sakai M, Kuroda Y, Kiyota Y, Kitabata Y, Kurosawa M. General condition of hikikomori (prolonged social withdrawal) in Japan: psychiatric diagnosis and outcome in mental health welfare centres. Int J Soc Psychiatry 2013;59:79-86.

13. Stip E, Thibault A, Beauchamp-Chatel A, Kisely S. Internet addiction, hikikomori syndrome, and the prodromal phase of psychosis. Front Psychiatry 2016;7:6.
14. Kato TA, Tateno M, Shinfuku N. Does the 'hikikomori' syndrome of social withdrawal exist outside Japan? A preliminary international investigation. Soc Psychiatry Psychiatr Epidemiol 2012;47:1061-75.
15. Lee YS, Lee JY, Choi TY. Home visitation program for detecting, evaluating and treating socially withdrawn youth in Korea. Psychiatry Clin Neurosci 2013;67:193-202.
16. H-yee Chan, T-wing Lo. Quality of life of the hidden youth in Hong Kong. Appl Res Qual Life 2014;9:951-69.
17. Wong PWC, Li TMH, Chan M, Law YW, Chau M, Cheng C, et al. The prevalence and correlates of severe social withdrawal (hikikomori) in Hong Kong: a cross-sectional telephone-based survey study. Int J Soc Psychiatry 2015;61:330-42.
18. Norasakkunkit V, Uchida Y. To conform or to maintain self-consistency? Hikikomori risk in Japan and the deviation from seeking harmony. J Soc Clin Psychol 2014;33:918-35.
19. Koyama A, Miyake Y, Kawakami N. Lifetime prevalence, psychiatric comorbidity and demographic correlates of "hikikomori" in a community population in Japan. Psychiatry Res 2010;176:69-74.
20. Hikikomori Italia. Chi sono gli hikikomori?, www.hikikomoriitalia.it/p/chi-sono-gli-hikikomori.html. Accessed June 20, 2020.
21. Poletto L. Hikikomori: growing number of young Italians choosing reclusive lives. La Stampa. 2019, www.lastampa.it/esteri/la-stampa-in-english/2018/07/30/news/hikikomori-growing-number-of-young-italians-choosing-reclusive-lives-1.34035351. Accessed June 20, 2020.
22. Chauliac N, Couillet A, Faivre S, Brochard N, Terra JL. Characteristics of socially withdrawn youth in France: a retrospective study. Int J Soc Psychiatry 2017;63:339-44.
23. Furuhashi T, Figueiredo C, Pionnié-Dax N, Fansten M, Vellut N, Castel PH. Pathology seen in French "Hikikomori". Seishin Shinkeigaku Zasshi 2012;114:1173-9.
24. Teo AR, Fetters MD, Stufflebam K, Tateno M, Balhara Y, Choi TY, et al. Identification of the hikikomori syndrome of social withdrawal: psychosocial features and treatment preferences in four countries. Int J Soc Psychiatry 2015;61:64-72.
25. Teo AR, Stufflebam K, Saha S. Psychopathology associated with social withdrawal: idiopathic and comorbid presentations. Psychiatry Res 2015;228:182-3.
26. Saito K. Hikikomori No Hyouka-Shien Ni Kansuru Gaido-Rain. Guideline of hikikomori for their evaluation and support. 2010. Tokyo, Japan: Ministry of Health, Labour and Welfare; 2010, www.ncgmkohnodai.go.jp/pdf/jidouseishin/22ncgm_hikikomori.pdf. Accessed June 20, 2020.
27. Corsello G, Ferrara P, Chiamenti G, Nigri L, Campanozzi A, Pettoello-Mantovani M. The child health care system in Italy. J Pediatr 2016;177S:S116-26.
28. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.

Changes in Routine Pediatric Practice in Light of Coronavirus 2019 (COVID-19)

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The outbreak of severe acute respiratory syndrome coronavirus 2 or coronavirus 2019 (COVID-19)[1] in the city of Wuhan, China, in December 2019 has rapidly emerged into a pandemic affecting national communities throughout the world.[2] As of May 17, 2020, more than 4.5 million people have been infected globally at a pace of 100 000/d, and 307 395 have died.[3] We will briefly discuss the effects of COVID-19 on routine pediatric practice that have surfaced during the months after the onset of the pandemic and the implications for children's health. Our aim is to raise awareness about the likely need to remodel routine pediatric practice, both in hospital and ambulatory services, in light of COVID-19, and in the event of future similar infectious emergencies.

The Magnitude of COVID-19 Infection in the Young Population

Although peer-reviewed reports and commentaries may not provide an exhaustive epidemiologic and clinical overview on how children respond to COVID-19, they provide a useful early look. Differences were observed between adults and children, which may have implications for the management of this disease in the younger population.

Information on morbidity and mortality by COVID-19 was first documented in adults.[4-6] Later studies have shown that infection rates in children are lower than in adults.[7-10] Three weeks after the start of the pandemic, the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report reported that in the US <2% of COVID-19 cases occurred in patients <18 years[11] and <1% in children <10 years of age.[12] The European Centre for Disease Prevention and Control reported that 1% of all cases were <10 years of age, and 4% were aged 10-19 years.[13] Early studies performed in China on relatively large pediatric cohorts showed that approximately two-thirds of the children had suspected cases of COVID-19, and the rest of the cases were laboratory-confirmed. According to these reports, approximately 4% of children were asymptomatic, 51% had mild illness, and 39% had moderate illness. About 6% had severe or critical illness, compared with 18.5% reported in adults.[9,11,14,15] In multiple settings of several countries, the majority of COVID-19 infections in subjects <18 years of age were mild to moderate and in general were associated with significantly lower rates of hospitalization and significantly lower rates of critical and severe illness.[12,13] However, recent reports do indicate the potential for severe disease in children and emphasize that children with severe symptoms usually belong to the most vulnerable age group, including infants who had greater hospitalization rates and intensive care admissions[11,16,17]

The reasons for the relatively milder viral phenotype in children remain elusive. Several factors were proposed as causative, including differences in angiotensin-converting enzyme 2 expression in children, simultaneous infection (coinfection) of competing viruses in children, and the age-related immature immune systems.[9,15,18] In the general population, although men and women have the same prevalence, men with COVID-19 are more at risk for worse outcomes and death, independent of age.[2,9] In children, the majority of COVID-19 cases were observed in male patients.[7,19] COVID-19 is reported to be highly transmissible, with high rates of asymptomatic-yet-contagious subjects.[20] Taken together, these observations suggest that changes may be necessary in the provision of healthcare for children.[21]

COVID-19 Prompting Changes in Routine Pediatric Practice

COVID-19 infection in children has important public health, social, and economic implications, and even though children may have considerably milder symptoms than individuals >18 years of age, those infected seem to have the same levels of circulating virus in their body and may be as infectious as adults.[22] However, other studies suggest that children have a

COVID-19	Coronavirus 2019
EPA-UNEPSA	European Paediatric Association, Union of National European Paediatric Societies and Associations

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small role in the spread of COVID-19.[23,24] Preventive regulations have been enacted by local and national authorities on the assumption that children are important in viral transmission and amplification. The majority of countries worldwide have established social and public health policies with the aim of slowing transmission and protecting vulnerable populations, including limiting interactions with adults and elderly people and issuing orders extending school closures. This unprecedented experience has brought enormous changes in routine pediatric practice, both in hospital and ambulatory services in Europe, as throughout the Western world. National public health authorities and professional organizations in Europe and in US have issued new rules and guidelines, which have led to redesigned pediatric practices in the different settings.[25-27]

Reports collected by the European Paediatric Association, Union of National European Paediatric Societies and Associations (EPA-UNEPSA) from its member national European pediatric societies show that the COVID-19 pandemic has produced a sharp decline in hospitalizations and emergency department visits for urgent and non-urgent care. The rate of decline in several hospitals is >70%, and there is a significant reduction of admissions and days of stay recorded in pediatric wards. Furthermore, most of the outpatient services in hospitals have been closed to reduce person-to-person contact. Reasons for such a decrease also may include parents' fear and apprehension about children's exposure to patients with COVID-19 in hospitals. Some children were referred to the emergency department in critical condition caused by acute illnesses, including severe ketoacidosis, full-blown sepsis, and other life-threatening situations, without previous medical assessment. However, a sharp decline in other common seasonal infectious diseases due to the general lockdown and reduced school activities also should be considered when analyzing COVID-19 data and their related epidemiologic implications.

These circumstances have brought a reorganization of pediatric services in many hospitals, which have reduced the services and the space previously assigned to pediatric wards to use pediatric beds for patients of all ages with COVID-19. In parallel, pediatric staff often have been reassigned to other duties.

Several factors have influenced also the routine practice of general pediatricians working in ambulatory settings during COVID-19. Many pediatricians belonging to high-risk groups limited their clinical exposure and direct clinical care of patients. Primary care pediatricians felt inadequately protected from COVID-19, as they were provided with insufficient personal protective equipment and because the virus-containment measures established by authorities were considered unable to effectively isolate suspected patients with COVID-19. Inefficient containment measures included the absence of negative-pressure rooms and the lack of space to effectively separate patients with respiratory symptoms, including those with greater COVID-19 index of suspicion, from patients with nonrespiratory symptoms.

Taken together, these factors may have contributed to the dramatic decline in direct pediatrician–patient encounters and the rise in telephonic and virtual consultations. As reported by the EPA-UNEPSA working group on social pediatrics, during the past 3 months, direct care has declined (**Figure**). Pediatric care has rapidly turned from direct to a predominantly virtual care practice, and pediatricians seem to have adapted to it, most likely including those who in the past may have objected to virtual-assisted care.

A significant limitation to telehealth is the availability of technical equipment. Although some hospitals and large physician practices are currently equipped to deliver care in virtual mode, many hospitals, public ambulatory settings, and private practices are not.[28] Additional factors included the level of training enabling clinicians to provide effective care in video visit modality and the costs for providing video-assisted care opportunities by the public health systems, which also needs to be regulated.[28] For instance, one of the health maintenance organizations in Israel announced that clinicians will be compensated for virtual calls only if they spend at least 50% of their time in the office to provide direct care for patients who are interested in this encounter. This statement caused deep dissatisfaction in many clinicians, who felt health maintenance organizations were forcing them to face patients without the provision of adequate personal protective equipment.

COVID-19 Influencing Standards of Practice in Pediatrics

Data collected by EPA-UNEPSA from its member societies show that in different European countries, many pediatricians during the pandemic have largely discontinued the practice of throat culture. Furthermore, referrals to laboratory tests, imaging, and consultations also have been reduced and primary care pediatricians have decided about treatment in absence of sufficient data. Ambulatory services dedicated to preventive care, including a variety of clinical services and programs, have been reduced. Periodic well child health examination and screening programs, including key newborn screening tests, were postponed, and physiotherapy, occupational therapy, and dietary consultations have declined.

The Future of Pediatric Practice after COVID-19

The pediatric practice changes and adjustments are most likely to remain after the pandemic is over.[29] Important discussions are ongoing in several European countries and the US on the effectiveness shown by telehealth and telephone care during the months of the pandemic.[30] Many consider them to be important tools, enabling pediatricians to connect with patients and families, especially in times of physical distancing. Public health services throughout Europe are also considering implementing this practice into national programs,[31] due to its cost effectiveness and efficiency to provide timely childcare in a less time-consuming manner than traditional in-person practice.[32] However, concerns exist regarding whether this form of healthcare

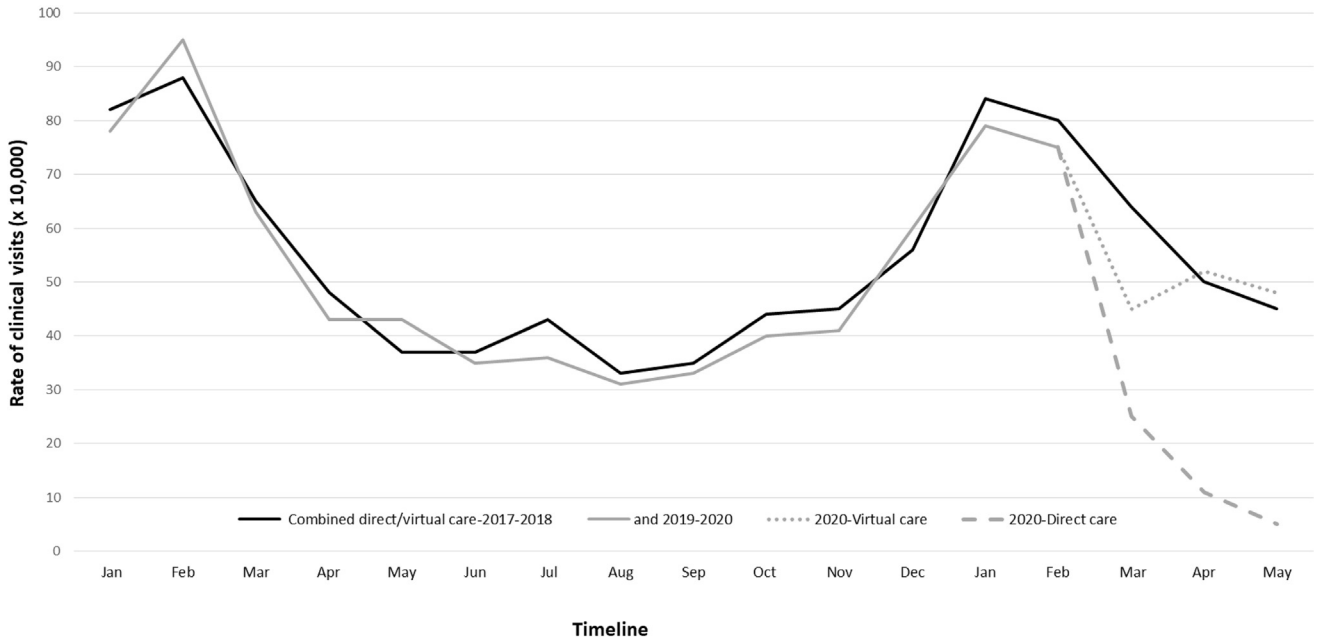

Figure. Pediatric primary care, hospital, and ambulatory settings. Comparison between direct and virtual pediatric clinical visits in European countries during the periods 2017-2018 and 2019-2020. Data were elaborated by the EPA-UNEPSA working group on social pediatrics based on preliminary reports from member societies. *Continued lines* indicate combined direct and virtual care. *Noncontinued lines* show separately the rates of virtual and direct care.

provision could be considered a main practice management resource in future child healthcare. In fact, many object, stating that medicine in general and pediatrics in particular is a human science, and the major part of healing is the direct encounter of the physician with the child and the patient's parents or caretakers.[33] Failure to create such conditions could result in less-effective clinical evaluations, which could lead to critical mistakes and to a decline in compliance with the physician's advice and recommendations. In accordance with this vision, telehealth and telephone care should be adopted only as an adjunctive to conventional health but not as the major resource in childcare provision. Reports to EPA-UNEPSA from its member societies indicate that previously and in the current crisis, to avoid direct encounters, physicians tend to overmedicate their patients to compensate for the inability to thoroughly evaluate their patients.[34]

However, protocols and algorithms for provision of telehealth and virtual care are developing, including relevant medical ethical issues and legal medicine implications. Pediatricians should be prepared by learning the advantages and disadvantages of distance medical practice and acquiring appropriate training.

Conclusions

Changes in pediatric practice driven by the COVID-19 pandemic are likely among the causes of delayed identification of serious illnesses, the failure to provide routine care for chronic conditions including mental and behavioral problems triggered during this period,[2] and the re-emergence of disorders due to uncompleted neonatal screening tests.[35] The pandemic has caused delays and significant disruption of standard vaccination programs.[36] Only time and future studies will show the real extent of collateral damages that have occurred due to the pandemic. ■

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References

1. Fauci AS, Lane C, Redfield RR. Covid-19—navigating the uncharted. N Engl J Med 2020;382:1268-9.
2. Jiao WY, Wang LN, Liu J, Fang SF, Jiao FY, Pettoello-Mantovani M, et al. Behavioral and emotional disorders in children during the COVID-19 epidemic. J Pediatr 2020;221:264-6.e1.
3. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report – 118. Geneva, Switzerland: World Health Organization; 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed May 18, 2020.
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382:1199-207.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
6. Lu R, Zhao X, Li J, Niu P, Yang B, Wuet H, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74.
7. Lu X, Zhang L, Du H, Jingjing Z, Li YY, Qu J, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663-5.

8. Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of dovid-19 in children in early January 2020 in Wuhan, China. N Engl J Med 2020;382:1370-1.
9. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics 2020. in press.
10. Zheng F, Liao C, Fan QH, Chen HB, Zhao XG, Xie ZG, et al. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. Curr Med Sci 2020;40:275-80.
11. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422-6.
12. Williams J, Namazova-Baranova L, Weber M, Vural M, Mestrovic M, Carrasco-Sanz, et al. The importance of continuing breastfeeding during COVID-19: in support to the WHO statement on breastfeeding during the pandemic. J Pediatr 2020;223:231-3.
13. European Centre for Disease Prevention and Control, ECDC. Are children also at risk of infection and what is their potential role in transmission? https://www.ecdc.europa.eu/en/covid-19/questions-answers. Accessed May 3, 2020.
14. Jenco M. American Academy of Pediatrics—COVID-19 less severe in children than adults: study. https://www.aappublications.org/news/2020/03/16/coronavirus031620. Accessed May 3, 2020.
15. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020. in press.
16. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr 2020. in press.
17. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. J Pediatr 2020. in press.
18. Brodin P. Why is COVID-19 so mild in children? Acta Paediatr 2020;109:1082-3.
19. Jian-Min J, Peng B, Wei H, Fei W, Xiao-Fang L, De-Min H, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health 2020;8:152.
20. Parmet WE, Sinha MS. Covid-19. The law and limits of quarantine. N Engl J Med 2020;382:e28.
21. Sepkowitz KA. Forever unprepared. The predictable unpredictability of pathogens. N Engl J Med 2009;361:120-1.
22. Jones TC, Mühlemann B, Veith T, Zuchowski M, Hofmann J, Stein A, et al. An analysis of SARS-CoV-2 viral load by patient age. https://zoonosen.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf. Accessed May 4, 2020.
23. Australian National Centre for Immunization Research and Surveillance (NCIRS). COVID-19 in schools—the experience in NSW. April 2020 Report. http://ncirs.org.au/sites/default/files/2020-04/NCIRS%20NSW%20Schools%20COVID_Summary_FINAL%20public_26%20April%202020.pdf. Accessed May 4, 2020.
24. UK National Institute for Public Health and the Environment. Children and COVID-19. https://www.rivm.nl/en/novel-coronavirus-covid-19/children-and-covid-19. Accessed May 4, 2020.
25. Ministry of Public Health, Italy. COVID-19: new directions and clarifications. https://www.sanitainformazione.it/wp-content/uploads/2020/02/LEGGI-LA-CIRCOLARE-DEL-MINISTERO-DELLA-SALUTE.pdf. Accessed May 9, 2020.
26. American Medical Association, AMA. A Physician's Guide to COVID-19. https://www.ama-assn.org/delivering-care/public-health/physicians-guide-covid-19. Accessed May 9, 2020.
27. American Academy of Pediatrics, AAP. Critical Updates on COVID-19. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/. Accessed May 9, 2020.
28. Board on Health Care Services, Institute of Medicine. The Role of Telehealth in an Evolving Health Care Environment: Workshop Summary. Washington (DC): National Academies Press (US); 2012. Nov 20. 4, Challenges in Telehealth. https://www.ncbi.nlm.nih.gov/books/NBK207146/. Accessed May 10, 2020.
29. Hollander JE, Carr BG. Virtually perfect? Telemedicine for covid-19. N Engl J Med 2020;382:1679-81.
30. Smith AC, Thomas E, Snoswell CL, Haydon H, Mehrotra A, Clemensen J, et al. Telehealth for global emergencies: implications for coronavirus disease 2019 (COVID-19). J Telemed Telecare 2020. in press.
31. Corsello G, Ferrara P, Chiamenti G, Nigri L, Campanozzi A, Pettoello-Mantovani M. The child health care system in Italy. J Pediatr 2016;177S:S116-26.
32. European Commission. Market study on telemedicine. https://ec.europa.eu/health/sites/health/files/ehealth/docs/2018_provision_marketstudy_telemedicine_en.pdf. Accessed May 10, 2020.
33. Society of Gynecology Oncology, SGO. Telemedicine Considerations During the COVID-19 Pandemic. https://www.sgo.org/wp-content/uploads/2020/04/telemedicine_considerations_v4.pdf. Accessed May 10, 2020.
34. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations." J Pediatr 2016;177S:S1-10.
35. Ehrich JH, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-8.e2.
36. McIntosh ED, Janda J, Ehrich JH, Pettoello-Mantovani M, Somekh E. Vaccine hesitancy and refusal. J Pediatr 2016;175:248-9.e1.

EUROPEAN PAEDIATRIC ASSOCIATION

The Importance of Continuing Breastfeeding during Coronavirus Disease-2019: In Support of the World Health Organization Statement on Breastfeeding during the Pandemic

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There are many questions and concerns about the coronavirus disease 2019 (COVID-19), including its implications for breastfeeding.[1] This commentary draws on a statement and recommendations recently issued by the Regional Office for Europe of the World Health Organization with the contribution of the European Pediatric Association-Union of National European Pediatric Societies and Associations and other main European pediatric organizations.[1] Our aim is to provide pediatricians with further guidance on breastfeeding and related safety measures during COVID-19, particularly in instances where a mother has or may have COVID-19.

The COVID-2019 epidemic, caused by severe acute respiratory syndrome coronavirus 2, was first identified in Hubei Province China in December 2019, and has subsequently spread globally, placing extensive pressure on health systems and posing a major public health challenge worldwide.[2] On March 11, 2020, the World Health Organization (WHO) declared the outbreak a pandemic.[3] At the time, little was known about COVID-19 or its effects on the general population, and even less was known about how it could influence specific populations such as pregnant women, infants, or children. Reports show that children at all ages are sensitive to COVID-19, with no significant gender difference.[4] Clinical manifestations of children's COVID-19 cases are less severe than in adults' patients, and a review of 72 314 cases by the Chinese Center for Disease Control and Prevention showed that <1% of the cases were in children <10 years of age.[5] Additional information about COVID-19 infection among children is increasing over time, but questions remain, including questions about breastfeeding, particularly in instances when a mother may be infected with COVID-19.[6,7] The protection, promotion, and support of breastfeeding are a priority for public health and WHO has been continuously compiling evidence on the effect of COVID on mothers and children.[3,8,9]

COVID-19	Coronavirus disease 2019
WHO	World Health Organization

Breastfeeding during the COVID-19 Pandemic

According to the WHO, mothers with COVID-19 (or suspected COVID-19) can breastfeed their babies as long as they take appropriate precautions.[9,10] Breast milk encloses various antimicrobial substances, anti-inflammatory components, and factors that promote the development of immune system and reduce the occurrence of respiratory tract infections.[11] The WHO statement[9] emphasizes again that breast milk contains all the nutriments in appropriate proportions essential for the healthy growth of infants, who can benefit from breastfeeding also from mothers with COVID-19 infection confirmed or suspected. Breastfeeding guarantees many health benefits for both the mother and infant and it is recognized as the ideal food for children in the first 6 months of life, constituting a primary form of promoting the child's health and development.[7] Breast milk is perfectly adjusted to the infant's nutrition requirements and growth, because it contains all the nutrients an infant needs.[12] It enhances the immature immune system of the infant and strengthens defense mechanisms against infectious and other agents throughout the breastfeeding period.[12] Several studies demonstrated that continued, frequent breastfeeding is associated with greater linear growth and further protects child health by delaying maternal fertility postpartum and decreasing the child's risk of morbidity and mortality.[13]

The Risk of COVID-19 Transmission during Pregnancy and Breastfeeding

Data are lacking about whether pregnant women who are infected by the novel coronavirus can pass it to their fetuses across the placenta during pregnancy. Current data do not

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support this possibility. Although vertical maternal-fetal transmission cannot be ruled out, several small studies of pregnant women infected with COVID-19 found no evidence of vertical transmission, because no infant tested positive at birth and it is likely that the sources of severe acute respiratory syndrome coronavirus in the neonates' upper respiratory tracts or anuses are maternal in origin.[14] Furthermore, the virus was not detected in samples of amniotic fluid, umbilical cord blood or placental tissue.[15-18] Few cases of newborns infected by the novel coronavirus have been reported; however, it remains unclear whether they were infected before, during, or after delivery and by what means.[14,19]

There is no evidence to date to suggest the novel coronavirus can pass to infants through breast milk, because the virus was not found in breast milk. This possibility cannot be completely ruled out, because the data available are based on limited clinical experience developed over few months during the novel COVID-19 pandemic, studies performed in women affected by COVID-19, and data collected during previous infectious outbreaks caused by other types of coronavirus, including severe acute respiratory syndrome, severe acute respiratory syndrome coronavirus, and Middle Eastern respiratory syndrome coronavirus. However, on the basis of available data, this circumstance is excluded.[10] Public health officials and healthcare professionals are intensely engaged in the process of learning while doing. Clinical features of the infection and the dynamics of the COVID-19 spread among human populations and between individuals and the risks for infants, including those whose mothers carry the infection, are key elements of this accelerated learning process. Breast milk samples collected at first lactation form mothers affected by COVID-19 during pregnancy were tested and proved negative for the presence of virus in a study performed in Wuhan, China, during the first 3 months of the local outbreak.[15] A case study from Australia described a mother with COVID-19 not separated from her infant; breast feeding seems to be possible and safe when viral precautions are observed.[20] Further studies are needed to confirm these results. Even if the virus is transmitted occasionally, the risks and benefits would have to be balanced, and the long-term risks of not breastfeeding would need to enter the equation. Because the data currently available show that the clinical features of COVID-19 in children and infants are generally mild and risks for viral transmission from mother to child are likely to be directly related to a COVID-19 infection affecting the respiratory tract of mothers, the potential risks for newborns seem to be minimal.[14]

How to Manage the Risk of Infection in Breastfed Infants

Women with confirmed or suspected COVID-19 infection are encouraged to breastfeed in absence of other limitations. However, precautions should be taken to minimize potential problems (Table). Room sharing and uninterrupted mother-infant proximity is recommended as an important factor for establishing good breastfeeding for mothers with COVID-19 as well, providing that specific and appropriate respiratory and skin hygiene measures are taken (Table). If mothers are unable to breastfeed owing to severe health conditions caused by COVID-19, they should receive support from competent health care professionals. They may be advised to provide breast milk to their infants via safe alternative methods, such as the provision of expressed milk or relactation (the process of restarting breastfeeding after a gap or very little breastfeeding). If that is not possible, other alternatives can be considered, such as the use of certified donor milk bank services, designed to protect the incoming milk supply by rigorous screening criteria for milk donors.[21,22]

The current WHO recommendations indicate that mothers should provide exclusive breastfeeding to their babies during the first 6 months of life.[23,24] After the addition of solid food, mothers are advised to continue breastfeeding for at least 6 additional months and, if possible, to continue this practice up to the age of 2 years and beyond. Therefore, COVID-19-affected or -suspected mothers should be informed about the importance to continue providing their infants breast milk, and that this goal can be achieved by adopting appropriate hygiene and safety practices.

Conclusions

The document on COVID-19 and breastfeeding developed by the WHO Regional Office for Europe strongly supports the

Table. COVID-19 safety measures: Essential advices for mothers and staff working in maternity and newborn services

Advised measures for breastfeeding mothers
Regularly practice respiratory hygiene including during feeding (covering mouth and nose with bent elbow or tissue when coughing or sneezing and promptly dispose of the used tissue)
In case of respiratory symptoms (ie, short breath): use a medical mask when near to breastfed infant.
Wash hands thoroughly with soap or sanitizer for a least 20 seconds before and after touching the baby.
Routinely clean and disinfect any surfaces have been touched.
If severely ill with COVID-19, if COVID-19 is suspected, or in case of other complications that are an obstacle to continue a direct breastfeeding, express milk to safely provide breastmilk to infants.
If clinical conditions prevent to breastfeed or express breastmilk, explore the possibility to practice relactation (restarting breastfeeding after a gap), or using donor human milk though certified donor milk banking. (The adopted approach will depend on cultural context, patients acceptability, and availability of services.)
Advised measures for staff working in maternity and newborn services
Breastmilk substitutes, feeding bottles, teats, pacifiers, or dummies should not be promoted by staff providing maternity and newborn services.
Mothers and infants should be enabled to remain together, practice skin-to-skin contact and room-in throughout the day and night, whether or not the mother or child has suspected, probable, or confirmed COVID-19, especially straight after birth during establishment of breastfeeding.

continuation of this practice during COVID-19, which is key for ensuring the health of children. European Paediatric Association-Union of National European Paediatric Societies and Associations, on behalf of its National European pediatric societies and associations, strongly and actively collaborates with the WHO regional office in promoting the position that breast milk is the ideal food for infants, because it is safe, clean, and provides all the energy and nutrients that the infant needs for the first months of life. Breast milk contains antibodies, which help to protect children against many common childhood illnesses, and breastfeeding confers many short- and long-term health benefits for both the mother and child. Efforts should be made to properly advise and support mothers with breastfeeding, even in instances when the mother has confirmed or suspected COVID-19 infection. ■

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References

1. European Pediatric Association/Union of National European Pediatric Societies and Associations (EPA/UNEPSA). www.epa-unepsa.org. Accessed April 6, 2020.
2. Fauci AS, Lane C, Redfield RR. Covid-19 — navigating the uncharted. N Engl J Med 2020;382:1268-9.
3. World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak. Coronavirus disease (COVID-19) outbreak. www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Accessed April 6, 2020.
4. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics 2020 Mar 16. in press.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 Feb 24. in press.
6. World Health Organization (WHO). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed April 6, 2020.
7. Centers for Disease Control and Prevention (CDC). Caring for children. www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children.html. Accessed April 6, 2020.
8. United Nations Children's Fund. Innocenti declaration on the protection, promotion and support of breastfeeding. 1990. New York: UNICEF's Nutrition Cluster; 1990. https://www.unicef.org/programme/breastfeeding/innocenti.htm. Accessed April 7, 2020.
9. World Health Organization (WHO). Coronavirus disease (COVID-19) technical guidance: Infection prevention and control. www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/infection-prevention-and-control. Accessed April 6, 2020.
10. Asadi L, Tabatabaei RS, Safinejad H, Mohammadi M. New corona virus (COVID-19) management in pregnancy and childbirth. Arch Clin Infect Dis 2020 Apr 6. in press.
11. Rebhan B, Kohlhuber M, Schwegler U, Fromme H, Abou-Dakn M, Koletzko BV. Breastfeeding duration and exclusivity associated with infants' health and growth: data from a prospective cohort study in Bavaria, Germany. Acta Paediatr 2009;98:974-80.
12. Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, et al. Breast-feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 2009;49:112-25.
13. World Health Organization (WHO). e-Library of Evidence for Nutrition Actions (eLENA). Continued breastfeeding for healthy growth and development of children. www.who.int/elena/titles/continued_breastfeeding/en/. Accessed April 7, 2020.
14. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr 2020 Mar 26. in press.
15. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020;395:809-15.
16. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, Xia S, Zhou W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020;9:51-60.
17. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China. Emerg Infect Dis 2020 Apr 2. in press.
18. Zhang L, Jiang Y, Wei M, Cheng BH, Zhou XC, Li J, et al. Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province. Zhonghua Fu Chan Ke Za Zhi 2020;55:E009.
19. Qiao J. What are the risks of COVID-19 infection in pregnant women? Lancet 2020;395:760-2.
20. Lowe B, Bopp B. COVID-19 vaginal delivery–a case report. Aust N Z J Obstet Gynaecol 2020;60:465-6.
21. Marinelli KA. International perspectives concerning donor milk banking during the SARS-CoV-2 (COVID-19) Pandemic. J Human Lactation 2020 Mar 30. in press.
22. European Milk Banking Association. COVID-19: EMBA position statement. 2020, February 25. https://europeanmilkbanking.com/covid-19-emba-position-statement/. Accessed April 7, 2020.
23. Human Milk Banking Association of North America. Milk banking and COVID-19. 2020, March 6. www.hmbana.org/news/statement-on-coronavirus.html. Accessed April 7, 2020.
24. World Heath Organization (WHO). Exclusive breastfeeding for six months best for babies everywhere. www.who.int/mediacentre/news/statements/2011/breastfeeding_20110115/en/. Accessed April 7, 2020.

Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic

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Since December 2019, health systems around the globe have struggled with an increasing number of cases of a viral respiratory syndrome that emerged in China. The cause is a new strain in the coronavirus family, provisionally named 2019 novel coronavirus (2019-nCoV)[1], SARS-CoV-2 or COVID-19.[2]

The European Paediatric Association–Union of National European Paediatric Societies and Associations (EPA-UNEPSA) has established a collaborative working group with key Chinese academic institutions and medical centers with the purpose of facilitating the reciprocal exchange of information and sharing scientific knowledge. The aim of this commentary by the China-EPA-UNEPSA working group is to raise awareness regarding children's psychological needs during epidemics and report early data collected in the COVID-19–affected areas in China during the current outbreak, emphasizing the role of families and caregivers in the timely recognition and management of negative emotions.

Epidemiology of COVID-19

The COVID-19 outbreak first erupted in the city of Wuhan in the Hubei Province of China, where several local health facilities reported clusters of patients with pneumonia of unknown cause; they were epidemiologically linked to a seafood and wet animal wholesale market.[3] COVID-19 infection rapidly spread throughout China, involving the provinces of Chongqing, Hunan, Anhui, Henan, Jiangxi, and Shaanxi.[4] Over the next 3 months, COVID-19 spread to other regions of the world, reaching >100 000 cases globally in the first week of March 2020, of which approximately 80% were reported in China, 6% in South Korea, 3% in Iran, and 0.2% in the US. In Europe, the first case of COVID-19 was registered in a patient hospitalized in Munich, Germany in early January 2020, following contact with a traveler from China.[5] Later, several other cases were reported in variable numbers in Germany, Spain, Italy, France, and other European countries, together representing roughly 5% of the cases of COVID-19 recorded worldwide.[4] Genetic studies on viral strains isolated from patients affected by Coronavirus infection throughout the world confirmed that they are all phylogenetically related to the original Chinese mutant strain.[6]

In contrast to seasonal influenza, COVID-19 seems to cause a milder clinical infection in children than in adults or older people. Early studies have suggested that children are just as likely as older age groups to become infected with the coronavirus but are far less likely to develop severe symptoms.[7] The risk of severe disease and death is highest for seniors and those with severe health conditions, such as heart disease, chronic lung disease, cancer, and diabetes.[7]

COVID-19 has been perceived worldwide as a major threat to health and a danger to the global economy, affecting people's lives by influencing their everyday behavior and causing feelings of panic anxiety, depression, and often triggering intense dread.

In China, COVID-19 has affected children aged 3 months to 17 years, most of whom had close contact with infected persons or were part of a family cluster of cases.[8] No official data are available on the number of symptomatic and asymptomatic individuals positive for COVID-19 in the <18 age group. Infected children might appear asymptomatic[9] or present with fever, dry cough, and fatigue, and few have upper respiratory symptoms including nasal congestion and running nose. Some patients present with gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea. Most infected children have mild clinical manifestations without fever or symptoms of pneumonia, and the majority recover within 1-2 weeks after disease onset. Few progress to lower respiratory infections.

Although children seem to be less vulnerable than adults to COVID-19, initial reports from Chinese areas hit by the outbreak indicate that children and adolescents have been impacted psychologically, manifesting behavioral problems, as discussed below.[10]

Early Investigation of Chinese Children's Behavioral and Emotional Reactions to COVID-19

Children are not indifferent to the dramatic impact of the COVID-19 epidemic. They experience fears, uncertainties,

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and physical and social isolation and may miss school for a prolonged period. Understanding their reactions and emotions is essential to properly address their needs. A preliminary study conducted in Shaanxi Province during the second week of February 2020, which was authorized by the local authorities, showed that the most common psychological and behavioral problems among 320 children and adolescents (168 girls and 142 boys) aged 3-18 were clinginess, distraction, irritability, and fear of asking questions about the epidemic (unpublished data). Because of the Chinese government's mobility restrictions related to epidemics, as enforced by local and national authorities, the study was performed using an online questionnaire to investigate the children's behavioral and emotional responses to the current epidemics. Several children were confined at home under protective isolation because they resided in highly affected areas.

The questionnaire, which was completed by the parents, incorporated the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria[10] commonly used for a cross-cultural assessment of anxiety disorders, including depression.[11] Fear of asking about the epidemics and the health of relatives, poor sleep including nightmares, poor appetite, physical discomfort, agitation and inattention, clinginess, and separation problems were among the main psychological conditions investigated. An important factor ensuring the reliability of results collected by questionnaires investigating mental disorders in general and particularly during emergencies is the procedure for data collection and statistical analysis followed by specialized personnel responsible for data collection, registration, and statistical processing, as in this case. The use of standard statistical methods ensures the comparability of the results with other studies.[12,13]

The purpose of the questionnaire used in the Chinese study was not to establish a final diagnosis of mental disorder and depression or to monitor depression severity, but rather to screen for behavioral and emotional disorders as a "first step" approach. Subjects who screened positive at preliminary investigation of their behavioral and emotional condition should be included in future programs to determine whether they meet criteria for a depressive disorder.

Psychological distress in Children Exposed to Adverse Events

Although the knowledge base regarding children's responses to trauma and adverse events in general has been expanding, descriptions of their responses during epidemics remain scarce.[14] Yet their vulnerability makes this an important group to study. Several studies have documented the damaging effects of psychological stress due to negative events in children. Anxiety, depression, lethargy, impaired social interaction, and reduced appetite are commonly reported manifestations. Physiological effects include a weakened or compromised immune system.[15-19] In the course of adverse events, children are often forced to stay home for long periods due to enforced isolation and school closure, resulting in limited connection with classmates and reduced physical activity.

A preliminary study conducted in the Shaanxi province during the COVID-19 epidemic by the China-EPA-UNEPSA collaborative working group showed that children in the younger age group (3-6 years) were more likely than older children to manifest symptoms, such as clinginess and fear that family members could contract the infection ($P = .002$). Children aged 6 to 18 years were more likely to show inattention ($P = .049$) and persistent inquiry ($P = .003$). Clinging, inattention, and irritability were the most severe psychological conditions demonstrated by the children in all age groups (**Figure**; available at www.jpeds.com). The rates of fear, anxiety, and other emotions were higher in children residing in highly epidemic areas; however, the differences between areas identified by different levels of epidemic risk were not statistically significant. Media entertainment was largely successfully used by families over reading and physical exercise as a means to relieve their children's distress and address their concerns regarding the negative condition they were experiencing (**Table**; available at www.jpeds.com).

The Importance of Nurturing Resilience in Children Exposed to Epidemics

Children facing unexpected and unknown events typically exhibit various stress reactions, as confirmed in the study performed in China during the COVID-19 epidemic. Resilience, the personal attributes that help children manage everything from little disappointments to big life traumas, should be nurtured and implemented by public health programs in children and teens living in areas hit by calamities such as epidemics. If properly supported by healthcare professionals, families, and other social connections, including school environment, children and adolescents can appropriately overcome a condition of distress and prospectively stabilize emotionally and physiologically.[20]

Conclusions

Pediatricians working in Shaanxi Province, China have pursued the strategy of nurturing resilience in children and adolescents hit by the psychological consequences of the COVID-19 epidemic. The measures suggested by Chinese pediatricians to parents and family members, included increasing communication with children to address their fears and concerns, playing collaborative games to alleviate loneliness, encouraging activities that promote physical activity, and using music therapy in the form of singing to reduce the worry, fear, and stress that the child may feel. All these measures are focused on supporting the child to

get through this difficult time. Furthermore, parents should pay attention to sleep difficulties and nightmares, prevent increased daytime sleep and suggest sleep hygiene and relaxation methods, model a positive psychological attitude to reduce stress, and divert attention to more productive and positive directions.

The effect of this outbreak is unclear at present, as the situation is rapidly evolving.[21] The China-EPA-UNEPSA working group believes that the preliminary report from the Chinese province of Shaanxi includes useful information for professionals involved in the care of children hit by the current and possible future epidemics.[22] ■

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References

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74.
2. Fauci AS, Lane HC, Redfield RR. Covid-19—Navigating the uncharted. N Engl J Med 2020. https://www.nejm.org/doi/full/10.1056/NEJMe2002387. Accessed March 6, 2020.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
4. World Health Organization. COVID-19 situation. https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd. Accessed March 6, 2020.
5. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020;382:970-1.
6. Nextstrain. Genomic epidemiology of novel coronavirus (HCoV-19). https://nextstrain.org/ncov. Accessed March 6, 2020.
7. Nature. Coronavirus latest: China study suggests children are as likely to be infected as adults. https://www.nature.com/articles/d41586-020-00154-w. Accessed March 7, 2020.
8. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020. https://doi.org/10.1007/s12519-020-00343-7 [Epub ahead of print].
9. Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa198 [Epub ahead of print].
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Publishing; 2013.
11. Petito A, Pop TL, Namazova-Baranova L, Mestrovic J, Nigri L, Vural M, et al. The burden of depression in adolescents and the importance of early recognition. J Pediatr 2020;218:265-7.e1.
12. Campanozzi A, Russo M, Catucci A, Rutigliano I, Canestrino G, Giardino I, et al. Hospital-acquired malnutrition in children with mild clinical conditions. Nutrition 2009;25:540-7.
13. Albenzio M, Campanozzi A, D'Apolito M, Santillo A, Pettoello Mantovani M, Sevi A. Differences in protein fraction from goat and cow milk and their role on cytokine production in children with cow's milk protein allergy. Small Rumin Res 2012;105:202-5.
14. Klein TP, Devoe ER, Miranda-Julian C, Linas K. Young children's responses to September 11th: the New York City experience. Infant Ment Health J 2009;30:1-22.
15. Hoven CW, Duarte CS, Lucas CP, Wu P, Mandell DJ, Goodwin RD, et al. Psychopathology among New York City public school children 6 months after September 11. Arch Gen Psychiatry 2005;62:545-52.
16. Laor N, Wolmer L, Mayes LC, Gershon A, Weizman R, Cohen DJ. Israeli preschool children under Scuds: a 30-month follow-up. J Am Acad Child Adolesc Psychiatry 1997;36:349-56.
17. Plourde A, Lavoie KL, Raddatz C, Bacon SL. Effects of acute psychological stress induced in laboratory on physiological responses in asthma populations: a systematic review. Respir Med 2017;127:21-32.
18. Park I, Oh SM, Lee KH, Kim S, Jeon JE, Lee HY, et al. The moderating effect of sleep disturbance on the association of stress with impulsivity and depressed mood. Psychiatry Investig 2020 https://doi.org/10.30773/pi.2019.0181 [Epub ahead of print].
19. Han JW, Lee H. Effects of parenting stress and controlling parenting attitudes on problem behaviors of preschool children: latent growth model analysis. J Korean Acad Nurs 2018;48:109-21.
20. Pettoello-Mantovani M, Pop TL, Mestrovic J, Ferrara P, Giardino I, Carrasco-Sanz A, et al. Fostering resilience in children: the essential role of healthcare professionals and families. J Pediatr 2019;205:298-9.e1.
21. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA 2020;323:707-8.
22. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.

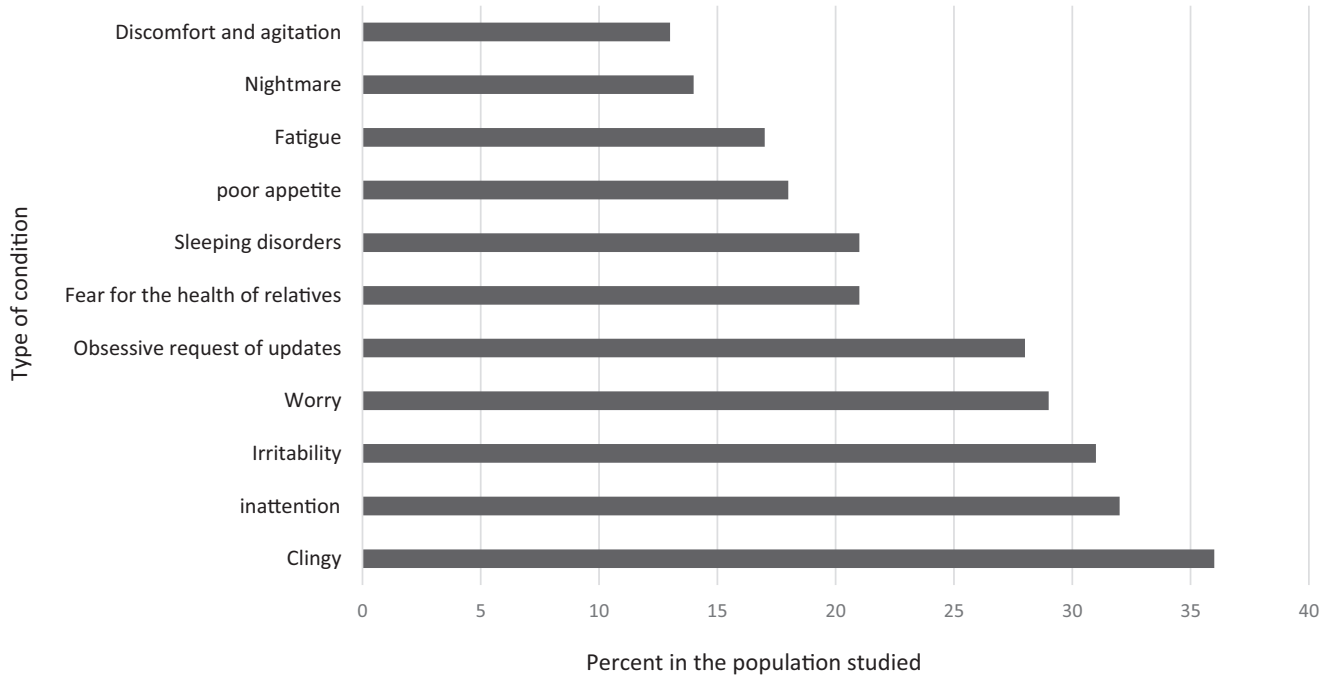

Figure. Psychological conditions studied in a population aged 3-18 during COVID-19 epidemic in the Shaanxi province, China. (January 25-February 8, 2020).

Table. Means used by families to address children's psychological problems and to mitigate their effects during COVID-19, evaluated on a 5-point rating scale

Option	Not used	Ineffective 1	2	3	4	Very effective 5
Media entertainment, %	18.77	0.97	5.83	11	37.86	25.57
Reading entertainment, %	19.09	3.56	12.3	17.48	28.8	18.77
Physical exercise, %	22.65	1.29	8.09	16.18	31.72	20.06

(Rating scale from HR-Survey, LLC for educational purposes: https://hr-survey.com/PfRatingScales.htm).

The Health Risks of Electronic Cigarettes Use in Adolescents

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The use of electronic cigarettes (e-cigarettes) and other types of vaping devices has risen in popularity, particularly among teenagers.[1] Several studies indicate that e-cigarettes might help smokers quit tobacco cigarettes, benefiting their long-term health.[2] However, further studies suggest that vaping may be driving an increase in nicotine use for teens, caused by their exposure to elevated levels of this alkaloid.[2,3] Due to the highly addictive nature of nicotine, it has been hypothesized that young vaping device users might switch from their initial use to traditional cigarettes, or that nicotine exposure may function as a gateway to drugs.[4] Concern also was raised on the risks of exposure to other chemicals through vaping. Acute respiratory distress syndrome, pulmonary illnesses, and asthma have been reported to be induced by vaping substances.[5-8] The Minnesota Department of Health reported that a significant number of patients have been classified as having e-cigarette, or vaping, product use–associated lung injury.[9]

The working group on social pediatrics and public health of the European Paediatric Association/Union of National European Paediatric Societies and Associations is actively engaged in monitoring health and wellbeing.[10,11] The purpose of this commentary is to raise the attention of healthcare professionals on the escalating use of e-cigarettes and vaping among adolescents, and the possible health implications of this broad social phenomenon.

Definition of Vaping and Vaping Products

E-cigarettes and similar devices, such as pens and other types of products, including advanced personal vaporizers or modified e-cigarettes, have been introduced and mass marketed in Europe (2006) and in the US (2007). A typical vaping device includes a mouthpiece, a battery, a cartridge to be filled with e-liquid or e-juice, and a heating component for the device. When the device is switched on, the battery heats up the heating component, which turns e-liquids into an aerosol vapor that is inhaled into the lungs and then exhaled. Vaping is the act of inhaling and exhaling this aerosol, which consists of many fine particles typically containing varying amounts of toxic chemicals that have been linked to harmful health events in individuals.[7,8,12] Commercialized e-liquids for use in vaporizer products usually contain a propylene glycol or vegetable glycerin–based liquid with nicotine, flavoring, and other chemicals and metals.

Epidemiology of Vaping in Teens and Adolescents

During the past 5 years, the popularity of vaping among adolescents has risen significantly.[13] The US National Institutes of Health (NIH) reports an increase in the use of vaping devices by high school seniors, from 27.8% in 2017 to 37.3% in 2018.[14] The NIH study estimates that the overall number of middle school and high school students reporting the use of e-cigarettes rose from approximately 2.1 million recorded in 2017 to 3.6 million documented in 2018, with a jump of 78% (from 11.7% to 20.8%), doubling rates of the past 2 years. The NIH data suggest that although it is illegal to sell e-cigarettes to anyone younger than 21 years of age in the US (18 or 19 years in some US states) and 18 years in the European Union[15,16] (**Table**; available at www.jpeds.com), age restrictions do not seems to be a limitation to widespread use.[14] Young people who have never smoked traditional cigarettes seem to be intrigued by the use of vaping, which is available in more than 1500 flavors, including fancy aromas like bubble gum and candy floss.[17-19] In a survey involving US youths aged 12-17 years, 81% of e-cigarette users reported that they have been prompted to vaping by the availability of flavored products. In Europe, the European Tobacco Products Directive legislation regulates the fundamental rules for the production of inhalation fluids.[15,16] Reliable statistics on the use of e-cigarettes in the European population younger than 18 years old are limited.[20] Among the available data, a study in Germany showed that the 1-year prevalence of subjects younger than the age of 18 who had ever used an e-cigarette was 14.6%.[21] Although 2.8% of them currently

NIH	National Institutes of Health

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used e-cigarettes, 0.2% had regularly used a vaping device in the past, and 11.6% had tried it at least once in the past.[21] The use of e-cigarettes among 11- to 15-year-olds in England increased from 22% in 2014 to 25% in 2016.[22,23] A 2018 report indicated that 16.0% of 11- to 18-year-olds in the United Kingdom had tried vaping at least once, an increase compared with 12.7% recorded in 2015.[22] In Italy, a study on the general consumption of nicotine by traditional cigarettes and vaping devices showed a 41.1% rate of use among students, which adding to the list the other available formulas (ie, snuff tobacco, water pipe, and cigarettes without combustion), reaches 47.3%, equal to a total of more than 1 million students.[24] Regarding the reasons for using vaping, 76.1% of e-cigarette smokers reported having tried it the first time out of curiosity, 15.7% because offered by friends, and 8.3% for quitting smoking.[24]

Potential Health Risks

Studies on e-cigarette products, including disposable and refillable commercial articles, and e-liquids, report that they contain an average of 6.2 flavoring chemicals, and that e-cigarettes with sweet flavors have a significantly greater number of flavoring chemicals when compared with tobacco- and menthol-flavored products.[25] More than 20% of commercial products were found to contain flavoring chemicals with a potential risk of inhalation toxicity, including benzyl alcohol, benzaldehyde, and vanillin.[25,26] Additional toxicants, such as acrolein and diacetyl, have been identified in several vaping products.[25] Measurable levels of tobacco-specific nitrosamines were detected in 70% of tested products.[25] Further studies suggest that use of e-cigarettes may negatively influence cardiovascular health[27] and that flavorants in e-cigarettes present potential hazards, such as risk of obstructive lung diseases.[28] In addition, nicotine, often used in vaping, confers a series of risks, including anomalies in the development of the hippocampus and cerebral cortex among adolescents.[29-31] Smoking is a highly efficient form of drug administration. Inhaled nicotine enters the circulation rapidly through the lungs and moves into the brain within seconds, with fast rates of absorption, reinforcing the effects of the drug.[32,33] Moreover, adolescent e-cigarettes users show increased rates of chronic bronchitis symptoms and asthma.[34] E-cigarettes contain several constituents, which may present potential risks for lung, stomach, bladder, and esophageal cancer.[35] Finally, e-cigarette vapor has been linked to cancer in mice.[36]

Conclusions

E-cigarettes and vaping devices have been introduced on the market as a safer and healthier alternative to traditional cigarettes, and available data suggest that they may help smokers to stop smoking long term, or to facilitate smokers unable to stop smoking entirely, to reduce their tobacco cigarette consumption.[37] Studies have shown that regular, daily e-cigarette use is positively associated with a significant decrease in the number of cigarettes smoked per day, as well as with an increase in smoking-cessation attempts.[38,39] However, substantial uncertainty surrounds the potential impact of e-cigarettes on health, and this important public health issue is currently widely debated. The evidence to date suggests that vaping is not a safe alternative to smoking tobacco.[40] This, coupled with the worrying trend of young nonsmokers being attracted to vaping, raises fears of yet another generation suffering from chronic lung disease and other acute and chronic health conditions.[41] Finally, due to the insufficient regulations in several countries,[42] up-to-date data on the prevalence of e-cigarette use and studies on the health's implications of their use are urgently needed to inform policy at a national and international level (ie, European Union). Pediatricians are typically on the front line for identifying emerging risks for children and adolescents; therefore, they may effectively help increase awareness about the potential danger of vaping on health.[43,44] Information on the use of vaping devices should be implemented worldwide and included in public health information and prevention programs.[45,46] ■

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References available at www.jpeds.com.

References

1. National Institute of Health (NIH). Teen e-cigarette use doubles since 2017. Researchers sound alarm on potential health effects of vaping. https://www.nih.gov/news-events/news-releases/teen-e-cigarette-use-doubles-since-2017. Accessed December 15, 2019.
2. Grana RA, Popova L, Ling PM. A longitudinal analysis of electronic cigarette use and smoking cessation. JAMA Intern Med 2014;174:812-3.
3. Kandel ER, Kandel DB. A molecular basis for nicotine as a gateway drug. N Engl J Med 2014;371:932-43.
4. Eaton DL, Kwan LY, Stratton K. Public Health Consequences of E-Cigarettes. Consensus study report. Washington (DC): National Academies Press (US); 2018.
5. Qarajeh R, Kitchen J. THC vaping-induced acute respiratory distress syndrome. Am J Med 2019 [Epub ahead of print].
6. Clapp PW, Peden DB, Jaspers I. E-cigarettes, vaping-related pulmonary illnesses, and asthma: a perspective from inhalation toxicologists. J Allergy Clin Immunol 2019 [Epub ahead of print].
7. Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. Lancet 2019;394:2073-83.
8. Alexander L, Perez MF. Identifying, tracking, and treating lung injury associated with e-cigarettes or vaping. Lancet 2019;394:2041-204.
9. Taylor J, Wiens T, Peterson J, Saravia S, Lunda M, Hanson K, et al. Lung Injury Response Task Force. Characteristics of E-cigarette, or vaping, products used by patients with associated lung injury and products seized by law enforcement—Minnesota, 2018 and 2019. MMWR Morb Mortal Wkly Rep 2019;68:1096-100.
10. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.
11. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
12. American College of Cardiology. E-Cigarettes Linked to Heart Attacks, Coronary Artery Disease and Depression. https://www.acc.org/about-acc/press-releases/2019/03/07/10/03/ecigarettes-linked-to-heart-attacks-coronary-artery-disease-and-depression. Accessed December 22, 2019.
13. Miech R, Johnston L, O'Malley PM, Bachman JG, Patrick ME. Trends in adolescent vaping, 2017-2019. N Engl J Med 2019;381:1490-1.
14. National Institutes of Health (NIH). Teens using vaping devices in record numbers. https://www.nih.gov/news-events/news-releases/teens-using-vaping-devices-record-numbers. Accessed December 22, 2019.
15. European Commission. The Tobacco Products Directive (2014/40/EU). https://ec.europa.eu/health/tobacco/products_en. Accessed December 29, 2019.
16. European Commission. Directive 2014/40/EU of the European Parliament and of the Council. https://ec.europa.eu/health/sites/health/files/tobacco/docs/dir_201440_en.pdf. Accessed December 24, 2019.
17. Chen JC, Das B, Mead EL, Borzekowski DLG. Flavored E-cigarette use and cigarette smoking susceptibility among youth. Tob Regul Sci 2017;3:68-80.
18. Thomas K, Kaplan S. E-cigarettes went unchecked in 10 years of federal inaction. https://www.nytimes.com/2019/10/14/health/vaping-e-cigarettes-fda.html. Accessed January 3, 2020.
19. Martin L, Reihill J. Here are all the valid health reasons why so many countries are banning vapes. https://www.sciencealert.com/more-and-more-countries-are-banning-e-cigarettes. Accessed January 3, 2020.
20. Filippidis FT, Laverty AA, Gerovasili V, Vardavas CI. Two-year trends and predictors of e-cigarette use in 27 European Union member states. Tob Control 2017;26:98-104.
21. Kotz D, Böckmann M, Kastaun S. The use of tobacco, e-cigarettes, and methods to quit smoking in Germany. Dtsch Arztebl Int 2018;115:235-42.
22. Action on Smoking and Health. ASH. June 2019 Report. Use of e-cigarettes among young people in Great Britain. https://ash.org.uk/wp-content/uploads/2019/06/ASH-Factsheet-Youth-E-cigarette-Use-2019.pdf. Accessed December 23, 2019.
23. Niblett P, National Health Service (NHS), England, Digital Statistical Service. Smoking, drinking and drug use among young people. England 2016. https://files.digital.nhs.uk/47/829A59/sdd-2016-rep-cor-new.pdf. Accessed January 3, 2020.
24. National Research Council (CNR). Italy. 2019 Report. Consiglio Nazionale delle Ricerche. Adolescenti in fumo. https://www.cnr.it/it/comunicato-stampa/9023/adolescenti-in-fumo. Accessed December 23, 2019.
25. Czoli CD, Goniewicz ML, Palumbo M, Leigh N, White CM, Hammond D. Identification of flavouring chemicals and potential toxicants in e-cigarette products in Ontario, Canada. Can J Public Health 2019;110:542-50.
26. Martin LS, Reihill JA. Promotion of a protease–antiprotease imbalance in the airways through chronic vaping. Am J Respir Crit Care Med 2019;200:1337-9.
27. Hammett E, Veldheer S, Yingst J, Hrabovsky S, Foulds J. Characteristics, use patterns and perceptions of electronic cigarette users who were never traditional cigarette smokers. Addict Behav 2017;65:92-7.
28. Lippi G, Favaloro EJ, Meschi T, Mattiuzzi C, Borghi L. Cervellin GE-cigarettes and cardiovascular risk: beyond science and mysticism. Semin Thromb Hemost 2014;40:60-5.
29. Barrington-Trimis JL, Samet JM, McConnell R. Flavorings in electronic cigarettes: an unrecognized respiratory health hazard? JAMA 2014;312:2493-4.
30. England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the developing human: a neglected element in the electronic cigarette debate. Am J Prev Med 2015;49:286-93.
31. Roditis ML, Halpern-Felsher B. Adolescents' perceptions of risks and benefits of conventional cigarettes, E-cigarettes, and marijuana: a qualitative analysis. J Adolesc Health 2015;57:179-85.
32. Benowitz NL. Nicotine addiction. N Engl J Med 2010;362:2295-303.
33. Albenzio M, Campanozzi A, D'Apolito M, Santillo A, Pettoello-Mantovani M, Sevi A. Differences in protein fraction from goat and cow milk and their role on cytokine production in children with cow's milk protein allergy. Small Ruminant Res 2012;105:202-5.
34. McConnell R, Barrington-Trimis JL, Wang K, Urman R, Hong H, Unger J, et al. Electronic cigarette use and respiratory symptoms in adolescents. Am J Respir Crit Care Med 2017;195:1043-149.
35. Cancer.Net. Cancer. Net Editorial Board, Health Risks of E-cigarettes, Smokeless Tobacco, and Waterpipes. https://www.cancer.net/navigating-cancer-care/prevention-and-healthy-living/stopping-tobacco-use-after-cancer-diagnosis/health-risks-e-cigarettes-smokeless-tobacco-and-waterpipes. Accessed December 23, 2019.
36. Tang M, Wu XR, Lee HW, Xia Y, Deng FM, Moreira AL, et al. Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. Proc Natl Acad Sci USA 2019;116:21727-31.
37. Schraufnagel DE, Blasi F, Drummond MB, Lam DC, Latif E, Rosen MJ, Forum of International Respiratory Societies. Electronic cigarettes. A position statement of the Forum of International Respiratory Societies. Am J Respir Crit Care Med 2014;190:611-8.
38. Zhu SH, Zhuang YL, Wong S. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ 2017;358:j3262.
39. Pasquereau A, Guignard R, Andler R. Electronic cigarettes, quit attempts and smoking cessation: a 6-month follow-up. Addiction 2017;112:1620-8.
40. Korfei M. The underestimated danger of E-cigarettes. Respir Res 2018;19:159-62.
41. Shmerling RH. Can vaping damage your lungs? What we do (and don't) know. Harvard Health Publishing. https://www.health.harvard.edu/

blog/can-vaping-damage-your-lungs-what-we-do-and-dont-know-2019090417734. Accessed December 29, 2019.
42. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
43. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
44. Ehrich J, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-8.e2.
45. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270-1.e1.
46. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, et al. the economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.

Table. Summary of rules on tobacco products and electronic cigarettes use, issued by the EU (Directive 2014/40/EU) and enforced in EU countries since 20 May 2016

General rules
- prohibits cigarettes and roll-your-own tobacco with characterizing flavors
- requires tobacco industry to report to EU countries on the ingredients used in tobacco products
- requires health warnings on tobacco and related products: combined health warnings (picture, text, and information on how to stop) must cover 65% of the front and back of cigarette and roll-your-own tobacco packages
- sets minimum dimensions for warnings and prohibits small packages for certain tobacco products
- bans promotional and misleading elements on tobacco products, e-cigarettes, and herbal products for smoking
- introduces EU-wide tracking and tracing to combat the illicit trade of tobacco products
- allows EU countries to prohibit internet sales of tobacco and related products
- sets out safety, quality, and notification requirements for electronic cigarettes
- obliges manufacturers and importers to notify EU countries about novel tobacco products before placing them on the EU market

Summary of rules for e-cigarettes sold as consumer products:

Safety and quality requirements for e-cigarettes
- The Directive sets a maximum nicotine concentration and volume for cartridges, tanks, and nicotine liquid containers.
- E-cigarettes should be child-resistant and tamper-evident and have a mechanism that allows refilling without spillage to protect consumers.
- E-cigarette ingredients must be of high purity
- E-cigarettes should deliver the same amount of nicotine when puffed at the same strength and duration.
- Manufacturers and importers must notify all products they place on the EU market through a standardized electronic format.

Packaging and labeling rules for e-cigarettes
- Health warnings for e-cigarettes advising consumers that they contain nicotine and should not be used by nonsmokers are mandatory
- Packaging must include a list of ingredients contained in the product, information on the product's nicotine content
- A leaflet with instructions for use and information on adverse effects, risk groups, addictiveness, and toxicity must be included in packaging
- Promotional elements are not allowed on e-cigarette packaging
- Cross-border advertising and promotion of e-cigarettes is prohibited.

EU, European Union.

The Burden of Depression in Adolescents and the Importance of Early Recognition

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Mental health disorders are frequent during the developmental years, particularly in adolescents. The leading cause of disability in young people are neuropsychiatric conditions, which if left untreated may severely affect development, including educational and social achievements. It has been reported that 10%-20% of individuals experience a form of mental disorder during childhood and adolescence worldwide.[1] One-half of them arise by 14 years of age.[2]

Among adolescent mental health disorders, depression is one of the most frequent conditions, and it is indicated as one of the most alarming "new morbidities."[3,4] The onset of depression is typically around mid-to-late adolescence, and it important to recognize its early warning signs and symptoms. Early intervention can often prevent the later development of a severe depressive illness. For instance, in adolescents, depression is a major risk factor for suicide, and more than one-half of adolescent suicide victims were reported to have a depressive disorder at the time of death.[5] Depression also leads to serious social and educational maladjustments in this age group, such as an increased rate of smoking, substance misuse, eating disorders, and obesity.[6,7] This commentary aims to further raise awareness of pediatricians on the burden and risks faced by adolescents developing depression. In particular, we emphasize that new morbidities should be part of the formal training in pediatrics worldwide, enabling the new generations of pediatricians to recognize these pathologic conditions in a timely manner and effectively deal with them.

Definition, Classification, and the Alarming Predictive Signs of Depression in Adolescents

Depression is identified by a cluster of specific symptoms with associated harms (**Table I**; available at www.jpeds.com). Adolescents and adults show similar clinical and diagnostic elements.[8,9] Depression in children is relatively infrequent; the prevalence is reported to be less than 1% in most studies, rising substantially throughout adolescence.[10,11] The postpubertal increase in the prevalence of depression can be explained by several factors related to the marked biological and social changes characterizing this developmental period. Among them, puberty, brain, and cognitive maturation have been frequently reported, together with the enhanced social understanding, sensibility, sensitivity, and self-awareness typical of this age period.[12-14] Neurophysiologic changes have a role in the unbalanced responses to reward and danger, and escalating feelings of stress and anxiety are registered, particularly in adolescent girls.[15,16]

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) includes a cross-cultural assessment of depression and an updated classification, providing a list of diagnostic symptoms.[17] As described in the DSM-5, major depressive disorders are characterized by marked episodes of a minimum 2 weeks' duration with at least 1 of 2 symptoms, which could be either depressed mood, loss of interest or pleasure, or alterations in affect and emotions, cognition, and neurovegetative functions.[17] Although the presence of a single episode could be sufficient to establish the diagnosis, in the majority of cases, this disorder is characterized by recurrent episodes alternating with remissions. The 2 main classification systems (DSM-5 and the International Classification of Diseases-11) define depression similarly, although in the DSM-5 irritability rather than depressed mood is accepted as a core diagnostic symptom.[17,18]

Depression in adolescents is frequently missed, possibly owing to the prevalence of irritability, mood instability, reactivity, and oscillating symptoms in this age group compared with adults.[19] However, depression can also be missed owing to a number of different initial problems, including unexplained physical symptoms, eating disorders, anxiety,

DSM	*Diagnostic and Statistical Manual of Mental Disorders*

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misconduct, refusal to attend school, decline in academic performance, and substance misuse.

The Onset of Depression throughout the Developmental Years

Population prevalence estimates for depression vary widely across studies and between different countries, possibly owing to the different classifications adopted, diagnostic procedures, and study methods.[20,21] The median 12-month prevalence rates (4%-5%), found in mid-to-late adolescence are similar to those observed in adults.[3,22] However, the aggregated published data show that the probability of depression rises from about 5% in early adolescence to as high as 20% by the end of this age period.[6,22] Depression typically leads individuals to become isolated from family and friends and to hazardous behaviors, such as irresponsible driving, alcohol and substance abuse, and inappropriate sexual behaviors.

The burden of depression on adolescents' health and social functioning could be severe and influence their adult life. Especially among the youngest children and adolescents, signs of depression are too often unrecognized, disregarded, overlooked, or purposely ignored by the family and by the primary care provider. This factor may represent a major obstacle in establishing timely effective preventive measures.

The Importance of Recognizing Early Signs of Depression

Depression in young children up to 6 years of age usually presents in minor or masked forms.[10] In these cases, the recurrent symptomatology concerns the psychosomatic sphere, including problems with the sleep-wake rhythm and nutrition, possibly accompanied by dermatologic and respiratory problems. Very young children can experience a particular form of depression involving interpersonal dependency, which is characterized by intense fears of abandonment and feelings of helplessness and weakness. At the base of this form of depression usually lies a family affective disorder, such as the absence of the mother or the father owing to illness, the death of one of the parents, or the loss of a close adult figure. Affective loss owing to separation from parents or other figures could also be caused by the child's disease and prolonged hospital admissions.[23]

With the growth and stabilization of emotional states, through social interactions within the family, in kindergarten, and later during primary school, the child may be able to develop compensatory mechanisms that can mitigate an initial depressive state. An important alarming sign predictive of a depressive state in children during primary school age is mood instability, with rapid oscillations of intense affect, and difficulty in regulating these oscillations and their behavioral consequences, rapidly switching from laughter to tears.[10,11]

The family environment represents a significant variable in the development of the child's depressed personality. Having 1 parent suffering from depression themselves provides the child with a learning model influencing their daily habits. Typically, children may also try to please the parents or caretakers in an attempt to develop interactions and attract their attention. Knowing the personal and family background story of the children they care for, and being able to recognize warning signs suggestive of depression, will allow pediatric healthcare professionals to predict the outcome.

The Value of a Multidisciplinary Team Approach

Depression is a complex condition of unclear causation.[24] Deficiency of certain neurotransmitters have been reported to play a role in causing or contributing to depression. Serotonin has attracted the most attention, but many others including norepinephrine and dopamine have also been considered as mediators (**Table II**; available at www.jpeds.com).[24] However, the current consensus is that there is no exclusive causative element such as neurotransmitter deficiency; instead, several different contributing factors may lead to depression, including psychological or social factors, life-changing events, and biological factors such as genetics, physical illness, and chemical imbalance.[24] Therefore, a multidisciplinary team approach is widely adopted in the management of depression during the developmental years. Primary care pediatric providers are key figures in these teams, which should consist of psychiatrists, clinical nurse specialists/community mental health nurses, psychologists, social workers, occupational therapists, and if advisable, other disciplines including counselors, drama therapists, art therapists, advocacy workers, and care workers.[25,26]

Conclusions

Children with depression frequently face major challenges with stigma, isolation, and discrimination.[27] These conditions are often complicated by difficult access to health care and education facilities. Depression can go unrecognized in adolescents if they are developing their personalities within the dynamics of the family context, struggling with independence, and facing difficult academic and career decisions.

The working group on social pediatrics and public health of the European Paediatric Association, the Union of National European Paediatric Societies and Associations, emphasizes that adequate training on new morbidities should be part of pediatric formal training worldwide.[28-31] Effectively addressing the new morbidities requires the training of new pediatricians to perceive themselves as advocates in the community as well as clinicians at the bedside.[32,33] ■

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References

1. WHO. Report on Adolescent Mental health (October 23, 2019). www.who.int/news-room/fact-sheets/detail/adolescent-mental-health. Accessed November 16, 2019.
2. Lopez A, Mathers C, Ezzati M, Jamison D, Murray C. Global burden of disease and risk factors. Washington (DC): Oxford University Press and the World Bank; 2006.
3. American Academy of Pediatrics. American Academy of Pediatrics the new morbidity revisited: a renewed commitment to the psychosocial aspects of pediatric care. Committee on Psychosocial Aspects of Child and Family Health. Pediatrics 2001;108:1227-30.
4. Windfuhr K, While D, Hunt I, Turnbull P, Lowe R, Burns J, et al. National confidential inquiry into suicide and homicide by people with mental illness. Suicide in juveniles and adolescents in the United Kingdom. J Child Psychol Psychiatry 2008;49:1155-65.
5. Hawton K, van Heeringen K. Suicide. Lancet 2009;373:1372-81.
6. Lewinsohn PM, Rohde P, Seeley JR. Major depressive disorder in older adolescents: prevalence, risk factors and clinical implications. Clin Psychol Rev 1988;18:765-94.
7. Keenan-Miller D, Hammen CL, Brennan PA. Health outcomes related to early adolescent depression. J Adolesc Health 2007;41:256-62.
8. Thapar A, Collishaw S, Potter R, Thapar AK. Managing and preventing depression in adolescents. BMJ 2010;340:c209.
9. Lewinsohn PM, Pettit JW, Joiner TE Jr, Seeley JR. The symptomatic expression of major depressive disorder in adolescents and young adults. J Abnorm Psychol 2003;112:244-52.
10. Kessler RC, Avenevoli S, Ries Merikangas K. Mood disorders in children and adolescents: an epidemiologic perspective. Biol Psychiatry 2001;49:1002-14.
11. Green H, McGinnity A, Meltzer H, Ford T, Goodman R. Mental health of children and young people in Great Britain, 2004. Basingstoke, UK: Palgrave Macmillan; 2005.
12. Patton GC, Viner R. Pubertal transitions in health. Lancet 2007;369:1130-9.
13. Cyranowski JM, Frank E, Young E, Shear K. Adolescent onset of the gender difference in lifetime rates of major depression. Arch Gen Psychiatry 2000;57:21-7.
14. Blakemore SJ. The social brain in adolescence. Nat Rev Neurosci 2008;9:267-77.
15. Silberg J, Pickles A, Rutter M, et al. The influence of genetic factors and life stress on depression among adolescent girls. Arch Gen Psychiatry 1999;56:225-32.
16. Nelson EE, Leibenluft E, McClure EB, Pine DS. The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. Psychol Med 2005;35:163-74.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
18. WHO. International classification of diseases, 11th revision. The global standard for diagnostic health information. https://icd.who.int/en. Accessed November 13, 2019.
19. Leaf PJ, Alegria M, Cohen P, Goodman SH, Horwitz SM, Hoven CW, et al. Mental health service use in the community and schools: results from the four-community MECA Study. Methods for the epidemiology of child and adolescent mental disorders study. J Am Acad Child Adolesc Psychiatry 1996;35:889-97.
20. Fleitlich-Bilyk B, Goodman R. Prevalence of child and adolescent psychiatric disorders in southeast Brazil. J Am Acad Child Adolesc Psychiatry 2004;43:727-34.
21. Pillai A, Patel V, Cardozo P, Goodman R, Weiss HA, Andrew G. Non-traditional lifestyles and prevalence of mental disorders in adolescents in Goa, India. Br J Psychiatry 2008;192:45-51.
22. Lewinsohn PM, Rohde P, Klein DN, Seeley JR. Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. J Am Acad Child Adolesc Psychiatry 1999;38:56-63.
23. Pettoello-Mantovani M, Pop TL, Mestrovic J, Ferrara P, Giardino I, Carrasco-Sanz A, et al. Fostering resilience in children: the essential role of healthcare professionals and families. J Pediatr 2019;205:298-9.e1.
24. Mullen S. Major depressive disorder in children and adolescents. Ment Health Clin 2018;8:275-83.
25. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet 2012;379:1056-67.
26. Cheung AH, Kozloff N, Sacks D. Pediatric depression: an evidence-based update on treatment interventions. Curr Psychiatry Rep 2013;15:381.
27. Birmaher B, Brent D, Bernet W, Bukstein O, Walter H, Benson RS. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 2007;46:1503-26.
28. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.
29. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
30. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
31. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
32. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, et al. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.
33. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270-1.e1.

Table I. Main revealing symptoms of depression

Depression symptoms can vary from mild to severe and may include:

- Feeling of sadness. Depressed mood throughout the day and almost every day.
- Marked loss of interest or pleasure in activities that were used to be enjoyed.
- Changes in daily nutrition habits and/or appetite. Significant weight loss or weight gaining unrelated to dieting.
- Sense of fatigue experienced nearly every day. Decline in common physical activities and slowing down of thought (evident to others).
- Increase in purposeless physical activity (ie, wandering, hand wringing) or slowed movements and speech (evident to others).
- Sleeping disorders. Including difficulty in falling and/or staying asleep, wake up frequently during the night or sleepiness.
- Sense of worthlessness or guiltiness, or feeling inadequate nearly every day.
- Reduced ability to think or concentrate, or sense of indecisiveness and difficulty in making decisions, nearly every day.
- Persistent thoughts of death. Experiencing suicidal feelings or manifesting suicidal purposes although in absence of specific plans.

Table II. Different neurotransmitters reported to play a role in depression

Neurotransmitters	Action
Acetylcholine	Enhances memory and it is involved in learning and recall.
Serotonin	Helps regulating sleep, appetite, and mood. Inhibits pain. Data report cases of depressed individual showing reduced serotonin transmission. Increased risk of suicide has been linked to low levels of a serotonin byproduct.
Norepinephrine	Constricts blood vessels, raising blood pressure. Certain forms of depression and anxiety status may be trigged by norepinephrine, which may also influence personal feelings of motivation and reward.
Dopamine	It is basic to movement. It plays a role in the perception of reality also influencing motivation. Psychosis and severe forms of distortion in thinking with hallucinations have been associated to dopamine transmission. It may play a role in substance abuse owing to its relation with the mechanisms involved in the brain's reward system.
Glutamate	It has been reported to act like an excitatory neurotransmitter and to play a role in bipolar disorder and schizophrenia.
Lithium carbonate	It is widely recognized as mood stabilizer and used to treat bipolar disorder. Experimentally, it has been shown to help preventing damage to neurons in the brains of rats exposed to high levels of glutamate. Further in vivo experimental data in animal suggests that lithium might stabilize glutamate reuptake, therefore providing a possible explanation on how in the long term the drug reduces the highs of mania and the lows of depression.
Gamma-aminobutyric acid	Reports indicate that by acting similarly to an inhibitory neurotransmitter, this amino acid helps controlling anxiety.

The Role of Healthy Lifestyle Promotion, Counseling, and Follow-up in Noncommunicable Diseases Prevention

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Several countries worldwide recently have experienced considerable transition in demography and disease epidemiology, characterized by falling rates of preventable communicable diseases and increased life expectancy. However, various factors, including the economy, education, food security, and access to proper healthcare and immunization programs, have led to unhealthy behaviors, inappropriate diets, and lack of physical activity, which have favored the development of noncommunicable diseases (NCD).[1] The term NCDs, often also referred to as "chronic diseases," describes medical conditions or diseases that are noninfectious, of long duration, and generally characterized by slow progression.[2] The global impact of NCDs on various populations has significantly increased during the last 2 decades to reach considerably greater incidence rates. The World Health Organization (WHO) statistics report that NCDs were responsible for 40.5 million, or 71%, of global deaths in 2016.[3]

Although NCDs have their major impact on global mortality and morbidity in adulthood, statistics also show a significant impact of NCDs on children and adolescents. The working group on social pediatrics and public health of the European Paediatric Association, the Union of National European Paediatric Societies and Associations is actively engaged in contrasting the expansion of NCDs through the promotion of preventive programs in collaboration with its members. The purpose of this commentary is to further raise the attention of healthcare professionals worldwide, and pediatricians in particular, about the importance of healthy lifestyle promotion, counseling, and follow-up in the prevention of NCDs during developmental years. Primary prevention offers the potential to reduce the continuous expansion of the social and economic burden related to NCDs, particularly within communities characterized by the presence of social and economic disparities.[4]

DALY	Disability-adjusted life year
NCD	Noncommunicable diseases
WHO	World Health Organization

Worldwide Mortality and Disease Burden of NCDs in Children

Data from the WHO estimate that in 2017, 3.9% of the 141 million children born every year died before their 5th birthday. Therefore, approximately 5.4 million children younger than 5 years die worldwide, many from preventable communicable diseases and malnutrition.[5] Of them, 4.1 million of all deaths younger than 5 years of age (75%) occur within the first year of life.[5] Although all WHO regions have significantly reduced their mortality rates for children younger than 5 years of age, over the past 30 years, the burden of mortality in this group of children remains unacceptably high and unevenly distributed.[6] Furthermore, the rates of NCDs are significantly high in children and adolescents, and the incidence of several NCDs and the prevalence of related risk factors in this population are rising rapidly, creating social and economic burdens across both developed and developing nations.[5,7] According to the WHO, the leading causes of mortality during the first year of life in 2016 were typically related to preventable newborn problems. In low-income countries, 45% of all deaths in this group of children are associated with undernutrition, and more than 80% of newborn deaths are associated with low birth weight. In general, 200 million children are estimated to be unable to achieve their full developmental potential.[5] NCDs occur due to a combination of genetic, physiological, environmental, and behaviors factors. The number of children with overweight or obesity younger than 5 years of age increased by 28% between 1990 and 2016, and cancer is currently a leading cause of death among children and adolescents globally. An estimated 25 million young people, ages 13-15 years,

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smoke cigarettes, and one-half of all mental illnesses begin by the age of 14 years.

Disease burden is measured in DALYs (disability-adjusted life years), which are used to estimate the total burden of a disease, both from years of life lost and years lived with a disability. One DALY equals 1 lost year of healthy life. The sum of these DALYs across the population, or the burden of disease, can be considered as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability.[8] The burden of NCDs in children younger than 14 years of age in selected North American and European countries is reported in the **Figure** (available at www.jpeds.com).

Social Determinants and NCDs

Common, yet preventable, risk factors lie behind most NCDs. The WHO focuses its attention and programs particularly on 4 groups of NCDs, including cardiovascular diseases (responsible for 46% of NCDs deaths), cancers (22%), chronic respiratory diseases (10%), and diabetes (4%).[1] These health conditions, which affect people globally, are rooted in modifiable behavioral risk factors: tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol.[2] Such behaviors, which may become addictions or habits in adulthood, frequently begin in childhood or adolescence.[9] Inequalities in social conditions may facilitate the development of NCDs, which can impact individuals from before birth, having long-lasting effects during a lifetime.[10] Development of brain areas associated with regulation and control of behaviors and thought, such as cognitive control over diet and activity levels, may be influenced by socioeconomic limitations suffered by individuals during their early years.[11] Populations living in economically advantaged areas characterized by middle and high income have more control of diet and physical activity, therefore reinforcing the speculation that social inequalities play a significant role in the development of NCDs.[4] Healthy eating programs, including dietary counseling, aimed at influencing eating behavior at an individual level are more effective in individuals of higher socioeconomic position, thus further increasing inequalities.[12]

Main Risk Factors

Children are particularly vulnerable to NCDs. The causes of obesity are complex and based on several elements, including genetic and physiological factors, eating and physical activity habits, and growth patterns in early life, all influenced by a variety of social determinants.[13] However, unhealthy diet and eating habits causing overweight and obesity[14] cannot be explained by defective cognitive control mechanisms only, as social gradients in these health conditions are observed in 5-year-old children whose choices are in large part governed by their family environment.[13]

Well-designed and planned preventive intervention programs are the primary measures to combat overweight and obesity, through targeting their related risk factors in children and adolescents.[15] Family, school, and local communities play a key role.[16] Isolated, although meritorious, initiatives or unplanned and noncoordinated interventions have shown to be insufficient, if not ineffective. For instance, simply providing diet sheets on healthy eating to patients is insufficient.

Several constraining factors, including social environmental, economic, political, and cultural factors, may interfere with preventive interventions and education programs aimed at influencing individual choices. For instance, an important limiting factor in correct food choice is the shortage of money. Not infrequently, renting and heating the home in addition to eating healthy appear to be irreconcilable ambitions. Affordability of a healthy diet may be a challenging issue for those on low incomes in all countries. In European countries, low-income households would have to spend more than 70% of their economic resources to follow healthy eating guidelines.[17] It is therefore important for pediatricians to be adequately trained in developing or taking part in appropriate and realistic community programs, which would enable them to break the barriers for successful planning of preventive programs and their implementation in different localities.[18,19]

Alcohol, drug abuse, and tobacco are also widely recognized to be important risk factors exposing children to NCDs. Most people who smoke or use tobacco products began at a young age, and teens who use tobacco and/or alcohol are more likely to use drugs. The risk of this increases if the child who begins using substances at an early age has a family history of substance abuse or friends who use or abuse substances and is sexually active.[20] Additional elements contributing to establishing negative habits in children and predisposing them to the development of NCDs are parental tobacco and alcohol use.[21]

Health education aimed at school aged children is considered the most effective way of implementing healthy lifestyle behavior and to decrease the risk of NCDs in adulthood. The school is the place in which the interventions programs could be implemented. For the last 20 years, the WHO has supported the role of schools in promoting health and the programs covering the most important challenges to health: nutrition problems and food safety, lack of physical activity, alcohol, tobacco, illicit drugs use, but also sexually transmitted diseases, unintended pregnancies and poor reproductive health, lack of immunization, and psychological problems. Programs for primary and secondary school children could improve the health of a nation, reducing the risk factors for NCDs and decreasing the morbidity of the future adult population.[22] Even though it is a known positive outcome of the integration of health education in school core curricula classes, there are different barriers that should be addressed to maximize the sustainability of educational goals.[23]

Conclusions

NCDs impact health in adulthood; however, most of them have their roots in behaviors introduced during childhood

and adolescence. Risk factors related to these diseases have been identified and are largely preventable. The European Paediatric Association, the Union of National European Paediatric Societies and Associations working group on social pediatrics and public health emphasizes the importance that pediatricians actively pursue the promotion of healthy lifestyle, counseling, and follow-up programs in children and adolescents. Establishing and promoting adequate health interventions throughout the developmental years, starting from pregnancy and continuing through childhood until adolescence, can significantly reduce NCDs. Preventive measures and health promotion should include the implementation of multidisciplinary approaches.[24] Health education in general, and healthy lifestyles in particular, and nutrition education in schools are essential components of an effective preventive strategy, as health outcomes may not be evident in the short term. If supported by well-planned learning-related interventions, such as student support services in schools and communities, these are highly effective when sustained over a lifetime.[24] ■

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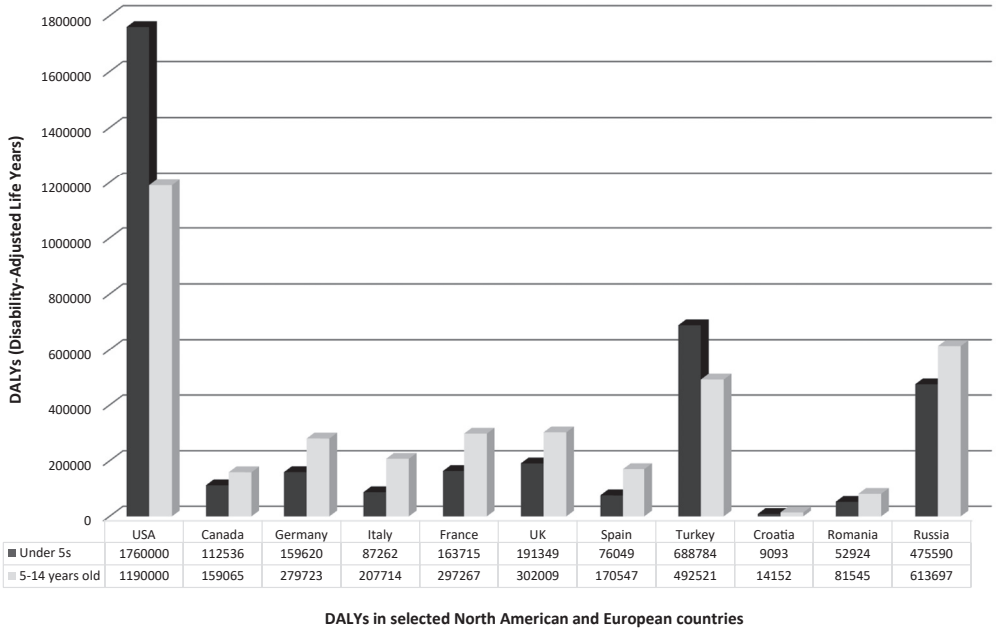
References

1. WHO. Global status report on noncommunicable disease, 2014. Geneva: World Health Organization; 2014. https://www.who.int/nmh/publications/ncd-status-report-2014/en/. Accessed June 11, 2019.
2. WHO. Global action plan for the prevention and control of noncommunicable diseases, 2013-2020. Geneva: World Health Organization; 2013. https://www.who.int/nmh/events/ncd_action_plan/en/. Accessed June 11, 2019.
3. Allen LN, Feigl AB. Reframing non-communicable diseases as socially transmitted conditions. Lancet Glob Health 2017;5:e644-6.
4. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, et al. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.
5. World Health Organization. Global Health Observatory (GHO) data. www.who.int/gho/child_health/en/index.html. Accessed October 12, 2019.
6. Roser M, Ritchie H, Dadonaite B. 2019 Child & Infant Mortality. OurWorldInData.org, ed. https://ourworldindata.org/child-mortality. Accessed October 12, 2019
7. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117-71.
8. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global burden of disease and risk factors. New York: Oxford University Press; 2006.
9. Shrestha R, Copenhaver M. Long-term effects of childhood risk factors on cardiovascular health during adulthood. Clin Med Rev Vasc Health 2015;12:1-5.
10. Prakash S. Non-communicable diseases (NCDs): a global challenge. Biomed J Sci & Tech Res. 2017;1:1-2.
11. Marteau TM, Hall PA. Breadlines, brains, and behaviour. BMJ 2013;347:f6750.
12. McGill R, Anwar E, Orton L. Are interventions to promote healthy eating equally effective for all? Systematic review of socioeconomic inequalities in impact. BMC Public Health 2015;15:457.
13. Butland B, Jebb S, Kopelman P. Tackling obesities: future choices—project report. 2nd ed. London: Government Office for Science; 2007. p. 1-161.
14. Albenzio M, Campanozzi A, D'Apolito M, Santillo A, Perttoello-Mantovani M, Sevi A. Differences in protein fraction from goat and cow milk and their role on cytokine production in children with cow's milk protein allergy. Small Ruminant Res 2012;105:202-5.
15. Pettoello-Mantovani M, Pop TL, Mestrovic J, Ferrara P, Giardino I, Carrasco-Sanz A, et al. Fostering resilience in children: the essential role of healthcare professionals and families. J Pediatr 2019;205:298-9.e1.
16. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
17. Scott C, Sutherland J, Taylor A. Affordability of the UK's Eatwell Guide. The Food Foundation; 2018. https://foodfoundation.org.uk/wp-content/uploads/2018/09/Affordability-of-the-Eatwell-Guide_Final_Web-Version.pdf. Accessed October 13, 2019.
18. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
19. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
20. Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia. https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia/contents/drug-types/tobacco. Accessed October 13, 2019.
21. Richter L, Richter DM. Exposure to parental tobacco and alcohol use: effects on children's health and development. Am J Orthopsychiatry 2001;71:182-203.
22. Pop TL, Rajka D, Stefanescu A, Racz O, Cainap S. Healthy lifestyle for a healthy childhood–a program of education for health in children. Arch Dis Child 2019;104(suppl 3):A279.
23. Rajan S, Roberts KJ, Guerra L, Pirsch M, Morrell E. Integrating health education in core curriculum classrooms: successes, challenges, and implications for urban middle schools. J Sch Health 2017;87:949-57.
24. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "diversity of child health care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.



	USA	Canada	Germany	Italy	France	UK	Spain	Turkey	Croatia	Romania	Russia
Under 5s	1760000	112536	159620	87262	163715	191349	76049	688784	9093	52924	475590
5-14 years old	1190000	159065	279723	207714	297267	302009	170547	492521	14152	81545	613697

Figure. Disease burden from NCDs in children 0-14 years old (2017).

Current and Future Perspectives of Child's Health Care in China

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Within the framework of membership in the International Pediatric Association representing the European national societies of pediatrics, the European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA/UNEPSA) actively interacts globally with similar organizations and centers of excellence of other continents. The aim is to create a world where all children, regardless of age, location, or family situation, can live healthy lives. EPA/UNEPSA has established an active collaboration with colleagues of a few key Chinese academic institutions and medical centers with the purpose of facilitating the reciprocal exchange of information and sharing scientific knowledge. The aim of this brief commentary is to present a summary of important key issues in the area of childcare in China.

Maternal and Child Health Care Services in China

The annual birth cohort in 2018 in China was 15.23 million births, a sharp decrease of 2 million compared with the previous year, according to China's National Bureau of Statistics. This represents a decrease for 2 consecutive years.

With the widespread usage of planned immunization, the incidence of common infectious diseases in children has decreased, although accidental injuries have increased correspondingly as a major cause for child mortality.

In 2019, the Chinese national health commission held a press conference to report on the development of maternal and child health undertaken in China from several aspects.[1] Key data of the report are summarized in the **Table** (available at www.jpeds.com). Over the past 2 decades, there has been an impressive decrease in central indices such as maternal mortality and mortality of newborns, infants, and children <5 years of age. The service network is more robust. By 2018, there were 3080 maternal and child health care institutions, 807 maternity hospitals, and 228 children's hospitals, with nearly 640 000 employees, 400 million outpatient visits annually, 13.79 million in patient visits annually, and 338 000 beds. The quality of services has been constantly improved and accessibility enhanced by narrowing gaps between urban and rural areas and between different regions, and guaranteeing basic health care that covers a wide range of areas and provides assistance to the needy.

EPA/UNEPSA	European Paediatric Association, the Union of National European Paediatric Societies and Associations
TCM	Traditional Chinese medicine

Traditional Chinese Medicine

In 2013, China's National Health and Family Planning Commission and the Chinese Medicine Administration jointly issued the "Health Management Service Specification of Traditional Chinese Medicine," which requires that the health management project of traditional Chinese medicine be added to the basic public health service projects. It was found that the health management services of traditional Chinese medicine can prevent common diseases of infants and young children.[2] It was also found that traditional Chinese medicine was comparable with oseltamivir in treating adolescents and young adults with H1N1 influenza.[3] However, there is a lack of relevant research to support whether traditional Chinese medicine health management services can be used as routine technology in community child health care. To validate its effectiveness, traditional Chinese medicine is approaching the stage of addressing many challenges in applying evidence-based medicine to traditional Chinese medicine.[4]

Child Growth and Development

In the mid-1980s, China paid attention to the development of low birth weight infants, confronting data indicating that low birth weight infants not only have low survival rate, but also have serious impairments in growth and development. There were disparities relating to survival of very low birth weight infants between coastal and inland areas.[5] Low birth weight rate is still prevalent and even increasing in China, and it is a leading cause of mortality in children and related to metabolic disease and hypertension later in life.[6] These data further emphasized the importance of adequate perinatal care in China.

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Shifting Focus Toward Adolescents

The child health work in the early days of the founding of New China was mainly for preschool children, with an emphasis on neonatal and infant health care, and less research focused on adolescent management. During the period of middle school, there has been puberty-related education on the growth and development of physical health. The courses included simple basic behavioral courses including mental health, basic knowledge of body and organs, basic sexual education, and knowledge of the endocrine system. Also, several children's and general hospitals set up clinics for the diagnosis and treatment of adolescence ailments.

Sexual Development and Sex Education

Over the past 30 years, the survey on the physical development and sexual development of Chinese teenagers demonstrated that puberty has begun to gradually occur at earlier ages similar to other countries. Mean age at menarche has decreased by 2.8 years, from 16.5 to 13.7 years of age, over an approximate 40-year time interval.[7] These phenomena, which could have been derived from better nutrition and living standards, have also raised concern regarding health products or foods containing sex hormones or sex hormone-like substances or pesticides exposure, which may cause pseudo-precocious puberty.

Child Nutrition

Owing to the availability of international formula in China, the rate of breast feeding in China has gradually decreased, especially in large cities. In the early 1980s, breast feeding rates decreased and only about one-half of infants in urban areas were predominantly breast fed under 6 months. In 2008, the exclusive breast feeding rate under 6 months was 28% in China.[8] Population-based studies showed that, although most pregnant women had intended to breastfeed, only 55.1% of infants were exclusively breastfed. It is essential to ensure that the health care system provides efficient antenatal and postnatal breastfeeding education and support.[9]

Micronutrient Research

In the last 20 years, research on the nutrition of children in China has received more attention. Many units across the country have carried out research on vitamins and trace elements. Chinese scholars showed that vitamin A can enhance cellular immunity and humoral immunity, and further explored cell receptors and the mechanism of action at the molecular level.[10] With the improvement of children's nutritional status, obvious vitamin A deficiency has been greatly decreased, especially in large and medium cities. The prevalence of subclinical vitamin A deficiency (serum retinol level ≤70 mmol/L or ≤20 mg/dL) decreased gradually from 40% to <10% from 1988 to 2009.[11] However, there are higher rates of vitamin A deficiency in rural areas and in children from low socioeconomic status. A short duration of breastfeeding and low consumption of vitamin A-rich foods were suggested as reasons for low serum retinol concentration among children with low socioeconomic status.[12]

Obesity and Its Prevention and Treatment

During the last 20 years in China, the prevalence of overweight and obesity among school-aged children has increased rapidly and over a shorter time period than in other countries.[13] Increased rates of the epidemic of overweight and obesity combined were greatest in large coastal cities: 32.6% and 19.1% among males and females, respectively.[14] In these locations the rates of overweight and obesity have increased from 3.4% and 1.0% in 1985 to 21% and 18% in 2010, respectively.

In response to these epidemics, food-based dietary guidelines were distributed in China, first in 1989 and revised in 1997, 2007, 2015, and 2016.[15] In addition, other programs are being studied such as the Chirpy Dragon study that includes the 12-month intervention among children 6-7 years of age in Guangzhou consisting of 4 components targeting diet, physical activity, behavior in and outside of school, and with family involvement.[13]

Common Diseases and Infectious Disease Prevention

The incidence of childhood infectious diseases has decreased. Since the late 1950s, China has been producing self-reliant vaccines and has promoted the immunization for common infectious diseases (measles, polio, tuberculosis, whooping cough, diphtheria, and tetanus). The national immunization coverage rate has reached >80% in the past 40 years, and the major cities such as Beijing and Shanghai have reached >99%, reaching the target of the 2000 Children's Program.[16] Vaccinations in China are free for BCG, whooping cough, diphtheria, tetanus, and some encephalitis vaccines, but other vaccines introduced in recent years such as pneumococcal vaccines are not.

Elimination of Infectious Diseases

China took the lead in eliminating filariasis in 83 endemic countries and regions. Since 2006, no cases of diphtheria have been reported. In 2017, for the first time China reported no local malaria cases nationwide.

Malnutrition Prevention

Severe malnutrition in children was common at the founding of the country. In the first national child health conference in 1961, a "nutrition" prevention and control program was formulated and implemented nationwide.[17] The incidence of malnutrition has decreased sharply in the past 40 years. In some cities, rates have decreased to 1%-2%, and mild

cases are more common.[18] Severe malnutrition is extremely rare. However, the incidence rate in many rural remote and poverty-stricken areas remains high.

Since 1980, the prevention and treatment of child nutritional anemia has been listed as a priority for children's health care in the country. Although the incidence of nutritional anemia has decreased significantly in the late 1990s, the prevalence of anemia in children is still high. A recent survey in rural areas revealed that 43% of 6- to 30-month-old children had anemia that derived from poor quality of the diets rather than insufficient quantities of food.[19]

Environmental Protection and Safety Issues

Environmental pollution has progressively become a challenging issue during the past decade. With the rapid expansion of industry and construction in China, the harm of environmental pollution to children's health has attracted attention. Since the 1990s, China's child health experts have conducted extensive research confirming that lead pollution has serious adverse effects on children's growth and development, and called for the use of unleaded gasoline. This measure reduced the lead pollution of children in Shanghai. The harmful effects of smoke, electromagnetic waves, and building materials scattering harmful substances have also begun to be investigated.[20-23]

Prevention of Accidental Injury

In recent years, accidental injuries have risen to be the third leading cause of infant deaths. In the past 10 years, child health workers have also paid attention to the prevention of accidents. Education of both parents and children for safety and accident prevention has greatly increased.

Conclusions

China has the largest number of children in the world and EPA/UNEPSA strongly believes that sharing the knowledge of problems related to child healthcare faced by nations, as well as discussing possible solutions, could lead to a global improvement in child and adolescent health. This commentary is a preliminary report of a larger study on maternal and child healthcare in China, which is currently under development as part of the EPA/UNEPSA efforts to collaborate with leading global health players in advocating globally, nationally, and locally for high quality, evidence-based and child-centered pediatric care. ■

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References

1. Social Survey Research Information Co. China medical news: May 2019 report. www.ssri.com/china/e/medicalnews/. Accessed October 13, 2019.
2. Zhang S. Playing the role of traditional Chinese medicine in protecting maternal and child health. Chin Med Clin Res 2018;10:149.
3. Wang C, Cao B, Liu QQ, Zou ZQ, Liang ZA, Gu L, et al. Oseltamivir compared with the Chinese traditional therapy maxingshigan-yinqiaosan in the treatment of H1N1 influenza: a randomized trial. Ann Intern Med 2011;155:217-25.
4. Fung FY, Linn YC. Developing traditional Chinese medicine in the era of evidence-based medicine: current evidences and challenges. Evid Based Complement Alternat Med 2015;2015:425037.
5. Lin HJ, Du LZ, Ma XL, Shi LP, Pan JH, Tong XM, et al. Mortality and morbidity of extremely low birth weight infants in the mainland of China: a multi-center study. Chin Med J 2015;128:2743-50.
6. Chen Y, Li G, Ruan Y, Zou L, Wang X, Zhang W. An epidemiological survey on low birth weight infants in China and analysis of outcomes of full-term low birth weight infants. BMC Pregnancy Childbirth 2013;13:242.
7. Graham MJ, Larsen U, Xu X. secular trend in age at menarche in china: a case study of two rural counties in Anhui province. J Biosoc Sci 1999;31:257-67.
8. Duan Y, Yang Z, Lai J, Yu D, Chang S, Pang X, et al. Exclusive breastfeeding rate and complementary feeding indicators in China: a national representative survey in 2013. Nutrients 2018;10:E249.
9. Huang P, Ren J, Liu Y, Luo B, Zhao X. Factors affecting breastfeeding adherence among Chinese mothers: a multicenter study. Medicine (Baltimore) 2017;96:e7619.
10. Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. J Clin Med 2018;7:E258.
11. Wong AY, Chan EW, Chui CS, Sutcliffe AG, Wong IC. The phenomenon of micronutrient deficiency among children in China: a systematic review of the literature. Public Health Nutr 2014;17:2605-18.
12. Jiang JX, Lin LM, Lian GL, Greiner T. Vitamin A deficiency and child feeding in Beijing and Guizhou, China. World J Pediatr 2008;4:20-5.
13. Li B, Liu WJ, Adab P, Pallan M, Hemming K, Frew E, et al. Cluster-randomised controlled trial to assess the effectiveness and cost-effectiveness of an obesity prevention programme for Chinese primary school-aged children: the CHIRPY DRAGON study protocol. BMJ Open 2017;7:e018415.
14. Ji CY, Chen TJ. Empirical changes in the prevalence of overweight and obesity among Chinese students from 1985 to 2010 and corresponding preventive strategies. Biomed Environ Sci 2013;26:1-12.
15. Food and Agricultural Organization of the United Nations (FAO). Food-based dietary guidelines: China. www.fao.org/nutrition/education/food-dietary-guidelines/regions/countries/china/en/. Accessed October 13, 2019.
16. Li Z, Wang P, Gao G, Xu C, Chen X. Age-period-cohort analysis of infectious disease mortality in urban-rural China, 1990-2010. Int J Equity Health 2016;15:55.
17. Qu P, Mi B, Wang D, Zhang R, Yang J, Liu D, et al. Association between the Infant and Child Feeding Index (ICFI) and nutritional status of 6- to 35-month-old children in rural western China. PLoS One 2017;12:e0171984.
18. Zhai L, Dong Y, Bai Y, Wei W, Jia L. Trends in obesity, overweight, and malnutrition among children and adolescents in Shenyang, China in 2010 and 2014: a multiple cross-sectional study. BMC Public Health 2017;17:151.
19. Wang L, Sun Y, Liu B, Zheng L, Li M, Bai Y, et al. Is infant/toddler anemia a problem across rural China? A mixed-methods analysis. Int J Environ Res Public Health 2018;15:e1825.
20. Jiao K, Xu M, Liu M. Health status and air pollution related socioeconomic concerns in urban China. Int J Equity Health 2018;17:18.
21. Li X, Zhang Y, Tan M, Liu J, Bao L, Zhang G, et al. Atmospheric lead pollution in fine particulate matter in Shanghai, China. J Environ Sci (China) 2009;21:1118-24.
22. Bina O. Environmental governance in China: weakness and potential from an environmental policy integration perspective. China Review 2010;10:207-39.
23. He JR, Li WD, Lu MS, Guo Y1, Chan FF, Lu JH, et al. Birth weight changes in a major city under rapid socioeconomic transition in China. Sci Rep 2017;7:1031.

Table. Summary of current official data on China population's health and healthcare released in 2018 by the China National Health Commission (NHC)

Total population: 1.406 billion
Annual birth cohort: 15.23 million
Population 0-14 y: 23.523 million
Population 15-24 y: 897.291.6 million
Population over 65 y: 16.658 million
Annual population growth rate: 3.81/1000
Population density: 145 people per square kilometer
Average family size: 3.02 person
Fertility rate: 1.63
Birth rate (per 1000 people): 12.94
Distribution of population (% rural/urban): 40.42/59.58
Life expectancy at birth: 76.4 y.
Life expectancy of Males: 75.0 y.
Life expectancy of females: 77.9 y.
Maternal mortality rate: decreased from 88.8/100 000 in 1990 to 18.3/100 000 women in 2018
Neonatal mortality rate: decreased from 33/1000 (1991) to 3.9/1000 (2018).
Infant mortality rate: decreased from 50.2/1000 (1991) to 6.1/1000 (2018).
Children <5 y mortality rate: decreased from 61/1000 (1991) to 8.4/1000 (2018)
Top 5 causes of death among children <5 years of age, accounting for 55.7% of all deaths (down 79.1% in 2000): prematurity or low birth weight, pneumonia, birth asphyxia, congenital heart disease, accidental asphyxia
Incidence of low birth weight: 6.1%
Incidence of small for gestational age in Guangzhou: decreased from 8.0% in 2001 to 6.2% in 2015
Immunization rates for measles: 95%

Lifelong Negative Influence of School Violence on Children

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Violence in the school environment is a constant concern for educators and parents and is a serious and often lifelong burden for the young victims. School violence is not just a limited problem, variously affecting specific or isolated communities in economic advantaged or disadvantaged areas, but a global modern phenomenon involving, to various degrees, one of the core social institutions of our society.[1-3] The European Paediatric Association-Union of National European Paediatric Societies and Associations (EPA/UNEPSA), through the working group on social pediatrics, supported by its European national pediatric societies members, is currently developing dedicated projects to investigate the physical, psychological, and social impacts of school violence on European children and its possible lifelong risks.[4] The purpose of this commentary is to raise awareness on this issue among healthcare professionals involved in childcare and to emphasize the importance of their participation in programs that are developed to monitor and prevent the negative, personal, and social impacts caused by this disturbing phenomenon on children.

School Violence

Violence against individuals during their developmental years (<18 years of age) is generally regarded as a circumstance including all forms of violence, whether perpetrated by parents or other caregivers, peers, partners, or strangers.[5] This broad definition of violence includes several types of interpersonal violence (**Table**; available at www.jpeds.com). They may occur in different circumstances during childhood.

The term school violence is commonly used to describe acts of interpersonal violence that occur in a school-associated environment or specifically within a school community. However, the issue of school violence is complex, and it should not be restricted to a narrow frame focusing on the interpersonal violence occurring between students or by students against their teachers. In fact, it is a consensus that analysis of this disturbing phenomenon should take in to consideration the wider context and forms of violence in school, together with the important interactive and causal effects resulting from the confluence of these factors.[6] This constructive approach leads to an integrated, multilevel definition of the problem and to a consequential multilevel causal analysis of school violence. This should include the full range of constitutive elements, which may ultimately allow for comprehensive and effective policy responses.[6] A widely accepted general definition of school violence refers to it as any activity that can create a disturbance in an educational organization or system.[6,7] This may involve verbal and physical altercations, threats, weapon use, or gang activity, favoring a range of extreme consequences, such as school shootings. It also incorporates the concept of cyber-bullying, perpetrated through electronic means or social media. Thus, school violence includes physical or verbal confrontations on the way to school, on the way home from school, or at school-related events that can cause physical or psychological harm to other individuals.[2,8]

EPA/UNEPSA European Pediatric Association-Union of National European Pediatric Societies and Associations

The Worldwide Phenomenon of School Violence

Data from the 2018 United Nations Children's Fund report, which includes 122 countries (51% of the global population of children between 13 and 15 years of age), confirm that school violence is a global phenomenon.[9] Schools are entrusted with providing a safe environment for children to learn, cultivating their education, and nurturing their skills. However, laws prohibiting violence in educational settings looks at least inadequate. For instance, one-half of the global population, about 732 million school-age children (aged 6-17 years), live in countries where they are not legally protected from corporal punishment at school. Furthermore, among the most alarming data of the United Nations report are those reporting episodes of shooting in school environments. During a 25-year period (1991-2016), children attending schools in countries that are not affected by

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conflicts, suffered 59 documented school shootings, that resulted in at least one reported fatality occurred in 14 countries across the world.[9] Over 75% of them took place in Western countries (Europe, United States).

About one-half of 13- to 15-year-old students worldwide, nearly 150 million of them, reported to have experienced violence, such as physical fights or various forms of bullying, from their peers in and around school. Bulling is probably the most common form of school violence suffered by children. The percentages of children bullied at school are based on geographical belonging: 25% in Europe, 31.7% in North America, 22.8% in Central America, 30.2% in South America, 41.1% in the Middle East, 30.3% in Asia, 42.7% in North Africa, and 48.2% in sub-Saharan Africa. In Europe, a recent report from Italy revealed that more than 50% of boys between 11 and 17 years of age have suffered at least 1 offensive or violent episode from their peers. Derisive nicknames (12.1%), derision for physical appearance (6.3%), defamation (5.1%), exclusion (4.7%), and violent physical gestures (3.8%) are most frequently reported.[10] In the US, the National Center for Education statistics reports more than 800 000 nonfatal victimizations at school among students 12-18 years of age, and approximately 7% of teachers have been threatened with injury or physically attacked by a student from their school.[11] Finally, data from the United Nations study,[9] which are similar to data observed in a preliminary study by EPA/UNEPSA, show that 3 in 10 young adolescents (17 million), from 39 countries in Europe and North America admit to bullying others at school (**Figure**; available at www.jpeds.com).

Prevention

Primary prevention should be the goal of any strategy tackling school violence, which should typically include the promotion of protective factors at various degrees of influence, with the general aim of building a culture of peace. An effective preventive strategy in the area of school violence is multidimensional, including 4 key levels: individual, relationship, community, and social.[12]

Strategies to prevent school violence at the individual level have 2 main objectives: (1) encouraging nonviolent behavior and conduct in children and young people, to prevent violence before it occurs, and (2) aiming at changing attitudes in students who have already manifested violent behaviors, or are at risk of harming themselves. Strategies to prevent school violence at the relationship level should primarily aim at influencing the type of relationships that both offenders and victims of school violence have with the individuals they regularly interact with, such as family members, teachers, mentors, and bystanders.

At the community level, strategies to prevent school violence should focus on raising public awareness and debate about typical school violence issues and discussing openly social and material causes of school violence in the various local environments. Furthermore, providing care and support for victims and encouraging community action by focusing particularly on developing supervising initiatives and promoting cultural and environmental activities should be a priority.

Finally, preventing school violence at the societal level should focus on key values, including the normative cultural, social, and economic determinants that shape societies, thus inspiring, and, where it is needed and when it is possible, influencing the educational systems and institutional policies that emerge from them.

Conclusions

Violence involving children in school-related environments often remains hidden, owing to the reluctance of many victims to disclose their abuse. This prevents them from seeking help to cope with their negative experiences or take action to protect themselves from further victimization. School violence can occur in both passive and physical forms, causing both bodily and psychological harm. An increasing awareness of this issue has been seen in public institutions over the past few years. However, interventions are still scarce and insufficient.[13] Several studies emphasize that besides the negative results of violent behaviors between children and adolescents, relationships based on violence from significant figures for the adolescent, such as peers and teachers, contribute to the emergence of aggressive behavior and depressive symptoms, which can have a lifelong negative impact on victims.[14] Teachers are the significant adult figures that should act as positive and stable socioemotional supports inside schools, and assist in preventing peer conflict during adolescence. They should be trained to deal with violence situations and to establish effective strategies to improve classroom climate and, in turn, enhance students' academic performance. Furthermore, pediatricians can play a key role in the supervision of cases of abuse such as school violence, as they can intercept the signs of discomfort and promote the adoption of the most appropriate measures to protect the physical or emotional health of children before any other subject. However, pediatricians may fail to intercept abused children, possibly owing to the lack of social culture and/or sufficient training in this area. It is important to promote dedicated educational programs during medical courses, involving all healthcare professionals.[15] Finally, the EPA/UNEPSA working group emphasizes that a key measure to counteract school violence is to further raise social awareness through developing efficient programs in communities, supported by appropriate statistical analysis of the results attained.[16,17] This would facilitate the interactions between families and community members with healthcare professionals, and help them to suspect and recognize abuse. ■

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References available at www.jpeds.com.

References

1. Dumitriu C. School violence around the world: a social phenomenon. Procedia Soc Behav Sci 2013;92:299-308.
2. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, et al. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.
3. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Diversity of child health care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations. J Pediatr 2016;177S:S1-10.
4. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270-1.e1.
5. Ferrara P, Guadagno C, Sbordone A, Amato M, Spina G, Perrone G, et al. Child abuse and neglect and its psycho-physical and social consequences: a review of the literature. Curr Pediatr Rev 2016;12:301-10.
6. Stuart HS. What is school violence? An integrated definition. Ann Am Acad Pol Soc Sci 2000;567:16-29.
7. United Nations Children's Fund. 2017 Annual report. A familiar face: violence in the lives of children and adolescents. New York: UNICEF; 2017.
8. Pettoello-Mantovani M, Pop TL, Mestrovic J, Ferrara P, Giardino I, Carrasco-Sanz A, et al. Fostering resilience in children: the essential role of healthcare professionals and families. J Pediatr 2019;205:298-9.e1.
9. United Nations Children's Fund. 2018 annual report. A familiar Face. Violence in the lives of children and adolescents. New York: UNICEF; 2018.
10. Ministry of Education (MIUR). Students welfare and youth policies. Bullismo, https://miur.gov.it/bullismo. Accessed September 19, 2019.
11. Robers S, Zhang J, Truman J, Snyder TD. Indicators of school violence and safety: 2012. Washington, DC: National Center for Education statistics and Bureau of Justice Statistics; 2012.
12. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
13. Burela A, Piazza M, Alvarado GF, Gushiken A, Fiestas F. Acceptability of physical punishment in child rearing by people who were victims of physical violence during childhood in Peru. Rev Peru Med Exp Salud Publica 2014;31:669-75.
14. Greenfield EA, Marks NF. Identifying experiences of physical and psychological violence in childhood that jeopardize mental health in adulthood. Child Abuse Negl 2010;34:161-71.
15. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
16. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
17. Silano M, Vincentini O, Luciani A, Felli C, Caserta S, Esposito S, Villella V, Pettoello-Mantovai M, Guido S, Maiuri L. Early tissue transglutaminase-mediated response underlies K562(S)-cell gliadin-dependent agglutination. Pediatr Res 2012;71:532-8.

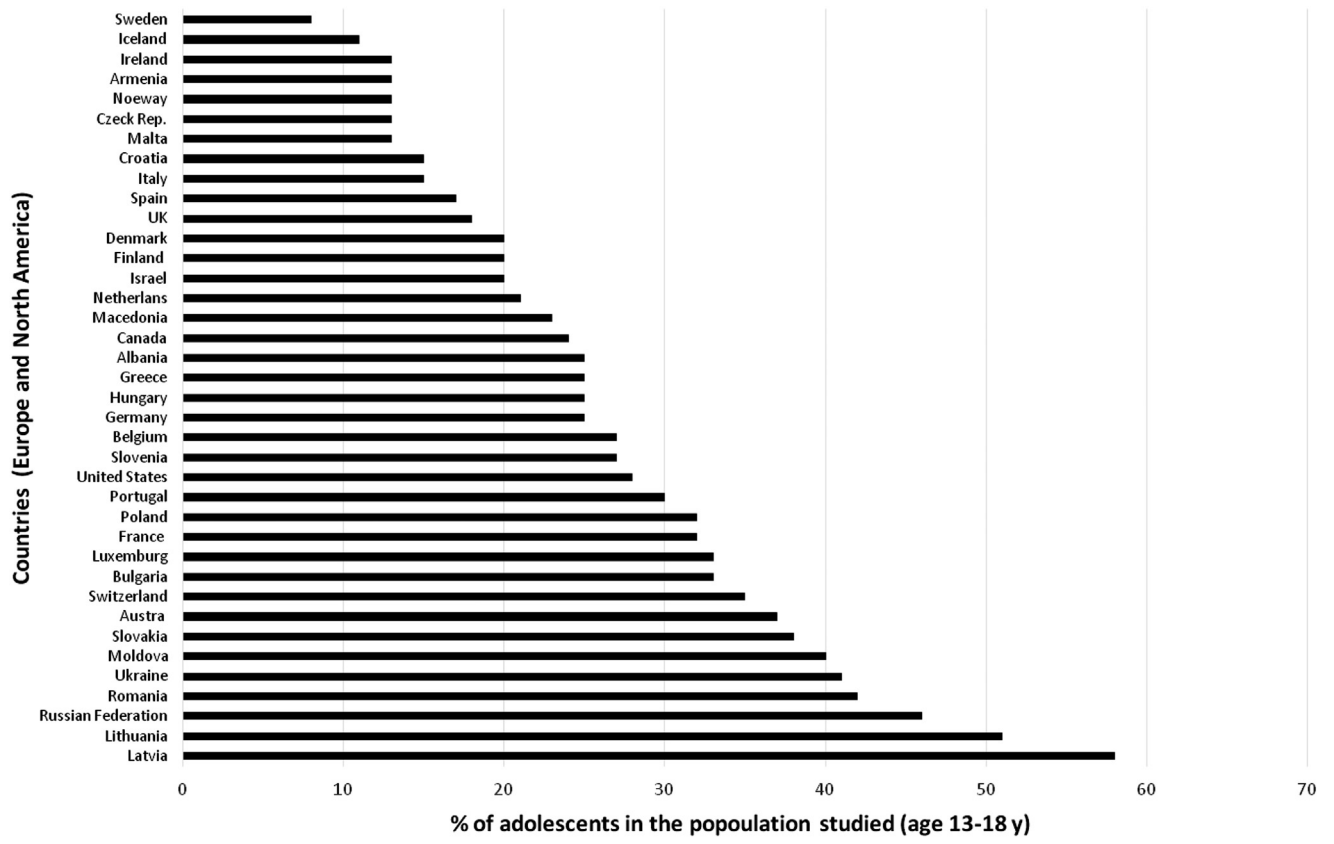

Figure. Adolescents admitting to bullying others at school in European and North American countries.

Table. Type of interpersonal violence

Maltreatment, including physical, sexual, psychological violence
Unethical educational measures (ie, violent punishment)
Unwanted, aggressive behavior involving a real or perceived power imbalance. Including mobbing (physical and emotional abuse in the workplace) and bullying (making threats, spreading rumors, attacking someone physically, verbally or by cyber means and excluding someone from a group on purpose)
Youth violence (frequent in community settings between associates and newcomers/strangers)
Domestic violence, including physical, sexual and emotional violence (frequently by an intimate or former partner)
Sexual violence, completed or attempted sexual nonconsensual acts (not necessarily involving contact)
Psychological and emotional pressure: nonphysical forms of hostile treatment (including child's movements restriction, denigration, derision, threats, intimidation, discrimination, and rejection)

Diversity of Serotype Replacement After Pneumococcal Conjugate Vaccine Implementation in Europe

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Streptococcus pneumoniae is the leading cause of bacterial infections in children, including meningitis, bacteremia, bacteremic pneumonia, empyema, and mucosal infections such as otitis media and non-bacteremic pneumonia. After the implementation of pneumococcal conjugate vaccines (PCVs), worldwide, the burden of invasive pneumococcal diseases (IPDs) and non-invasive pneumococcal diseases due to vaccine serotypes (VTs) greatly decreased in children.[1] However, since 2015, several European countries have reported an increased incidence of IPDs due to non-vaccine serotypes (NVTs), which seemed variable across countries in terms of magnitude, serotypes involved, and clinical entities.[1-4] This led to questions regarding the long-term benefit of PCVs.

This commentary presents an overview of serotype replacement in pneumococcal carriage and diseases in Europe, with a focus on IPDs. The aim is to raise awareness among pediatricians and healthcare professionals of the potential factors involved in the phenomenon of serotype replacement diversity after PCV implementation. In addition, we analyze the potential factors involved in this phenomenon. We selected European observational studies assessing the impact of PCV10 and PCV13 beyond 5 years after their implementation at the population level in children. We reviewed the literature in MEDLINE via PubMed, with no time or language restriction (last search June 30, 2019). The search algorithm was based on a combination of terms related to "13-or 10-valent PCV," "pneumococcal diseases or pneumococcal carriage," and "impact/effect/change." We completed this search by screening the reference lists of the selected articles.

Diversity of Nasopharyngeal Emerging Serotypes

In the nasopharyngeal microbiota, following the striking collapse of VTs, several NVTs emerged, which resulted in an overall pneumococcal carriage rate close to or identical to the pre-PCV level.[5,6] In European countries where nasopharyngeal carriage studies have been performed, the main predominant serotypes are now 15B/C, 11A, 23B, 15A, 35B, 10A, 21, and 23A.[5-7] This distribution seems relatively similar among countries.[5-7]

Diversity of Emerging Serotypes in IPDs

If we consider IPDs as a unique clinical entity, the serotypes implicated in replacement are more diverse among countries. The **Table**[2-4,7-12] (available at www.jpeds.com) lists the relevant selected articles reporting the main replacement serotypes. In England and Wales, the overall IPD incidence increased after 2015,[2] but young children were less affected.[2] In infected children <2 years old, the main NVTs were 12F, 8, and 10A. A study from the United Kingdom reported an increase in incidence of serotypes 12F, 24F, and 23B in 2015.[7] In Israel, Rokney et al described a steady increase in incidence of IPDs due to serotype 12F, in all age groups, including children <2 years old.[3] In addition, the frequency of serotype 2 in IPD increased, but with an epidemic evolution. In Germany, the main NVTs involved were serotypes 10A and 24F during 2014-2016.[12,13] In France, there was an increase in pneumococcal meningitis incidence after 2015, mainly affecting children <2 years old.[4] This increase was related to serotype 24F, which accounted for 23% of cases in children <2 years old in 2016.[4] The other main NVTs reported were 15B/C, 23B, and 12F.[4]

Among European countries where PCV10 was implemented, some differences in the replacement dynamics were reported. In Belgium, PCV13 was implemented in 2011 and switched to PCV10 during 2015-2016. Since 2016, the IPD incidence due to serotype 19A has increased in children <2 years.[10] This serotype became the first serotype in IPD.[10] Finland introduced PCV10 in 2010. The incidence of 19A IPD did not significantly change from 2010 to 2016, but this serotype ranked first during this period.[14] Also in Sweden, where PCV13 or PCV10 was implemented depending on the county, the incidence of 19A IPD did not differ among counties with PCV10 and those with PCV13.[11]

Overall, for countries implementing PCV13 or PCV10, reports highlighted the marked heterogeneity both in

IPD	Invasive pneumococcal disease
NVT	Non-vaccine serotype
PCV	Pneumococcal conjugate vaccine
VT	Vaccine serotype

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magnitude of replacement in IPD and serotypes involved. In the 2017 annual report of the European Centre for Disease Prevention and Control,[8] based on data from 29 European countries, when summarizing serotypes implicated in IPD in children <5 years old, serotype 24F ranked first (10.6% of cases), followed by serotypes 3 (8.5%), 12F (7.8%), 19A (7.2%), and 10A (6.9%).[8]

Diversity Among the Spectrum of Pneumococcal Diseases

It has become evident that IPD cannot be considered a homogeneous entity; moreover, we have to assess the impact of PCV implementation on noninvasive pneumococcal disease cases. For meningitis, a systematic review[15] highlighted a marked increase in number of cases due to emerging NVTs in several countries, especially France.[4,15] By contrast, for bacteremic pneumonia and pneumonia with pleural effusion, no increase in cases was reported in France[16] and England,[17] with a small increase in cases of empyema in Germany.[18] These different trends between these clinical entities agree with a recent study comparing the spectrum of IPD over time in the PCV13 era and the specific tropism of VTs and NVTs.[9] The frequency of pneumonia greatly decreased but not that of meningitis or bacteremia without source.[9] Finally, the incidence of noninvasive pneumonia and otitis media seems not affected by the serotype replacement.[19,20]

Hypotheses Explaining Discrepancies in Serotype Replacement in Pneumococcal Diseases

Several data have suggest that the PCV implemented (PCV10 or PCV13) may affect the distribution of NVTs in IPD.[1,10] Vaccine schedules or vaccine coverage also can affect the evolution of pneumococcal epidemiology, but they do not seem very different across European countries (**Table**). Because antibiotic use also induces a selective pressure on pneumococcal strains from nasopharyngeal microbiota and because some NVT strains are resistant to antibiotics, the level of antibiotic consumption in a country undoubtedly plays a role,[21] with large differences in antibiotic use in Europe. Ten years ago, after PCV7 implementation, the emergence of multidrug-resistant serotype 19A was worrying in many countries. This increase seemed more marked in countries with a high antibiotic consumption, which offered an ecologic advantage for this serotype. Similarly, we hypothesize that the prevalence of penicillin non-susceptible serotype 24F has significantly increased in France, in part because of high antibiotic consumption.

Several other epidemiologic factors pre-existing to PCV implementation must be considered (**Figure**; available at www.jpeds.com). In the pre-PCV7 era, the variability in prevalence of NVTs was notable throughout Europe and obviously has affected the serotype distribution after PCV implementation consecutive to the collapse of VTs.[22] Furthermore, young children, the main pneumococcus carriers, are largely involved in its transmission. Thus, the factors affecting both carriage and transmission (day care center attendance, birth rate, crowding, etc) can play a role in the serotype replacement.[22] Dynamic models may be suitable to better assess the specific role of each factor in the complex phenomenon of replacement. The link between the serotype distribution in carriage and diversity in pneumococcal disease strongly depends on the respective disease potential of each serotype.[23] Of note, serotypes 12F and 24F, the predominant emerging NVTs causing IPD in children in Europe, have high disease potential. Indeed, even a small increase in carriage prevalence can have a strong impact on IPD incidence and serotype distribution,[23] which may explain why countries with similar overall carriage distribution can exhibit various trends in IPD serotype distribution. Furthermore, recent studies showed that among pneumococcal isolates of a given serotype, several clonal lineages can be represented, with a likely difference in their disease potential.[22,24] Conversely, these studies also revealed that one single lineage can result in a country-specific different serotype.[24]

Next-Generation PCVs. Which Potential Benefit Expected?

After more than 5 years of PCV10 or PCV13 implementation, the serotype-replacement scenario still seems highly dynamic. Regardless, the magnitude and diversity of serotype replacement invite us to consider next-generation PCVs. The PCV15 formulation includes serotypes 22F and 33F, which to date may not represent a high disease burden in Europe in young children. Nevertheless, an expected better immunogenicity of this vaccine against serotype 3, which remains highly prevalent, gives hope for a greater impact on pneumococcal disease.[25] PCV20, with 5 additional serotypes (8, 10A, 11A, 12F, 15B), might have substantial benefit in countries reporting a recent increase in IPD incidence in children. Neither next-generation PCVs nor the pneumococcal polysaccharidic 23-valent vaccine include serotype 24F in their formulation, which could become a major issue for European countries in the near future. Lastly, assessing the impact of next-generation PCVs cannot be limited to IPDs. ■

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References available at www.jpeds.com.

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References

1. Savulescu C, Krizova P, Lepoutre A, Mereckiene J, Vestrheim DF, Ciruela P, et al. Effect of high-valency pneumococcal conjugate vaccines on invasive pneumococcal disease in children in SpIDnet countries: an observational multicentre study. Lancet Respir Med 2017;5:648-56.
2. Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis 2018;18:441-51.
3. Rokney A, Ben-Shimol S, Korenman Z, Porat N, Gorodnitzky Z, Givon-Lavi N, et al. Emergence of *Streptococcus pneumoniae* serotype 12F after sequential introduction of 7- and 13-valent vaccines, Israel. Emerg Infect Dis 2018;24:453-61.
4. Ouldali N, Levy C, Varon E, Bonacorsi S, Béchet S, Cohen R, et al. Incidence of paediatric pneumococcal meningitis and emergence of new serotypes: a time-series analysis of a 16-year French national survey. Lancet Infect Dis 2018;18:983-91.
5. Rybak A, Levy C, Bonacorsi S, Béchet S, Vié le Sage F, Elbez A, et al. Antibiotic resistance of potential otopathogens isolated from nasopharyngeal flora of children with acute otitis media before, during and after pneumococcal conjugate vaccines implementation. Pediatr Infect Dis J 2018;37:e72-8.
6. Ben-Shimol S, Givon-Lavi N, Greenberg D, Dagan R. Pneumococcal nasopharyngeal carriage in children <5 years of age visiting the pediatric emergency room in relation to PCV7 and PCV13 introduction in southern Israel. Hum Vaccines Immunother 2016;12:268-76.
7. Kandasamy R, Voysey M, Collins S, Berbers G, Robinson H, Noel I, et al. Persistent circulation of vaccine serotypes and serotype replacement after five years of UK infant immunisation with PCV13. J Infect Dis 2019. in press.
8. European Centre for Disease Prevention and Control. Invasive pneumococcal disease - annual epidemiological report for 2017. Solna, Sweden: ECDC; 2017. https://ecdc.europa.eu/en/publications-data/invasive-pneumococcal-disease-annual-epidemiological-report-2017. Accessed November 8, 2019.
9. Levy C, Varon E, Ouldali N, Béchet S, Bonacorsi S, Cohen R. Changes in invasive pneumococcal disease spectrum after 13 valent pneumococcal conjugate vaccine implementation. Clin Infect Dis 2019. in press.
10. Desmet S, Verhaegen J, Van Ranst M, Peetermans W, Lagrou K. Switch in a childhood pneumococcal vaccination programme from PCV13 to PCV10: a defendable approach? Lancet Infect Dis 2018;18:830-1.
11. Naucler P, Galanis I, Morfeldt E, Darenberg J, Örtqvist Å, Henriques-Normark B. Comparison of the impact of pneumococcal conjugate vaccine 10 or pneumococcal conjugate vaccine 13 on invasive pneumococcal disease in equivalent populations. Clin Infect Dis 2017;65:1780-9.
12. Weinberger R, von Kries R, van der Linden M, Rieck T, Siedler A, Falkenhorst G. Invasive pneumococcal disease in children under 16 years of age: incomplete rebound in incidence after the maximum effect of PCV13 in 2012/13 in Germany. Vaccine 2018;36:572-7.
13. Perniciaro S, Imöhl M, Fitzner C, van der Linden M. Regional variations in serotype distribution and vaccination status in children under six years of age with invasive pneumococcal disease in Germany. PLoS One 2019;14:e0210278.
14. Rinta-Kokko H, Palmu AA, Auranen K, Nuorti JP, Toropainen M, Siira L, et al. Long-term impact of 10-valent pneumococcal conjugate vaccination on invasive pneumococcal disease among children in Finland. Vaccine 2018;36:1934-40.
15. Koelman DLH, Brouwer MC, van de Beek D. Resurgence of pneumococcal meningitis in Europe and Northern America. Clin Microbiol Infect 2019. in press.
16. Ouldali N, Levy C, Minodier P, Morin L, Biscardi S, Aurel M, et al. Long-term association of 13-valent pneumococcal conjugate vaccine implementation with rates of community-acquired pneumonia in children. JAMA Pediatr 2019;173:362-70.
17. Thorrington D, Andrews N, Stowe J, Miller E, van Hoek AJ. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. BMC Med 2018;16:13.
18. Liese JG, Schoen C, van der Linden M, Lehmann L, Goettler D, Keller S, et al. Changes in the incidence and bacterial aetiology of paediatric parapneumonic pleural effusions/empyema in Germany, 2010-2017: a nationwide surveillance study. Clin Microbiol Infect 2019;25:857-64.
19. Wiese AD, Huang X, Yu C, Mitchel EF, Kyaw MH, Griffin MR, et al. Changes in otitis media episodes and pressure equalization tube insertions among young children following introduction of the 13-valent pneumococcal conjugate vaccine: a birth-cohort based study. Clin Infect Dis 2019. in press.
20. Fortanier AC, Venekamp RP, Hoes AW, Schilder AGM. Does pneumococcal conjugate vaccination affect onset and risk of first acute otitis media and recurrences? A primary care-based cohort study. Vaccine 2019;37:1528-32.
21. Ouldali N, Cohen R, Levy C, Gelbert-Baudino N, Seror E, Corrard F, et al. Pneumococcal susceptibility to antibiotics in carriage: a 17 year time series analysis of the adaptive evolution of non-vaccine emerging serotypes to a new selective pressure environment. J Antimicrob Chemother 2019. in press.
22. Lewnard JA, Hanage WP. Making sense of differences in pneumococcal serotype replacement. Lancet Infect Dis 2019;19:e213-20.

23. Balsells E, Dagan R, Yildirim I, Gounder PP, Steens A, Muñoz-Almagro C, et al. The relative invasive disease potential of Streptococcus pneumoniae among children after PCV introduction: a systematic review and meta-analysis. J Infect 2018;77:368-78.
24. Lo SW, Gladstone RA, van Tonder AJ, Lees JA, du Plessis M, Benisty R, et al. Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole-genome sequencing study. Lancet Infect Dis 2019;19:759-69.
25. Hurtado K, Platt H, Shekar T, et al. A phase 2, double-blind, randomized, multicenter trial to evaluate the safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (pcv15) compared to pcv13 in healthy infants. In: Paper presented at the 37th Annual Meeting of the European Society for Paediatric Infectious Diseases, Abstract N° ESPID19-0162. May 6-11; 2019. Ljubljana, Slovenia.

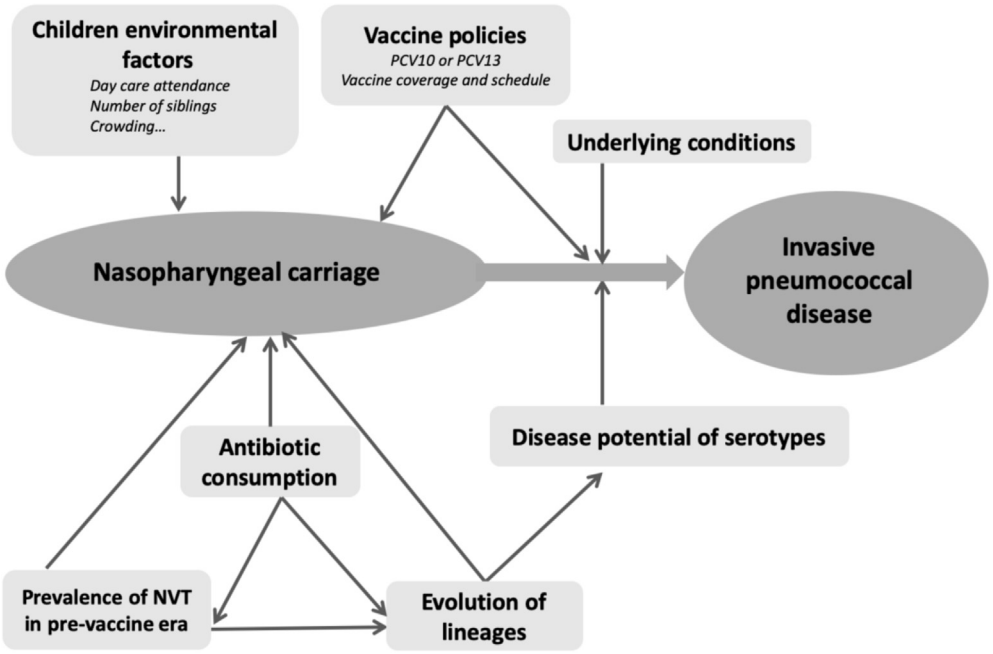

Figure. Potential factors involved in serotype replacement diversity after PCV implementation.

Table. Serotype distribution in IPDs in European countries 5 years after high-valence PCV implementation in children

Countries/schedules/ vaccination coverages	Study years	Type of IPD	Type of study	Population of serotype distribution	Sample size	Serotypes involved in the last available year or period
ECDC 2017 report[8]	2013-2017	Overall IPD	National IPD surveillance system of 29 European countries	Children <1 y old in 2017	528	3 (10.0%) 10A (8.9%) 8 (8.7%) 24F (8.1%) 19A (6.5%)
				Children 1-4 y old in 2017	812	24F (12.1%) 12F (9.2%) 19A (7.6%) 3 (7.4%) 23B (6.4%)
				Children <5 y old in 2017	1340	24F (10.5%) 3 (8.4%) 12F (7.8%) 19A (7.2%) 10A (6.9%)
England/Wales (Ladhani et al)[2] PCV7 in 2006, PCV13 in 2010 2, 4, 13 mo VC ≥3 doses: >92% since their introduction	2000-2017	Overall IPD	National prospective laboratory-based surveillance	Children <5 years old in 2016-2017	331	12F (14.2%) 8 (10.0%) 10A (8.2%) 15B/C (7.9%) 23B (6.3%)
England/Wales (Kandasamy et al)[7]	2010-2015	Overall IPD	Regional prospective laboratory-based surveillance	Children <5 y old in 2015	408	12F (12.0%) 24F (7.4%) 23B (6.9%) 15B/C (6.6%) 22F (5.9%)
France (Ouldali et al)[4] PCV7 in 2003, PCV13 in 2010 2, 4, 12 mo VC ≥3 doses: >91% since 2011	2001-2016	Meningitis	National prospective active laboratory and hospital-based surveillance	Children <15 y old in 2015-2016	143	24F (21%) 15B/C (8%) 23B (6%) 22F (6%) 12F (5%)
France (Levy et al)[9]	2011-2016	Overall IPD	National prospective active laboratory-based surveillance	Children <15 y old in 2016	152	24F (16.1%) 15B/C (7.1%) 23B (7.1%) 12F (6.6%) 10A (6.6%)
Israel (Rokney et al)[3] PCV7 in 2009, PCV13 in 2010 2, 4, 12 mo VC ≥2 doses: >95% since 2011	2009-2016	Overall IPD	National prospective active population-based surveillance	Children <15 y old in 2016	119	12F (26%)
Belgium (Desmet et al)[10]	2006-2017	Overall IPD	Passive laboratory-based surveillance	Children <2 y old in 2017	154	19A (13.6%)
Sweden (Naucler et al)[11] PCV7 in 2007, PCV10 or 13 in 2010. 3, 5, 12 mo VC ≥3 doses: ≥97%	2005-2016	Overall IPD	National prospective laboratory and hospital-based surveillance	Children <5 y old in 2013-2016	120	NVT (32.7%) 3 (13.7%) 19A (11.8%)
Germany (Weinberger et al)[12] PCV7 in 2001, PCV10 in 2009, PCV13 in 2010 2, 4, 11/14 months VC ≥2 doses: ≥96%	1997-2016	Overall IPD	National prospective laboratory and hospital-based surveillance	Children <15 y old in 2014-2016	164	10A (17.1%) 24F (13.4%) 15C (9.1%) 12F (8.5%) 38 (7.3%)

ECDC, European Centre for Disease Prevention and Control; *VC*, vaccination coverage.

The Clinician Scientist, a Distinct and Disappearing Entity

Ido Somekh, MD[1], Eli Somekh, MD[2,3,4], Massimo Pettoello-Mantovani, MD[4,5], and Raz Somech, MD, PhD[6,7,8]

Clinician scientists are commonly defined as those individuals holding an MD or MD/PhD degree who perform biomedical research of any type as their primary professional activity.[1] Here we discuss issues that affect the choice to pursue a clinician scientist career in the various areas of medical research, including pediatrics, and how these issues are changing in light of recent developments in the biomedical research environment and the practice of medicine.

The clinician scientist has become a rare and distinct entity, or an "endangered species" as James Wyngaarden, former director of the National Institutes of Health stated 4 decades ago.[2] Recent data show a consistent worldwide decrease in the rate of medical doctors pursuing this path.[3] For instance, reports from the US have emphasized that although an absolute increase in medical students has been observed during the past few years, the number of MD/PhD applicants has plateaued.[4,5] According to the National Institutes of Health Physician Scientist Workforce report, in 2012 physician scientists comprised only 1.5% of the total physician workforce in the US.[6] Also of concern is the aging of the clinician scientist workforce. The average age of the workforce has increased, as has the age of independence for researchers (grant holders), suggesting a decrease in the pool of young researchers and an inability to compete with PhDs for grants. Notably, an overall gender inequality was also reported, with females representing only 22% of MD/PhD physician scientists.

The Need for Clinician Scientists

There are divergent opinions on this issue. Some claim that an MD should concentrate on clinical work, and a basic research scientist should pursue their scientific career. A general growing perception is that there is more than enough work for both professional figures. The training to become a clinician scientist is time consuming, and each field is a challenging career by itself. Therefore, whether a hybrid of these 2 fields is truly necessary is a legitimate question. It is true that a clinician with training as a research scientist usually does not have the same wide technical education or the basic skills of an experienced scientist. However, having clinical experience offers several advantages. A clinician scientist who deeply understands a disease, its complications, and implications may raise specific questions and develop focused research projects, which can be more effectively translated into clinical benefits.[7] Being a clinician scientist may facilitate access to patient samples and thereby promote bench to bedside research projects, linking basic and clinical science. Physician scientists have the capability to transpose clinical observations into testable research hypotheses and translate research findings into medical advances. A clinician who is familiar with research can establish better links with patients, as well as medical staffs. Clinician scientists are able to better introduce patients to the objective of a cross-disciplinary study. This combination can result in good patient compliance and strengthen patient–clinician interactions.[8]

Factors Negatively Influencing the Choice to Become a Clinician Scientist

Several reasons may account for the declining number of medical graduates who opt for a career as clinician scientists (**Table**; available at www.jpeds.com). In general, MD/PhD dual programs require extensive training and are demanding in terms of time and emotional commitment, making the integration of these 2 fields of practice a difficult task to pursue. Furthermore, different types of skills are needed to succeed in each field, which need to be integrated. Both fields share common denominators, purposes, and patient care goals, whether by treating disease or through shedding light on the mechanisms involved, however, substantial differences exist. Although the primary work of most physicians involves a direct caregiver–patient encounter and the responsibility for the patient as a whole, the basic research scientist rarely has interacts directly with patients and the benefits of successful research usually impact patients' health. A further important difference between the MD and PhD fields relates to the immediate vs prospective satisfaction in patient care. Although the physician may get an immediate satisfaction from helping a patient, the results of scientific research are usually seen after a longer time period.

Reconciling a distinctive approach to the work performance and expectations between MD and PhD professionals is also an issue. MDs are typically trained to follow and implement consolidated standards of practice and research scientists are typically encouraged to challenge existing paradigms through novel ideas.

Economic factors play a role in the choice to pursue a clinician scientist career, because it could hinder economic opportunities, such as private clinical practice. Students may also hesitate to pursue a career involving research owing to

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the burden of debt they may incur and the need to repay the loans they receive during this period.[9]

The expectations from a clinician scientist can be stringent and at times unrealistic. A clinician scientist is typically involved in 2 different yet demanding professional settings, involving different personnel. Different teams might feel dissatisfied owing to a perceived lack of commitment, often caused by the need for clinician scientists to divide their time, which could lead to conflicts.

MD/PhD dual programs are long, tiring, and complex; the candidate is required to learn new techniques, new approaches, and new technical languages. Moreover, the professional competence that MD physicians gain after graduation and completing their residency may look unhelpful or underused when they are required to interact in the laboratory settings with partners from different fields of science who are trained in basic research.

These factors may have independently contributed to the gradual reduction in the number of MDs who decide to gain a PhD degree and pursue a clinician scientist career in favor of a more economically secure and less complicated, although demanding clinical career.

Factors Positively Influencing the Decision to Pursue a Clinician Scientist Career

Diversity is one of the main factors that may favor the decision of MDs to pursue a basic science path. In fact, MDs typically concentrate on a specific path and subspecialize in a certain field. However, the routine of practice, although often professionally and economically satisfying, could become monotonous, leading to professional frustration. This could generate a decrease in interest, satisfaction, and excitement, and ultimately impair the motivation to pursue personal and professional goals in the clinical field. Integrating different, yet complementary fields in an MD/PhD career could stimulate the desire to engage in translational research with the goal of applying knowledge from basic biology and clinical trials to techniques and tools that address critical medical needs.

Recent reports have emphasized the importance for MDs to participate in basic research projects aimed at developing new therapies, medical procedures, or diagnostics.[10] A study from Israel documented that translational research served as an anti-burnout remedy for Israeli pediatricians.[11] Tutoring students and conducting research were shown to be the 2 activities that brought high satisfaction, and the academic status was also correlated with high satisfaction among pediatricians.[12] The awareness about the importance of basic research for the advancement of clinical knowledge in the area of developmental medicine is growing.[13] Such informational activities and programs need to be developed and further implemented, and the European Paediatric Association/Union of National European Paediatric Societies and Associations is actively engaged in this task.

Conditions Necessary to Facilitate the Choice to Become Clinician Scientists

A key element for attracting students to pursue a career as clinician scientists is the creation of well-structured MD/PhD dual programs focused on developing a strong competence in translational medicine and regularly updated to include cutting-edge medical advances. The quality of mentorship, the availability of a stimulating research environment, and well-equipped facilities are also crucial conditions for the success of dual programs. Medical schools, hospitals, and research centers should be aware of the advantages of promoting physicians to grow as clinician scientists.[14] Several medical schools have created specific educational channels for clinician scientists, including financial benefits for clinicians who choose this career path.[11] This strategic approach is based on the awareness that such investments would ultimately have a high rate of positive return in terms of both research grants and prestige for the university. The selection of clinician candidates for this combined career should be done during residency. In fact, some European residency programs in pediatrics include periods specifically dedicated to research.[15] Planning for a future pediatric workforce should include an efficient use of periods dedicated to research during medical studies and residency, to identify potential candidates for a dual program.

The entity of clinician scientist is in danger of vanishing.[16,17] The overall pattern is clear and consistent; biomedical research has been expanding, but the rates of physician scientists have not kept pace.[16,18] As we approach an era of personalized medicine, prompted by a better understanding of disease mechanisms and the use of novel therapeutic approaches, there is an increased need for a closer collaboration between research scientists and clinicians, and for clinician scientists who speak both languages fluently.[19] The career of a clinician scientist may be challenging, interesting, fulfilling, diverse, and ultimately rewarding owing to the unique opportunity to impact patient health through an effective and combined bench-to-bedside and bedside-to-bench approach.[20]

The quality of pediatric research may reflect the quality of clinical care in a given country.[21] The European Paediatric Association is actively exploring methods to improve child health care in Europe. This includes the expansion and updating of training programs for pediatricians.[22] Pediatric research activities in Europe should take a life course perspective on child development, health, and disease, thus aiming to increase pediatric research activities.[23] Finally, in the view of European Paediatric Association/Union of National European Paediatric Societies and Associations, research projects should become integrated into long-term health care projects involving all age groups.[24,25] As written previously, "Clinicians know all of the problems, but none of the solutions; scientists know all of the solutions, but none of the problems."[26] One of the ways to close this gap is to encourage a generation of clinician scientists. ■

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References available at www.jpeds.com.

References

1. Zemlo TR, Garrison HH, Partridge NC, Ley AJ. The physician-scientist: career issues and challenges at the year 2000. FASEB J 2000;14:221-30.
2. Wyngaarden JB. The clinical investigator as an endangered species. N Engl J Med 1979;301:1254-9.
3. Gordon R. The vanishing physician scientist: a critical review and analysis. Account Res 2012;19:89-113.
4. Davila JR. The physician-scientist: past trends and future directions. Mich J Med 2016;1:66-73.
5. Schafer AI. The vanishing physician-scientist? Transl Res 2010;155:1-2.
6. National Institute of Health. Physician-Scientist Workforce Working Group report. 2014. https://acd.od.nih.gov/documents/reports/PSW_Report_ACD_06042014.pdf. Accessed June 21, 2019.
7. Yap KK. The clinician-scientist: uniquely poised to integrate science and medicine. AMSJ 2012;3.
8. Eisenberg MJ. Is a physician-scientist career right for you? The physician scientist's career guide; 2010. 13-25. https://link.springer.com/chapter/10.1007%2F978-1-60327-908-6_2. Accessed June 24, 2019.
9. Donath E, Filion KB, Eisenberg MJ. Improving the clinician-scientist pathway: a survey of clinician-scientists. Arch Intern Med 2009;169:1241-7.
10. Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. Int J Cell Biol 2016;7:19-43.
11. Grossman Z, Chodick G, Kushnir T, Cohen HA, Chapnick G, Ashkenazi S. Burnout and intentions to quit the practice among community pediatricians: associations with specific professional activities. Isr J Health Policy Res 2019;8:2.
12. Kennedy PGE. My life as a clinician-scientist: trying to bridge the perceived gap between medicine and science. DNA Cell Biol 2015;34:383-90.
13. Somekh E, Katz M, Grossman Z. Planning the pediatric workforce in Israel. J Pediatr 2019;206:308-9.
14. Kushnir T, Cohen HA. Job structure and burnout among primary care pediatricians. Work 2006;27:67.
15. Corsello G, Ferrara P, Chiamenti G, Nigri L, Campanozzi A, Pettoello-Mantovani M. The child health care system in Italy. J Pediatr 2016;177:S116-26.
16. Goldsmith LA. The physician-scientist. A vanishing oxymoron? Arch Dermatol 1992;128:474.
17. Schrier RW. A Ph.D. in clinical science for physicians: one solution to the vanishing breed of the physician-scientist. Proc Assoc Am Physicians 1998;110:88-9.
18. Coller BS. Translational research and the physician-scientist. In: Schafer AI, ed. The vanishing physician-scientist? Ithaca (NY): Cornell University Press; 2009. p. 67-83.
19. Molloy EJ, Modi N, Greenough A, Lagercrantz H, Bearer CF, Turner M. The future of pediatric research: European perspective. Pediatr Res 2017;81:138-9.
20. Oates JC. The magic of the Southern Society for Clinical Investigation: can we make the vanishing physician-scientist reappear? Am J Med Sci 2013;345:259.
21. Ehrich J, Tenore A, Del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of Pediatric Workforce and Education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
22. Hoey H, Stephenson T, Namazova-Baranova L, Pettoello-Mantovani M, Mestrovic J, Vural M, et al. Prevention and therapeutic innovation in the management of child health. J Pediatr 2019;208:300-1.
23. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: a Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.
24. Ehrich J, Pettoello-Mantovani M. Views of the Presidents of National European Pediatric Societies on evolving challenges of child health care. J Pediatr 2016;177:336-7.e1.
25. Beck AF, Cohen AJ, Colvin JD, Fichtenberg CM, Fleegler EW, Garg A, et al. The future of pediatric research: European perspective. Pediatr Res 2017;81:138-9.
26. Heit WN. Translating research into clinical practice: deliberations from the American Association for Cancer Research. Clin Cancer Res 2005;11:4275-7.

Table. Perceived limiting factors influencing the choice for MD/PhD dual programs

Extensive and intensive training causing energy depletion or exhaustion
Increased limitations in personal time availability
Risk of work-related stress exposing to burnout
Struggling to integrate different skills required for succeeding in a combined MD/PhD's career
Immediate vs prospective satisfaction in patient's care
Economic issues, including limitations in salary and difficulty to repay educational loans
Need to reconcile different approaches to work performance. Encouraged application of consolidated standard practices vs encouraged exploitation of novel solutions
Difficulty in planning the work in 2 different yet demanding professional settings (clinical and laboratory)
Complexity in handling different teams working in separate clinical and research settings

The Risk of Gambling Disorders in Children and Adolescents

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Gambling disorders should be regarded as a public health issue, with adverse consequences for individuals and families. Over the past 25 years, the phenomenon of gambling among children and adolescents has grown, particularly in economically advantaged countries. Reports on youth gambling performed during this period have revealed increasing incidence and prevalence rates, which emphasize the possibility that negative effects related to gambling disorders will progressively impact children and adolescents' health and well-being.[1] Thus, although gambling has become a significant public health issue, it remains a hidden event for too many in civil society and even among healthcare professionals. Although adolescents with gambling-related problems frequently present psychological and mental health problems, including substance use, they are often underrepresented in treatment. In fact, despite gambling addiction being recognized by the World Health Organization as a behavioral disorder, most national health systems do not currently fund specialist treatment.[2]

The problem of gambling among youths is among the main focuses of the working group on social pediatrics supported by several European national pediatric societies, members of the European Paediatric Association, and the Union of National European Paediatric Societies and Associations. The aim of this commentary is to raise pediatricians' attention to this phenomenon and its implications for the health of the children and adolescents. Given the multitude of risk factors faced by youths exposed to gambling, it is important to emphasize the role of pediatricians in monitoring. Working closely with families and providing early screening, assessment, and treatment for problem gambling is essential for the effective control of gambling disorders in children and adolescents to decrease the risk of negative impacts on their present and future lives.

The Gambling Disorder Condition

Gambling disorders refer to a range of problems, from the subclinical to full-scale clinical disorders; a variety of terms are commonly used, often interchangeably, to describe this condition, including "problem gambling," "pathological gambling," and "compulsive gambling," which have often generated confusion.[3,4] Problem gambling is used to describe a condition in which persons are generally afflicted by an urge to gamble continuously, despite harmful negative consequences. Unlike problem gambling, compulsive gambling is commonly referred to as a condition in which persons present impulse control disorders that they are unable to stop.[3,5] Compulsive gambling is described as a mental disorder that in youths involves specific symptoms, including a preoccupation with gambling, a need to keep using money or other goods on gambling to get excited about it, trying unsuccessfully to stop gambling, experiencing restlessness or irritability when trying to refrain from this activity, using gambling as a coping mechanism to escape problems or to manage feelings of helplessness or sadness, being deceptive to family members or others to hide the extent of the gambling, committing misconduct or theft to support gambling activities, compromising family and friends' relationships or school opportunities, and asking others for money.[4,5]

Pathological gambling was initially described as an impulse control disorder characterizing persons experiencing progressive loss of control.[6] This definition was later changed to reflect its similarity to substance dependence, such as the addition of repeated unsuccessful attempts to control, cut back, or stop gambling.[7] Pathological gambling has been reclassified by the *Diagnostic and Statistical Manual of Mental Disorders*[8] (DSM-V) as an addictive disorder, because the persons affected show many similarities to those who have substance addictions. In this regard, data suggest that the behaviors observed in problematic gambling and most primary substance use disorders aim to activate similar reward mechanisms in the brain.[9] The official revision, changing the term "pathological gambling" to "gambling disorder" in the *DSM-V*, has been welcomed by many researchers and clinicians, given a general concern that the term "pathological" would

DSM	Diagnostic and Statistical Manual of Mental Disorders
SOGS-RA	South Oaks Gambling Screen revised for adolescents

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give a pejorative connotation to the persons affected. This wording is particularly important for children and adolescents, among whom the social stigma of being a problem gambler would significantly complicate social and clinical interventions and re-education.

As with adults, we can observe that gambling behavior in children and adolescent forms a continuum that ranges from a nongambling status to an occasional, recreational, nonproblematic, or social gambling panel of situations, to at-risk gambling circumstances, and finally, to a problem, pathological, compulsive, or disordered gambling, as described in the DSM-V.[8] Also in analogy to adults, these excessive forms of gambling may typically result in moderate to severe psychosocial, behavioral, economic, interpersonal, and legal difficulties.

Assessment of Gambling Disorders in Youth

Studies on gambling disorders in the general population are relatively limited.[1] In particular, data on children and adolescents are scarce and refer to population-based cross-sectional studies conducted with the support of diagnostic questionnaires. Currently, there are a number of validated diagnostic questionnaires available worldwide to assess gambling disorders in youths. However, the majority are used to evaluate the presence of a gambling condition in adolescents and are based on self-report surveys, often using paper-pen forms, that have been directly adapted from adult versions. Among them, the most widely used diagnostic tool is the South Oaks Gambling Screen revised for adolescents[10] (SOGS-RA), a 20-item self-report questionnaire based on the DSM-III[6] and developed to identify probable gambling disorders. Its primitive diagnostic criteria focusing on pathological gambling have been later modified over the years to include the changes made in the fourth[7] and fifth[8] editions of the DSM. The SOGS is currently largely used as a diagnostic instrument in epidemiological research, despite a growing literature suggesting that the SOGS tends to overestimate the prevalence of the gambling disorders.[11] Further available diagnostic methods include the DSM-IV adapted format for juveniles,[12] the Lie/Bet Scale,[13] the Canadian Adolescent Gambling Inventory,[14] and the Gamblers Anonymous Twenty Questions revised for adolescents.[15]

Worldwide Prevalence of Gambling Disorders in Youths

Statistics about gambling disorders in children and adolescents show great variation in the data depending on the country, the measuring methods used, and the target subpopulations. A systematic review emphasized that many countries have never carried out studies on gambling disorders in minors.[16] Reliable reports on gambling disorders in children younger than 12 years of age are scarce, suggesting that methodological complexity in both the correct identification of this problem and data collection in this age group may play a role in limiting an extensive analysis of the phenomenon in this population. However, data on adolescents (12-18 years of age) are available from systematic reviews of national studies, which have reported a high prevalence of gambling disorders in this age group. The prevalence of this condition in European adolescents shows a wide range among nations, from 0.2 to 12.3%. For instance, in Italy,[17] out of a total population of 9 910 710 minors (0-18 years of age) residing in the country in 2017, 695 000 (7%) reported having performed a gambling activity at least once during the past year. In Romania, a Romanian National Prevalence Study on problem gambling and pathological gambling in children and adolescents[18] performed using the SOGS-RA method and classification indicated that in 2018, 7.1% of youths were classified as at risk of gambling, and 4% showed pathological gambling behavior. The same population was analyzed by the Gamblers Anonymous Twenty Questions revised for adolescents method, which showed a prevalence of problem gambling and pathological gambling respectively of 10.1% and 2.6%. In Croatia, a recent study on adolescents reported that 16.9% of the population studied showed low to moderate problematic gambling disorders, and 12.3% presented severe gambling behavior.[19] A study of online gambling recently performed in Turkey[20] showed that 12.4% of the adolescents studied reported online betting; however, only 2.9% of them were classified as problematic Internet users. An important piece of information reported by this study is that 61% of participants revealed that they preferred to be online because they did not have better things to do, stressing the social implications of this phenomenon.

Particularly alarming are the data reported by the UK Gambling Commission[21] in 2018, which revealed that the number of child gamblers in the UK quadrupled in just 2 years. In particular, according to this report, 55 000 11- to 16-year-olds have been classified as problem gamblers. It is also of deep concern to learn that an additional 70 000 11- to 16-year-old persons are considered at risk of developing a gambling problem and that, compared with other potentially harmful activities, the rate of gambling among young people is higher than the rates of drinking alcohol, smoking cigarettes, or taking illegal drugs. These data are similar to those observed in other nations throughout Europe and further emphasize the need to treat gambling as a serious public health issue. There are also variations in the prevalence rates of gambling disorders among different continents. For instance, in North America, the reported prevalence rates of gambling disorders range from 2.1% to 2.6%, whereas in Oceania, they range from 0.2% to 4.4%.[22]

The Importance of Establishing Preventive Intervention Programs

Preventive intervention programs are the primary social preventive measures to counter the rampant phenomenon of gambling disorders in youths and to decrease its burden on society and families at the global level. Many social[23] and economic[24] factors are driving the incidence of gambling disorders in children and adolescents; however, preventive

measures seem to be far less than the burden requires and need to be significantly implemented, as there is currently no empirically validated treatment program available for adolescent problem gamblers worldwide.[25]

Primary targets for the implementation of preventive programs are families and schools. Preventive intervention programs should aim to identify children and adolescents with positive attitudes toward gambling and to sensitize families and communities to better use and control their parenting resources. Prevention programs should focus on increasing the quality of relations within families, and the first step in these programs is typically to involve and stimulate parental attention in children's whereabouts, friend choices, and day-to-day activities. A multidisciplinary approach in these programs is essential[26] and pediatricians are key professional figures in the teams that work with parents,[27] who need to understand what is age appropriate to develop reasonable expectations of children. It is in fact important to develop adequate strategies aimed at increasing parents' knowledge of development norms, reducing age-inappropriate expectations or dysfunctional attributions, and increasing parents' capacity to regulate their own emotions.

Parental knowledge depends on the cooperation of young people to disclose what they are doing and thinking to their parents, and it is not realistic to expect adolescents to spontaneously cease engaging in risky behaviors that are common in their community of friends. In general, an important goal of social preventive intervention programs in the area of gambling disorders is educating adolescents to become informed, analytic consumers whose choice to participate in risky activities will cause potentially fewer problematic behaviors. Finally, it is important to report that pharmacological interventions should be discouraged, because there are no data or studies investigating the safety and efficacy of pharmacological treatments for gambling disorders in children and adolescents.

Conclusions

International studies have consistently shown that gambling is part of the life experiences of most young people, although it is unacceptable that so many young people are struggling with gambling problems.[3,21] Underage gambling seems to be related to alcohol, tobacco, and other substance use, as well as with other negative individual behaviors.[28] Therefore, collaborative efforts between scientific societies, governments, and stakeholders seem to be essential to influence the uptake of research findings that can be used to implement social policies and design effective public health intervention options. Educational-based gambling disorder prevention programs are important measures in targeting at-risk behaviors among children and adolescents to prevent an escalation of problematic behaviors into adulthood.[29] In this regard, the European Working Group on Social Pediatrics is actively engaged with the national institutions and government authorities to ensure that appropriate preventive programs are more easily available and free at the point of delivery.[30] ■

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References available at www.jpeds.com

References

1. Calado F, Griffiths MD. Problem gambling worldwide: An update and systematic review of empirical research (2000–2015). J Behav Addict 2016;5:592-613.
2. Abbot M. The epidemiology and impact of gambling disorder and other gambling-related harm. 2017 WHO Forum on alcohol, drugs and addictive behaviours. Geneva, Switzerland: World Health Organization; 2017.
3. Fong TW. More adolescents are gambling with addiction. Curr Psychiatry 2016;5:59-70.
4. Yau YH, Potenza MN. Gambling disorder and other behavioral addictions: recognition and treatment. Harv Rev Psychiatry 2015;23:134-46.
5. Reilly C. Challenges of treating addiction and gambling disorders. In: What clinicians need to know about gambling disorders. Beverly (MA): NCRG; 2014.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd ed. Washington (DC): American Psychiatric Association; 1980.
7. American Psychiatric Association Committee on Nomenclature and Statistics. Diagnostic and statistical manual of mental disorders, 4th ed, text revision. Washington (DC): American Psychiatric Association; 2000.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington (DC): American Psychiatric Publishing; 2013.
9. Potenza MN. The neurobiology of pathological gambling and drug addiction: an overview and new findings. Philos Trans R Soc Lond B Biol Sci 2008;363:3181-9.
10. Lesieur HR, Blume SB. The South Oaks Gambling Screen (The SOGS). A new instrument for the identification of pathological gamblers. Am J Psychiatry 1987;144:1184-8.
11. Ladouceur R, Bouchard C, Rhéaume N, et al. Is the SOGS an accurate measure of pathological gambling among children, adolescents and adults? J Gambl Stud 2000;16:1-24.
12. Fisher S. Measuring pathological gambling in children: the case of fruit machines in the UK. J Gambl Stud 1992;8:263-85.
13. Johnson EE, Hamer R, Nora RM, Tan B, Eisenstein N, Engelhart C. The Lie/Bet Questionnaire for screening pathological gamblers. Psychol Rep 1997;80:83-8.
14. Tremblay J, Stinchfield R, Wiebe J, Wynne H. Canadian Adolescent Gambling Inventory (CAGI) Phase III Final Report. Alberta (Canada): Alberta Gaming Research Institute; 2010.
15. Gamblers Anonymous, 3rd ed. Los Angeles: Gamblers Anonymous Publishing; 1984.
16. Ferrara P, Franceschini G, Corsello G. Gambling disorder in adolescents: what do we know about this social problem and its consequences? Ital J Pediatr 2018;44:146-50.
17. Cerrai S, Resce G, Molinaro S. Consumi d'azzardo 2017. Rapporto di Ricerca sulla diffusione del gioco d'azzardo fra gli italiani attraverso gli studi IPSAD ed ESPAD Italia. Consiglio Nazionale delle Ricerche; 2017. www.epid.ifc.cnr.it/images/downloads/Report/Gioco/Consumi_azzardo_2017.pdf. Accessed March 24, 2019.
18. Lupu V, Lupu IR. Romanian National Prevalence Study - problem and pathological gambling in children and adolescents. Clujul Med 2018;91:435-40.
19. Dodig D. Assessment challenges and determinants of adolescents' adverse psychosocial consequences of gambling. Kriminologija i Socijalna Integracija 2013;21:1-29.
20. Aricak OT. Problematic online betting among Turkish adolescents. J Gambl Stud 2018. in press.
21. UK Gambling Commission. 2018 report on children and gambling trends. www.gamblingcommission.gov.uk/home.aspx. Accessed March 24, 2019.
22. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;73:270-1.e1.
23. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
24. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, Pettoello-Mantovani M. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.
25. Gupta R, Derevensky JL. A treatment approach for adolescents with gambling problems. In: Gambling problems in youth. Cham (Switzerland): Springer; 2005, p. 165-88.
26. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177:S1-10.
27. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12-9.
28. Floros GD. Gambling disorder in adolescents: prevalence, new developments, and treatment challenges. Review. Adolesc Health Med Ther 2018;9:43-51.
29. Oh BC, Ong YJ, Loo JMY. A review of educational-based gambling prevention programs for adolescents. Asian J Gambl Issues Public Health 2017;7:4.
30. Ehrich J, Tenore A, Del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.

The State of Children's Health in Europe

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The health status of the European population is supervised constantly through the national public health agencies in their respective countries and monitored by the several nongovernmental organizations dedicated to public health active in Europe.[1] In particular, the European Union (EU) supervises the health of the population in its 28 member nations by means of the Directorate for Health and Food Safety.[2] The Directorate bases its proposals and legislative interventions both on data from the single nations and the statistical analysis provided by Eurostat, the official statistical office of the EU, situated in Luxembourg, whose mission is to provide high-quality statistics for Europe.

On February 5, 2019, Eurostat released its most recent general report on children's health in the EU.[3] The document, which describes the status of health of the population 0-16 years of age, includes reassuring information, which were collected from household members. This commentary briefly discusses the significant positive data reported by Eurostat. Our aim is to share the encouraging information included in the report while emphasizing the importance for pediatricians not to rely exclusively on the family members' perception to assess the quality of pediatric care. We believe that it is important to never lower one's guard on children's health and therefore to regularly follow social and legislative changes to constantly provide adequate children's care that is focused and organized around the needs and expectations of their families.

Data on the General State of Children's Health in EU States

European data on children's health are released by Eurostat. They are based on information collected through the "EU–Statistics on Income and Living Conditions" (EU-SILC) system,[4] which is anchored in the European Statistical Structure, and represents the EU reference source for comparative statistics on income distribution, poverty, and living conditions. EU-SILC is a consolidated methodologic instrument designed to collect timely and comparable cross-sectional and longitudinal multidimensional microdata on income, poverty, social exclusion, and living conditions.

EU	European Union
EU-SILC	European Union–Statistics on Income and Living Conditions

In the Eurostat document, more than 95% of children between 0 and 16 years of age living in the EU are reported to be in good or very good general health. Children whose general health was classified to be good or very good were further grouped according to age, and only slight differences were registered between those aged younger than 5 (96.5%), subjects aged 5-9 (95.9%), and those aged 10-15 (95.2%) years.

Children with limitations in activities due to health problems were less than 5%, of whom 3.7% had moderate limitations and 1.2% had severe limitations. However, the percentage of children with both moderate and severe limitation of activities increased proportionally in the 3 age groups. In those aged younger than 5 years, 2.2% had moderate and 0.6% had severe limitations in activities, whereas in those aged 5-9 years, the proportions were 4.1% and 1.2%, respectively, and 4.4% and 1.6% for those aged 10-15 years. The general health of children was reported to be bad or very bad in only 1% of the subjects in the 3 age groups, and less than 1% of children younger than 5 years were reported to suffer from severe limitations in activity due to health problems. Particularly positive data were registered by Eurostat in Spain, Bulgaria, Romania, and Italy, where the percentage of children considered to be in good or very good health in the 3 age groups was reported to be greater than 98%.

The Value of Pediatric Primary Care for Children's Health and Well-Being

The data published by Eurostat are based on the statistical analysis of preliminary indicators gathered from the various nations.[5] However, we would like to emphasize that the 4 countries showing a better level of children's health reported by households are characterized by the presence of a well-structured primary care system that is efficiently coordinated with secondary and tertiary pediatric care

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centers.[6,7] Pediatric care in the 53 European countries is provided variously. A study by the European Paediatric Association/Union of National European Paediatric Societies and Associations[6] described that the spectrum of primary pediatric care systems in Europe shows a large variation between countries. However, in general at least 3 different pediatric care systems currently coexist in Europe: a pediatric system in which greater than 75% of primary care is provided by pediatricians, an intermediate system with 50/50 care provided by pediatricians and general practitioners, and the family doctor system, with 75% of primary pediatric care provided by general practitioners.[6,8] Debate exists regarding which system is able to provide better care for European children. The answer to this question depends on several socioeconomic factors,[8] many of them closely related to the evidence of a profound multinational diversity.[9] However, the data by Eurostat seem to offer elements in support of the notion that an active and efficient primary care pediatrics better guarantee children's health and it is also well perceived by households.

Multiple Factors Contribute to a Comprehensive Evaluation of European Children's Health

Data reported by Eurostat were collected by the EU-SILC questionnaires from the reference population living in private households and their current members, residing in the territory of the countries at the time of data collection. In EU-SILC data collection system, each country may implement the most efficient solution from a national perspective to deliver the data corresponding to each variable.[4] The EU-SILC is based on common concepts and definitions, and the evolution of some of these concepts reflect the complexity as well as the diversity of the national situations, which can be consulted in the annual methodologic guidelines.[4] The cross-sectional and longitudinal analysis is based on data from 130 000 and 100 000 households, respectively. The EU-SILC methodology is very rigorous. However, other important factors should be assessed and considered to achieve a complete and comprehensive analysis on the status children's health. For instance, these factors should include the extent to which children receive developmentally appropriate and age appropriate health care services,[10] including clinical preventive services, whether children have ready access to primary and specialty pediatric care, and the assessment of the quality and accessibility of hospital structures available to children. The Eurostat report should be therefore regarded as an important component of a comprehensive multifactorial analysis on the European children's health state.

Conclusions

Children and youth represent about 25% of the European population and 100% of the continent's future. Supporting their health from birth is at the same time a responsibility and a great opportunity to foster future generations of healthy Europeans.[11] Many healthcare systems in Europe are undergoing significant reconfigurations toward a more population-oriented delivery model to manage old and new morbidities more adequately.[12] Health starts outside the medical system, as supportive families and communities, education, hygiene, proper nutrition, and adequate housing and income are only a part of the multiple key determinants of health. Healthcare systems, constantly evolving and renovating to properly adapt to socioeconomic changes and scientific innovation,[13] are indubitably central in this process.

The authors of this commentary would like to emphasize that growing scientific reports and statistical data indicate that primary care pediatrics will become an increasingly important factor in the future of European pediatric care. The important data published by Eurostat regarding children's heath in Europe reinforce the importance of well-developed primary care pediatrics, properly coordinated with secondary and tertiary care centers, as a key element for the quality of any healthcare system. ■

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References available at www.jpeds.com

References

1. Jansen D, Saxena S, Azzopardi-Muscat N. Public health practice and policy to improve child and adolescent health in Europe. J Pediatr 2017;190:293-4.e2.
2. European Commission. Directorate General of Health and Food Safety—Public Health. https://ec.europa.eu/health/location_en. Accessed February 25, 2019.
3. European Commission. Eurostat. News releases. https://ec.europa.eu/eurostat/news/news-releases. Accessed February 25, 2019.
4. European Commission. Eurostat. European Union Statistics on Income and Living Conditions (EU-SILC). https://ec.europa.eu/eurostat/web/microdata/european-union-statistics-on-income-and-living-conditions. Accessed February 25, 2019.
5. European Commission, Eurostat. Key to European statistics. Ad-hoc modules. https://ec.europa.eu/eurostat/web/income-and-living-conditions/data/ad-hoc-modules. Accessed February 25, 2019.
6. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations". J Pediatr 2016;177S:S1-10.
7. Bienkowska-Gibbs T, King S, Saunders CL, Henham ML. New organizational models of primary care to meet the future needs of the NHS. Santa Monica (CA) and Cambridge (UK): RAND Corporation; 2015.
8. Ehrich J, Tenore A, Del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.e4.
9. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, Pettoello-Mantovani M. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.
10. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270-1.e1.
11. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
12. Lenton S, Namazova L, Vural M, Pettoello-Mantovani M. Improving community and primary care services for children, adolescents, and their families in Europe. J Pediatr 2017;185:256-7.
13. Silano M, Vincentini O, Luciani A, Felli C, Caserta S, Esposito S, Villella VR, et al. Early tissue transglutaminase-mediated response underlies K562(S)-cell gliadin-dependent agglutination. Pediatr Res 2012;71:532-8.

Prevention and Therapeutic Innovation in the Management of Child Health

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The topics of prevention and therapeutic innovation in the management of infant, child, and adolescent health have progressively acquired global importance for their direct effects on the lifelong health and well-being of populations. If appropriately implemented, they have the potential to positively impact various areas of the public health sector,[1] generating beneficial outcomes, which include major economic implications for local healthcare systems. Responding to the emerging preventive and health promotion needs of infants, children, and adolesents has become a priority for pediatrics, and together with therapeutic innovation, represents an important part of any strategic healthcare plan.

The main objective of pediatric practice is to prevent disease and disability through primary, secondary, and tertiary methods,[2] and where prevention is not possible to provide up-to-date evidence-based treatment to optimize the health and well-being of the child and family.

Prevention encompasses a range of factors including prenatal health, newborn screening, nutrition, early assessment and treatment, vaccine development, a healthy lifestyle including obesity prevention, physical activity, child surveillance, child protection, and promotion of children's rights to health, equity, and social justice.[3] This commentary briefly discusses prevention and therapeutic innovation in pediatrics, with the aim to further raise the attention of pediatricians to these topics, and to the importance of pursuing both an effective continuing exchange of high-quality clinical information, including basic science, and the promotion of efficient international collaboration in clinical practice, education, and research.

Prevention in the Context of Child Health

As described by the World Health Organization,[4] child health is a state of physical, mental, intellectual, social, and emotional well-being and not merely the absence of disease or infirmity. Children grow if they have the opportunity to live in families, communities, and environments that provide them with the right conditions and opportunities to reach their fullest developmental potential. A fundamental key factor supporting the achievement of an optimal health status for children is ensuring unrestricted access to good healthcare.

The general perception is that children's health has improved greatly on many fronts over recent decades—from more effective interventions in the areas of cancer treatment and infectious diseases, along with better control of noncommunicable diseases. However, there is indisputable evidence that many diseases are increasing in frequency, including new and reemerging infectious diseases, as well as new pathologic conditions because of environmental contaminants.

Prevention activities are typically categorized by 3 main areas of intervention: primary, secondary, and tertiary (**Table**). Individual, local, national, and international efforts to prevent environmentally and nonenvironmentally caused illness and disease have had some success. However, more comprehensive efforts, supported by increasing the awareness of pediatricians on these themes through continuing education activities, programs, and training courses, would be useful in combatting current and future health challenges in children's care.

The Value of Therapeutic Innovation in Child Healthcare

The need for better treatments and advanced therapeutic innovation for infants, children, and adolescents is universally acknowledged. From a public health perspective, the value of new treatment strategies in pediatrics lies in their therapeutic value, and in the health benefits, including survival rates, better quality of life or better drug tolerance, that they can generate for children, their families, and the community.

Although evidence-based practice provides a framework for identifying and disseminating effective treatments, therapeutic innovation is more likely to come from translational research. As research progressively moves from the laboratory to clinical care, behavioral and social sciences are used to apply biomedical science, and multidisciplinary and interdisciplinary teams seem to be replacing single discipline investigators. In a general

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Table. Prevention activities

1. Primary prevention: intervening before health effects occur, through appropriate measures (ie, vaccinations), correcting detrimental behaviors (ie, poor nutritional habits), or educational programs directed to children and their caretakers (ie: banning substances or practices known to be associated with a disease or poor health condition)
2. Secondary prevention: screening practices to identify diseases in the earliest stages, before the onset of signs and symptoms (ie, periodical health checkups)
3. Tertiary prevention: management of diseases post diagnosis to slow or stop disease progression (ie, chemotherapy, rehabilitation, screening for complications)

healthcare context in which research moves from the laboratory to clinics, an effective collaboration between basic science, community, and primary care is essential not only to provide optimal care, but also to help identify new treatment targets and promote the tailoring of new therapeutic agents and their dissemination in clinical practice. Educational and information programs and activities regarding advancements in therapeutic innovation are also an essential factor in achieving a valuable exchange of data between research and healthcare professionals providing clinical care.

The Role of Family and Community in Supporting Children's Health and Preventive Programs

Children are not able to achieve optimal health alone. They are dependent upon adults in their family and community to ensure that they grow in a healthy milieu.[5] Because they are continually growing physically and mentally, monitoring the achievement of optimal child health will be challenging in the absence of healthcare systems favoring a close collaboration between families and healthcare professionals, and without the support of adequate information about optimal preventive programs and new therapeutic opportunities. The involvement of families in childcare is, therefore, an essential factor in pursuing child health. Even maternal health status, habits, and environment during and before pregnancy profoundly impact the health and well-being of a child. Pediatricians should be provided with high quality continuing educational opportunities to update them on relevant best practice preventive measures and on effective therapeutic innovations.[6] When children's health is suitably nurtured and appropriate opportunities are provided to acquire habits that support good health during childhood, the stage is set for a healthy adulthood less likely to include chronic health problems.

Conclusions

The challenges posed by the growing importance of prevention and therapeutic innovation in the management of child health emphasize the value of exchanging experiences and the collaboration between pediatricians and health professionals caring for children. Enabling the exchange of experiences and the sharing of best practices is a key factor in responding effectively to the growing challenges of our society, such as the increasing incidence and prevalence of chronic diseases. The mission of the European Paediatric Association-Union of National European Paediatric Societies and Associations includes encouraging education of patients, families, and caregivers by sharing specialist knowledge with generalists, and promoting activities aimed at improving the quality of pediatric patient care in all European countries through excellent clinical research and the implementation of research into practice.[7] The Ninth Europaediatrics meeting in Dublin on June 13-15, 2019 will focus on the question of how the effectiveness of prevention, medical research, and therapeutic innovation can be used to ensure the optimal health and well-being of children, and to widen opportunities and access to adequate innovative treatment options for all. ■

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References

1. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to Diversity of Child Health Care in Europe: A Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations. J Pediatr 2016;177S:S1-10.
2. Stiris T, Huss G, Namazova-Baranova L. Consensus on the improvement of community and primary care services for children, adolescents and their families in Europe 2016. A joint statement from the European Academy of Paediatrics (EAP) European Confederation of Primary Care Paediatricians (ECPCP) European Paediatric Association (EPA). http://www.epa-unepsa.org/EPA%20EAP%20ECPCP_A%20consensus%20on%20improvement%20of%20community%20and%20primary%20care%20services%20for%20children%20in%20Europe%20Novemeber%202016.pdf. Accessed 19 November 2018.
3. Bundy DAP, Silva Nd, Horton S, Jamison DT, Patton GC, eds. Child and Adolescent Health and Development. 3rd ed. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; 2017.
4. World Health Organization. Maternal, newborn, child and adolescent health. https://www.who.int/maternal_child_adolescent/child/en/. Accessed 22 January 2019.
5. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270-1.e1.
6. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6.e2.
7. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, et al. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.

The Evolution of the European Young Pediatricians Association (EURYPA)

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The European Young Pediatricians Association (EURYPA) is a pan-European scientific association created with the vision to support the efforts of young European pediatricians, residents, and trainees to promote children's health, equity, and social justice through mutual collaboration in science, clinical research, and education.[1] The strength of this association lies in the diversity of interests, experience, and training of its members and ongoing collaboration to work toward these common goals. The association is still in its infancy as an independent scientific aggregation; however, recent significant progresses in the development of this association indicates its growing importance and role for pediatrics in Europe. Our aim is to describe the progress of EURYPA to date and to further support its development by working in collaboration with the national pediatric societies and their boards.

Foundation and Initial Activities of EURYPA

The widespread use of social media and the internet favor greater communication across countries, which allows for timely information and preparation to address emerging challenges, including, for instance, migration, that are faced by professionals involved in children's health in Europe as well as globally. Recently, residents in pediatrics and young pediatricians from several European nations worked closely with Board members of the European Pediatric Association, the Union of the National European Pediatric Societies and Associations (EPA/UNEPSA) to identify and work on the emerging challenges in pediatrics and to develop effective strategies aimed at better supporting children's health and well-being. Developing and promoting the professional use of new information and communication technologies among the new generations of pediatricians is part of this joint effort. Particular attention has been dedicated to properly sustain the education and professional role of young pediatricians. The important collaboration of young pediatricians active in several European nations with EPA/UNEPSA and its Board, particularly with Profs Fugen Cullu Cokugras and Julie Mestrovic, led to the foundation of EURYPA. The founding principles were inspired by simple yet powerful concepts: encouraging and sustaining young doctors in their educational programs is a key factor to promote competence and dynamism and inspire new visions and positive changes, therefore encouraging progress. Based on these values, EURYPA was founded on January 31, 2015, in Istanbul during a meeting promoted by young pediatricians of the Turkish Pediatric Association and the Italian National Observatory of Residents in Pediatrics. The EURYPA project was developed with the support and endorsement of the EPA/UNEPSA. Members of EURYPA are young medical doctors, residents in pediatrics, and specialists and subspecialists in pediatrics who are within 5 years of their certification or qualification.[2]

The first official meeting of EURYPA was held on May 15, 2015, in Florence during the Seventh Europaediatrics Congress. The second meeting took place in October of the same year, hosted by the Italian National Observatory of Residents in Pediatrics National Congress at the University of Padova, Italy. The first European congress of EURYPA was held in December 2015 in Istanbul with the participation of nearly 600 participants, members of EURYPA, from 10 different countries. The congress included several educational sessions, which provided a useful platform for scientific discussion. Furthermore, it represented an opportunity for the young pediatricians who convened to meet and share their research and discuss specific issues selected for their high relevance by the participants, such as equality issues in pediatrics and diversity of training programs in Europe.

Information about EURYPA and its foundation was first described in an article published in *The Journal* in April 2016.[3] In that article, members of EURYPA discussed the issues related to the differences in training modalities and requirements across Europe, entry requirements and competition to attain resident positions, and the discrepancies between the various structures of training programs throughout Europe.[4,5] The main challenges and issues faced by EURYPA discussed in the article are still objects of debate among the members of the organization, including financial support and the locations and cost of venues hosting congresses and working groups, which could limit the participation of delegates to the meetings and determine which nations would be able to be more active in EURYPA.[4]

EPA/UNEPSA	European Pediatric Association, the Union of the National European Pediatric Societies and Associations
EURYPA	European Young Pediatricians Association

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The Consolidation of EURYPA

EURYPA works in close relation with EPA-UNESPA and collaborates on its projects. EURYPA is also part of the General Assembly of EPA-UNESPA, joining its work and projects as an Affiliated Member. In collaboration with EPA/UNEPSA, during the past 4 years EURYPA developed an active international network that facilitates dynamic communications among young pediatricians though establishing e-mail, Facebook, and WhatsApp groups. EURYPA's ambition is to provide a common platform for all young pediatricians in Europe, offering them the necessary tools, useful, up-to-date information, and a feeling of empowerment to achieve their personal professional endeavors. The collaboration between EURYPA and EPA/UNEPSA also includes a plan to associate young pediatricians with the EPA/UNEPSA board members to establish a useful exchange of information and actively contribute to realize the projects in which the organization is involved.[6]

In 2017, EURYPA was represented officially at the Eighth Europediatrics Congress in Bucharest, Romania, and delegates of EURYPA had the opportunity to present their projects at the EPA/UNEPSA General Assembly. Young pediatricians, representing 9 countries (Turkey, Italy, United Kingdom, Romania, Hungary, Armenia, Ireland, Czech Republic, and Croatia) presented case reports in the EURYPA Symposium "Pediatric Emergencies," which included roundtable sessions and debates. During the official board meeting of EURYPA, the delegates analyzed the activities performed during the past years and shared ideas about planning for future projects and activities, with the aim of joining forces to further develop better educational platforms and activities and the best strategies to effectively advocate for European children's health and well-being.

Looking to the Future

The next official EURYPA meeting will take place in 2019 during the Ninth Europaediatrics Congress in Dublin, Ireland. As discussed and agreed at the meeting in Bucharest in 2017, the first permanent executive committee of the organization will be established. The Turkish representatives have volunteered to provide an interim executive leadership and to temporarily coordinate the activity and communication among EURYPA members until the permanent executive committee will take office.

The Facebook group will be used as the primary mean of communication among EURYPA members, to inform the European community of young pediatricians about courses or events taking place across Europe. Each nation will have 2 representatives active in the communications committee, who will have the role of administrators in the Facebook group. They will circulate information to the colleagues in their countries and solicit them to join and become active in the EURYPA community. Furthermore, a WhatsApp group has been established to further facilitate the interactions between delegates and among EURYPA members.

The statute of the organization has been discussed extensively during the previous meetings of EURYPA, and it has been agreed that the final draft will be developed and circulated to the EURYPA members by the interim executive leadership before the meeting planned in 2019, where it will be further discussed, finalized, and voted. The statue will provide a description of roles and responsibilities of its officers, who will be elected at the meeting in Dublin. In addition to national representatives, the EURYPA statute will include working committees with specific aims.

EURYPA is currently represented in 18 European countries. The goal is to further and significantly expand the number of nations represented in EURYPA by the time of the meeting in Ireland by involving a large number of members from the 50 European nations.

EURYPA has already actively engaged in research projects, and members of EURYPA from Turkey have completed a survey on the training experience of their pediatric residents. This study has collected responses from about 250 trainees in Turkey, and an analysis of the preliminary data allowed us to gather useful information, including demographics of trainees, experience of working conditions, mental health, and involvement in malpractice cases. EURYPA plans to extend this survey to trainees across other European countries. Barriers and challenges of training also will be the topic of a roundtable and discussion at the 2019 EURYPA symposium during Europaediatrics in Dublin.[6,7] The session will be chaired by members of EURYPA,[6,7] and senior speakers will be invited to share their insights and experience on training in pediatrics. An EURYPA poster session open to entrants younger than 35 years of age is programmed during the conference, and a prize for best presentation will be awarded.

Conclusions

Despite the challenges of maintaining contacts and collaboration across a distance, a number of important steps have been taken. With the ongoing commitment of its members, we anticipate that EURYPA will continue to grow. In the years to come, our organization looks forward to further expanding its cooperation with the young generations of European and non-European pediatricians, with the aim to join forces to improve children's health and well-being in Europe and worldwide.[8,9] ■

We thank members of the EPA Council for their support and all members of EURYPA who were involved in developing this project. EURYPA currently is represented in these countries: Albania, Armenia, Belgium, Croatia, Czech Republic, Denmark, France, Hungary, Ireland, Italy, Latvia, Moldova, Poland, Portugal, Romania, Serbia, Turkey, and the United Kingdom. All authors contributed equally to this article.

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References available at www.jpeds.com

References

1. European Paediatric Association, Union of National European Paediatric Societies and Association. EURYPA. http://www.epa-unepsa.org/sites/default/files/EURYPA_WEBSITE.pdf. Accessed February 4, 2019.
2. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424.e2-426.e2.
3. Gray S, Raschetti R, Beşer ÖF, Elicin PU, Aversa S, Pamuk G, et al. European Young Pediatricians Association: laying the foundations for collaboration, integration, and networking among pediatricians of the future. J Pediatr 2016;171:324.e1-5.e1.
4. Ehrich JHH, Pettoello-Mantovani M. Views of the presidents of National European Pediatric Societies on evolving challenges of child health care. J Pediatr 2016;177:336.e1-337.e1.
5. Gray S, Raschetti R, Beşer ÖF, Elicin PU, Aversa S, Pamuk G, et al. European Young Paediatricians Association: laying the foundations for collaboration, integration and networking amongst paediatricians of the future. J Pediatr 2016;171:324-5.
6. Ehrich JHH, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: a Study of the European Paediatric Association/Union of National European Paediatric Societies and Associations." J Pediatr 2016;177S:S1-10.
7. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471.e4-6.e4.
8. Goldhagen J, Mercer R, Robinson G, Duran E, Webb E, Ehrich J. Establishing a child rights, health equity, and social justice-based practice of pediatrics. J Pediatr 2015;166:1098.e1-3-9.e1-3.
9. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270.e1-271.e1.

Planning the Pediatric Workforce in Israel

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Israel provides a useful model for effective and efficient pediatric workforce planning. Israel is a child-oriented society and 33% of the population are children with the highest fertility rate in the Organization for Economic Cooperation and Development (OECD) countries.[1] Although infant mortality in Israel is one of the lowest in the world, child poverty level and disparities in healthcare are in the top of OECD nations. Being a child-oriented society, the demand for pediatric services characterized by availability and qualified expertise is very high, including the demand for primary care services to be provided by pediatricians.

The major challenges associated with planning of the pediatric work force in Israel and its training include future planning of an adequate number of pediatric graduates to cope with the increasing demands for pediatric services in Israel; updating the pediatric training to enable the pediatricians to address the changing requirements; recruitment of pediatricians to serve in preventive and public healthcare services in view of poverty rates and disparities in health services in Israel; and promoting clinical and especially basic research in pediatrics.

Planning an Adequate Number of Pediatric Residency Graduates

In Israel, the rate of practicing physicians per 1000 people is 3.11, close to the OECD average of 3.2. However, compared with most other OECD countries, the number of per capita physicians in Israel has declined since 2000. Until recently, the supply of Israeli physicians relied heavily on physicians who were trained in other countries. However, that source is now drying up. To address the projected shortage, Israel has expanded its 4 existing medical schools and an additional medical school is scheduled to open in October 2019.

In 2014, there were 2687 licensed pediatricians in Israel; 52% of them were younger than 55 years of age. The ratio of pediatricians aged <65 years per 1000 children age 0-14 years was 0.799 in 2014. The number of pediatricians with a subspecialty increased from 20% of total pediatricians in 1995 to 27% of total pediatricians in 2006 and to 41.5% of total pediatricians in 2014, an increase of 330%.[2-4]

Community primary care is provided for children at community based Health Fund clinics. Pediatricians care for more than 75% of children and family physicians treat the remaining children.[5]

Even though the number of pediatricians has increased recently, the number of children <14 years of age per 1 pediatrician has increased because the growth of the child population in Israel (because of the high fertility rate) is higher than the growth of the number of active pediatricians in the country.[3]

There are several assumptions specific to the Israeli system that may assist in the prediction of needed physicians, including an influx of immigrant physicians does not significantly change the number of graduating pediatricians, 5% of pediatricians do not practice in their profession because of emigration or career change, ~50% of all subspecialists will have part-time jobs in a primary pediatric clinic, the increase of pediatricians working part-time will decrease the pediatrician workforce by 1.5% a year, and changes in technology will increase the demand for pediatricians by 1% per year.[4]

Another difference from some other European countries is that although the formal retirement age in Israel is 67 years, many pediatricians continue to practice pediatrics either part time or full time beyond that age. This phenomenon has assisted in alleviating the shortage of pediatricians in Israel.

One of the main obstacles for increasing the number of pediatric graduates has been the financial limits on recruitment of more pediatric residents each year.

There have been several suggestions for overcoming this budget associated restrains including a cooperation with the acting 4 Health Maintenance Organizations in Israel so that they will sponsor the residency salary of a significant number of residents and in return they will be provided by pediatricians upon their graduation which they desperately need.[6]

Updating Pediatric Training

Residency in pediatrics in Israel lasts 4.5 years, with one-half of the time spent in a university-affiliated inpatient hospital department and 6 months training in an ambulatory primary care facility or a secondary care (advisory referral) general pediatrics outpatient clinic. In addition, residents devote 6 months of their training to basic science or clinical research.[6]

Although traditionally residency in pediatrics was supposed to provide the graduate with up-to-date scientific knowledge and experience in different illnesses and malformations, there has been a growing demand to revise the pediatric curriculum so that the pediatric residency graduate will be able to successfully address the new morbidities in pediatrics. This includes focused training in areas that include advocacy, public health, adolescence, chronic illness, health promotion,

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behavioral issues, parenting and family dynamics, social influences, and health and social inequalities. The pediatric graduate is also expected to provide a culture sensitive healthcare. Israel includes several ethnic groups with very different backgrounds. There is a need for a cultural formulation in the healthcare setting. A sensitive assessment provides recognition of how the patient's cultural roots affect care delivery. Cooperation and compliance to the advice given by healthcare professionals may be enhanced by understanding the patient's cultural perceptions.

Facing these challenges, several health organizations in Israel launched the Goshen Project,[7] aimed at bolstering residents' and postgraduate pediatric training with developmental, behavioral, and psychosocial situations. It has been shown that training in developmental and behavioral pediatrics has given Israeli pediatricians a greater satisfaction with their ability to care for children.[8,9]

Recruitment of Pediatricians to Serve in Preventive and Public Health Services

Traditionally, public health matters are supposed to be handled by experts in public health and public health officials. However, several features in pediatric healthcare in Israel call for deeper involvement of pediatricians in pediatric public health services and policy shaping, which include disparities, immunizations and infectious diseases outbreaks, and nutrition. About the disparities factor, it is important to report that infant mortality is Israel is relatively low (3:1 deaths per 1000 live births), and Israeli figures have already attained and exceeded the United Nations Sustainable Development Goal 2030 targets for child mortality and improved maternal health. However, the overall infant mortality among Arab children is consistently more than double that of Jewish infants. This difference can be attributed primarily to the almost 4-time excess of deaths because of congenital malformations and inherited diseases among Arab infants relative to Jewish infants, and much of the excess mortality from congenital malformations and inherited diseases can be attributed to the 31% occurrence of consanguinity in the Arab population. Even though Israel is a developed, industrialized country, it has the highest level of child poverty among OECD countries. In 2014, 35% of children were living in poverty.[1]

In reference to immunizations and infectious diseases outbreaks, the greatest challenges to ensuring and maintaining high coverage and concomitant herd protection are the active antivaccine movements, vaccine hesitancy, large family structures and irregular vaccination coverage in some communities, and the enclaves of asylum-seekers whose vaccination status is unknown. Several recent outbreaks of measles and mumps, as well as the silent circulation of wild poliovirus in 2013, demonstrate the susceptibility to outbreaks even when there is a relatively minor decline in vaccination coverage or where there are pockets of undervaccinated groups. Israel is now experiencing a major measles outbreak, and the number of cases as of the end of December 2018 was more than 3150.[10]

Finally, nutrition makes a significant impact on the health and well-being of the Israeli population, which is facing a rising prevalence of obesity and its complications. At present, approximately 1 in 4 children in school grades 7-12 are overweight or obese, with the highest prevalence among young Arabs.[1]

A deeper and increased involvement of pediatricians in public health practice and preventive medicine is extremely important because addressing these problems is essential for maintaining health gains in children. Therefore, pediatric work force planning should include allocation of a certain number of pediatric residency graduates for public health practice because early community interventions are cost effective and the most profitable expenses.

Conclusions

Promoting clinical, community-based care and basic research plays an essential role in pediatrics. Similar to other European countries, Israel is also suffering from decreased interests and investments in pediatric research as fewer graduates invest time and career in basic research. Although there has been increased interest in community-based research,[11] this research should be also encouraged. Investment in research is an investment in the future and is one of the most fruitful investments.

Residency in Israel contains a 6-month period dedicated to research. Planning of the pediatric workforce should include an efficient usage of this period to identify and promote the relevant candidates who are expected to have a significant and successful career in research and to allocate a sufficient number of pediatric residency program graduates to spend time in research, especially in basic sciences research. ■

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References available at www.jpeds.com

References

1. Rubin L, Belmaker I, Somekh E, Urkin J, Rudolf M, Honovich M, et al. Maternal and child health in Israel: building lives. Lancet 2017;389:2514-30.
2. Gofin Y, Afek A, Derazne E, Toker A, Shamiss A. A model for assessing the gap between physician residency demand and present status. Isr Med Assoc J 2012;14:275-80.
3. Porter B, Urkin J. Community pediatrics in Israel: time for change? Isr Med Assoc J 2011;13:133-6.
4. Laufer M, Perry ZH, Reuveni H, Toker A. Pediatrician workforce planning: the Israeli experience and projections of pediatric manpower 1995-2025. J Hosp Adm 2014;3:140-8.
5. Van Esso D, del Torso S, Hadjipanayis A, Biver A, Jaeger Roman E, Wettergren B, et al. Pediatric primary care in Europe, variation between countries. Arch Dis Child 2010;95:791-5.
6. Tasher D, Rubin L, Grossman Z, Grotto I, Dahan D, Berlowitz Y, et al. Child health care in Israel. J Pediatr 2016;177S:S107-15.
7. Porter B, Gadassi H, Grossman Z, Kerem E, Katz M, Oberklaid F. Community paediatrics in Israel: the 'Goshen' model for change. Arch Dis Child 2017;102:795-7.
8. Haggerty RJ. Child health 2000: new pediatrics in the changing environment of children's needs in the 21st century. Pediatrics 1995;96:12-804.
9. Senecky Y, Inbar D, Diamond G, Grossman Z, Apter A, Kahan E. Pediatricians' satisfaction with their abilities to care for children with developmental, behavioral and psychosocial problems. Pediatr Int 2007;49:472-8.
10. State of Israel Ministry of health. Measles. https://www.health.gov.il/English/Topics/Pregnancy/Vaccination_of_infants/Pages/measles.aspx. Accessed January 27, 2019.
11. Grossman Z. IPROS—Israel Pediatric Research in Office Setting. Archiv Med Fam 2007;9:17-9.

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Fostering Resilience in Children: The Essential Role of Healthcare Professionals and Families

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In our complex society, stressful or negative life experiences have typically been considered to induce a substantial change from one set of living conditions to another. Life remodeling, resulting from adversities, involves significant challenges because of the need to adapt to new circumstances. That may often impair the ability to cope with new life settings, exposing the risk of clinical distress and possible long-term psychological illnesses, resulting in symptoms of depression, anxiety, fatigue and stress.[1]

Children and adolescents who have suffered adversities are considered to be at risk of failing to succeed.[2] There has been an increasing attention toward understanding the condition of children and adolescents faced with adversities. Several studies have assessed children's ability to manage their well-being and develop resilience to adapt and cope with unfavorable events. The scientific literature in this area is expanding, however, there is limited integration of the findings into proactive strategies designed to relieve the impact of adverse experiences suffered by individuals during their developmental years.[3,4]

The process of developing resilience in children and adolescents has progressively become of particular interest to healthcare professionals and families because of its implications for the health of children and adolescents they care for. The authors of this commentary are part of a working group on social pediatrics supported by European national pediatric societies, members of the European Paediatric Association/Union of National European Paediatric Societies and Associations. Herein we outline the relationship between resilience and health to further emphasize the joint role that healthcare professionals and families may play in identifying the sources and degree of stress experienced by children. This would facilitate the ability of children and adolescents to discover and use their own strengths and resources to better cope with adversities, and most importantly to reduce the possible long-term effects of negative events in life.

Definition of Resilience

The term resilience identifies the process of properly adapting to adversity, trauma, individual, or society tragedies, and in general, react positively to significant sources of stress, including family and relationship problems, as well as significant health threats.[4,5] It is a commonly accepted notion that resilience consists of a balance between stressful events and the ability to cope.[1,4]

Resilience is effectively defined in children and adolescents as the capacity to successfully preserve or recuperate their mental and physical health in the face of significant negative events or risks.[4]

The Relationship between Resilience and Health

Increased attention has been devoted toward positive psychology and mental health promotion and their protective potentials in establishing a general status of good health and well-being in children and adolescents. The majority of scientific studies on resilience have been published within the last 2 decades.[3-5] However, although predominantly focusing on children, the literature in this field describes the role of resilience related to children and adolescents faced by different conditions and occurrences. They may include poverty, maltreatment, chronic illness, needs of individuals from cultural minorities, or children and adolescents at risk for behavioral problems and substance abuse.[2-5] Less frequently, the focus is on the role that resilience may play in children's health as a whole, and also in health systems.[6,7] It is in fact important for pediatric healthcare systems and structures to exhibit absorptive, adaptive, or transformational capacity in the face of challenges related to children's health.

It is a well-established notion that the absence of physical sickness is insufficient to properly describe a status of good health in children and adolescents.[4] In fact, as part of a holistic approach to health, the physical and psychological state should be considered when evaluating the condition of well-being. Following this methodologic line of thought, building resilience is a central element in the efforts to develop

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essential factors contributing to establishment and maintenance of health status. Significant factors include the capability to build and maintain interpersonal relationships, shape efficient problem solving skills, and identify realistic goal setting. The capacity of adopting this behavioral format is considered to beneficially contribute to an individual's ability to preserve and sustain one's mental and physical health status, and to enhance one's aptitude to perform and contribute meaningfully in one's current and future daily life.[8]

Assessing Resilience in Children, Adolescents, and their Families

The assessment of resilience in children, adolescents, and their families is of fundamental importance to health systems to develop efficient programs of intervention. The goal should be to recognize difficulties to be addressed and potential protective factors to be developed[2] within the frame of their competences. Assessing resilience would enable healthcare professionals to identify the proper strategies of intervention, as well as enhance existing capabilities, encourage healthy adjustment trajectories, and nurture resilient adaptation. A multidimensional yet focused approach to intervention would be advisable, as it will help to identify potential risks and protective factors, then favoring positive adjustments.[2,9] Various methods to assess resilience have been proposed, including scales, questionnaires, personal interviews, and checklists; however, the use of standardized, scientifically validated approaches for measuring resilience is recommended to properly collect and analyze data.[10]

An example of a standardized rating scale, which can be used to assess resilience in children between 2 and 5 years of age is the Devereux Early Childhood Assessment,[11] which explores the 2 informative dimensions of protective factors and behavioral concerns. A major goal of this system is to help healthcare professionals establish if children have developed acceptable skills in the area of initiative, self-control, and attachment, which are 3 key elements associated with resilience. A further extension of the Devereux rating scale is the Devereux Early Childhood Assessment Clinical Form,[12] which is a clinical assessment designed to evaluate factors associated with resilience, including the nature and severity of preschooler's behavioral, emotional, or social problems.[8,10]

In adolescents, the most appropriate system to assess the level of resilience[2,13] is the Resilience Scale, consisting of a 25-item scale based on 2 factors recognized to be associated with resilience: personal competence and acceptance of self and life.[2,14] This scale has been tested and successfully validated with various ages and ethnic groups.[2,15]

The purpose of assessing resilience in families is to facilitate interactions and dialogs within them about the different roles of their members, as well as the potentials and characteristics of internal dynamics and functioning.[16] Examples of appropriate standardize tools for measuring family functioning include the McMaster Family Assessment Device[17] and the Family Environment Scale.[18] The first is based on a 7-dimensions scale including problem solving, communication, roles, affective responsiveness, affective involvement, behavior control, and general functioning, whereas the latter evaluates perceptions across relationship, personal growth, and system maintenance dimensions.

The Role of Healthcare Professionals and Families in Fostering Resilience in Childhood and Youth

With the combined support of healthcare professionals, families, and other social connections, including friends and the school environment, children and adolescents can appropriately overcome a condition of distress and prospectively stabilize emotionally and physiologically.[16,19,20]

Pediatricians play a positive role in the lives of their patients and families,[19,21] as they may help to identify and increase protective factors and build resiliency even before children's birth. Pediatricians are seen by families as a trusted font of information,[20] therefore, they are in a privileged position to explain the essential role that families may play in helping raise children and adolescents to be resilient.

Conclusions

When children are resilient, they are confident, curious, able to adapt to new situations, and better skilled to extend their reach into the world. The goal for healthcare professionals, as well trained gatekeepers of children's and adolescent's health,[22] should be to promote their balance and resilience with the collaboration of their families, which in turn will contribute to improving their health and well-being. ■

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References available at www.jpeds.com

References

1. Armstrong AR, Galligan RF, Critchley CR. Emotional intelligence and psychological resilience to negative life events. Pers Individ Dif 2011;51:331-6.
2. Zolkoski SM, Bullock LM. Resilience in children and youth: a review. Child Youth Serv Rev 2012;34:2295-303.
3. Bosqui TJ, Marshoud B. Mechanisms of change for interventions aimed at improving the well-being, mental health and resilience of children and adolescents affected by war and armed conflict: a systematic review of reviews. Confl Health 2018;12:1-17.
4. Stewart M, Reid G, Mangham C. Fostering children's resilience. J Pediatr Nurs 1997;12:21-31.
5. Traub F, Boynton-Jarrett R. Modifiable resilience factors to childhood adversity for clinical pediatric practice. Pediatrics 2017;139:e20162569.
6. Christopher Nemeth C, Wears R, Woods D, Hollnagel E, Cook R. Minding the gaps: creating resilience in healthcare. In: Henriksen K, Battles JB, Keyes MA, eds. Advances in patient safety: new directions and alternative approaches (Performance and tools), Vol. 3. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
7. Blanchet K, Nam SL, Ramalingam B, Pozo-Martin F. Governance and capacity to manage resilience of health systems: towards a new conceptual framework. Int J Health Policy Manag 2017;6:431-5.
8. Stewart DE, Yuen T. A systematic review of resilience in the physically ill. Psychosomatics 2011;52:199-209.
9. Luthar SS, Cicchetti D. The construct of resilience: implications for interventions and social policies. Dev Psychopathol 2000;12:857-85.
10. Naglieri JA, LeBuffle PA. Measuring resilience in children. In: Goldstein S, Brooks RB, eds. Handbook of resilience in children. New York: Springer; 2005. p. 107-21.
11. Brinkman TM, Wigent CA, Tomac RA, Pham AV, Carlson JS. Using the Devereux early childhood assessment to identify behavioral risk and protective factors within a head start population. Can J Sch Psychol 2007;22:136.
12. The Devereux Early Childhood Assessment Clinical Form (DECA-C). Devereux Center for Resilient Children (DCRC) assessment tools. https://www.centerforresilientchildren.org/wp-content/uploads/2014/01/DECA-C-full-version.pdf. Accessed June 27, 2018.
13. Ahern NR, Kiehl EM, Sole ML, Byers J. A review of instruments measuring resilience. Issues Compr Pediatr Nurs 2006;29:103-25.
14. Wagnild GM, Young HM. Development and psychometric evaluation of the resilience scale. J Nurs Meas 1993;1:165-78.
15. Wagnild GM. A review of the resilience scale. J Nurs Meas 2009;17:105-13.
16. Walsh F. Family resilience: a framework for clinical practice. Fam Process 2003;42:1-18.
17. Mansfield KA, Keitner KG, Dealy J. The family assessment device: an update. Fam Process 2015;54:82-93.
18. Vostanis P, Nicholls J. The family environment scale: comparison with the construct of expressed emotion. J Fam Ther 1995;17:299-315.
19. American Academy of Pediatrics. The resilience project. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Resilience-Project.aspx. Accessed June 28, 2018.
20. Ferrara P, Corsello G, Basile MC, Nigri L, Campanozzi A, Ehrich J, et al. The economic burden of child maltreatment in high income countries. J Pediatr 2015;167:1457-9.
21. Ferrara P, Corsello G, Sbordone A, Nigri L, Ehrich J, Pettoello-Mantovani M. Foster care: a fragile reality needing social attention, and economic investments. J Pediatr 2016;173:270.e1-271.e1.
22. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424.e2-426.e2.

As Few Pediatricians as Possible and as Many Pediatricians as Necessary?

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A common mantra is "as little as possible and as much as necessary." This perception can be applied to all kinds of different projects in everyday life in order to help achieve a good outcome. It also applies to medicine, for example, "as little antibiotics as possible and as much/many antibiotics as necessary." However, does this "rule" also apply to the pediatric workforce, that is, "as few pediatricians as possible and as many pediatricians as necessary"? How can we develop a sustainable pediatric workforce to meet the healthcare needs of children? We previously offered different equations for calculating the needed numbers of annually trained pediatricians to keep the actual number of pediatricians in a country stable in view of variable working conditions such as full-time or part-time working equivalents[1,2] and weekly working hours and night shifts.[3] We now describe pediatric workforces in 2013-2018 in 16 European countries, 11 European Union and 5 non-European Union countries.

National child healthcare systems are embedded in the underlying political and economic systems such as capitalistic, liberal, monarchic, socialistic, or social market system. National pediatric workforces can be analyzed according to the triangle of need–supply–demand. Our analysis neither intended to compare national pediatric workforces with the underlying political systems nor did it investigate the role of different types of health insurance systems, for example, financed by levies to insurance funds (Bismarck system) or by taxes (Beveridge system). We also tried to avoid a single-sided view of pediatricians whose understandable aim is to defend their own needs and to improve working conditions. Instead, we wanted to look at the child healthcare services through the eyes of families and their children. The priority of families is to have an available, adequate/appropriate, affordable, and easily accessible healthcare service provided by highly qualified personnel on all levels ranging from generalists to specialists. Families wish to have a well-functioning and competent child healthcare system that—if fragmented—should be well-coordinated. Different bodies and institutions involved in the care of children should communicate and cooperate well, reaching a consensus wherever and whenever possible.

Human Resource Planning in Pediatrics

The factors that must be taken into account in the process of calculating the pediatric workforce include geography, population density, transport links, relationship between child health centers, political readiness for change, and cooperation between different types of clinicians. Critical to the discussion is the number of children requiring community care, hospital care, and public healthcare by pediatricians to adapt the different competences of pediatrics to the needs of young patients and their families.

Results of a Survey on National Pediatric Workforce in 2013-2018

Responses to a questionnaire on national pediatric workforce were received from pediatricians (see author list) of 16 European countries and subsequently analyzed (data on individual countries will be published in an upcoming European Paediatric Association article). Results were also compared for the 3 subgroups of child healthcare systems as described by Katz et al[4] and the World Health Organization[5]: pediatric system = 6 countries (Croatia, Czech Republic, Germany, Israel, Russia, Spain), mixed care system = 6 countries (Armenia, Austria, France, Italy, Switzerland, Turkey), and general practitioner system = 4 countries (Bulgaria, Ireland, The Netherlands, Romania). In the 16 countries there were 95 559 853 children <14 years of age and the total number of pediatricians was 116 840, a ratio of 818:1. The mean percentage of primary care pediatricians was 41%; hospital pediatricians equaled 56%, and other types of pediatricians 3% (eg, working in public healthcare services). The mean proportion of trained and accredited pediatric subspecialists was 27%. The median of lifelong working years was 36 years. The median percentage of pediatricians working part time equivalents was 17%; 71% were female and the mean percentage of female pediatricians

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currently in training was 76%. Eight countries reported an increase of pediatricians from 2013 to 2018 ranging from 1% to 10%; 5 countries reported no change and 2 a decrease. No data were available for 1 country. In 6 of the 16 countries, the number of pediatricians leaving the national workforce and migrating exceeded the number of immigrating physicians; in 3 countries there was an equal balance of incoming and outgoing pediatricians, and there was a surplus of immigrating physicians in 5 countries; no data were available for 2 countries. Data on the influence of new medical technologies or increasing multidisciplinary care by other caregivers than pediatricians on the numbers of pediatricians were unknown. The annual number of active pediatricians leaving child healthcare services for other professions was negligible in all but 1 of the 16 countries.

From 2013 to 2018, the mean number of annually trained pediatricians per country was 319. In 2018, there will be 347 trainees, reflecting the accuracy of the equations used when compared with 339 as predicted by using our previously published equations.[1,2] In 2013, the presidents of national pediatric societies had been asked to predict the future numbers of pediatricians in their countries. Eight of the 16 presidents correctly predicted the number of pediatricians.

The median ratio of children <14 years per pediatrician in 6 countries with a pediatric system was 722:1. This ratio was 1342:1 for primary care pediatricians and 1446:1 for hospital pediatricians. When comparing the mixed care system with the pediatric system, higher numbers of children were treated by 1 pediatrician working in a mixed system, 860:1 vs 722:1 for all pediatricians, 1625:1 vs 1342:1 for primary care pediatricians, and 2540:1 vs 1446:1 for hospital pediatricians. There were no major differences between these 2 groups concerning lifelong working years of pediatricians and percentages of subspecialists, primary care pediatricians, and hospital pediatricians. Countries with the general practitioner system had the highest percentage of hospital pediatricians (90%) and subspecialists (31%), and the highest mean ratio of children per pediatrician, namely 2250:1.

Conclusions

What is the best model for testing how to calculate the ideal number of children in the community who should be cared for by a single pediatrician? We may be naive when using the existing statistics on numbers of pediatricians of 16 European countries as indicators for solving the challenges of a highly complex service system also including other caregivers for children.

The status of the pediatric workforce in child healthcare has been discussed for several years, debating oversupply and inefficient services.[6-8] These debates are influenced by the widely accepted assumption that the future child population will require more pediatric and more general healthcare. The ratio of 4000 children per pediatrician that was regarded to be appropriate in the 1980s has decreased to 1400:1 in recent years.[6] This ongoing trend is supported by our findings from 2013 to 2018 in 16 European countries, irrespective of the underlying child healthcare system.

One of the basic questions deals with the assumption that the calculation of needed numbers of pediatricians should either be based on the supply and demand model or on estimating specific needs. Avoiding the complex and contradictory triangle of need–supply–demand for calculating an adequate pediatric workforce may lead to the general conclusion that the ideal system must be characterized by a decentralized provision of general care and treatment by the most experienced physicians whenever possible, with centralized specialization for treating rare diseases and severely ill children. From the patients' perspectives, all parts of child healthcare services should be available, affordable, and adequate. These services must be as close to home as possible.

This strategy requires a constant update of statistical data in national institutes. Moreover, good governance of federal and national ministries of health and social affairs is mandatory, as well as of health insurance companies. The joint forces of all national pediatric organizations must prepare a forum in which their representatives will speak with "one voice." Our own analyses in 16 countries discovered substantial gaps of requested data that could not be filled with documented data by different national institutions.

In our opinion, future strategies also require a mixture of centralized and subsidiary institutions being involved in a constant exchange of top-down and bottom-up decision making. This means that ministerial proposals will have to be tested by regional committees before being implemented. Regional experts must return the results of their findings, conclusions, and proposals to the central ministries to allow the adaptation of theoretical to practicable solutions. In this network solution, all pediatricians must actively collaborate and constantly strive to improve safety and outcomes. Local teams of pediatricians must organize and evaluate every day care as well as liaison with social care and 2-way communication with specialized pediatric centers. These pediatric specialist centers should not be seen as standalone institutions, but as part of a well-managed clinical network, promptly accepting the most urgent and appropriate cases for treatment and subsequently sending children back into the local system for rehabilitation after specialist care. Clinical leadership for gate-keeping and basic child healthcare resides with the community pediatrician who organizes shared care with clear patient pathways and clinical care plans, including training and joint clinics by specialized teams.

We think that most countries in Europe need more well-trained general pediatricians and pediatric subspecialists to achieve the goals of improving child healthcare on different levels. The "total is more than the sum of all single parts." By contrast, the motto "better care by fewer pediatricians" is unrealistic. Our objective is to alert healthcare officials regarding the necessity to optimize the issue of calculating the needed numbers of pediatricians in different settings and services of each national healthcare system. ■

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References

1. Ehrich J, Pettoello-Mantovani M. Never ending stories: the loop in pediatrics. How many pediatricians need to be trained in European countries to keep the pediatric workforce stable? J Pediatr 2018;196:332-3.
2. Ehrich J, Fruth J, Jansen D, Gerber-Grote A, Pettoello-Mantovani M. The loop in pediatrics: how to calculate the risk of shortage and surplus of pediatric workforce? J Pediatr 2018;199:286-7.
3. Machtey E, Ehrich J, Somekh E. Regulations of night shifts of pediatric residents: review of responses to a European survey. J Pediatr 2018;201:302-3.
4. Katz M, Rubino A, Collier J, Rosen J, Ehrich JH. Demography of pediatricprimary care in Europe: delivery of care and training. Pediatrics 2002;109:788-96.
5. Weber M, Backhaus S, Chukwujana O, Fenski F, Henking G, Schatte L, et al. Pädiatrische Versorgungskonzepte in Europa. Monatsschrift Kinderheilkunde 2018;166:131-40.
6. Fiser DH. Increasing utilization of general pediatricians and pediatric subspecialists: can the workforce meet the need? J Pediatr 2005;146:3-5.
7. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.
8. Stapleton B. How do we create the best pediatric workforce? Questions abroad and at home. J Pediatr 2015;167:227-8.

Regulations of Night Shifts of Pediatric Residents: Review of Responses to a European Survey

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The regulation of residents' night shifts and weekly working hours increasingly is being questioned and investigated to better understand the benefits and harms. Studies on the effects of fatigue on function appeared in the media in the early 1970s in the US (**Table I**; available at www.jpeds.com); one of the first studies demonstrated that interns "deprived of sleep were significantly less able to recognize arrhythmias on the electrocardiographic task" and "judged themselves to have abnormalities in cognitive, perceptual, and physiologic areas of function."[1] A review of the current literature questions the effect of subsequent American changes in the night shift hours and weekly work hours of the residents.[2] The critical comments deal especially with the changes in the American Accreditation Council for Graduate Medical Education reforms from 2003 and 2011 and their implications on the safety and quality of patient care, the implications on the quality of life of residents, and also on the quality of the residency training. A large meta-analysis found that most studies concluded that the restrictions of duty hours had no negative impact on patient care or residents' wellness but had a negative impact on residents' education and training.[2]

In 2003, the Council of Europe issued "the general working time directives on working hours and maximum hours of duty, rest time during working hours, and maximum weekly working hours" for all professions. These directives stated that the average working time should not exceed 48 hours for each 7-day period; a daily rest of 11 consecutive hours per 24-hour period; and a rest period for every 6 hours set by legislation or collective agreement.[3] To the best of our knowledge, there are currently no European data available regarding the degree of compliance with the Council of Europe regulations or data regarding working hours and shifts of pediatric residents in children's hospitals of different countries in the European Union (EU). Similarly, there are no data comparing the status in EU countries with those that are not part of the EU.

The objectives of this study were to collect data on the regular working hours of pediatric residents during residency and to gather information regarding the enforcement of European regulations on this issue in European countries. We also endeavored to understand whether changes have been made in the residency program to meet these regulations and how they have affected residency programs and the workload of senior pediatricians.

EU European Union

Methods

In cooperation with the Scientific Advisory Board of the European Pediatric Association,[4] we sent questionnaires to 25 presidents of national pediatric associations and societies in Europe (17 from countries in the EU and 8 from countries not in the EU). The questionnaire included questions about work arrangements and night shifts on weekdays and weekends, questions regarding the maximum weekly working hours, as well as questions about the extent to which changes in regulation in this area have affected the residency program in recent years.

Results

The regulations and conditions of night shifts and maximal weekly work hours in a week differed considerably between EU and non-EU countries (**Table II**; available at www.jpeds.com). The fulfillment of EU regulations was not complete in all 17 EU countries reporting to the questionnaire, eg, the night shift duration exceeded 11 hours in 92% of EU responders (**Table II**). Five of 17 presidents of national pediatric associations reported that EU regulations had positively influenced the quality of their residency program, 4 reported no changes, and 2 reported a worsening of residency quality; no data were reported from 6 of 17 countries. However, the residency program had to be modified to overcome the effect of changing shift regulations in one-third of countries, eg, by increasing the number of residents. Two-thirds of countries reported that the new regulations had led to an increased workload for senior pediatricians.

Discussion

The answers to the questionnaires revealed that there were considerable differences between EU and non-EU countries with regard to the existence of regulation and the conditions of night shifts and maximal weekly working hours. However, even

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among nations in the EU, the fulfillment of EU regulations was not complete, for example, the shift duration was longer than 11 hours in 92% of EU responders. Even the regulation regarding working following a night shift was not well implemented, and 31% of responders from EU countries and 50% of responders from non-EU countries stated that the residents continued to work a regular working day after the night shift.

Even though shift regulations were enacted to improve quality of life of the residents and to improve the quality of the residency experience and patient care, the effects of these regulations on these parameters were ambiguous, as reflected in the literature and from responses to our questionnaire. For example, of 11 responders from EU countries that fulfill the regulations, only 5 stated that regulations have improved the quality of residency but 6 stated that quality has not changed or was worse. These regulations have brought about changes in the routine work of pediatric departments. For example, the implementation of regulations also has increased the work burden of senior pediatricians according to two-thirds of responders.

Our aim was to inform healthcare officials regarding the need to optimize the work burden of young residents during their postgraduate training. The partial compliance with EU regulations suggests that either the work force was not sufficient to fulfill these regulations or other issues, such as continuity of care or scheduling and planning the working hours, have surpassed the commitment to these regulations.

Night shift regulations have been a continuous issue and a source of dissatisfaction for decades and a reason for "rebellions" among residents—as seen recently in Israel, when residents applied to the supreme court to shorten the duration of night shift hours.[5] Issues such as continuity of care, having enough hours of supervision, and flexibility of working hours challenge values such as "sane" working conditions, physician burn out, and the wellbeing of the residents. In addition, differences among the various generations involved in routine hospital assignments with different attitudes of each generation toward work, responsibility, and lifestyle may account for some misunderstandings among the different "players."[6,7]

Our data indicate that these issues are far from reaching a consensus. Research regarding the effects of the various interventions and the reasons for deviations from these regulations may assist in creating a convention that could fit the various, and opposing needs and interests, of young patients, young pediatricians, experienced pediatricians, and hospital managers. ■

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References

1. Friedman RC, Bigger JT, Kornfeld DS. The intern and sleep loss. N Engl J Med 1971;285:201-3.
2. Bolster L, Rourke L. The effect of restricting residents' duty hours on patient safety, resident well-being, and resident education: an updated systematic review. J Grad Med Educ 2015;7:349-63.
3. Directive 2003/88/EC of the European Parliament and of the Council of 4 November 2003 concerning certain aspects of the organisation of working time (Official Journal L 299, 18/11/2003 P. 0009-0019).
4. EPA-UNEPSA. EPA-UNEPSA. http://www.epa-unepsa.org/?q=page/epa-council. Accessed August 31, 2018.
5. Linder-Ganz R. Medical Residents Sue State to Shorten Hospital Shifts. https://www.haaretz.com/1.5182759. Accessed August 31, 2018.
6. Johnson SA, Romanello ML. Generational diversity: teaching and learning approaches. Nurse Educ 2005;30:212-6.
7. Evans KH, Ozdalga E, Ahuja N. The medical education of generation Y. Acad Psychiatry 2016;40:382-5.
8. Asch DA, Parker RM. The Libby Zion case. N Engl J Med 1988;318:771-5.
9. Spritz N. Oversight of physicians' conduct by state licensing agencies: lessons from New York's Libby Zion case. Ann Intern Med 1991;115:219-22.
10. Accreditation Council for Graduate Medical Education. The 2011 ACGME Duty Hour Standard. https://www.acgme.org/Portals/0/PDFs/jgme-monograph[1].pdf. Accessed August 31, 2018.
11. Asch DA, Bilimoria KY, Desai SV. Resident duty hours and medical education policy—raising the evidence bar. N Engl J Med 2017;376:1704-6.

Table I. Short summary of US recommendations and regulations regarding resident working hours and supervision of residency

In the mid-1980, after the tragic death of Libby Zion, a campaign began to counter the heavy workload of internships. In 1986, a New York State jury determined that the death of Zion was linked to shifts of 36 hours in a row and due to an inadequate supervision of her quality of care and by senior physicians. The jury called for a reform of the internship program. Consequently, the New York City Health Commissioner appointed an advisory committee, known as the Bell Committee.

In 1987, the committee's findings were published, including a recommendation with a maximum of 80 weekly working hours, a maximum of 24 consecutive working hours, and a demand for the supervision by senior physicians in the hospital. Despite the controversy and opposition of the hospital community, the recommendations were incorporated into the New York State Health Code in 1989, making New York the first country to regulate its population hours.[8,9]

In 2002, the ACGME adopted new restrictions, which included in-house call no more frequently than every third night and 1 day of rest of 7 days. Night shifts will last for a maximum of 24 hours, and 4 additional hours may be required if necessary. Teaching assignments, shift hand-over (ensuring continuity of patient care), and weekly working hours should not exceed 80 hours per week on 4 successive weeks.

In July 2011, the ACGME issued new restrictions: Those in the first year of residency will work for up to 16 hours during night shifts. Residences from the second year of residency will work up to 24 hours with a recommendation to sleep after 16 hours (between 10:00 p.m. and 8:00 a.m.). It is possible to stay for up to a maximum of 4 additional hours after night shift for the continuation of the treatment and for the training of the resident. However, it is possible to stay longer when treating unstable patients, providing social assistance to patients or their families, or for the purpose of professional study and understanding of clinical events.[10]

In 2017, the ACGME issued new rules maintaining an 80-hour-per-week cap on residents' work, averaged over 4 weeks, but extending the permissible work shifts for first-year residents from 16 to 24 hours and permitting more within-shift flexibility as long as weekly duty-hour limits are not expanded.[11]

ACGME, Accreditation Council for Graduate Medical Education.

Table II. Responses from national delegates of 25 European countries to a questionnaire on night shifts and weekly working hours of young pediatric residents undergoing postgraduate training in children's hospitals

1. Do you have national regulations for night shifts of residents in hospitals?
   - EU countries responders: Yes = 88%
   - Non-EU responders: Yes = 25%
2. Do you know the regulations of night shifts of the EU?
   - EU countries responders: Yes = 64%
   - Non-EU responders: Yes = 13%
   - 2A. If yes, do your national regulations comply with those of the EU:
     - Yes = 90% in those countries declaring that they know the EU regulations
3. According to your national regulations, is there a maximum duration for weekly working hours of residents?
   - EU countries responders: Yes = 76%
   - Non-EU responders: Yes = 14%
   - 3A. If yes, how many hours are allowed per week
     - EU countries responders: Median = 48 hours
     - Non-EU responders: Lack of responses
4. According to your national regulation, is there a maximum total duration of a night shift following the work on a normal weekday?
   - EU countries responders: Yes = 81%
   - Non-EU responders: Yes = 85%
   - 4A. If yes, how many hours?
     - EU countries responders: Mean = 18 hours
     - Non-EU responders: Mean = 19 hours
5. Do the residents continue to work the next day after having worked a night shift?
   - Non-EU responders: Yes = 50%
   - All responders: Yes = 38%
6. According to your national regulation, is there a maximum total duration of a shift on a weekend?
   - All responders: Yes = 88%. No difference between EU and non-EU countries.
   - 6A. If yes, how many hours?
     - All responders: median = 24 hours. No difference between EU and non-EU countries.
7. Does your hospital comply with these regulations?
   - All responders: Always = 70%; Most of the time = 20%; Sometimes = 10%
8. When analyzing 100 night shifts of pediatric residents in your hospital, please give an estimate on the percentage of nights that the doctors will be able to get some sleep of: (1/2/3/4/none)
   - No sleep: mean 29%
   - 1-hour sleep: mean = 13%
   - 2-hour sleep: mean = 18%
   - 3-hour sleep: mean = 20%
   - 4-hour sleep: mean = 20%
   - Total = 100%

An Appeal for Implementing Social Assistance and Welfare Programs for European Children Challenged by Parental Loss

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The loss of a parent is a severe crisis for children and adolescents. According to the life cycle model, the crisis originates from different roots and causes and leads to a large spectrum of acute psychomental and physical effects on child health and later may induce long-term effects on adult health. There are several scenarios that involve the separation of children and adolescents from their mothers and fathers (**Table I**; available at www.jpeds.com), and there are short- and long-term effects of parental loss on health (**Tables II** and **III**; available at www.jpeds.com).

Sociology defines the family as a group that is made up of people who are related to each another by blood and legal bonds. In the history of humankind, family and clan structures are a resilient social unit that has adapted successfully to the external threats and to the changing world. However, the structure of families differs from culture to culture and from one nation to the other. Ongoing research in family sociology has expanded our understanding of the diversity of family life according to nations, regions, classes, ethnic groups, and religions. In the affluent Western world, there have been many reports on the fact that traditional types of families are in decline. In a 2013 survey of the European Paediatric Association–Union of National European Paediatric Societies and Associations (EPA-UNEPSA) on new types of families, pediatricians from 26 European countries reported the alarming signal that ~20% of all children were born out of wedlock, one-fifth of families lived in poverty, and 50% of all mothers with children younger than 3 years were working outside their own home, leaving the care of their young children to nurseries, other family members, or babysitters.

The authors of this commentary, many of whom are part of a working group on social pediatrics supported by some of the European national pediatric societies member of EPA-UNEPSA, conclude that more studies are needed to cross the boundaries between disciplines, for example, looking at the inter-relationship of family life and child health and how parental loss is affecting the micro and macro level of child healthcare service systems. Therefore, this article aims to alert pediatricians to the impact of parental loss on child health and wellbeing. It emphasizes the importance of implementing preventive and social support programs for achieving health promotion and health-protective effects.

Parental Loss during Childhood and Adolescence as a Negative Impact for Health, General Health Care Services, and Pediatric Care

Whatever the roots and causes may be, parental loss is a negative stress factor[1,2] on the health and well-being of children, thus playing a negative role in the mental and physical development if coping mechanisms such as resilience fail to establish a new balance between stress and stress management. The sudden loss of a parent triggers grief responses leading to symptoms of sadness, anxiety, lack of concentration ability, poor impulse control, episodes of psychosomatic pain, etc. These symptoms may persist after early grief coping and may lead to delayed consultations in the practices of pediatricians and psychologists. These symptoms are summarized by the term "vulnerable children with new morbidities." In the EPA-UNEPSA survey on new medical problems, pediatricians from 10 of 26 countries listed new morbidities as among the top 3 pediatric challenges and reported an increase of young patients attending their ambulatory care unit for behavioral disorders. It is unclear to what extent these patients suffered from symptoms that were related to parental loss or "incomplete" families. Parental loss during childhood has been associated with a number of psychiatric disorders, including anxiety,[3] a spectrum of personality disorders,[4] addiction to drugs and alcoholism,[5] and most notably depression.[5,6] The event of a parent's death during childhood is a traumatic experience that can generate difficulties in adaptation to normal life, and it can induce psychopathologic problems occurring throughout the developmental age channels until adulthood.

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Association of Parental Loss during Childhood with Subsequent Adult Mental Disorders

Recent studies described psychobiological alterations related to parental loss suffered in childhood, which could manifest their effects later in life.[7-9] There is a wide range of findings reported regarding the impact of parental loss on the mental health of individuals through their life and the existence of early "windows of vulnerability" in certain areas of the developing brain that are more susceptible to adversity than other areas.

Developmental and psychodynamic theories[10,11] have indicated childhood parental loss as a key element in the genesis of affective psychopathology. This relation is still being debated. Although a large number of clinical studies have shown that early parental death and prolonged parental separations are associated with depression and anxiety disorders,[10,11] other studies have reported that mental disorders are not related to childhood parental death or separation.[2] This suggests that methodologic differences, including the difficulty in identifying a commonly accepted definition of parental loss, multiple factors contributing to it (ie, death, desertion, prolonged separations, divorce), and the composition of control groups, play a role in preventing conclusive analyses.[12]

Challenges and Chances for Health Services to Offer Preventive and Therapeutic Care

The likelihood of experiencing a different impact from parental loss varies according to locality and social circumstances.[13,14] Ethnicity, social positioning, and economic circumstances have received little attention in previous surveys.[15] For instance, migration, poverty, and discrimination may increase the children's vulnerability when dealing with parental loss. The complexity of confounding factors explains the absence of conclusive analyses on the causal role of single factors such as the loss of a person. Moreover, the scarcity of evidence-based data on long-term outcomes[14] makes it difficult to develop guidelines for supporting healthy children with parental loss and for treating symptomatic children with subsequent disturbances.

The loss of parents or family members is a major stressful experience for children.[3] If symptoms of grief and pain coping are neglected and left untreated, the damage and suffering experienced by individuals during childhood may persist and amplify during their adult life.[16] Different theoretical frameworks and psychosocial interventions have been proposed to offer adequate care,[16] including pharmacotherapy, self-help, family interventions, support groups, as well as coaching in community resilience groups.[16]

The therapeutic interventions in adult age were performed by a variety of professionals (eg, general practitioners, social workers, psychologists, nurses, pastoral teams) using different methods (eg, individual or group therapeutic meetings, home visiting, the Internet, telephone).[16] These interventions were moderately effective.[17] By contrast, pediatric support programs that targeted treating high-risk children as early as possible after parental loss were more effective.[17] In summary, some studies indicated the importance of respecting the short time frame for initiating the interventions, eg, less than 1 year after the parental loss. Fewer studies suggested a time interval of 5 years to be sufficient in establishing effective supportive interventions.

Primary care pediatricians should be the gatekeepers and coordinators of multidisciplinary teams including members of local public healthcare services, such as school teachers, social workers, career advisers, and other similar figures in planning social programs of interventions, which should be initiated as soon as possible after parental loss.[18,19] Preventive and early psychological and social interventions for bereaved children and their parents can lower acute distress and prevent future psychopathology, such as posttraumatic and complicated grief effects.[20] A "family-oriented approach" of the support programs should unite the whole family, the pediatrician, and a multidisciplinary team, preferably within the neighborhood of the patients.[21] ■

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References available at www.jpeds.com

References

1. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 2009;10:434-45.
2. Cerniglia L, Cimino S, Ballarotto G, Monniello G. Parental loss during childhood and outcomes on adolescents' psychological profiles: a longitudinal study. Curr Psychol 2014;33:545-56.
3. Otowa T, York TP, Gardner CO, Kendler KS, Hettema JM. The impact of childhood parental loss on risk for mood, anxiety and substance use disorders in a population-based sample of male twins. Psychiatry Res 2014;220:404-9.
4. Pert L, Ferriter M, Saul C. Parental loss before the age of 16 years: a comparative study of patients with personality disorder and patients with schizophrenia in a high secure hospital's population. Psychol Psychother 2004;77:403-7.
5. Kendler KS, Sheth K, Gardner CO, Prescott CA. Childhood parental loss and risk for first-onset of major depression and alcohol dependence: the time-decay of risk and sex differences. Psychol Med 2002;32:1187-94.
6. Berg L, Rostila M, Hjern A. Parental death during childhood and depression in young adults—a national cohort study. J Child Psychol Psychiatry 2016;57:1092-8.
7. Herberth G, Weber A, Röder S, Elvers HD, Krämer U, Schins RP, et al. Relation between stressful life events, neuropeptides and cytokines: results from the LISA birth cohort study. Pediatr Allergy Immunol 2008;19:722-9.
8. Kraft AJ, Luecken LJ. Childhood parental divorce and cortisol in young adulthood: evidence for mediation by family income. Psychoneuroendocrinology 2009;34:1363-9.
9. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry 2016;21:642-9.
10. Bowlby J. Separation: anxiety and anger. New York: Basic Books; 1973.
11. Bowlby J. Loss: sadness and depression. New York: Basic Books; 1980.
12. Tyrka AR, Wier L, Price LH, Ross NS, Carpenter LL. Childhood parental loss and adult psychopathology: effects of loss characteristics and contextual factors. Int J Psychiatry Med 2008;38:329-44.
13. Ellis J, Dowrick C, Lloyd-Williams M. The long-term impact of early parental death: lessons from a narrative study. J R Soc Med 2013;106:57-67.
14. Mitchell R, Dorling D, Shaw M. Inequalities in life and death: what if Britain were more equal? Bristol: Polity Press and Joseph Rowntree Foundation; 2000.
15. Amato PR. The consequences of divorce for adults and children. J Marriage Fam 2000;62:1269-87.
16. Pereira M, Johnsen I, Hauken MA, Kristensen P, Dyregrov A. Early interventions following the death of a parent: protocol of a mixed methods systematic review. JMIR Res Protoc 2017;6:e127.
17. Currier JM, Holland JM, Neimeyer RA. The effectiveness of bereavement interventions with children: a meta-analytic review of controlled outcome research. J Clin Child Adolesc Psychol 2007;36:253-9.
18. Black D. Childhood bereavement: distress and long term sequelae can be lessened by early intervention. BMJ 1996;312:1496.
19. Pettoello-Mantovani M, Ehrich J, Romondi A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424.e2-426.e2.
20. Kirwin KM, Hamrin V. Decreasing the risk of complicated bereavement and future psychiatric disorders in children. J Child Adolesc Psychiatr Nurs 2005;18:62-78.
21. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12. Article number 12.

Table I. Major roots and causes for parental loss affecting children and adolescents

Selection of reasons for transient, prolonged, or permanent absence of parents from the family
- Working place of mothers or fathers differing from the place of residence of the family
- Fathers and mothers working in the military and going to war
- Fathers and mothers migrating to other countries because of political crises
- Imprisonment of mothers or fathers
- Long-term hospitalization of parents according to diseases, alcoholism, and drug addiction
- Divorce of parents
- Death of mother and/or father
- Other

Selection of reasons for transient, prolonged, or permanent separation of children and adolescents from parents
- Behavioral disorders of the child requiring foster care in other families or in institutions
- Boarding school
- Other

Table II. Selection of short- and long-term effects of parental loss on health of all family members

- Learning disabilities
- Inattention
- Impulsivity
- Psychosocial growth retardation
- Anxiety
- Depression
- Sadness
- Anxiety
- Low concentration ability
- Lack of endurance
- Poor impulse control
- Episodes of psychosomatic pain
- Dysthymic disorder
- Panic disorders
- Social phobia
- Obsessive–compulsive disorder
- Substance disorders

Table III. Short- and long-time effects of separation and loss on children's development

First year (0-12 mo)	Short-term effects • Psychological regression related to dependency needs. • Loss of sense of security and trust in the adults' availability. • Pause or discontinuing acquisition in the process of sequencing information and in the basic cause–effect learning process, related to the change in caregivers and the introduction of new routines. Long-term effects • False or wrong expectations of the child toward life due to dependency needs not satisfied (persistence of feelings that life owes him/her). • Difficulties in meeting the dependency needs of others. • Impaired trust in others. • Learning disabilities, secondary to unclear analysis of cause–effect inputs (possibly also developing later in time during preschool and elementary school years).
Toddlerhood (13-36 mo)	Short-term effects • Disruption in the balance between age appropriate dependency and independency. • Disruption in the typical children's "ego" development, consequential to an interference with the child identity, due to possible changes in family position. • Possible psychological and behavioral regression and loss of recently acquired skills, due to scarcity of internal and external stimuli related to the social changes. • Temporary block in the normal acquisition of language, particularly if the lost parent or caregiver was the child's figure of reference. Long-term effects • Developing a role of victim or victimizer to better cope with the new situation. • Signs revealing an initial development of difficulties in personality control. • Disruption in ego development, with increasing risk of "borderline personality" problems. • Lack of self-awareness. • Moderate-to-complicated language problems. • Possibility in adulthood of developing an inflexible, rigid personality unable to deal appropriately with aggressive impulses.
Preschool period (37-72 mo)	Short-term effects • Development of a personal world of egocentric magical thinking that generates a misunderstanding for the causes of the separation and loss of the familiar figure. • Displaying indiscriminate attachment to adults and developing conflicting feelings about the "good" and "bad" qualities related to themselves and others. Long-term effects • Development of a sense of guilt in reference to the loss suffered, due to the combination of magical thinking and a "good vs bad" inner conflict. • Relating the loss suffered to the wanting of the parent of the opposite sex all to him/herself (combined effects of the magical thinking and possible presence of Oedipal conflicts), with the risk of developing sexual identify issues. (This occurrence may be amplified in cases of sexual abuse.) • Charging him/herself with the responsibility for the loss of the familiar figure.
Elementary school years	Short-term effects • Reduction of psychological and physical energies needed for attending the usual tasks of this age, due to the unresolved grieving process. • Development of problem behaviors with their peers, due to the a progressive awareness of possible differences between themselves and the peers. Long-term effects • Development of psychological and behavioral problem related to the internalization of conscience. • Development of a long-term series of disruptions in schooling and peer relationships throughout adulthood.
Adolescence	Short-term effects • Disruption of the classical tasks of psychological separation during the adolescence years usually "practiced" to come up against and oppose parental figures, who are nonetheless consistently available and caring. • Developing a sense of impotence related to the feeling that a large part of the decisions about his or her life are out of their control (control issues). Long-term effects • Risk of destructive conducts leading to suicidal tendencies or to a variety of antisocial behaviors, due to the feeling perceived by the individuals that they have lost all control over their life.

How to Calculate the Risk of Shortage and Surplus of Pediatric Workforce?

Jochen Ehrich, MD, DCMT (London)[1,2], Jana Fruth, PhD[3], Danielle Jansen, PhD[4], Andreas Gerber-Grote, MD[1,5], and Massimo Pettoello-Mantovani, MD, PhD[1,6]

In the first part of this series debating the required pediatric workforce in different European child healthcare systems, the European Paediatric Association (EPA) presented the equations for calculating the need of annual number of newly certified pediatricians in the different European national contexts, and for keeping their national pediatric workforce stable.[1] This article provides further equations for calculating dynamically the risk of shortage and surplus in numbers of pediatricians, and its impact on child healthcare services. We also debate how to develop and to provide sustainable pediatric services for European children by training a nationally tailored pediatric workforce, competent to undertake the child healthcare able to meet the expectations of the families of healthy, sick, or children with disabilities.

Selection of Demographic Factors Influencing the Need for Training Pediatricians

Young pediatricians working in hospitals complained about an inordinately high work load during and after normal working hours and about unsatisfactory working conditions with an increasing administrative burden and decreasing clinical and research pediatric activity.[2] Considering increasing treatment numbers of children in practices and hospitals, because of an increased individual demand for healthcare, the slight increase of pediatric workforce in some European countries may not lead to a reduced work load for individual pediatricians. The median age of primary care pediatricians increased to almost 55 years in some countries like Germany and Italy. Thus, nearly 50% of all pediatricians working in private practices may plan to retire from their practice over the next 5-10 years. Furthermore, an increasing number of employed female pediatricians in different European countries decided against a full-time job because of several factors, including significant cultural, social, and economic constraints for female pediatricians, therefore, emphasizing the likely persistence of sex disparities and unequal opportunities to unrestricted accessibility to work in pediatrics.[3] In 2016, the proportion of pediatricians working part-time ranged from 0% to 15% in a selected group of 10 European countries. Politicians should decisively acknowledge this connection between more part-time work and fewer medical working hours. Therefore, the number of training places in pediatrics must be adequately planned and increased if necessary.

EPA	European Paediatric Association
UNEPSA	Union of National European Paediatric Societies and Associations

This means that there is an economic question of needs and that it cannot be left solely to a market system of supply and demand. The migration of pediatricians from Eastern European countries across borders to fill the gaps in Western European countries, particularly within the European Union 28 where the circulation of professionals is unrestricted, appears often to be unfair for those countries that have paid for the training of pediatricians. Other factors influencing the calculation of the need for training pediatricians seem to be less critical (eg, the unemployment rate of pediatricians in 2016 was almost 0 in most West European countries). Furthermore, the percentage of pediatricians changing their profession or having no intention to work was insignificant.

Calculating the Adequate Balance of Annually Trained and Retired Pediatricians

The number of practicing pediatricians in the various nations could stay stable throughout the years, providing that the number of annually certified young pediatricians will match exactly the number of annual retirements. Whereas the number of newly certified pediatricians (NewPed) and their median age at certification (CerAge) should easily be available by the national medical associations at the end of each year, it may be more complicated to estimate the number of retiring pediatricians several years in advance because of variable retirement ages (RetAge).

Therefore, we propose to use a model of 2 equations for estimating the number of retiring pediatricians (RetPED) at intervals of 1, 5, and 10 years, which may allow for a prospective planning. National medical associations are able to calculate the median age of all practicing pediatricians (MedAge). This statistical data enables calculating the number of expected RetPED in 2 steps (**Table I**; available at www.jpeds.com). The RetAge in Europe ranges between 60 and 70 years with a lower age for female pediatricians also differing across jurisdictions. The median age of all practicing pediatricians (MedAge) can be annually calculated by National Medical Associations and/or the National Institutes of Medical Statistics as well as the

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median age of newly certified pediatricians (NewAge). For instance, in a simulation case where RetAge is equal to 65 years, MedAge is equal to 55 years and NewAge is equal to 30 years, one- half of all pediatricians will have to work 10-35 more years whereas the other one-half will have to work for another 1-10 years only.

Annually Retiring Pediatricians (Step 1)

Assuming that the numbers of annually certified and retired pediatricians do not change and that the age of all pediatricians above the age of MedAge is uniformly distributed, the number of annually retiring pediatricians (RetPed) can be calculated by equation 1 shown in **Table I**.

Estimated Total Number of All Practicing Pediatricians (Step 2)

The estimated total number of all practicing pediatricians after a specific number (k) of years (PracPedk) is given by equation 2 shown in **Table I**. For instance, using the same figures used in the simulation case of step 1 (**Table I**), if RetPed is equal to 600 and NewPed is equal to 400, the annual deficit of pediatricians will be 200, thus, accumulating to 1000 missing pediatricians after 5 years if the number of trained pediatricians is not adjusted accordingly.

Developing and Providing Sustainable Child Healthcare Services for European Children by Training Nationally Tailored Pediatric Workforces

The number of lifelong working years is defined by the period of full-time work without interruptions between certification as a general pediatrician and the age of retirement. This means that the above algorithm on a stable number of pediatricians will only be realistic if all pediatricians are working full-time without intermittent longer leave of absence such as parental leave, etc. Furthermore, the proportion of immigrants/emigrants of all annually trained pediatricians will have an influence on the number of all practicing pediatricians. In addition, there are other variables, such as career changes, influencing the calculations. These variables, however, will only matter if the new generation of pediatricians is developing new working habits differing from the traditional ones. Moreover, digitalization and other newly developed medical technologies may lessen the number of required pediatricians in the near future. Likewise, expanding solo practices for community care by multidisciplinary teams including nonpediatric care givers such as nurse practitioners will contribute to the above mentioned demand for a nationally tailored replacement of retired pediatricians.

One way of adding the possibly influencing variables identified by the EPA/Union of National European Paediatric Societies and Associations (UNEPSA) (**Table II**; available at www.jpeds.com) to the equation 2 is to calculate the estimated or calculated gradual influence by specific factors, to be multiplied with numbers of PracPed, NewPed, and RetPed. The factor of 1 indicates no influence. A factor of 0.9 will indicate a negative influence of 5% reduction of the future number of any type of pediatrician. Vice versa a factor of 1.1 will indicate a 5% positive influence on the respective numbers of pediatricians.

Part-Time Work: A Confounding Variable Influencing the Equation for Developing and Providing Stable Child Healthcare Services for European Children

Several variable factors (**Table II**) may influence the calculation for the required number of certified pediatricians in different European countries, which should be taken in account when applying the equations proposed to the various local contexts. Among them, the part-time factor plays an important role, which may possibly influence the basic equations 1 and 2 used to calculate the pediatric workforce needed in a given nation. In this case, a model of 3-step corrective equations can be used to minimize the impact of this factor on the final figure.

For instance, using the same example and figures as in steps 1 and 2, and assuming the number of PracPed to be 12 000, RetPed equal to 600, and NewPed equal to 400, in the event that 20% of all NewPed are planning to work half-time during the next 5 years and 100% of RetPed have worked full-time, then equation 2 (**Table I**) must be adapted by a part-time factor (partF). This factor corrects the total number of full-time and half-time pediatricians to a total number of (virtual) full-time pediatricians (**Table III**, equation A, B, and C; available at www.jpeds.com).

Conclusions

The EPA/UNEPSA proposes a functional method for possibly calculating the adequate balance of annually trained and retired pediatricians, aiming at keeping the number of practicing pediatricians stable, yet responding to the needs of pediatric workforce in the different European countries, which are typically characterized by diverse socioeconomic contexts and different healthcare systems. Furthermore, EPA/UNEPSA emphasizes the importance to develop sustainable national child healthcare service systems for European children. One goal could be obtained by training an adequate nationally tailored pediatric workforce. Compatibility and consistency could be determined by the use of selected factors to be applied to the equations proposed. These were satisfactorily tested in different European countries by a recent EPA/UNEPSA internal pilot survey. A further report will describe the application of equations developed in an expanded survey made by the EPA/UNPSA member societies and association. ■

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References available at www.jpeds.com

References

1. Ehrich J, Pettoello-Mantovani M. Never ending stories: the loop in pediatrics. How many pediatricians need to be trained in European countries to keep the pediatric workforce stable? J Pediatr 2018;196:332-3.
2. Rao SK, Kimball AB, Lehrhoff SR, Hidrue MK, Colton DG, Ferris TG, et al. The impact of administrative burden on academic physicians: results of a hospital-wide physician survey. Acad Med 2017;92:237-43.
3. Cull WL, Mulvey HJ, O'Connor KG, Sowell DR, Berkowitz CD, Britton CV. Pediatricians working part-time: past, present, and future. Pediatrics 2002;109:1015-20.

Table I. Two-step calculation of the balance between annually trained and retired pediatricians

Equation 1 (annually retiring pediatricians):

$$\text{RetPed} = \frac{\text{PracPed}}{2 * (\text{RetAge} - \text{MedAge})}.$$

with PracPred representing the number of all practicing pediatricians.

Example: RetAge = 65 y, MedAge = 55 y, and NewAge = 30 y
Considering the numbers above and assuming the number of all practicing pediatricians equals 12 000, the number of annually retiring pediatricians will be:

$$\frac{12\,000}{2 * (65 - 55)} = 600.$$

Equation 2 (practicing pediatricians after *k* y):

$$\text{PracPedk} = \text{PracPed} + k * (\text{NewPed} - \text{RetPed}).$$

Example: if RetPed = 600 and NewPed = 400, when applying the numbers in equation 1 into equation 2, the total number of pediatricians after 5 years will be:

$$12\,000 + 5 * (400 - 600) = 11\,000.$$

*Results are based on the simulation case described in **Table III**.

Table II. List of variable factors identified by EPA/UNEPSA to be influencing the equations for calculating the required number of certified pediatricians in European Nations

	Variables	Mathematic terms
(1)	Actual number of all practicing pediatricians working full time	PracPed
(2)	practicing pediatricians after (k) years	PracPedk*
(3)	Number of annually certified pediatricians	NewPed
(4)	Number of required new pediatricians to keep the number of practicing pediatricians stable	NewPed*
(5)	Number of annually retiring pediatricians	RetPed
(6)	Median age of all practicing pediatricians	MedAge
(7)	Median age of newly certified pediatricians	NewAge
(8)	Median age of retiring pediatricians	RetAge
(9)	Part-time working factor	partF
(10)	Percentage of full-time pediatricians	PercFull
(11)	Percentage of half-time pediatricians	PercHalf

*Results are based on the simulation case described in **Table III** and do not represent original data.

Table III. Corrective 3-step equations to minimize the influence of part-time factor on the calculation for developing stable child healthcare services for European children

Step1)
Equation A (part-time factor):

$$\text{partF} = \frac{\text{PercFull} + 0.5 * \text{PercHalf}}{100}$$

with PercFull being the percentage of full-time pediatricians and PercHalf the percentage of half-time pediatrians respectively.

Example: Assuming the number of PracPed = 12 000, RetPed = 600, newly certified pediatricians (NewPed) = 400.
If 20% of all NewPed are planning to work half-time during the next five years and 100% of RetPed have worked full-time, the part-time factor of

$$\frac{80 + 0.5 * 20}{100} = 0.9$$

Step 2)
To determine the number of full-time equivalents of NewPed, the number of NewPed must be multiplied by partF = 0.9. This is applied in the following adapted equation for the practicing pediatricians after *k* years (PracPedk*):
Equation B (equation 2 adapted for part-time working new pediatricians):

$$\text{PracPedk*} = \text{PracPed} + k * (\text{partF} * \text{NewPed} - \text{RetPed})$$

Example: for the simulation case proposed in step 1, the total number of pediatricians after 1 y will be:

$$12\,000 + 1 * (0.9 * 400 - 600) = 11\,760.$$

Step 3)
To obtain the number of annually certified pediatricians necessary to keep the total number pediatricians at the actual height of 12 000, Equation B has to be rearranged to solve for NewPed:
Equation C (equation B adapted to calculate the number of required new pediatricians to keep the number of practicing pediatricians stable):

$$\text{NewPed*} = \frac{1}{\text{partF}} * \text{RetPed},$$

Example: in the simulation case of steps 1 and 2, after one year the number of required pediatricians is:

$$\frac{1}{0.9} * 600 \approx 667.$$

Thus, about 667 newly certified pediatricians (20% of them working half-time) are necessary to replace 600 RetPed full-time working .
If, however, 50% instead of 20% of all newly certified pediatricians are planning to work half-time, partF will be 0.75. Then for the example, after 1 y we need a number of:

$$\frac{1}{0.75} * 600 = 800$$

newly certified pediatricians (50% of them working half-time) to replace 600 RetPed full-time working. This means that 400 pediatricians are working full-time and 400 half-time, however, the latter 50% provide only 33.3% of the total care.
If, however, 50% of the total work load should be performed by half-time working pediatricians the required total number of pediatricians would be 900 (300 full-time and 600 half-time). This means that two thirds of all pediatricians would work half-day and do 50% of the total work of pediatricians.

*Results are based on the simulation case described in **Table III** and do not represent original data.

Food Insecurity and Children's Rights to Adequate Nutrition in Europe

Massimo Pettoello-Mantovani, MD, PhD[1,2], Jochen Ehrich, MD, DCMT[3,4], Michele Sacco, MD[5], Pietro Ferrara, MD[6], Ida Giardino, MD[7], and Tudor Lucian Pop, MD[2,8]

Advocating for European children's rights to health and well-being has characterized the wide spectrum of efforts of the European Pediatric Association-Union of National European Pediatric Societies and Associations (EPA/UNEPSA) since its founding in 1976. These activities aim to intensify the learning processes of child health care service systems across European borders. Food security has been defined as a situation in which all community residents can obtain a safe, culturally acceptable, nutritionally adequate diet through a sustainable food system that maximizes self-reliance and social justice.[1] Food insecurity, which refers to a lack of food access based on financial and other resources, is a never-ending issue impacting especially the health of young individuals and their development. Inadequate nutrition negatively influences children's well-being by hampering the accomplishment of their complete physical, mental, and social comfort. The aim of this commentary is to raise pediatricians' awareness on the emerging issue of children's food insecurity and its risks in Europe.

Definition of Food Insecurity and Its Prevalence in Europe

The broad-based and accepted definition of household food insecurity is the limited or uncertain availability of nutritionally adequate and safe food, or having to acquire foods in socially unacceptable ways.[2] Conditions strictly related to food insecurity include hunger, undernutrition, overnutrition with low-quality food, and a disordered intake of macronutrients and micronutrients (malnutrition), as well as physical harms (chronic disease) and psychological harms (personal, family, and social disturbances).[3]

The prevalence of food insecurity has increased during recent years in several European countries.[4] To measure moderate to severe food insecurity in different global areas, a 2017 study performed by the United Nations Children's Fund (UNICEF) used the Food Insecurity Experience Scale indicator, an experience-based metric that reported food-related behaviors on the inability to access food owing to resource constraints.[4,5] In the 28 European Union (EU) countries, the regional estimates of food insecurity among households with children <15 years of age showed a Food Insecurity Experience Scale prevalence of 18% of households experiencing a moderate (4%) to severe (14%) inability to access food, and 20% prevalence of households reporting not enough money to buy food.[6] In the European Commonwealth of Independent States identifying former parts of the Soviet Union, the same UNICEF study reported a Food Insecurity Experience Scale prevalence of 17% of households with moderate (2%) to severe (15%) inability to access food and 28% prevalence of households with an economic-related inability to buy food.

Data from the EU Commission database, Eurostat, also showed remarkable disparities in food security among countries of the union that were heterogeneous regarding their socioeconomic background.[7] Food insecurity began to increase in the EU between 2009 and 2012, likely as a result of the 2008 global economic turmoil. Eurostat 2015 data showed a substantial variations in food insecurity across EU countries during the posteconomic crisis period that were confirmed in later reports.[7] A high prevalence of household food insecurity, ranging from 10% to 22% and increasing, was reported for the Czech Republic, Hungary, and Slovakia. During the same period in Poland and Slovenia, the prevalence of food insecurity showed a significant (>1%) decrease, as also shown by Austria, Germany, and Portugal, where the prevalence of food insecurity ranged from 3% to 8% after a decade-long decreasing trend.[7] However, during the same period, other European countries showed a significant increase in food insecurity, ranging from 2% to 10%, which was documented in the UK, Hungary, Greece, and Italy, where food insecurity increased from 7% to 17%.

Experiencing a low unemployment rate (<6%), well-meaning citizens in Germany established food banks and soup kitchens even in small towns. The food pantry movement has some 60 000 volunteers and about 3000 food banks—a larger network than some of the supermarket chains. The number of people receiving meals for free has approximately doubled to >1 million.

Taken together, these data suggest that food insecurity in Europe is a current severe issue impacting children's well-being

EPA/UNEPSA	European Pediatric Association-Union of National European Pediatric Societies and Associations
EU	European Union
UNICEF	United Nations Children's Fund

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in a generalized way and involving several European countries regardless of their geographical location, political background, socioeconomic status, and gross domestic product.

Malnutrition and Its Relation to the Recent Economic Turmoil and Food Insecurity in Europe

An important issue related to food insecurity is malnutrition.[8] Significant changes in the diet of the European population have been observed during the past 3 decades. Data from the Food and Agriculture Organization of the United Nations indicated a shift toward a different dietetic regimen defined as the "Western diet," characterized by high content of sweeteners, vegetables, and animal fat, and a low content in grains.[8,9] The nutritional effects and general impact on the population's health are currently unclear and under study, particularly in children. Although undernutrition and micronutrient deficiencies have declined in parallel to a general increase in household incomes, malnutrition as an indicator of nutritional disorders related to the consumption of low-quality food has become an increasing health problem in children, particularly for the implication of this condition in the development of chronic diseases, such as diabetes.

Malnutrition affected each country differently, depending primarily on its level of income at the time of the onset of the 2008 economic crises, and on how the economy of various countries reacted. For instance, in the Balkan countries, a recent multivariate analysis by the Food and Agriculture Organization Regional Office for Europe emphasized the presence of significant nutritional changes in diets, as well as a more sedentary lifestyle.[10] The report correlated the changes to several socioeconomic factors and food insecurity leading to a specific nutritional profile for the countries of this geographical area, characterized by the coexistence of 3 important nutritional factors: undernutrition, micronutrient deficiency, and overnutrition (the triple burden of malnutrition).

Increasing Disparities and Inequities Influencing Food Security and European Children's Well-Being

The essential elements of children's health and well-being are ingrained in socioeconomic, political, environmental, and behavioral factors, and they depend on how these factors will progress, stagnate, or regress within the context of the local, regional, or global economy.[11] This has proven to be true for Europe when the global economic turmoil distressed the world during the past decade, producing a significant impact on national health care systems that are supposed to preside over the children's well-being throughout Europe.[12] The impact of the crisis is still being felt, and one of its significant outcomes has been the development of a large variation in the socioeconomic condition of the European countries that, in combination with specific local factors, has produced differences in the social status of various groups of population within the same country. Such disparities were generated by inequities in socioeconomic, cultural, political, and environmental conditions induced by the crisis. The widening of the gaps in parity and equality between the populations living in Europe, have created disparities in the health status of children that can be typically described as unfair, unjust, avoidable, and unnecessary.[13]

Food insecurity in Europe seems to be solidly rooted in inequities in social and environmental determinants of health, which followed the global economic turmoil of 2008 generating poverty, income inequality, environmental deterioration, and decline in educational and other resources. To this regard, the European countries have shown a substantial inability to produce effective public policies, collectively implemented and capable to efficiently contrast the decline in children well-being observed in various countries, and in particular food vulnerability as a condition that places vulnerable people at risk of becoming food insecure.

Conclusions

The number of children being marginalized in Europe is progressively increasing, and child poverty and other indicators of children's well-being, like food insecurity, position Europe in the lowest rank among the world's most industrialized nations.[14,15]

Health care equity has been identified as a fundamental component of The EPA/UNEPSA's strategic plan and agenda, which also focuses on factors such as food insecurity contributing to influence children's health and well-being in addition to health care. As part of its programs and policies addressing child health disparities through practice, advocacy, education, research, and policy formulation, EPA/UNEPSA will raise awareness of pediatricians on the escalating food insecurity in several geographical areas and populations in Europe, and on their potential role in responding. In addition to their efforts in pediatric and community settings, pediatricians can serve as advocates for policies that improve access to nutritious food. Pediatricians can therefore educate their local or national decision makers about the impact of food insecurity on children's health, education, and outcomes in relation to the life cycle model.[16] Pediatricians can network with other advocates of child health to support policies that strengthen child nutrition programs. ■

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References available at www.jpeds.com

References

1. Hamm M, Bellows A. Community food security: background and future directions. J Nutr Educ Behav 2003;35:37-43.
2. Holben DH. Position of the American Dietetic Association: food insecurity and hunger in the United States. J Am Diet Assoc 2006;106:446-58.
3. Gagné MH, Drapeau S, Melançon C, Saint-Jacques MC, Lépine R. Links between parental psychological violence, other family disturbances, and children's adjustment. Fam Process 2007;46:523-42.
4. Loopstra R, Reeves A, Stuckler D. Rising food insecurity in Europe. Lancet 2015;385:2041.
5. Food and Agriculture Organization of the United Nations (FAP). The Food Insecurity Experience Scale. http://www.fao.org/3/a-bl354e.pdf. Accessed March 18, 2018.
6. Audrey L, Pereira L, Handa S, Holmqvist G. Prevalence and correlates of food insecurity among children across the globe. Office of Research — Innocenti Working Paper WP-2017-09 | June 2017. New York: UNICEF. 2017.
7. European Union. European commission database. EUROSTAT. http://ec.europa.eu/eurostat/data/database. Accessed March 18, 2018.
8. Thompson B, Cohen MJ, Meerman J. World food insecurity and malnutrition: scope, trends, causes and consequences. In: The impact of climate change and bioenergy on nutrition. FAO United Nations Edition and Springer Science+Business Media B.V Publisher; Dordrecht, Netherlands: 2012.
9. Pettoello-Mantovani M, Guandalini S, Ecuba P, Corvino C, di Martino L. Lactose malabsorption in children with symptomatic giardia lamblia infection: feasibility of yogurt supplementation. J Pediatr Gastroenterol Nutr 1989;9:295-300.
10. Capacci S, Mazzocchi M, Shankar B, Traill B. The triple burden of malnutrition in Europe and Central Asia: a multivariate analysis. FAO Regional Office for Europe and Central Asia Policy Studies on Rural Transition No. 2013-7; 2013.
11. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:Article number 12.
12. Wolfe I, Thompson M, Gill P, Tamburlini G, Blair M, van den Bruel A, et al. Health services for children in Western Europe. Lancet 2013;381:1224-34.
13. Krieger N. A glossary for social epidemiology. J Epidemiol Community Health 2001;55:693-700.
14. Food and Agriculture Organization (FAO). Report of the world food summit. Rome Food and Agriculture Organization of the United Nations; 1996. http://www.fao.org/docrep/003/w3548e/w3548e00.htm. Accessed March 20, 2018.
15. UNICEF Office of Research. Child well-being in rich countries: a comparative overview. Innocenti Report Card 11, UNICEF Office of Research, Florence; 2013.
16. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6, e2.

Pediatric Healthcare for Refugee Minors in Europe: Steps for Better Insight and Appropriate Treatment

Reinhold Kerbl, MD[1,2], Nicole Grois, MD[2,3], Christian Popow[2,4], Eli Somekh[5,6,7], and Jochen Ehrich, MD, DCMT[5,8]

Children on the Move

In recent years, "children on the move" have become a major issue in Europe. Among more than 1 million migrants, asylum seekers, and refugees arriving in Europe in 2015, about one-third were children and about 90,000 of these were unaccompanied.[1,2] Politicians, health authorities, and health providers were equally unprepared for this challenge. As a consequence, healthcare for this group was often not adequately scheduled and until now it has been uncoordinated. In several countries, nongovernmental organizations and individual persons started initiatives for better healthcare provision for children on the move. It was requested that the health status of these children should be carefully evaluated and systematically documented, and that access to the healthcare system should be the same for refugee and resident minors. However, to date, no uniform procedures have been developed throughout Europe.

Current Sources of Information

Currently, few scientific healthcare data are available about refugee minors in Europe. A PubMed literature search performed in January 2018 combining the items "refugees/children/Europe" resulted in 742 papers with a clear publication peak in 2016 (77 papers). Most of these studies deal with children only as "subgroup," have small numbers of investigated refugee minors, were restricted to limited areas/regions, and concentrate on single aspects of health or sickness. Large-scale studies, cross-border investigations, and meta-analyses/reviews are lacking.

Medical Problems of Refugee Minors

The spectrum of medical problems of refugee minors is broad and can be divided into noninfectious somatic problems, infectious diseases, trauma/injuries, and mental health disorders. Although the occurrence of many diseases is comparable for refugee and resident minors,[3-5] others are specific for refugees and dependent on the country of origin, hygienic conditions on the move, and other flight-related circumstances.

Noninfectious Somatic Problems

Few publications focus on this issue; however, with the exceptions of malnutrition,[2] genital mutilation,[6] anemia,[7] and dental disorders,[8] there is no major difference between refugee and resident minors.

Trauma/Injuries

These may have been acquired in the country of origin owing to war and torture or on the way to Europe. Depending on the time, kind, and severity of affliction, visible residuals (wounds, scars, mutilation) show wide variation.[9]

Infections

Numerous publications describe the increased prevalence of infectious diseases in refugees. This holds true for tuberculosis, particularly for refugees from high-incidence countries,[10-13] human immunodeficiency virus/AIDS,[14,15] malaria,[16] infections caused by (multidrug-resistant) gram-negative bacteria,[17-19] parasitoses,[20] measles,[21] and tinea capitis.[22] One study reported that 19.6% of unaccompanied refugee minors had infections requiring treatment, mostly owing to *Giardia*, intestinal helminths, and schistosomiasis.[23] Additionally, an increased prevalence was reported for syphilis, different types of hepatitis, poliovirus, and other viral infections.[24-27] The clusters or outbreaks of infectious diseases may spread to the local population and may result in higher rates of these infections in susceptible individuals.

Mental Disorders

Many studies have investigated the mental health status of refugee minors; depending on the study design, applied tools, and investigated groups, different results have been reported.[20,28-38] The prevalence of mental disorders is significantly increased in refugees, peaking in a rate of 77% in a Danish study.[36] The symptoms described range from anxiety over sleep disorders, adjustment disorders, dysthymia, depression to post-traumatic stress disorder. For an assessment of mental health status, the SDQ (Strength and Difficulties Questionnaire) is a useful tool.

Immunity/Vaccination

For most refugees, no documents about previous immunizations are available. Some studies have demonstrated low

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seroprevalence for measles, mumps, rubella, and varicella immunity in children, although the majority of adult migrants revealed satisfactory measles, mumps, and rubella immunity.[39] Similarly, insufficient tetanus and diphtheria immunity was found in a German study of 6 refugee centers, and protective serum IgG levels were found in only 56% for tetanus and 48% for diphtheria.[40] Thus, the risk for these infections and for a measles outbreak seems to be increased in refugee minors.[41] For other infections like hepatitis A virus (HAV), data are controversial. Although 1 study described an outbreak of HAV in asylum seekers,[42] another publication considered this risk relatively low owing to a high anti-HAV seroprevalence.[43] Frequently, individual protection through immunization cannot be reliably assessed. As a consequence, most European countries have developed strategies to deal with refugees without immunization documents.[44] These strategies, however, vary even within a country.[45]

Age Assessment—Necessary or Unethical?

In accordance with the UN Convention on the Rights of the Child, persons under 18 years of age have special privileges of social support and medical treatment. This is the reason why many adult refugees pretend to be younger than 18 years of age and maintain to be born earlier than the required deadline. As a consequence, many of them are referred to and treated at pediatric departments. The question of whether such behavior may be justified remains a controversial issue among professionals. Although some consider the false claim of being "underage" a misuse of children's rights endangering the real minors, others consider this justified and bring the argument forward that the mental development of these persons may correspond with that of underage persons. They demand a multidisciplinary, holistic approach for age assessment.[46] Currently, age assessment is based on somatic findings—hand skeletal age, third molar mineralization, and ossification of the medial clavicular epiphysis.[47] However, these methods do not allow reliable age assessment. This is one of the reasons why some groups argue against any age assessment in minors,[2] and others request better methods and more research on this issue.[48]

The Role of Pediatricians

Pediatricians of all levels (primary, secondary, and tertiary care) are confronted with refugee minors. Some of the problems eventually arising during consultation are a consequence of communication deficits, whereas others are caused by incomplete preparedness of institutions or inadequate numbers of pediatricians to deal with this specific group. In primary care, missing health records, lack of time, language problems, and unclear governmental and/or social insurance regulations make a proper patient approach difficult. For example, specific immunizations sometimes are officially recommended, but the costs are not covered by the public healthcare system. This brings pediatricians into the dilemma whether or not to administer these vaccinations. Another important problem of daily pediatric routine is that of communication. Usually, general pediatricians have no access to medical interpreters. Thus, investigations and treatment are often limited. Patients are frequently referred to another physician or institution and the vicious circle of lacking information and documentation is prolonged.

Better Information as a Prerequisite for Appropriate Healthcare for Refugee Minors

A lack of epidemiologic data results in inappropriate treatment and preventive measures for refugees as a group. Thus, any improvement in healthcare for refugee minors has to start with routine evaluation of health status in every refugee minor and the systematic collection of health data. The following assessments are a prerequisite for further appropriate management: (1) somatic/organ status, (2) previous and chronic diseases, (3) mental health status, (4) dental status, (5) developmental status/stage of puberty, (6) immunity/vaccinations, and (7) infectious diseases.

Some regions have developed extended programs for these evaluations. However, these protocols vary even within single countries.[45] Their use is time consuming. Therefore, they are frequently neglected by those providing primary care, namely, general pediatricians and practitioners. To improve insight and treatment quality, the following steps seem to be necessary: (1) development of easy-to-use standardized evaluation protocols/forms, (2) information on their use, (3) cross-border use of these protocols/forms, and (4) systematic collection and analysis of data. Preferably, electronic documentation should be provided; however, this raises the limitations of data protection. Additionally, there is a need for well-coordinated international surveys exploring current diversities in healthcare services, evaluating deficits and demonstrating the need for European standards on age assessment, vaccination recommendations, and electronic health records.

Conclusion

A coordinated and well-planned healthcare system for refugee minors is urgently needed in Europe. Pediatricians and healthcare institutions are confronted with new medical and psychosocial challenges. National child healthcare service systems must be equipped with the appropriate tools and personnel to address the challenges of previously underrecognized medical, social, and cultural roots of the complex problems. The availability, accessibility, and affordability of adequate pediatric care will result in better health of refugee minors, and also will prevent the spread of problems deriving from minor refugees to local populations. ■

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References available at www.jpeds.com

References

1. Hodes M, Vasquez MM, Anagnostopoulos D, Triantafyllou K, Abdelhady D, Weiss K, et al. Refugees in Europe: national overviews from key countries with a special focus on child and adolescent mental health. Eur Child Adolesc Psychiatry 2018;27:389-99.
2. ISSOP Migration Working Group. ISSOP position statement on migrant child health. Child Care Health Dev 2018;44:161-70.
3. Pohl C, Mack I, Schmitz T, Ritz N. The spectrum of care for pediatric refugees and asylum seekers at a tertiary health care facility in Switzerland in 2015. Eur J Pediatr 2017;176:1681-7.
4. van Berlaer G, Bohle Carbonell F, Manantsoa S, de Béthune X, Buyl R, Debacker M, et al. A refugee camp in the centre of Europe: clinical characteristics of asylum seekers arriving in Brussels. BMJ Open 2016;6:e013963.
5. Alberer M, Wendeborn M, Loscher T, Seilmaier M. [Spectrum of diseases occurring in refugees and asylum seekers: data from three different medical institutions in the Munich area from 2014 and 2015]. Dtsch Med Wochenschr 2016;141:e8-15.
6. Dettmeyer R, Laux J, Friedl H, Zedler B, Bratzke H, Parzeller M. [Medical and legal aspects of genital mutilation and circumcision part I: female genital mutilation (FGM)]. Arch Kriminol 2011;227:1-22.
7. Zur B. [Increase in genetically determined anemia as a result of migration in Germany]. Internist (Berl) 2016;57:444-51.
8. Josefsson E. Immigrant background and orthodontic treatment need. Quantitative and qualitative studies in Swedish adolescents. Swed Dent J Suppl 2010;207:1-92.
9. Clement R, Lebosse D, Barrios L, Rodat O. Asylum seekers alleging torture in their countries: evaluation of a French center. J Forensic Leg Med 2017;46:24-9.
10. Bennet R, Eriksson M. Tuberculosis infection and disease in the 2015 cohort of unaccompanied minors seeking asylum in Northern Stockholm, Sweden. Infect Dis (Lond) 2017;49:501-6.
11. Schaberg T, Völker M, Weizsäcker K. [TB screening of pregnant women in accordance with the German protection against infection act]. Pneumologie 2016;70:777-80.
12. Helbling P, Altpeter E, Egger JM, Zellweger JP. Treatment outcomes of multidrug-resistant tuberculosis in Switzerland. Swiss Med Wkly 2014;144:w14053.
13. Schneeberger GS, Helbling P, Zellweger JP, Altpeter ES. Screening for tuberculosis in asylum seekers: comparison of chest radiography with an interview-based system. Int J Tuberc Lung Dis 2010;14:1388-94.
14. Hufton E, Raven J. Exploring the infant feeding practices of immigrant women in the North West of England: a case study of asylum seekers and refugees in Liverpool and Manchester. Matern Child Nutr 2016;12:299-313.
15. Madden HC, Phillips-Howard PA, Hargreaves SC, Downing J, Bellis MA, Vivancos R, et al. Access to HIV community services by vulnerable populations: evidence from an enhanced HIV/AIDS surveillance system. AIDS Care 2011;23:542-9.
16. Sonden K, Castro E, Tornnberg L, Stenstrom C, Tegnell A, Farnert A. High incidence of Plasmodium vivax malaria in newly arrived Eritrean refugees in Sweden since May 2014. Euro Surveill 2014;19:35.
17. Maltezou HC, Elhadad D, Glikman D. Monitoring and managing antibiotic resistance in refugee children. Expert Rev Anti Infect Ther 2017;15:1015-25.
18. Angeletti S, Ceccarelli G, Vita S, Dicuonzo G, Lopalco M, Dedej E, et al. Unusual microorganisms and antimicrobial resistances in a group of Syrian migrants: sentinel surveillance data from an asylum seekers centre in Italy. Travel Med Infect Dis 2016;14:115-22.
19. Heudorf U, Krackhardt B, Karathana M, Kleinkauf N, Zinn C. Multidrug-resistant bacteria in unaccompanied refugee minors arriving in Frankfurt am Main, Germany, October to November 2015. Euro Surveill 2016;21:30109.
20. Monpierre O, Baudino P, Rio-Rene P, Maurice S, Malvy D, Receveur MC. [Global health of unaccompanied refugee minors in Gironde (France) between 2011 and 2013]. Bull Soc Pathol Exot 2016;109:99-106.
21. Kopel E, Amitai Z, Savion M, Aboudy Y, Mendelson E, Sheffer R. Ongoing African measles virus genotype outbreak in Tel Aviv district since April, Israel, 2012. Euro Surveill 2012;17:pii: 20272.
22. Kopel E, Amitai Z, Sprecher H, Predescu S, Kaliner E, Volovik I. Tinea capitis outbreak in a paediatric refugee population, Tel Aviv, Israel. Mycoses 2012;55:e36-9.
23. Theuring S, Friedrich-Janicke B, Portner K, Trebesch I, Durst A, Dieckmann S, et al. Screening for infectious diseases among unaccompanied minor refugees in Berlin, 2014-2015. Eur J Epidemiol 2016;31:707-10.
24. Jablonka A, Solbach P, Wobse M, Manns MP, Schmidt RE, Wedemeyer H, et al. Seroprevalence of antibodies and antigens against hepatitis A-E viruses in refugees and asylum seekers in Germany in 2015. Eur J Gastroenterol Hepatol 2017;29:939-45.
25. Bottcher S, Neubauer K, Baillot A, Rieder G, Adam M, Diedrich S. Stool screening of Syrian refugees and asylum seekers in Germany, 2013/2014: identification of Sabin like polioviruses. Int J Med Microbiol 2015;305:601-6.
26. Tafuri S, Prato R, Martinelli D, Melpignano L, De Palma M, Quarto M, et al. Prevalence of Hepatitis B, C, HIV and syphilis markers among refugees in Bari, Italy. BMC Infect Dis 2010;10:213.
27. Tafuri S, Martinelli D, Melpignano L, Balducci MT, Calvario A, Bozzi A, et al. High level immunity against poliomyelitis in African and Asian refugees in southern Italy. J Travel Med 2010;17:203-5.
28. Sijbrandij M, Acarturk C, Bird M, Bryant RA, Burchert S, Carswell K, et al. Strengthening mental health care systems for Syrian refugees in Europe and the Middle East: integrating scalable psychological interventions in eight countries. Eur J Psychotraumatol 2017;8:1388102.
29. Horlings A, Hein I. Psychiatric screening and interventions for minor refugees in Europe: an overview of approaches and tools. Eur J Pediatr 2017;177:163-9.
30. Salari R, Malekian C, Linck L, Kristiansson R, Sarkadi A. Screening for PTSD symptoms in unaccompanied refugee minors: a test of the CRIES-8 questionnaire in routine care. Scand J Public Health 2017;45:605-11.
31. Arsenijevic J, Schillberg E, Ponthieu A, Malvisi L, Ahmed WAE, Argenziano S, et al. A crisis of protection and safe passage: violence experienced by migrants/refugees travelling along the Western Balkan corridor to Northern Europe. Confl Health 2017;11:6.
32. Jensen TK, Fjermestad KW, Granly L, Wilhelmsen NH. Stressful life experiences and mental health problems among unaccompanied asylum-seeking children. Clin Child Psychol Psychiatry 2015;20:106-16.
33. Eide K, Hjern A. Unaccompanied refugee children—vulnerability and agency. Acta Paediatr 2013;102:666-8.
34. Dura-Vila G, Klasen H, Makatini Z, Rahimi Z, Hodes M. Mental health problems of young refugees: duration of settlement, risk factors and community-based interventions. Clin Child Psychol Psychiatry 2013;18:604-23.
35. Bronstein I, Montgomery P, Dobrowolski S. PTSD in asylum-seeking male adolescents from Afghanistan. J Trauma Stress 2012;25:551-7.
36. Montgomery E. Trauma, exile and mental health in young refugees. Acta Psychiatr Scand Suppl 2011;440:1-46.
37. Huemer J, Karnik N, Voelkl-Kernstock S, Granditsch E, Plattner B, Friedrich M, et al. Psychopathology in African unaccompanied refugee minors in Austria. Child Psychiatry Hum Dev 2011;42:307-19.
38. Wiegersma PA, Stellinga-Boelen AA, Reijneveld SA. Psychosocial problems in asylum seekers' children: the parent, child, and teacher perspective using the Strength and Difficulties Questionnaire. J Nerv Ment Dis 2011;199:85-90.
39. Jablonka A, Happle C, Grote U, Schleenvoigt BT, Hampel A, Dopfer C, et al. Measles, mumps, rubella, and varicella seroprevalence in refugees in Germany in 2015. Infection 2016;44:781-7.
40. Jablonka A, Behrens GM, Stange M, Dopfer C, Grote U, Hansen G, et al. Tetanus and diphtheria immunity in refugees in Europe in 2015. Infection 2017;45:157-64.
41. Jones G, Haeghebaert S, Merlin B, Antona D, Simon N, Elmouden M, et al. Measles outbreak in a refugee settlement in Calais, France: January to February 2016. Euro Surveill 2016;21:30167.

42. Michaelis K, Wenzel JJ, Stark K, Faber M. Hepatitis A virus infections and outbreaks in asylum seekers arriving to Germany, September 2015 to March 2016. Emerg Microbes Infect 2017;6:e26.
43. Jablonka A, Solbach P, Happle C, Hampel A, Schmidt RE, Behrens GMN. [Hepatitis A immunity in refugees in Germany during the current exodus]. Med Klin Intensivmed Notfmed 2017;112:347-51.
44. Giambi C, Del MM, Dente MG, Napoli C, Montano-Remacha C, Riccardo F, et al. Immunization strategies targeting newly arrived migrants in non-EU countries of the Mediterranean Basin and Black Sea. Int J Environ Res Public Health 2017;14:pii: E459.
45. Wahedi K, Nost S, Bozorgmehr K. [Health examination of asylum seekers: a nationwide analysis of state policies in Germany: section sign 62 of the asylum law]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2017;60:108-17.
46. Aynsley-Green A, Cole TJ, Crawley H, Lessof N, Boag LR, Wallace RM. Medical, statistical, ethical and human rights considerations in the assessment of age in children and young people subject to immigration control. Br Med Bull 2012;102:17-42.
47. Schmidt S, Schramm D, Ribbecke S, Schulz R, Wittschieber D, Olze A, et al. [Forensic age estimation in juveniles and young adults: reducing the range of scatter in age diagnosis by combining different methods]. Arch Kriminol 2016;237:25-37.
48. Hjern A, Brendler-Lindqvist M, Norredam M. Age assessment of young asylum seekers. Acta Paediatr 2012;101:4-7.

Never-Ending Stories, the Loop in Pediatrics—How Many Pediatricians Need to be Trained in European Countries to Keep the Pediatric Workforce Stable?

Jochen Ehrich, MD, DCMT[1,2], and Massimo Pettoello-Mantovani, MD, PhD[1,3]

In today's world, looping seems to be a universal constant in many contexts—whether in music, media, politics, or healthcare. In pediatrics, the self-contained loop is an essential part of the never-ending question "What is the scope of pediatrics?" It is highly questionable whether any positive advantage exists for society when pediatricians from different countries practice endless, unresolved discussions within relatively closed circles about questions such as "what is a pediatrician?" or "how many pediatricians are needed nationally to keep the pediatric workforce stable and effective?"

This commentary aims to raise the attention of legislators and the pediatric community on the risk of a shortage of pediatricians and its negative social impact that the civil society will face shortly, particularly in the Western world. In Europe, not enough pediatric graduates are currently entering the profession to replace those who retire. The task force of the European Paediatric Association/Union of National European Paediatric Societies and Associations' (EPA/UNEPSA) Scientific Advisory Board, which is studying this circumstance, has developed an equation for estimating the needed annual number of newly trained pediatricians. This equation could be adapted to different national European contexts, assisting national stakeholders in determining the ideal annual pediatric workforce that would serve the need of the different European child healthcare systems.

Nationally Tailored and Properly Trained Pediatricians Are Needed to Sustain Child Healthcare Services in Europe

Recent articles from EPA/UNEPSA in *The Journal* have documented that more research will be necessary to harmonize the different child healthcare service systems in Europe.[1] The question remains open as to how to develop and to provide a sustainable child healthcare service to European children by training nationally tailored pediatric workforces that are competent to undertake the child healthcare expected of them by families. International ratios of pediatricians per 1000 children range between 0.38 and 0.78.[2] The number of European children per pediatrician ranges from 600 to 20 000 (= 0.05-1.6 pediatricians per 1000 children).[1] The list of the underlying causes for different numbers of caregivers is long. The same applies for the different availability, accessibility, affordability, and quality of pediatric care.[1]

The pediatric workforce consists of 3 different groups: generalists, specialists, and subspecialists. The members of each of the 3 groups usually see different groups of patients; however, there is a considerable overlap of responsibilities as well as fragmentation of care, reflecting the gaps between primary child healthcare, secondary, and tertiary health care. It is a widely accepted concept that neonates, hospitalized children, and adolescents should be treated by specially trained physicians, such as neonatologists and specialized pediatricians (**Table I**; available at www.jpeds.com). However, it is debatable whether pediatric community care should be offered by pediatricians, general practitioners (GPs), or both.[3] It was shown that >70% of children <5 years were cared for by primary care pediatricians in two-thirds of European countries. In one third of countries healthcare was provided to >70% of these children by GPs. The median percentage of children receiving primary healthcare by GPs increased with the age of the children.[4]

There is no Europe-wide accepted age of retirement for pediatricians.[5] Furthermore, there is no generally accepted upper age limit of young people who should be treated by pediatricians working in 1 of the 53 different European countries.[4] Moreover, the child population is not always stable, and several countries have reported a decrease in birth rates, which will become an important demographic factor when extrapolating the future child population and the number of required care givers. In contrast, there may be an increased demand for pediatricians because there will be an increasing number of elderly people requiring more care by GPs. Thus, the steadily growing "clientele" of GPs may have to be compensated by pediatricians who will have to look after young adults up to age 25 years. These young adults may accept to be treated by pediatric specialists in adolescent care because many young people are still depending financially on their parents due to high unemployment rates.

EPA/UNEPSA	European Paediatric Association/Union of National European Paediatric Societies and Associations
GP	General practitioner

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The Increasing Shortage of Pediatricians in Europe

In 2016, the World Health Organization predicted a worldwide physician shortage.[6] According to the surveys of EPA/UNEPSA, this development currently affects pediatric generalists and specialists in European countries.[4] The underlying multiple factors for a shortage of pediatricians have different roots and causes. Pediatric residents of European countries like Turkey feared that too few hospitals provided comprehensive services to mitigate the risks associated with night work and also claimed that long working hours might negatively affect the health of both pediatricians and their young patients. The number of daily working hours of hospital pediatricians with effective and rewarding patient contacts had gone down in many countries because of ever-increasing effort to cope with bureaucratic duties, which may result in demotivation and the decision to change from pediatric work to other occupations. The future could result in the vanishing pediatrician scientist if the time for creative research will be adversely affected.

Looking for the Right Balance of Prevention Versus Cure in Pediatrics

Currently, a looping debate is also ongoing within the scientific community, particularly following the 2008 global economic crisis, on what would be the right balance of prevention vs cure,[7,8] in terms of effectiveness and costs. In fact, the costly "wonders" of modern medicine have possibly not only had an effect on child health but also a negative effect on the countries' wealth. In some countries, depending on contingent-economics, less money may go to preventive medicine, because it is hard for preventive measures to compete with an expensive cancer medication or new technology that may affect few patients. In other countries, more money would be spent for safer roads and better support for poor families with children, including better housing, hygiene, and nutrition. Moreover, pediatricians would be reimbursed mainly for preventive practices, and curative measures would be rationed. It is not inconceivable that this development would result in less income for pediatricians, leading to the fact that fewer postgraduate students will choose pediatrics for postgraduate training.

Last but not least, there is also a need to plan the pediatric subspecialty workforce. There is no European consensus on the question of whether the training recommendations for pediatricians are meant to generate generalists or specialists or subspecialists in child healthcare. In fact, this dilemma reflects more than a semantic question. The lack of a consensus is one of the reasons for different primary child healthcare services in Europe that may be delivered either by pediatricians, by GPs/family doctors, or a mixture of both (**Table II**; available at www.jpeds.com).

Contrary to internal medicine, few private practices are offering pediatric subspecialty services for outpatients.[1] These services, such as renal or cardiac care, are mostly located in children's hospitals or highly specialized pediatric centers of competence.[9] The proportion of pediatric subspecialists in relation to the number of all pediatricians per country is not known for all European countries.

In summary, forecasting the needed pediatric workforce for a given country has become increasingly complex because of multiple parameters that are influencing the models for determining the demand for pediatricians.[2,10,11]

Human Resource Planning in Pediatrics

In 2014, an equation for pediatric workforce planning was published based on a study assumption that was adjusted with Israeli parameters.[2] The authors concluded that "since planning is a very complex task, decision makers in different health care systems need more indices to plan a cost effective pediatric workforce in their own country." Therefore, the Scientific Advisory Board of EPA/UNEPSA has worked to adjust the existing Israeli equation to other countries and according to the European diversity and complexity of child healthcare service systems (**Table III**; available at www.jpeds.com).

When calculating the total number of full-time equivalent pediatricians needed per country, there is no one-size-fits-all equation for all European countries and for all types of pediatricians. Due to the shortage of space, we decided to present a simplistic equation for calculating the annual number of newly trained pediatricians (and pediatric subspecialists) necessary to keep up the existing number of pediatricians (**Table IV**; available at www.jpeds.com). In a follow-up article, we shall add additional equations that are needed to calculate a threatening shortage or surplus of pediatricians according to several confounding factors, which are listed in **Table III**.

Conclusions

The question arises whether it is necessary to calculate the number of needed pediatric generalists, specialists, and subspecialists because the past has shown that it worked more or less well by market rules. It is unclear whether careful planning may be advantageous. According to sociologists, our generation lives in a postmodern world that is characterized by loosening binding rules and by rapid structural changes. We conclude that the stable world with embedding of individual developments into long-time existing societal structures is over and that rapid societal changes and tensions will require careful planning of future investments and workforce in pediatrics. ■

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References available at www.jpeds.com

References

1. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "Diversity of Child Health Care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations." J Pediatr 2016;177S:S1-10.
2. Laufer M, Perry ZH, Reuveni H, Toker A. Pediatrician workforce planning: the Israeli experience and projections of pediatric manpower 1995-2015. J Hosp Adm 2014;3:140-8.
3. Katz M, Rubino A, Collier J, Rosen J, Ehrich JH. Demography of pediatric primary care in Europe: delivery of care and training. Pediatrics 2002;109:788-96.
4. Ehrich J, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton DS, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.
5. Ehrich J, Nwaneri N, de Santo N. The role of retired pediatric professors in European child healthcare services. J Pediatr 2017;181:332-3.
6. World Health Organization. The world health report 2016—working together for health. Geneva, Switzerland: WHO; 2006.
7. Cohen J, Neumann P, Weinstein M. Does preventive care cave money? Health economics and the presidential candidates. N Engl J Med 2008;358:661-3.
8. Faust H, Menzel P. Prevention versus treatment: what's the right balance? Oxford (UK): Oxford University Press; 2012.
9. Ehrich J, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-80.
10. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
11. Pettoello-Mantovani M, Ehrich J, Romondia A, Nigri L, Pettoello-Mantovani L, Giardino I. Diversity and differences of postgraduate training in general and subspecialty pediatrics in the European Union. J Pediatr 2014;165:424-6, e2.

Table I. Proposed reclassication of pediatric healthcare expanding the concept of primary, secondary, and tertiary pediatric care

1. **Maternal and neonatal care:** neonatal and maternal care require juxtaposition of a pediatric unit and an obstetric unit within a general hospital or mother-and-child hospital.
2. **Community child health care:** deals with protection, prevention, and provision of individual care in the vicinity of the child and his or her family. Primary care may be offered in private practices or state-owned polyclinics or in other institutions such as kindergarten or schools.
3. **Hospital pediatrics:** ranges from small pediatric units within general hospitals to large and stand-alone children's hospitals or mother-and-child hospitals offering both inpatient and outpatient care.
4. **Highly specialized pediatric care:** in national and international centers of competence, means treating children with rare and/or complicated diseases in centers in Europe providing highly specialized expertise, sophisticated infrastructure, academic processes, and research. They also offer cross-border care.

Table II. What is a pediatrician?

Pediatricians in Europe are differentiated into *generalists* and *specialists*, both of whom have been given also other synonyms

Generalists were named:
- general pediatricians
- primary care pediatricians
- ambulatory pediatricians
- community care pediatricians
- social pediatricians
- others

Specialists were named:
- hospital pediatricians
- secondary care pediatricians
- tertiary care pediatricians
- academic/university pediatricians
- pediatric public health officer
- others

Pediatric subspecialists

Pediatric subspecialists can be differentiated into several groups
- Adolescent medicine
- Allergology
- Cardiology
- Community pediatrics
- Developmental pediatrics
- Emergency pediatrics
- Endocrinology
- Gastroenterology
- Genetics
- Hematology
- Hepatology
- Immunology
- Infectious diseases
- Intensive care
- Mental health
- Metabolic diseases
- Neonatology
- Nephrology
- Neurology
- Oncology
- Palliative pediatrics
- Others

Other medical specialists with a subspecialty in child healthcare
- Pediatric surgeons (cardiac surgeons neurosurgeons, orthopedic surgeons, etc)
- Pediatric anesthetists
- Pediatric dermatologists
- Child psychiatrists
- Pediatric gynecologists
- Pediatric ophthalmologists
- Pediatric otorhinolaryngologists
- Pediatric pharmacologists
- Others

Table III. Factors influencing the equations for calculating the required number of annually certified pediatricians according to different countries and different pediatric specialties*

	Criteria	Mathematic term	Italy	Germany
1	Number of lifelong working years = period without interruption between accreditation as a general pediatrician and age at retirement (or subspecialist)	LLWY	37	34 (32)
2	Actual number of all pediatricians (actual number of full time equivalent pediatrician)	APed	14 953	13 000 (12 350)
3	Percentage of general, primary care pediatricians of all pediatricians	PCPed	60%	50%
4	Percentage of hospital pediatricians of all pediatricians	HCPed	36%	45%
5	Percentage of other types of pediatricians (eg, public health pediatricians) of all pediatricians	OCPed	4%	5%
6	Percentage of subspecialized pediatricians of all pediatricians	All SSPed Neonatologists Nephrologists	NA	25% 10% 1%
7	Percentage of pediatricians working full time or part time equivalents	FT Full time Part time	 90% 10%	 90% 10%
8	Sex factor: female/male ratio of recently trained pediatricians (required if affecting number of lifelong working years)	GF Female Male	 90% 10%	 70% 30%
9	Mean percentage of annually increasing (+) or decreasing (–) numbers of pediatricians in the previous 5 years	PedID	–1.8%	0% = stable with 13 000 pediatricians
10	Number of pediatricians with annual career change per year	PedCC	Negligible	Negligible
11	Percentage of **immigrant** pediatricians of all annually trained pediatricians (%/year) Percentage of **emigrant** pediatricians of all annually trained pediatricians (%/year)	IPed EPed	>0.02% >0.1%	Stable and balanced ratio of immigrating vs emigrating pediatricians
12	Estimated decreasing number of pediatricians per year following future digitalization and other newly developed medical technology	PedTech	Unknown	Unknown
13	Estimated decreasing number of pediatricians per year following increasing multidisciplinary care by other care givers such as nurse practitioners, etc	PedMult	Unknown	Unknown
14	Number of annually certified pediatricians	NewPed	366 (average of last 6 years)	450-500 (because of expected shortage)
15	Calculated number of annually needed pediatricians	cNewPed	405	382
16	Planned number of trained pediatricians in 2018	pNewPed	427 (because of expected shortage)	450

*The number in brackets are estimates that were taken from Italy and Germany.

Table IV. Annual number of newly trained pediatricians

Three different equations are needed to calculate the annual number of newly trained pediatricians:

1) The number of full-time lifelong working years (LLWY) for pediatricians must be calculated separately for different countries according to the mean age at Baccalaureate Diploma (A-level, Matura, matriculation exam), the mean duration of waiting time before starting medical school, duration of compulsory military or social service, duration of undergraduate training, and duration of postgraduate pediatric training (and pediatric subspecialty training for subspecialists).

LLWY = Age of retirement minus mean age at Baccalaureate Diploma minus mean duration in years of waiting time for starting medical school minus mean duration of military/social service minus (if any) mean duration of undergraduate training minus mean duration of postgraduate pediatric training.

2) The country-specific factor (CSF) on different working conditions must include data on the percentage of pediatricians working part time as well the influence of sex on life-long working years. If sex affects the number of LLWY, this factor has to be adjusted accordingly. For example if the female/male ratio is 50/50, LLWY of females and male must be added and divided by 2. If LLWY is shorter in females and female/male ratio is 90/10, the calculation is 90 × LLWY of females and 10 × LLWY of males divided by 100.

CSF = 1 divided by LLWY.

3a) The number of annually certified pediatricians is calculated by the equation:

NewPed/year = actual number of all full time pediatricians (APed) × CSF

3b) The number of annually certified **subspecialized pediatricians (SSPed)** which is necessary to keep the existing number of experts stable can be calculated by adjusting the **country specific factor (CSF)** for SSPed according to criteria which are listed in rows 15-17 in **Table III**.

The number of annually certified **subspecialized pediatricians is calculated by the equation:**

New SSPed/year = actual number of full time SSPed × CSF_{SSPed}.

EPA

The Importance of Expert Opinion–Based Data: Lessons from the European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA/UNEPSA) Research on European Child Healthcare Services

Jochen Ehrich, MD[1,2], Eli Somekh, MD[1,3], and Massimo Pettoello-Mantovani, MD, PhD[1,4]

Evidence-based medicine (EBM) has gained great importance in child healthcare.[1] Yet, the practical process of clinical decision-making is far more complex and ranges from highly sophisticated clinical trials to personal experience of a pediatrician on previously treated individual patients. Furthermore, the necessary participation of young patients and their families in decision-making is based on their feelings, wishes, medical knowledge, and health beliefs.[2,3] Decision-making processes in child healthcare service systems are even more complex because of a lack of evidence-based data. Long-term observational studies on the benefit and risk of new models of child healthcare are scarce, and there is no guarantee that a successful model in 1 country will work in different countries with different health system characteristics. Last but not least, the group of opinion makers involves—in addition to pediatricians—other professionals, who have different interests and biases.

Pediatric expert advice appears to have become an old style of authority in decision-making. Indeed, expert opinion can be wrong, and there are occasions when experts do not agree with each other.

The concept of EBM also has its limits with regard to the process of medical decision-making, as it tends to place medicine in the field of the exact sciences such as mathematics. However, unlike exact sciences, child healthcare is less characterized by accurate quantitative expression, predictions, and hypotheses that can be tested by rigorous methods involving precise measurements.

We will stress the importance of the role of expert opinion in the planning of child healthcare services in an era when EBM is mainly sought. Plato wrote that "opinion is something intermediary between knowledge and ignorance." We conclude that pediatric expert opinions should be used complementary to evidence-based pediatrics. Opinions may change the pediatric world if based on solid data, practical experience, theoretical knowledge, and creative visions. Our experience of gathering information and expert opinions from our European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA/UNEPSA) members for improving child healthcare in Europe is summarized in this article.

EBM	Evidence-based medicine
EPA/UNEPSA	European Paediatric Association, Union of National European Paediatric Societies and Associations

Contributions of European Experts to EPA/UNEPSA Surveys on Child Healthcare

Since 1998, EPA/UNEPSA has performed 14 surveys that asked for data on the diversity of child healthcare and on health policy performance[4] in Europe. The answers were provided by the presidents of national pediatric societies and associations. The results of the surveys were discussed with the presidents during Europaediatrics Congresses to identify biases and interests interfering with the accuracy of data and/or if they were published in international journals.[5,6]

Most questionnaires targeted data on how European countries organized different aspects of child healthcare service systems. Each questionnaire aimed at collecting data that were based on official national medical statistics. In the case of missing statistical data, the responders were asked to fill in estimated data based on their own or other national experts' opinions. Health policy organizers could benefit from identifying the experts' opinions on health policy performance, quality of care, strengths and failures of healthcare services, and future needs such as workforce development.[6]

Our retrospective evaluation supports the concept that the knowledge-based pediatric expert's opinion is necessary to fill the data gap between a high level of evidence provided by long-term medical statistics and little systematic empirical evidence.[7,8]

Strengths and Weaknesses of Collecting European Pediatric Data from National Institutes of Medical Statistics

The quality of pediatric data depends on completeness and accuracy of reporting. "Detailed assessments of mortality patterns, particularly age-specific mortality, represent a crucial input that enables health systems to target interventions to specific populations."[9] However, completeness of data was not achieved in the Global Burden of Diseases, Injuries, and Risk factors Study (GBD).[8] The retrospective analysis of our own 14 European surveys led us to believe that many questions were difficult to answer by

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the presidents or experts of national pediatric societies because of a lack of a broad basis of medical statistics relevant to child healthcare. Furthermore, the accuracy of official data was sometimes questioned by the national experts. In some countries like Russia and other parts of the former Soviet Union, it was assumed that the quality of official data had improved since the 1990s. Individual presidents reported it difficult to access official national data and/or difficulties in obtaining the permission by local authorities to report national data to EPA/UNEPSA. In many cases of requested national data on demography, the presidents reported data from the medical data banks of World Health Organization or World Bank. In summary, the heterogeneity of availability, accessibility, and quality of data had been a considerable limiting factor, exposing the surveys to the risks of incompleteness and inaccuracy of data on child health, which had to be compensated by expert opinions.

Strengths and Weaknesses of Collecting European Pediatric Data from National Pediatric Experts

Since 1998, EPA/UNEPSA has asked the presidents of national pediatric societies to answer 14 questionnaires on the diversity of child healthcare in Europe.[5] Some of the early reporting presidents remained on this panel as liaisons for EPA/UNEPSA. In retrospect, this turned out to be successful because they created continuity of the interactive panel of experts, resulting in a lively exchange of ideas and mutual trust in the quality of data, and last but not least providing the basis for exchanging confidential personal views that may deviate from official statements.

A further step to improve the accessibility of valuable information on child healthcare was the initiative to ask national "EPA Ambassadors" to represent their own country on the scientific advisory board.[10] Strengthening experience meant that retired pediatric professors also had been asked to work as members of EPA scientific advisory board.[11]

Examples of the Value of Pediatric Expert Opinion for European Child Healthcare Service Systems

Combating the Threatening Shortage of Numbers of European Pediatricians

In the 1990s, the number of pediatricians had increased in 14 of 18 European countries; however, pediatric experts anticipated a scenario leading to a deficit of pediatricians for the year 2010 in 10 of 18 countries.[12] This alarming signal was largely discussed by expert pediatricians during national and Europaediatrics Congresses and the impact of a shortage in pediatricians on public health was carefully described and stressed at political levels. The 2012 follow-up survey on the pediatric workforce revealed that the decrease of the number of pediatricians was prevented in 9 of these 10 countries. This provides concrete evidence that knowledge-based pediatric expert opinion had been transferred successfully from theory into practice. However, the policy of pediatric experts should not stop here, because a stable number of all pediatricians in a given country does not necessarily mean that there are also enough primary care pediatricians (PCPeds) or subspecialists. As the mean age of PCPed has increased by 5 years or more during recent years in several countries, there is great concern that there will be a shortage of PCPeds in 7-10 years in countries such as Italy and Germany.

Monitoring the Efficiency of Health Services in Pediatric Subspecialties

The recent EPA/UNEPSA follow-up survey on pediatric renal care showed that the percentage of pediatric nephrologists/all pediatricians had increased from 0.7% in 1998 to 1.0% in 2017.[13] The estimated total number of European pediatricians in 2017 was close to 175 000; thus, approximately 1750 highly specialized pediatric nephrologists took care of all European children with kidney diseases, including dialysis and renal transplantation.

Evaluating Pediatric Healthcare Services during Political Transition Periods

One study revealed that those countries that had become independent after the collapse of the Soviet Union in the 1990s had changed from the pediatric primary care system to the general practitioner system.[14] Fifteen years later, presidents of national pediatric societies of 10 of 14 countries reported a partial worsening of the quality of primary child healthcare because well-functioning, pre-existing structures had been destroyed. Three countries did not follow the recommendations of the World Bank to switch from the pediatric to the general practitioner system.

Identifying Priorities in Child Healthcare

In 2012, the presidents of national pediatric societies reported 3 areas that had become a priority among all challenges of their national healthcare systems: (1) the migrant child population, (2) the role of new types of families and lifestyles resulting in mental disorders, and (3) complex healthcare for children with long-term conditions. National pediatric societies should therefore aim at creating cross-border ventures to cope with these challenges together. These activities should not stop at the outer border of the European Union countries.

Conclusions

Evidence-based data derive from answers to questions that were put forward by experts. Thus, the quality of answers in the questionnaires depends on the quality of questions, and the quality of evidence-based data depends on the completeness and accuracy of answers to the questions. In conclusion, expert opinion plays an important role in many areas of pediatrics. Particularly, it can help to identify priorities of care, to plan surveys on healthcare services in all European countries, to help analyze data and develop new models of care, and to transfer theory into practice by providing advice for decision makers and legislators. The European cooperation of pediatric experts must be based on international social responsibility and on cross-border discussions. ■

References available at www.jpeds.com

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References

1. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:371.
2. Ehrich J, Pettoello-Mantovani M, Lenton S, Damm L, Goldhagen J. Participation of children and young people in their health care: understanding the potential and limitations. J Pediatr 2015;167:783-4.
3. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr 2009;35:12.
4. Mackenbach JP, McKee M. A comparative analysis of health policy performance in 43 European countries. Eur J Public Health 2013;23:195-201.
5. Ehrich JHH, Pettoello-Mantovani M. Views of the presidents of national European pediatric societies on evolving challenges of child health care. J Pediatr 2016;177:336-7.
6. Ehrich JH, Tenore A, del Torso S, Pettoello-Mantovani M, Lenton S, Grossman Z. Diversity of pediatric workforce and education in 2012 in Europe: a need for unifying concepts or accepting enjoyable differences? J Pediatr 2015;167:471-6.
7. Tonelli MR. In defense of expert opinion. Acad Med 1999;74:1187-92.
8. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305-10.
9. Global Buren of Diseases 2016 Mortality Collaborators. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1084-150.
10. Gerber-Grote A, Namazova-Baranova L, Hoey H, Pettoello-Mantovani M, Vural M, Mestrovic J, et al. European Paediatric Association, the Union of National European Paediatric Societies and Associations Turns 40 years: what this European platform offers to pediatricians. J Pediatr 2017;186:217-8.
11. Ehrich J, Nwaneri N, de Santo N. The role of retired pediatric professors in European child healthcare services. J Pediatr 2017;181:332-3.
12. Helwig H. Als kinderarzt in Europa. Kinderarzt 1998;29:1441-5.
13. Ehrich JH, El Gendi AA, Drukker A, Janda J, Stefanidis C, Verrier-Jones K, et al. Demography of paediatric renal care in Europe: organization and delivery. Nephrol Dial Transplant 2005;20:297-305.
14. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "diversity of child health care in Europe: a study of the European Paediatric Association/Union of National European Paediatric Societies and Associations." J Pediatr 2016;177S:S1-10.

Pediatric Ambulatory and Hospital Networks for Surveillance and Clinical Epidemiology of Community-Acquired Infections

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Care of infectious diseases (prevention, diagnosis, and treatment) represents a large part of the activity of pediatric practices as well as primary care, emergency departments, and hospitals. The bacterial and viral species involved in pediatric community-acquired infections (CAIs) can induce severe, moderate, or mild diseases, which require care by hospitalization, emergency departments, or first-line clinicians. For example, pneumococcus manifests as a spectrum of diseases ranging from severe invasive diseases, such as meningitis, bacteremic pneumonia, and bacteremia, to less severe but more frequent diseases, such as acute otitis media (AOM), sinusitis, and pneumonia (**Figure**; available at www.jpeds.com).[1,2] Therefore, outpatient use of antibiotics also involves antibiotic resistance for CAIs; hence, infection management becomes even more complex, often leading to hospitalizations. Moreover, some vaccines, for which the main objective is reducing invasive and severe diseases, have an additional impact on less severe diseases and also change the carriage.[3] Trying to study the bacterial and clinical epidemiology of organisms such as Pneumococcus, Group A *Streptococcus*, or *Escherichia coli*, involved in a large spectrum of CAIs, requires a focus on both the ambulatory setting and on the hospital.

We review the efforts to build a French pediatric research network that focused on CAIs.

Before the 1990s, in France, first-line clinicians and notably ambulatory pediatricians were not involved in clinical research, which was performed mainly by universities and hospitals. Because of a lack of surveillance systems in ambulatory settings, we created a nonprofit ambulatory-pediatric research network, Pediatric Clinical and Therapeutic Association of Val de Marne (ACTIV). This regional network (Paris area) was extended at the national level via a strong collaboration with the Association of French Ambulatory Pediatricians. A link with a preexisting hospital network, the Pathology Pediatric Infectious Disease Group of the French Pediatrics Society, was established several years later. The network has complied with the high-quality standards required by good clinical practice for industrial trials by European and North American drug regulators and the "feasibility in real life," taking into account medical practice with ambulatory care and hospital constraints. With ACTIV, we have designed study protocols aimed at simplifying the procedures, while maintaining a high standard of quality. This approach facilitated the publication of scientific data that were widely used by the European and American medical markets.

ACTIV	Pediatric Clinical and Therapeutic Association of Val de Marne
AOM	Acute otitis media
CAI	Community-acquired infection
PCV	Pneumococcal Conjugate Vaccine

From Antibiotic Treatment to Prevention with Vaccines

To compare the efficacy of different therapeutic options (type of drug, dosage, duration of antibiotic treatments, etc), in AOM we have performed several clinical trials using rigorous criteria to standardize the AOM diagnosis along with otoscopy training sessions.[4-6] Our research group evaluated the impact of antibiotics on the composition and antibiotic resistance in nasopharyngeal flora that involved a network of almost 100 primary care pediatricians.[5,6] The bacteriological samples were centralized in the National Reference Center for Pneumococci. The advantage of the expertise acquired in this area (several thousand nasopharyngeal samples collected in 10 years) allowed us to perform our pivotal study on nasopharyngeal carriage after the 7-valent pneumococcal conjugate vaccine (PCV) implementation in France in 2001.[7] This study was performed as a postlicensing commitment requested by the European Medicines Agency to determine the impact of the 7-valent pneumococcal conjugate vaccine. Although other studies reported similar results for the PCV impact, none were comparable with those we have conducted since 2001 in terms of design, duration (>17 years), and number of patients enrolled (>15 000).[7]

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Keys to Success

Several factors could explain the success of this network lasting more than 30 years (**Table**; available at www.jpeds.com). The important outcome of the studies performed by the research network has been the implementation of clinical conclusions and recommendations by pediatricians in their practice. This includes the duration of antibiotic therapy for children with AOM or group A *Streptococcus* pharyngitis as well as the use of biomarkers or rapid diagnostic tests to improve diagnostic performance and use of appropriate antibiotics for different infectious diseases.[8-11] Finally, the best proof of success was that pediatricians' behavior was correlated with the research they conducted. Particularly, our group, which promptly implemented the proposed recommendations, showed less prescription of antibiotics and greater vaccination coverage for their patients than other physicians who applied the recommendations later.[12]

We have recently moved to a new method that allows us to even more easily perform studies by directly obtaining data from pediatricians' computers. With 100 pediatricians using the same software (Infansoft, CompuGroup Medical, Koblenz, Germany), we have automated data capture from electronic medical records for children in ambulatory settings, the Panel in Ambulatory Research Infectiology. The participants benefit in real time from the epidemiology of several infectious diseases on a dedicated Website. They can also improve their diagnosis with e-learning sessions specifically dedicated to each pathology.

Link with the Hospital Network

Linking ambulatory and hospital networks is important. For instance, to determine the multifaceted impact of pneumococcal vaccine implementation on invasive pneumococcal infections, we linked the ambulatory with the hospital-based surveillance systems by reconciling separate databases, and we created a national hospital network for bacterial meningitis with the Pathology Pediatric Infectious Disease Group of the French Pediatrics Society.[13,14] More than 230 pediatricians and 168 microbiologists nationally were involved in this study. Microbiologists agreed to voluntarily send each bacterial species isolated from meningitis samples to the corresponding national reference center, which performed serotyping and genotyping, as well as extensive standardized susceptibility testing. The strong participation and motivation of hospital pediatricians and microbiologists were related to the lack of a prior surveillance system that included clinical, therapeutic, and microbiological data for invasive diseases in France. Moreover, the originality and the relevance of our system lies in the fact that we used our research platform that was initially created for outpatient infectious diseases. We identified a team of pediatricians and microbiologists in each participating center and organized a close collaboration with the experts of the national reference centers for the different bacterial species. The research has improved the quality of care, and the network has been regularly asked to perform ancillary studies and specific analyses for each bacteria involved. The bacterial meningitis study surveillance, with more than 6500 cases enrolled since 2001, allowed for the publication of several articles, also involving the contribution of young pediatricians.[15] Moreover, our ambulatory and hospital network initially built for pneumococcal infections was extended to study other diseases and pathogens, such as the increasing incidence of CAIs owing to extended-spectrum β-lactamase-producing *E coli*. These studies provided useful public health data and recommendations.

French Vaccine Network

In 2003, following the Infovac-Swiss model, we developed InfoVac-France, a website designed by Clair-Anne Siegrist of the University of Geneve, providing physicians with a direct source of information on vaccinations.[16-18] In the context of vaccine hesitancy in the world and particularly in France, here again this network helps provide optimal vaccine support and represents a good opportunity for the release of validated scientific information on vaccines.

Conclusion

Rather than providing guidance for better surveillance of pediatric infectious diseases, herein we present an overview of our surveillance system for diseases and highlight why, in the French context, it was successful beyond our hopes. Owing to different clinical practices and healthcare systems, epidemiology, and vaccination programs worldwide, results from studies performed in other countries cannot always be extracted or transposed to one's own country. This factor has led to each country performing its own clinical research. The strength of our surveillance systems lies in the multiplicity of funding (governmental, university, and pharmaceutical industry). Our challenges are to rigorously maintain several well-established surveillance systems with resources specifically allocated and increase the involvement of young researcher-pediatricians. Our networks are not always representative of all French pediatricians, because our researcher-pediatricians are well-informed and particularly well-trained to follow the latest recommendations. However, we believe in this model, which can easily evolve with themes of research prioritized according to epidemiologic changes. Without competing with the different preexisting research groups in our country, we have federated and involve all the volunteers in our networks. Hence, this "ambulatory/hospital" research network, which is unique in Europe, contributes greatly to answering public health questions, particularly for vaccination strategies and antibiotic resistance.[15] ■

References available at www.jpeds.com

References

1. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis 2004;4:144-54.
2. Simell B, Auranen K, Kayhty H, Goldblatt D, Dagan R, O'Brien KL, et al. The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 2012;11:841-55.
3. Dagan R. The diversity of pneumococcal conjugate vaccine impact observed through their implementation. Hum Vaccin Immunother 2016;12:266-7.
4. Cohen R, Levy C, Boucherat M, Langue J, de La Rocque F. A multicenter, randomized, double-blind trial of 5 versus 10 days of antibiotic therapy for acute otitis media in young children. J Pediatr 1998;133:634-9.
5. Varon E, Levy C, De La Rocque F, Boucherat M, Deforche D, Podglajen I, et al. Impact of antimicrobial therapy on nasopharyngeal carriage of Streptococcus pneumoniae, Haemophilus influenzae, and Branhamella catarrhalis in children with respiratory tract infections. Clin Infect Dis 2000;31:477-81.
6. Cohen R, Bingen E, Varon E, de La Rocque F, Brahimi N, Levy C, et al. Change in nasopharyngeal carriage of Streptococcus pneumoniae resulting from antibiotic therapy for acute otitis media in children. Pediatr Infect Dis J 1997;16:555-60.
7. Cohen R, Varon E, Doit C, Schlemmer C, Romain O, Thollot F, et al. A 13-year survey of pneumococcal nasopharyngeal carriage in children with acute otitis media following PCV7 and PCV13 implementation. Vaccine 2015;33:5118-26.
8. Cohen R, Reinert P, De La Rocque F, Levy C, Boucherat M, Robert M, et al. Comparison of two dosages of azithromycin for three days versus penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. Pediatr Infect Dis J 2002;21:297-303.
9. Cohen JF, Cohen R, Bidet P, Levy C, Deberdt P, d'Humières C, et al. Rapid-antigen detection tests for group a streptococcal pharyngitis: revisiting false-positive results using polymerase chain reaction testing. J Pediatr 2013;162:1282-4, 4 e1.
10. Cohen R, Levy C, Chalumeau M. Shortened antimicrobial treatment for acute otitis media. N Engl J Med 2017;376:e24.
11. Levy C, Biscardi S, Dommergues MA, Dubos F, Hees L, Levieux K, et al. Impact of PCV13 on community-acquired pneumonia by C-reactive protein and procalcitonin levels in children. Vaccine 2017;35:5058-64.
12. Levy C, Pereira M, Guedj R, Abt-Nord C, Gelbert NB, Cohen R, et al. Impact of 2011 French guidelines on antibiotic prescription for acute otitis media in infants. Med Mal Infect 2014;44:102-6.
13. Cohen R, Biscardi S, Levy C. The multifaceted impact of pneumococcal conjugate vaccine implementation in children in France between 2001 to 2014. Hum Vaccin Immunother 2016;12:277-84.
14. Bingen E, Levy C, de la Rocque F, Boucherat M, Varon E, Alonso JM, et al. Bacterial meningitis in children: a French prospective study. Clin Infect Dis 2005;41:1059-63.
15. Association Clinique et Thérapeutique Infantile du Val de Marne (ACTIV). http://activ-france.com/Publis_en.php. Accessed December 18, 2017.
16. InfoVac Suisse. La ligne directe d'information sur la vaccination! https://www.infovac.ch/fr/. Accessed December 18, 2017.
17. InfoVac-France. La ligne directe d'information et de consultation sur les vaccinations. https://www.infovac.fr/. Accessed December 18, 2017.
18. Cohen R, Siegrist CA. Vaccines' adverse events: questions and answers brought by InfoVac. Arch Pediatr 2006;13:650-2.

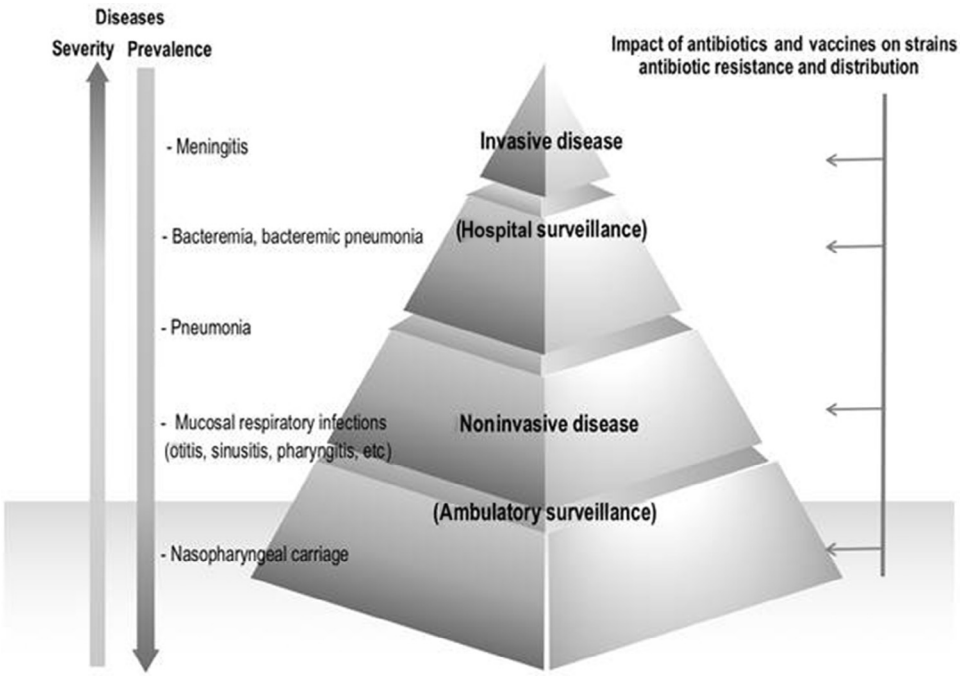

Figure. Spectrum of *Streptococcus pneumoniae* disease.

Table. Factors determining the successful outcome of pediatric ambulatory and hospital networks for surveillance and clinical epidemiology of CAIs

Addressing areas of typical concern for primary care physicians (ie, improvement in diagnosis and/or management of pediatric infectious diseases).
Developing projects aimed at providing answers to common clinical question related to professional practice and promoting pediatric best practice for the benefit of children (ie, studies involving respiratory tract infections, owing to their frequency and easiness in obtaining oropharyngeal or nasopharyngeal samples).
Placing investigators and their training programs at the cornerstone of the research system (investigators easily recognize that contributing to the projects proposed provides a real benefit to their daily practice and professional continuing education).
Building and establishing preliminary relationships between parents and their family pediatricians, which largely favor parental adherence to protocols and facilitate the collection of parental written informed consent to the studies (very few patients are lost to follow-up).

Effective School Health Service: A Response to Adolescent Health Needs in Europe

Pierre-André Michaud, MD[1], Leyla Namazova-Baranova, MD[2], Martin Weber, MD[3], and Anne-Emmanuelle Ambresin, MD, MEpi[4]

The World Health Organization defines "adolescents" as people aged 10-19 years; "youth" (also named "AYA" for "adolescents and young adults") as those aged 15 to 24 years; and "young people" as those aged 10-24 years.[1] Several of the main health problems affecting adolescents in the whole world have changed, with a lessening of the prevalence of most infectious diseases, an increase in mental health problems and intentional or unintentional violence, the persistence of sexually transmitted infections, unplanned pregnancies and abortions, and an increase in problems linked with substance misuse.[2,3] Also, more adolescents survive a potentially lethal chronic condition, which raises issues such as adherence problems or short- and long-term physical or psychosocial consequences that must be addressed. Despite an improvement in the health of the adolescent population globally, several European countries face troublesome trends in specific areas, such as the increasing rate of obesity as well as of the death rate by suicide, and an increase in the proportion of adolescents with recurrent health complaints.[4]

The school health services are particularly well-placed to respond to this situation. They are potentially able to reach the majority of adolescents to deliver health information or care and promote well-being and safe lifestyles through effective interventions. However, as shown by several recent publications[5-7] and as discussed during a symposium of the European Paediatric Association held during the EUROPAEDIATRICS congress in 2017, there remains room for improvement. Investments in adolescent health and well-being are cost effective.[8] We briefly review the organizational aspects of school health services in Europe and how they should evolve in the future to meet the new morbidities of adolescents.

What Is Known About the Effectiveness of School Health Services?

School health services can provide a variety of interventions such as vaccination, and screening for developmental disability and occult or poorly symptomatic conditions (high blood pressure, vision or ear defect, scoliosis, etc). Over the years, given the evolution of the epidemiologic situation of adolescents, they tend to focus also on mental health problems and behavioral and health-compromising behavior through counselling activities and group or class interventions. There are good reviews available showing that interventions in the field of mental health are effective,[9,10] as well as those targeting the use of tobacco[11] or alcohol.[12] Sexual education and various preventive programs focusing on the use of contraception, and the prevention of unplanned pregnancy or dating violence, have shown encouraging results.[13-16] A promising avenue is the development of policies aimed at the improvement of the ethos or climate of the school, with an emphasis on connectedness, respect, and a positive view at the pupils achievement and future, all grouped together into the concept of health-promoting schools.[9,17,18] In other terms, as far as adolescents are concerned, the overall trend is an increase in group-based preventive interventions and health promotion, and a lessening of screening procedures for conditions that are either not followed up properly or have become less prevalent, or have been already identified.

Variation of European School Health Structure and Services

The World Health Organization has shown similarities and differences across 37 European countries, both in terms or organization and types of services provided.[5,19] Most countries had a staff of health professionals attached to and working in the school, and some provided some services outside the school environment by identified school health professionals. A few countries did not have any formal school-based services and relied on the primary care system, and some had a mixed kind of organization. One of the conclusions of the reports is that the most effective services were those who provided their services from inside the school. Most countries delivered their services to adolescents up to the age of 18 years.

Many countries still performed regular screening, most of the time as a check of weight and height, visual and hearing testing, or blood pressure measurement. It is puzzling that some countries have chosen to concentrate on other types of screening such as sexually transmitted infections, lung and heart auscultation, proteinuria, or body temperature, for which we have little evidence of effectiveness.

Out of the 37 countries surveyed, most run vaccination programs (~90%) and 3 of 4 propose individual counselling. Moreover, some 60% provided training in the field of emergency

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basic care. Nearly all countries provided some sort of preventive activities in the field of mental health, life styles, and behavioral problems, but the nature and extent of these activities was unknown. Also, more than three-quarters of countries have set up preventive interventions in the field of healthy nutrition, smoking, alcohol and other drug prevention, and sex education.

Training School Health Professionals and Building Partnerships

One of the main challenges still is to assess the extent to which the diversity of organizational models and health content of school health services have an impact on the health outcomes of the adolescent population. Indeed, although we have evidence of the effectiveness of a variety of interventions, these well-controlled evaluations took place on a limited scale. The external validity of these approaches (eg, introduction on a large scale in the "real" environment) must still be demonstrated. The implementation of preventive intervention depends heavily on the availability of a well-trained and motivated staff, in general school nurses and doctors, as well as their collaboration with the teaching staff of the school. The European Union for School and University Medicine and the World Health Organization recently developed a series of quality standards in the field, focusing largely on the competence of the school health professionals.[20] This document, based on a survey of European countries and a consensus conference held in 2012, outlines the main roles of the school health expert, based on the CanMEDS model. It also insists on the importance of a collaboration between the administration of education and of health at all levels (ministries, regions, cities) as well as some cornerstone values, such as respect for integrity, equity, privacy, confidentiality, and access. To a large extent, these norms are applied in other contexts of care under the denomination of "adolescent-friendly services and care,"[21] and are well-accepted and used in many countries of the world.

The Future of School Services in Europe: A Challenge for Pediatricians

Because pediatricians are heavily involved in the area of school health in most countries, they have a responsibility to advocate for improving the quality of health interventions within the school setting.[22-25] The following suggestions emerged from the meeting on school health organized by the World Health organization during the 2017 congress of the European Paediatric Association held during the EUROPAEDIATRICS congress in 2017.

First, it was suggested to use in the future the term of school health or school health and medicine instead of school medicine alone, which does reflect the evolution of adolescent health needs and how to respond. Also, school health professionals should be less driven in the future by the detection of diseases, but more by the emergence of new health needs in the fields of life style, mental health, substance abuse, sexual and reproductive health, or eating disorders and obesity. Given the paucity of financial resources in many countries, the positive net effect of large-scale interventions by school health services on the health of the adolescents[8] may be more cost effective than discrete individual screening procedures, so that school health professionals should restrict these screening interventions to those diagnostic methods for which there is evidence of their effective potential impact on the current and future health of the pupils. An important consideration here is the necessity for a good collaboration of school health services with the primary care sector to ensure that any condition for which students are screened is subsequently addressed appropriately.

Although a school health system is in place, access to services may still be poor. Therefore, school health services should strive to improve the pupils' access to any service in place as well as their health literacy. As far as health literacy is concerned, a major challenge is to assist the adolescents in the proper use of Internet, especially of those website concerning health issues.

As mentioned, an approach stressing prevention and health promotion requires an interdisciplinary approach, that is, a close collaboration between the teaching staff and the health team, and respect for their roles, responsibilities, and professional cultures.[20] The school health staff, in collaboration with the educational sector, should aim at working not only on the individual pupils' health, but more globally at the level of the whole institution, for instance, on the climate of the school, for example, within the context of the World Health Organization European Network of Health Promoting Schools.

The issue of the rights of the pupils (eg, UN Convention on the Rights of the Child[26]) should be put high on the agenda. Any school should ensure the fair participation of the pupils in the life of their school, discourage bullying and violence, and promote positive values such as connectedness and respect. The participation of pupils to the life of their institution through youth councils working in a democratic way is an essential aspect of the promotion of their rights.

Finally, decision makers should provide school health professionals with adequate and updated training; they should also ensure that working conditions make school health care an attractive profession. ■

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References available at www.jpeds.com

References

1. Sawyer SM, Afifi RA, Bearinger LH, Blakemore SJ, Dick B, Ezeh AC, et al. Adolescence: a foundation for future health. Lancet 2012;379:1630-40.
2. Mokdad AH, Forouzanfar MH, Daoud F, Mokdad AA, El Bcheraoui C, Moradi-Lakeh M, et al. Global burden of diseases, injuries, and risk factors for young people's health during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2016;387:2383-401.
3. Patton GC, Sawyer SM, Santelli JS, Ross DA, Afifi R, Allen NB, et al. Our future: a Lancet commission on adolescent health and wellbeing. Lancet 2016;387:2423-78.
4. Kuntsche E, Ravens-Sieberer U. Monitoring adolescent health behaviours and social determinants cross-nationally over more than a decade: introducing the Health Behaviour in School-aged Children (HBSC) study supplement on trends. Eur J Public Health 2015;25(Suppl 2):1-3.
5. Baltag V, Levi M. Organizational models of school health services in the WHO European Region. J Health Organ Manag 2013;27:733-46.
6. Baltag V, Pachyna A, Hall J. Global overview of school health services: data from 102 countries. Health Behav Policy Rev 2015;2:268-83.
7. World Health Organization. Pairing children with health services: the results of a survey on school health services in the WHO European region. Secondary pairing children with health services: the results of a survey on school health services in the WHO European region. Copenhagen: World Health Organization; 2010 http://www.euro.who.int/__data/assets/pdf_file/0006/112389/E93576.pdf?ua=1.
8. Sheehan P, Sweeny K, Rasmussen B, Wils A, Friedman HS, Mahon J, et al. Building the foundations for sustainable development: a case for global investment in the capabilities of adolescents. Lancet 2017;doi:10.1016/S0140-6736(17)30872-3. pii: S0140-6736(17)30872-3, [Epub ahead of print].
9. Langford R, Bonell CP, Jones HE, Pouliou T, Murphy SM, Waters E, et al. The WHO Health Promoting School framework for improving the health and well-being of students and their academic achievement. Cochrane Database Syst Rev 2014;(4):CD008958.
10. Mason-Jones AJ, Crisp C, Momberg M, Koech J, De Koker P, Mathews C. A systematic review of the role of school-based healthcare in adolescent sexual, reproductive, and mental health. Syst Rev 2012;1:49.
11. Thomas R, Perera R. School-based programmes for preventing smoking. Cochrane Database Syst Rev 2006;(3):CD001293.
12. Foxcroft DR, Tsertsvadze A. Universal school-based prevention programs for alcohol misuse in young people. Cochrane Database Syst Rev 2011;(5):CD009113.
13. Lopez LM, Bernholc A, Chen M, Tolley EE. School-based interventions for improving contraceptive use in adolescents. Cochrane Database Syst Rev 2016;(6):CD012249.
14. Mason-Jones AJ, Sinclair D, Mathews C, Kagee A, Hillman A, Lombard C. School-based interventions for preventing HIV, sexually transmitted infections, and pregnancy in adolescents. Cochrane Database Syst Rev 2016;(11):CD006417.
15. Oringanje C, Meremikwu MM, Eko H, Esu E, Meremikwu A, Ehiri JE. Interventions for preventing unintended pregnancies among adolescents. Cochrane Database Syst Rev 2016;(2):CD005215.
16. De Koker P, Mathews C, Zuch M, Bastien S, Mason-Jones AJ. A systematic review of interventions for preventing adolescent intimate partner violence. J Adolesc Health 2014;54:3-13.
17. Langford R, Bonell C, Komro K, Murphy S, Magnus D, Waters E, et al. The health promoting schools framework: known unknowns and an agenda for future research. Health Educ Behav 2017;44:463-75.
18. Shackleton N, Jamal F, Viner RM, Dickson K, Patton G, Bonell C. School-based interventions going beyond health education to promote adolescent health: systematic review of reviews. J Adolesc Health 2016;58:382-96.
19. Baltag V, Levi M. Pairing children with health services: results of a survey on school health services in the WHO European region. Copenhagen: World Health Organization; 2010 http://www.euro.who.int/__data/assets/pdf_file/0006/112389/E93576.pdf?ua=1.
20. World Health Organization. European framework for quality standards in school health services and competences for school health professionals. Copenhagen: World Health Organization Regional Office for Europe; 2014. p. 11 http://www.euro.who.int/__data/assets/pdf_file/0003/246981/European-framework-for-quality-standards-in-school-health-services-and-competences-for-school-health-professionals.pdf?ua=1.
21. Ambresin AE, Bennett K, Patton GC, Sanci LA, Sawyer SM. Assessment of youth-friendly health care: a systematic review of indicators drawn from young people's perspectives. J Adolesc Health 2013;52.
22. World Health Organization. Investing in children: the European child and adolescent health strategy 2015-2020. 2014:20 pp. Copenhagen, http://www.euro.who.int/__data/assets/pdf_file/0010/253729/64wd12e_InvestCAHstrategy_140440.pdf?ua=1.
23. World Health Organization. Global standards for quality health-care services for adolescents: a guide to implement a standards-driven approach to improve the quality of health care services for adolescents, Vol. 1. Standards and criteria. Geneva: World health organization; 2015 http://apps.who.int/iris/bitstream/10665/183935/1/9789241549332_vol1_eng.pdf.
24. World Health Organization. Improving the quality of care for reproductive, maternal, neonatal, child and adolescent health in the WHO European region. Copenhagen: World Health Organization; 2016 http://www.euro.who.int/__data/assets/pdf_file/0009/330957/RMNCAH-QI-Framework.pdf?ua=1.
25. World Health Organization. Global Accelerated Action for the Health of Adolescents (AA-HA!): guidance to support country implementation: guidance to support country implementation. Geneva: World Health Organization; 2017 http://www.who.int/maternal_child_adolescent/topics/adolescence/framework-accelerated-action/en/.
26. United Nations General Assembly. United Nations General Assembly, ed. United Nations convention on the rights of the child. New York (NY): 1990.

Diversity of Service Systems in Pediatric Surgery for Fetuses, Neonates, Infants, Children, and Adolescents in Europe

Bernd Tillig, MD[1], Jochen Ehrich, MD, DCMT[2,3], and Udo Rolle, MD[4]

Dramatic improvements in surgical care have allowed neonates, children, and adolescents who once would have perished to survive.[1] For example, there are novel therapeutic approaches to organ failure or congenital anomalies managed by surgeons that have led to improvements in survival and quality of life.[1] These changes have been driven by evidence in most cases. The clinical management of children with rare diseases was often based on registries and multicenter trials, for example, the European biliary atresia registry.[2]

However, the same cannot be said of the models and pathways of surgical care used in different European child health care service systems. These systems were often products of history and not of science.[3] Arbitrary divisions, such as which services are provided in a general hospital, in a children's hospital, or in the community, may have their origins in professional boundaries established decades ago. "Many things that should be done are not."[3]

To avoid fragmentation of child health care services and to integrate surgical centers into the organizational structure of primary, secondary, and tertiary pediatric care is of utmost importance. A successful approach should include centralized organization, coordination, and decision making by special designated centers of pediatric surgery and a decentralized provision of treatment whenever possible to guarantee child-friendly health care.[4] We offer a grounded basis for discussion on which the future of pediatric surgery in Europe should be organized. We provide a short summary of 3 published surveys and 1 ongoing survey on the organization of pediatric surgery in a representative number of European countries.

Pediatric Surgery and Different Service Systems in Europe

In 1995, the Section of Pediatric Surgery of the Union of European Medical Subspecialists (UEMS) stated that "the field of pediatric surgery encompasses the surgical care of the growing individual. . .from before birth up till the final stages of development."[5]

Parigi reported organizational data on pediatric surgery in 2002 in Europe[5] and noted that pediatric surgery was not recognized as an independent specialty in Denmark, Belgium, and The Netherlands. In countries with an accredited pediatric surgery specialty, there were controversies among surgeons about the definition of the field of competence of a pediatric surgeon. Parigi reached the conclusion that quality of data on diversity of pediatric surgical systems in Europe was low because of incompleteness and inaccuracy.

Therefore, in 2013 the Section and Board of Pediatric Surgery of the UEMS and the European Pediatric Surgeons' Association (EUPSA) jointly organized the first official census of the European centers of pediatric surgery, with the mandate to gather data that could be made available to all European pediatric surgeons and stakeholders involved in designing the future of pediatric surgery in Europe.[6] A questionnaire eliciting data on location of center, workload, workforce and other specific surgical aspects was answered by 251 pediatric surgery centers from 25 European countries. One-half of the centers were located in university hospitals, and one-quarter were affiliated with universities. A mean population of 177 000 children aged <14 years were treated at the centers; however, there was a wide range across countries (92 000 to 475 000). The number of children per 1 fully trained pediatric surgeon ranged from 15 000 to 95 000 children aged <14 years or from 1000 to 5600 neonates. Almost all centers provided emergency services and trauma care on different levels. Minimally invasive procedures were widely applied throughout Europe. Fetal and robotic surgery were performed by pediatric surgery in <20% of countries, and transplant surgery was performed in <30% of countries. It was concluded that harmonization of pediatric surgery in Europe had not reached the highest possible standard. It was hoped that comparisons of national data among the different regions of Europe would induce a harmonization process, in the sense that colleagues working in countries in which some facilities are below the European average would be encouraged to stimulate their health authorities to fill existing gaps, ultimately leading to improved quality of pediatric surgical care for all children.

Postgraduate Training of Pediatric Surgeons

Twenty-nine of 37 (78%) national associations of pediatric surgery in Europe answered the questionnaire on the national training conditions of pediatric surgeons.[7] In 2014, training usually started with a common surgical trunk in 75% of countries lasting 1 to 2 years, with complete training taking

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up to 6 years. The training comprised general pediatric surgery and newborn surgery in all countries, pediatric surgical oncology and pediatric urology in most countries, and pediatric traumatology and pediatric neurosurgery in some countries. Nonsurgical parts of the training included pediatrics, neonatology, and pediatric intensive care and were part of the training program in only 54% of countries. More than 90% of countries used a training logbook, and 79% required a final examination. The European Board of Pediatric Surgery examination was recognized in 54% of European countries. It was concluded that a uniform training schedule in pediatric surgery had not yet been achieved throughout Europe, and that attempts should be made to harmonize both training curricula and examination at a European level.

Cross-Border Care, Integrated Care, and Cross-Functional Collaboration between Pediatric Surgery and Pediatrics

The concept of cross-border care and of cross-functional collaboration between pediatrics and pediatric surgery as the basis of high-quality child health care is unknown in many countries. Therefore, the European Pediatric Association (EPA)/Union of National European Paediatric Societies and Associations (UNEPSA) started in 2017 a joint project with EUPSA and the German Association of Paediatric Surgery (DGKCH) to study the European status A questionnaire targeted data from the viewpoint of both national pediatric associations and pediatric surgical associations regarding how European countries organize surgical care for children. The unpublished responses, which were reported by presidents of national pediatric societies and/or a leading pediatric surgeon in 22 countries, revealed that 6 countries were lacking pediatric surgeons and 10 countries were lacking specialized nurses. Cross-border care programs existed in 9 countries. In 7 of 22 countries, children with serious surgical problems were sent to foreign centers because of a lack of national expertise or technical facilities. Both pediatric surgeons and pediatricians agreed that pediatric surgery wards should be located in children's hospitals. The professional relation between pediatric surgeons and pediatricians within hospitals was judged by the representatives of 17-19 out of 22 countries as constructive, essential, and collegial; however, only 11 of 22 countries reported satisfactory cooperation, and 14 of 22 reported supportive cooperation, indicating needs and challenges for further improvement.

Several ways to improve cooperation between pediatric surgery and pediatrics were proposed by surgeons and pediatricians from different countries, including regular joint meetings within hospitals (18 countries), joint research projects (n = 16), joint annual congresses (n = 14), rotation of trainees (n = 13), shared infrastructures, and joint curriculum for training (n = 11). Future analyses will focus on subspecialty care within pediatric surgery, guidelines of care and regulations for the cooperation between pediatric surgeons and general surgeons and also between pediatric surgeons and organ specialists, such as neurosurgeons and cardiac surgeons.

Summary and Conclusions

The present data show a heterogeneous situation in European pediatric surgery, in alignment with the diversification and fragmentation of child health care services in general.[8] Pediatric surgery and pediatrics can grow even closer in many countries. It was the aim of the published surveys to create a basis for analyzing strengths and weaknesses of national service systems to propose to those countries recommendations for improving their systems. The ongoing surveys of EPA/UNEPSA, EUPSA, and DGKCH aim to fill the knowledge gaps and to stimulate debate on transforming theory into practice. The joint efforts of surgeons and pediatricians should focus on children and child-friendly treatment, and not on the caregivers with their diverging interests. ■

References

1. Wessel LM, Fuchs J, Rolle U. The surgical correction of congenital deformities: the treatment of diaphragmatic hernie, esophageal atresia and small bowel atresia. Dtsch Arztebl Int 2015;112:357-64.
2. Petersen C, Harder D, Abola Z, Alberti D, Becker T, Chardot C, et al. European biliary atresia registries: summary of a symposium. Eur J Pediatr Surg 2008;18:111-6.
3. McKee M, Nolte E. Learning from others: child health and the European Observatory on Health Systems and Policies. J Pediatr 2017;188:316-17.e1.
4. Ehrich J, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the debate on pediatric subspecialties and specialist centers: opportunities for better care or risks of care fragmentation? J Pediatr 2015;167:1177-8.
5. Parigi GB. Pediatric surgery in Europe: problems and perspectives. J Indian Assoc Pediatr Surg 2002;7:121-9.
6. Parigi GB, Czauderna P, Rolle U, Zachariou Z. European census on pediatric surgery. Eur J Pediatr Surg 2017. doi: 10.1055/s-0037-1600524. Epub ahead of print.
7. Schmedding A, Rolle U, Czauderna P. European pediatric surgical training. Eur J Paediatr Surg 2017;3:245-50.
8. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to Diversity of child health care in Europe: a study of the European Paediatric Association/Union of National Paediatric Societies and Associations. J Pediatr 2016;177S:S1-10.

TÜRK PEDİATRİ ARŞİVİ
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Editorial

The role of paediatricians in implementing adequate social programs to assist children suffering parental loss

Ebeveyn kaybı yaşayan çocuklara yardımcı olmak için uygun sosyal programların gerçekleştirilmesinde pediatristlerin rolü

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Parental loss in children describes several circumstances, which besides death, are related to a prolonged absence of one or both parents or caregivers. Separation from familiar figures due to divorce, incarceration, prolonged absence for work or removal to foster care, are only few of the several factors that have been identified to contribute establishing a condition of parental loss.

During recent years the cases of parental loss have progressively grown among children living in the European area, likely reflecting substantial changes in the civil society, mainly related to several social, economic, cultural and technological trends that have impacted the traditional family structure, particularly during the last few decades. To this regard, factors like the recent 2008 economic turmoil and a progressive dissemination of undifferentiated and globalized social models have further favored the increasing negative impact of parental loss in children living in the European countries. In fact, the progressive homogenization of social and welfare programs, proposing generalized solutions to specific issues, seem to be often unable to effectively integrate at local level with the typical cultural diversities characterizing the various European social backgrounds. Social interventions applying the same operational models in different countries, appears in many circumstances insufficient to properly assist children coping with parental loss. Therefore, suggesting that the "*one fits all*" type of approach to deal with social challenges, may not provide efficient and long lasting solutions.

The authors of this commentary are part of a social pediatrics working group supported by European national pediatric societies (Turkish Paediatric Association, Italian Federation of Paediatricians, Romanian Social Pediatrics Society, Italian Society of Paediatrics) member of the European Paediatric Association, the Union of National Pediatric Societies and Associations (EPA/UNEPSA). The commentary aims at further raising the attention of pediatricians on the increasing impact of parental loss on children's life and in particular on their present and future health and wellbeing. To this regards the working group

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emphasizes the importance of assisting children challenged by parental loss, with adequate social programs of prevention and support, as well as the role that paediatricians may play in implementing these interventions. Such programs should be designed to properly adapting to different local needs, taking in account the cultural diversity and social backgrounds characterizing the Nations of the European area, in which families differs from culture to culture and from one nation to the other.

Definition of parental loss

Parental loss, in its wider meaning, also includes the concept of separation variously articulated in its several dimensions. Currently, there is no unifying definition of parental loss reported in literature. Parental loss is in fact the result of several different elements and independent circumstances, which are often difficult to be correlated. Whatever the cause, the impact of parental loss on the health and well been of children, seems however to be significant and possibly playing an important role in the pathogenesis of pathologic conditions in adulthood. For instance, parental loss has been associated with a variety of psychiatric disorders in adulthood (1), including a range of personality disorders (2), anxiety (1), addiction to drugs and alcoholism (3), and particularly depression (3, 4). Recent studies have also described psychobiological alterations related to parental loss suffered in childhood, which could manifest their effects later in life (5–7).

Childhood parental loss and adult mental disorders

There is a wide range of findings reported in literature about the impact of parental loss on the mental health of individuals through their life, which appear in many cases conflicting. It is however a general accepted notion that parental loss is a stress-causing event (8). To such regard, a large number of animal and human studies suggest long lasting effects of chronic stress on the brain structure involved in psychiatric disorders (8), and that certain areas of developing brain show the existence of early windows of vulnerability that are most susceptible to adversity than others (9).

Childhood parental loss has been suggested by various psychodynamic and developmental theories throughout the years, to be a main determining factor in the geneses of affective psychopathology disorders (9). The debate around this relation is still open, as a considerable number of clinical reports have indicated an existing association of depression and anxiety disorders with early parental death and prolonged parental separations, while other studies have reported that childhood parental death or separation are not related with mental disorders (9). Such different conclusions reported in literature may be due to the presence of significant methodology variants adopted by the studies published in literature. Among them, the heterogeneous composition of control groups adopted in the different studies, and most of all the lack of consensus in defining parental loss, possibly due to the variety and difference of causal conditions, may have been an obstacle to formulate conclusive analysis on the impact of this condition in the development of affective psychopathology disorders. Further factors, such as age or gender of the individual or the loss parent have been also indicated to possible influence the risk for mental illness in the wake of parental loss, but the scientific evidence for this is currently considered inconsistent, due to the lack of convincing data (10).

Among the range of conditions included in the state of parental loss, the event of a parent's death during childhood is certainly a most important traumatic experience that can frequently generate difficulties in adaptation and psychopathological problems occurring throughout the developmental age channels to the adulthood. The impact of parental death on children's health it also influenced by several concurring factors. For instance, it is a commonly accepted concept that the likelihood of experiencing a different impact from parental loss varies by locality and social circumstances (11). To such regard, ethnicity, social positioning or material circumstances have received little attention, as for instance migrations, economic disadvantages and discrimination may increase the children's vulnerability when dealing with parental loss. This can explain the absence of conclusive analysis for these factors, probably due to the scarcity of data about the long-term outcomes.

Thus while there is a consensus regarding the parental loss, considered in its wider meaning, been a stress causing events, a long lasting debate on its role in impacting children's mental health, and in generating adult psychopathologies is still open, due to the complexity of this multifactorial condition.

Psychobiological alterations related to parental loss

Stress-related perturbation of immunologic processes have been related to adult risk for morbidity and mortality in disease susceptibility through inflammatory mediators with a dysregulation of immune-modulating systems (i.e.: the sympathetic–adrenal–medullary system and the hypothalamic–pituitary–adrenal axis) (5). Parental loss suffered during childhood has been associated to increased levels of inflammatory molecules shown by the same subjects during their adulthood, as well as a disproportion of inflammatory mediators has been reported in the occasion of illnesses (ie, asthma, cardiovascular dis-

ease and cancer,) (5). Furthermore, a lower output of hormone cortisol has been described in individuals who had suffered a parental separation, and elevated levels of the inflammatory marker C-reactive protein were also documented among individuals who had experienced parental separation during childhood compared with those who had not (6, 7).

Several reports from the literature also emphasize that parental loss and in general early life events play a role on the onset of childhood functional gastrointestinal disorders (12). These reports indicate that early life events represent a significant risk factors in the development of an abnormal response to pain during adolescence and later in adulthood. Experimental and clinical studies provide evidences that early childhood is a critical time period in which psychological or physical trauma can induce visceral hyperalgesia. The important notion that complicated pathogenesis of functional gastrointestinal conditions may be in part related to early life events it is of great significance, since a timely intervention by establishing adequate clinical and social programs, may have a critical impact in the prevention of this group of chronic incapacitating conditions.

Thus, significant evidence has been provided by literature for the link at a neurobiological level between parental death and risk for psychopathology. However, future larger studies which should include an extended control for confounding factors, may offer additional insights and further elements to expand the knowledge on the mechanisms of the effects of loss on the development and prevention of depressive and anxiety disorders.

Conclusions

The loss of parents, family members or caregivers in general has been documented to be a major stressful and disturbing experience for children (1). Parentally bereaved children are more exposed to functional impairment and other multiple negative outcomes, including psychobiological, behavioral and mental problems. The damage and suffering, experienced by individuals during childhood are amplified in adult life when appropriate levels of support are not provided timely (12). Mainly due to the multiple dimension of parental loss and the different social and cultural contexts in which this condition takes place, a diversity of frameworks and psychosocial interventions have been proposed (12). They consist in a range of different types of approaches which include, besides a classic pharmacologic therapy, self-help, family interventions, support groups, counseling, and community resilience groups (13).

In most cases the interventions are delivered by a multiplicity of professionals and para-professional figures (eg, psychologists, nurses, social workers, pastoral groups) in varied formats (ie. individual or group support meetings, home visiting programs, online or telephone support teams), which effectiveness showed small to moderate effects (14). However, it has been shown that support programs targeting high-risk children and starting closer to the loss they have suffered, have been more effective (14). To such regard a substantial number of studies indicate the importance of respecting a specific time-frames for initiating the interventions, which is indicated to be within a year and a half after a death or in general a loss is suffered by children. However, there is no general consensus on this point, as few studies suggest a time interval of 5 years post-loss to be sufficient in establishing effective supportive interventions.

The social pediatrics working group collaborating with EPA/UNEPSA on the effects of parental loss in children, would like to stress the importance for pediatricians to be aware of the impact caused by this condition on the well-being of children. Pediatricians and particularly family pediatricians should be part and help local public health care systems in planning social programs of interventions, which should be initiated early after the loss (15). In fact, early psychological and social interventions for bereaved children and their families have been described to be an effective mean able to prevent acute distress levels and future psychopathology, such as post-traumatic and complicated grief effects (13). bereaved children should be provided with early information and involvement. Finally, following the correct notion of the "family oriented approach" in pediatric care, effective support programs should include the whole family.

References

1. Otowa T, York TP, Gardner CO, Kendler KS, Hettema JM. The impact of childhood parental loss on risk for mood, anxiety and substance use disorders in a population-based sample of male twins. Psychiatry Res 2014; 220: 404–9.
2. Pert L, Ferriter M, Saul C. Parental loss before the age of 16 years: a comparative study of patients with personality disorder and patients with schizophrenia in a high secure hospital's population. Psychol Psychother 2004; 77: 403–7.
3. Kendler KS, Sheth K, Gardner CO, Prescott CA. Childhood parental loss and risk for first-onset of major depression and alcohol dependence: the time-decay of risk and sex differences. Psychol Med 2002; 32: 1187–94.
4. Berg L, Rostila M, Hjern A. Parental death during childhood and depression in young adults - a national cohort study. J Child Psychol Psychiatry 2016; 57: 1092–8.

5. Herberth G, Weber A, Röder S, et al; LISAplus study group. Relation between stressful life events, neuropeptides and cytokines: Results from the LISA birth cohort study. Pediatr Allergy Immunol 2008; 19: 722–9.
6. Kraft AJ, Luecken LJ. Childhood parental divorce and cortisol in young adulthood: Evidence for mediation by family income. Psychoneuroendocrinology 2009; 34: 1363–9.
7. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α Mol Psychiatry 2016; 21: 642–9.
8. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 2009; 10: 434–45.
9. Cerniglia L, Cimino S, Ballarotto G, Monniello G. Parental Loss During Childhood and Outcomes on Adolescents' Psychological Profiles: A Longitudinal Study. Curr Psychol 2014; 33: 545–56.
10. Tyrka AR, Wier L, Price LH, Ross NS, Carpenter LL. Childhood parental loss and adult psychopathology: effects of loss characteristics and contextual factors. Int J Psychiatry Med 2008; 38: 329–44.
11. Ellis J, Dowrick C, Lloyd-Williams M. The long-term impact of early parental death: lessons from a narrative study. J R Soc Med 2013; 106: 57–67.
12. Bonilla S, Saps M. Early life events predispose the onset of childhood functional gastrointestinal disorders. Rev Gastroenterol Mex 2013; 78: 82–91.
13. Kirwin KM, Hamrin V. Decreasing the risk of complicated bereavement and future psychiatric disorders in children. J Child Adolesc Psychiatr Nurs 2005; 18: 62–78.
14. Currier JM, Holland JM, Neimeyer RA. The effectiveness of bereavement interventions with children: a meta-analytic review of controlled outcome research. J Clin Child Adolesc Psychol 2007; 36: 253–9.
15. Black D. Childhood bereavement: distress and long term sequelae can be lessened by early intervention. BMJ 1996; 312: 1496.

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Pilot study for the understanding and use of probiotics by different paediatric healthcare professionals working in different European countries

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Abstract

Background: Consumers' conviction of the benefits of probiotics is influenced by their existing beliefs and by the information they receive from healthcare professionals. The attitude of healthcare professionals towards commercially available probiotics will, therefore, determine how trustworthy and beneficial these products are perceived by consumers. Furthermore, due to European Union legislation, companies are prohibited from displaying information on product packaging; therefore, consumers are dependent primarily on healthcare professionals for correct information and guidance on the use of these products. The aim of this pilot study was to explore the understanding and use of probiotics in clinical practice by professionals who are involved in child healthcare in different European countries and to assess how much they value the scientific evidence behind these products.

Methods: The study was performed using a cross-sectional, descriptive, 30-question online questionnaire circulated among healthcare professionals belonging to three professional categories that are typically involved in childhood probiotic prescription: paediatricians, dieticians and general practitioners. The questionnaire was developed using web-based standard guidelines, and the questions were modelled on those used in previously published probiotics studies.

Results: Overall, 27,287 healthcare professionals belonging to three major European scientific societies were contacted by the organizations participating in the study. In total, 1360 valid questionnaires were recorded, and the results were statistically analysed.

Conclusions: The results emphasize the importance for healthcare professionals to be properly educated and updated on probiotics. An improved knowledge about probiotics led to increased prescriptive confidence. To disseminate accurate information on probiotics, healthcare professionals look for appropriate and scientifically validated educational platforms to acquire information, explore concerns and barriers and look for positive approaches towards recommending probiotics.

Keywords: Probiotics, Survey, Healthcare

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Introduction

Probiotics [1–3] are currently prescribed for a variety of clinical conditions [4, 5] with which there is credible evidence to support their use [5–8]. Guidelines have been developed by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) for the use of probiotics in the management of acute gastroenteritis [8, 9], and their use in the form of fermented products such as yogurt has been reported by ESPGHAN to prevent the occurrence of antibiotic-associated diarrhoea (AAD) [10]. Furthermore, meta-analyses [4, 11, 12] have shown probiotics to be effective in decreasing both the incidence and duration of common infectious diseases, such as upper respiratory tract infections, with a substantial impact on public health and socioeconomics [6]. Their beneficial use in clinical practice has been recently described in children for selected clinical conditions and in specific vulnerable groups [5]. However, the correct use of probiotics in clinical practice by healthcare professionals (HCPs) appears to be complicated by a limited knowledge of the scientific basis for their use and by the ample, yet confusing, information provided by industry on commercially available probiotic products. In general, primary care professionals do not rate their understanding of probiotics as very high, and they report being confused by the terminology used to describe the gut microbiological environment and the properties of probiotic-containing products, as in the case of live yogurts [13]. Consumers' conviction of the benefits of probiotics is influenced by their existing beliefs and by the information they receive from HCPs [14]. The attitude of HCPs towards commercially available probiotics will therefore determine how trustworthy and beneficial these products are perceived by consumers [15]. Furthermore, European Union (EU) [7] legislation prohibits companies from including informational text on probiotic packaging; thus, consumers are dependent primarily on HCPs for correct information and guidance on probiotic use.

In Europe, the field of paediatrics is characterized by a large amount of diversity, variation, and heterogeneity in the healthcare that is provided to the more than 200 million children below 18 years of age within the 53 European countries. This implies a significant diversity in the availability of commercially prescribed products and in the available information and prescription attitudes regarding these products [16]. The aim of this pilot study was to investigate the levels of understanding and use of probiotics in the clinical practice of European professionals who are involved in paediatric healthcare who work in different European countries (characterized by diverse medical training backgrounds) and to evaluate how much HCPs value the evidence behind these probiotics. A further aim was to investigate which educational platforms are considered by HCPs to be useful for acquiring information and exploring concerns and barriers and for providing positive approaches towards recommending probiotics. The results of this preliminary study help to decide whether to further engage in similar investigations involving additional countries and different types of HCPs in order to develop useful recommendations on how to disseminate accurate information on probiotics to the population and overcome possible local cultural barriers and/or insufficient medical communication.

Methods

This study was planned by the working group on nutrition of the Union of National European Paediatric Societies and Associations/European Paediatric Association (EPA/UNEPSA) and performed during July–October 2016. A questionnaire focusing on the understanding and attitude towards commercially available probiotic products was circulated among HCPs belonging to three professional categories that are typically involved in childhood probiotics prescription: paediatricians, dieticians and general practitioners.

Design of the questionnaire

A cross-sectional, descriptive, 30 question online was developed and validated in 2016 at the University of Nottingham School of Biosciences within the frame of the Master of Science degree programme in Advanced Dietetic Practice. It was designed in DanSurvey, a licenced product of LimeSurvey (Symfony, England), which is a free and open source online survey application written in PHP, based on a MySQL, PostgreSQL or MSSQL database, and distributed under the GNU general public license [17].

The questionnaire was developed using web-based standard guidelines [18], and the questions were modelled on those used in previously published studies on probiotics [19]. Factors that may influence the choice of probiotics, including demographics (country of work, gender, profession), areas of expertise, the association between nutrition and clinical practice and the attitude towards probiotics, were considered in the choice of questions [20].

In accordance with previous studies, the questionnaire was designed to take less than 30 min to complete in order to reach an acceptable compliance and response rate [21]. The 30 questions were divided into three sections: *About you* (*n.6*), *Probiotics* (*n.21*) and *How to get information to you* (*n.3*). The questionnaire was based predominantly on multiple choice questions with an open field to clarify the answer where required.

Survey participants and data collection

The Union of National European Paediatric Societies and Associations promoted the questionnaire among the 50 national European paediatric societies belonging to the organization. The national paediatric societies of Croatia, Italy, Turkey and Russia agreed to participate in the survey and circulated the questionnaire among their paediatrician members. In these four countries, only doctors certified in paediatrics are allowed to be involved in paediatric healthcare. Dieticians participating in the survey were from United Kingdom (UK), including members of the British Dietetic Association (BDA), which agreed to collaborate in the survey. Primary care gastroenterologists were also included in the study, as they are also involved in paediatric healthcare and are classified in the survey data analysis as general practitioners (GPs). The GPs were members of the European Society for Primary Care in Gastroenterology (ESPCG), a professional scientific society that also agreed to collaborate in the data collection by circulating the questionnaire among their European associates who are involved in paediatric care in hospital, community or primary care settings.

To facilitate data collection, the questionnaire was translated into the national language of the participating organizations (Croatian, Italian, Turkish and Russian). To ensure that the respondents accurately understood the authors' intention, the translated questionnaires were validated by the paediatrics and statistics departments of the following institutions: the Scientific Centre of Children's Health, Moscow, Russia; the University of Foggia, Italy; the University of Split Medical School, Croatia; and the University of Istanbul, Turkey. The participants were allowed to forward the link to the questionnaire to colleagues practising in European countries who were also involved in paediatric care and belonged to the same professional area (dieticians working in paediatric healthcare, paediatricians and GPs with expertise in paediatrics), thereby soliciting additional, completed questionnaires. This resulted in responses from countries in addition to the UK, Italy, Croatia, Turkey and Russia and is reported in the results section.

Statistics

Frequency analyses were applied to check for data errors, and any values outside of this range were easily identified [22] and recoded to fit into existing categories, otherwise new categories were created to group the responses. Most of the data were described using univariate analysis. Chi-squared tests were used to compare the respondents. A significance level of $p \leq 0.05$ was used. The 'other please specify' responses were subjected to content analysis, coded and added to the quantitative data.

SPSS software (version 23. 2015, IBM, USA) was used for statistical analysis, with a license obtained from Nottingham University for the purpose of this research. A convenience sample was used to compare the three groups (dietitians involved in paediatric care, GPs involved in paediatric care and paediatricians) [23].

The statistical analysis was validated at the University of Nottingham School of Biosciences in the UK within the frame of the Master of Science degree programme in Advanced Dietetic Practice and was further elaborated and confirmed by the statistical analysis unit of the European Association of Paediatrics and the University of Foggia Department of Paediatrics in Italy.

Ethics

Ethical approval was received from the School of Biosciences Research Ethics Committee (SBREC150106A, 12/10/2015). The survey was anonymous, with no personal or identifiable data being collected. The study was approved by the Ethics Committee of the European Paediatric Association/Union of National European Paediatric Societies, Office of Presidency.

Results

A total of 27,287 HCPs were contacted by the six scientific societies participating in the study, including 7000 dietitians contacted by BDA, 20,000 by the national paediatric societies of Croatia, Italy, Russia and Turkey, and 287 by ESPCG. In the study, 1604 responses were recorded; of these, 244 were removed due to insufficient data recorded on the forms, leaving 1360 valid questionnaires (Table 1). The highest absolute number of respondents ($n = 846$) were paediatricians, followed by dieticians ($n = 426$). Of the 287 GPs who received the questionnaire circulated by ESPCG among its members, 36 responded. GPs made up 2.6% of respondents, dietitians 31.3% ($n = 426$) and paediatricians 62.3% ($n = 846$). For the other 52 (3.8%) respondents, it was not possible to determine the profession, and their data were reported separately.

Respondent profile

All healthcare professionals enrolled in the study worked in the field of child healthcare. Of those who declared their gender, more women ($n = 1018$, 76.2%) than men ($n = 305$, 22.8%) contributed to the study (Table 1). The highest total number of respondents were from the UK ($n = 426$, 31.6%), followed by Russia ($n = 352$, 26.1%), Italy ($n = 227$, 16.9%), Turkey ($n = 224$, 16.7%) and Croatia ($n = 66$, 4.8). The remainder of respondents (54, 3.9%) were from different European countries, including 19 from Greece (1.3%). The majority of respondent dietitians were from the UK, while the respondent paediatricians were variously distributed among the four

Table 1 Characteristics of survey respondents. Breakdown by profession, country of origin, gender and year of graduation

Country	Dietitian N (%)	Paediatrician N (%)	GP N (%)	Other N(%)	Total N (% of respondents)
United Kingdom	409 (95.6)	10 (2.2)	5 (13.9)	2 (3.9)	426 (31.6)
Russia	2 (0.5)	342 (40.2)	2 (5.5)	6 (11.5)	352 (26.1)
Italy	2 (0.9)	201 (23.5)	7 (19.5)	17 (32.7)	227 (16.9)
Turkey	0	223 (26.2)	0	1 (1.9)	224 (16.7)
Croatia	0	66 (7.6)	0	0	66 (4.8)
Other country	13 (3.0)	4 (0.3)	22 (61.1)	26 (50.0)	54 (3.9)
Total	426 (100)	846 (100)	36 (100)	52 (100)	1360 (100)
Gender					
Female	388 (93.3)	585 (70.2)	15 (42.8)	30 (57.7)	1018 (76.2)
Male	24 (5.8)	240 (28.8)	20 (57.2)	21 (42.3)	305 (22.8)
Prefer not to say	4 (0.9)	9 (1.0)	0	0	13 (1.0)
Total	416 (100)	834 (100)	35 (100)	52 (100)	1336 (100)
When graduated					
last 5 years	158 (37.1)	330 (39.1)	6 (17.2)	14 (26.9)	508 (37.4)
5–15 years ago	118 (27.7)	197 (23.2)	5 (14.3)	17 (32.8)	337 (24.9)
> 15 years ago	150 (35.2)	316 (37.3)	24 (68.5)	21 (40.3)	511 (37.6)
Did not declare	0	1 (0.4)	0	0	1 (0.1)
Total	426 (100)	844 (100)	35 (100)	52 (100)	1357

European countries of the paediatric national societies that participated in the study. Only 14 paediatricians were from other European countries, of which 10 were from the UK (Table 1). The 36 respondent GPs were variously distributed among several European countries.

The respondents worked in different healthcare settings [16], which are reported in Fig. 1.

Dietitians mainly worked in hospitals ($n = 224$), followed by the community ($n = 199$). Overall, most of the paediatricians were hospital-based ($n = 611$), while the rest worked in primary care settings ($n = 235$).

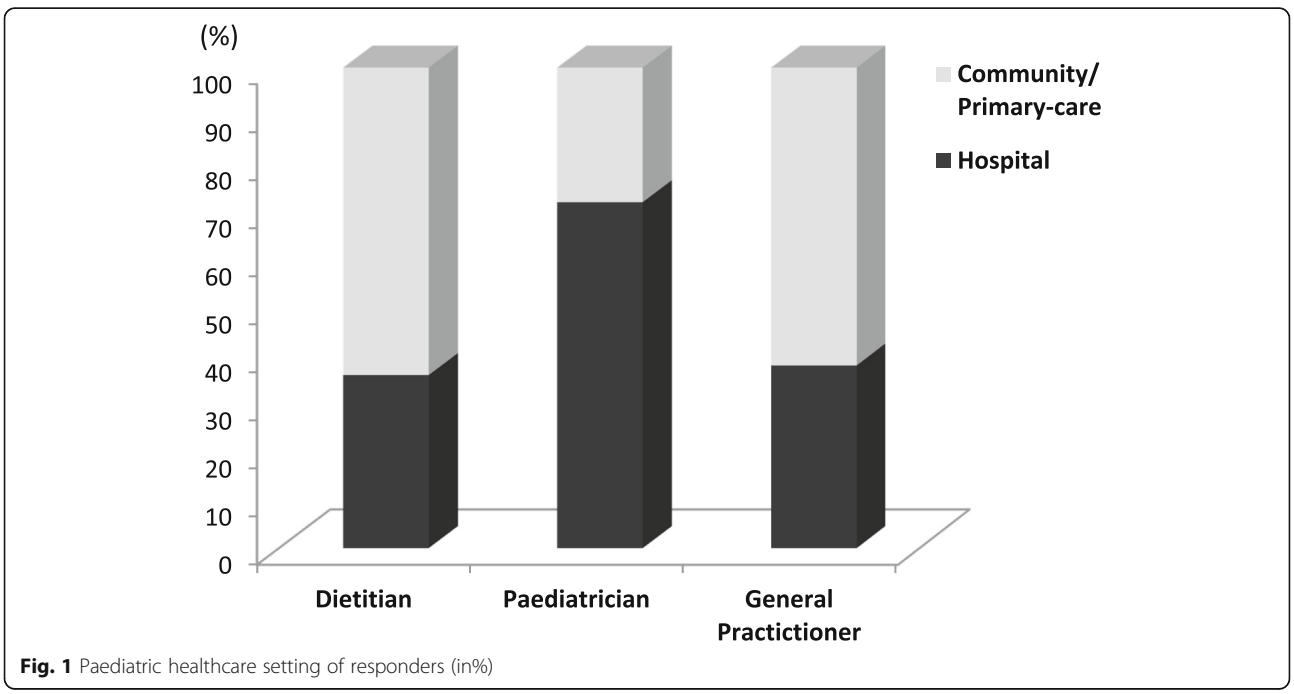

Fig. 1 Paediatric healthcare setting of responders (in%)

Regarding professional qualifications, 1357 respondents completed this question. The majority qualified more than 5 years ago (Table 1). In particular, 337 (24.9%) received their professional qualifications between 5 and 15 years ago, while 511 (37.6%) qualified more than 15 years ago.

Attitudes towards probiotics among different professions

Regarding the statement that nutritional advice plays an important role in clinical practice, there was a high level of agreement amongst the dietitians ($n = 298$, 83.2%), paediatricians ($n = 753$, 93.5%) and GPs ($n = 24$, 77.4%). Conversely, the dietitians also disagreed the most with this statement ($n = 57$, 15.9%), as shown in Table 2.

Of those who completed the question on whether probiotics have a place in clinical medicine, 86.3% ($n = 1068$) agreed. In contrast, 21.2% ($n = 78$) of the dietitians did not agree that probiotics had a place in clinical medicine. When respondents were asked whether they believed probiotics to be an evidence-based intervention for health, there was a higher level of agreement amongst paediatricians (76.4%, $n = 618$) and GPs (71%, $n = 22$), than dietitians (63.3%, $n = 223$). Dietitians who responded negatively totalled 37.5% ($n = 134$) as opposed to 23.6% ($n = 191$) of paediatricians and 29.1% ($n = 9$) of GPs.

Overall, HCPs are likely to suggest a probiotic food or drink ($n = 882$, 72.1%) in comparison to freeze-dried probiotics in tablet form. Dietitians ($n = 157$, 44.7%) were more likely to not recommend a probiotic food or drink (combined responses to 'don't know' or 'unlikely'), in comparison to 20% ($n = 163$) of paediatricians and 25% ($n = 8$) of GPs (Table 2). HCPs seem to be largely unaware that in Europe companies are legally prohibited from communicating about probiotics directly with consumers ($n = 842$, 78%).

HCPs rating their knowledge of the gut microbiota

When asked whether there is a need to educate HCPs about probiotics, 91% ($n = 1120$) of the respondents answered positively. The survey asked the respondents to rate their level of training in probiotics and their knowledge of the gut microbiota. When comparing the three professional groups, dietitians had the least training in

Table 2 Attitude of HCPs towards nutritional advice and probiotics

		Dietitian	Paediatrician	General Practitioner	other	did not declare	Total
Nutritional advice plays an important role in my clinical practice.	Disagree	57	34	3	0	1	95
		15.9%	4.2%	9.7%	0.0%	4.8%	7.7%
	Neutral	3	18	4	1	0	26
		.8%	2.2%	12.9%	5.6%	0.0%	2.1%
	Agree	298	753	24	17	20	1112
		83.2%	93.5%	77.4%	94.4%	95.2%	90.2%
Probiotics have a place in clinical medicine.	Disagree	14	47	5	0	0	66
		3.9%	5.8%	16.1%	0.0%	0.0%	5.3%
	Neutral	64	36	0	1	2	103
		17.9%	4.4%	0.0%	5.6%	9.5%	8.3%
	Agree	279	727	26	17	19	1068
		78.2%	89.8%	83.9%	94.4%	90.5%	86.3%
Probiotics are an evidence based intervention for health?	Disagree	34	38	3	0	2	77
		9.5%	4.7%	9.7%	0.0%	9.5%	6.2%
	Not sure	100	153	6	8	5	272
		28.0%	18.9%	19.4%	47.1%	23.8%	22.0%
	Agree	223	618	22	9	14	886
		62.5%	76.4%	71.0%	52.9%	66.7%	71.7%
How likely are you to suggest a probiotic food or drink?	Unlikely	98	103	7	4	5	217
		27.9%	12.8%	22.6%	23.5%	23.8%	17.7%
	Don't know	59	60	1	2	3	125
		16.8%	7.5%	3.2%	11.8%	14.3%	10.2%
	Likely	194	641	23	11	13	882
		55.3%	79.7%	74.2%	64.7%	61.9%	72.1%

probiotics, with 91.9% ($n = 328$) describing their training in probiotics as some/a little versus 51.3% ($n = 416$) of paediatricians (Fig. 2).

When assessing how HCPs rate their knowledge of gut microbiota/intestinal flora, 16.5% ($n = 59$) of dietitians rated their knowledge as quite high. This is in contrast to paediatricians, where 54.3% ($n = 437$) rated their knowledge as quite high (Table 3).

Looking at how the level of training in probiotics correlates to the likelihood of recommending a probiotic food or drink, the data analysis indicates a moderate but significant positive correlation ($r = 0.241$) with the highest level of training ("quite a lot"). The chi-squared tests suggested that HCPs who had much training were more likely to recommend probiotics ($p < 0.005$) (Fig. 3).

Health disorders indicated by HCPs to benefit from probiotic prescriptions

The patient groups that paediatricians and dietitians are most likely to recommend probiotics for are children with irregular bowel movements and diarrhoea ($n = 705$, 51.8%). Within this result, 72.9% ($n = 617$) of paediatricians, as opposed to 12.4% ($n = 53$) of dietitians, would recommend a probiotic for children with irregular bowel movement and diarrhoea. Pertaining to diarrhoea in young children, 73.8% ($n = 624$) of paediatricians, as opposed to 14.1% ($n = 60$) of dietitians and 47% ($n = 17$) of GPs, would recommend a probiotic. Among the dietitians, 48.4% ($n = 206$) would recommend a probiotic for bloating and 58.5% ($n = 249$) for irritable bowel syndrome (IBS) across the general population. For allergies in the general population, 42% ($n = 355$) of paediatricians, as opposed to 7.7% ($n = 33$) of dietitians and 11% ($n = 4$) of GPs, would recommend a probiotic.

HCPs' evaluation about the evidence supporting probiotics

The areas where the majority of HCPs ($n = 957$, 81.5%) agreed on the efficacy of probiotics include the role of probiotics in balancing the intestinal flora and enhancing its functionality. The majority of paediatricians confirmed their belief in the evidence behind AAD ($n = 553$, 71.1%). Overall, 67.6% of HCPs agreed with the evidence ($n = 803$, 67.6%) for AAD. Forty percent ($n = 313$) of paediatricians stated that probiotics alleviated thrush, compared to 18% ($n = 63$) of dietitians and 26.7% ($n = 4$) of GPs. The questions did not specify oral thrush. A large percentage of HCPs neither agreed nor disagreed with the statements that probiotics alleviate thrush ($n = 512$, 43.8%), allergic psoriasis ($n = 696$, 59.4%), improve infection control ($n = 538$, 45.6%) and reduce the risk of a light common cold ($n = 520$, 44.8%).

Position of HCPs on probiotic information

The survey contained 10 statements on probiotics where respondents could select whether they agreed with the statement. Figure 4 summarizes the results by percentage of the responses from each of the HCP groups (dietitians, paediatricians and GPs). Over 76% ($n = 482$, 76.3%) of paediatricians were familiar with the World Health Organization (WHO) definition of probiotics [16], as opposed to 55.7% ($n = 230$) of dietitians. The majority of dietitians agreed that not all yogurts have proven clinical evidence of health benefits (67.8%, $n = 280$), as did 70% of GPs ($n = 21$), while 44.5% ($n = 281$) of paediatricians

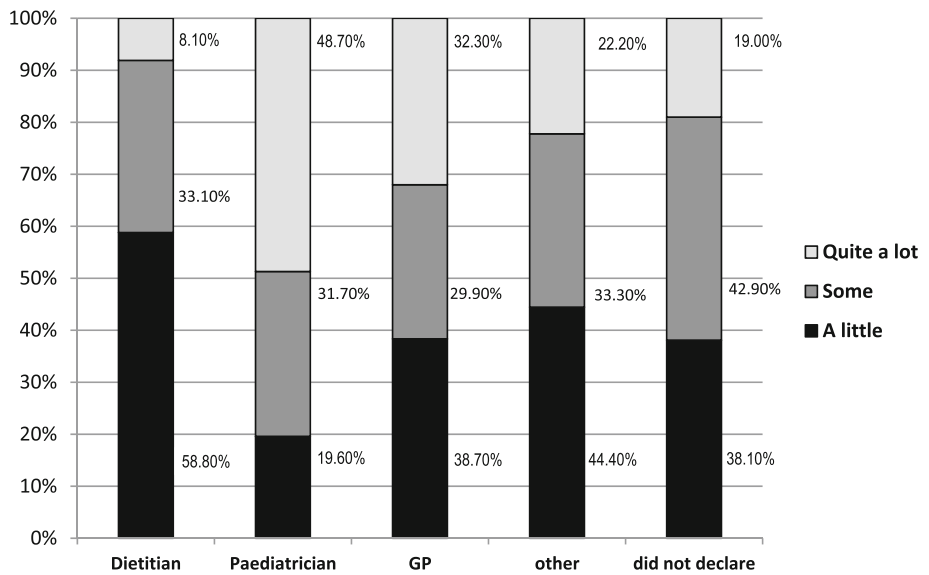

Fig. 2 Level of training in probiotics reported by HCPs

Table 3 How HCPs rate their knowledge of the gut microbiota

	Dietitian N (% of respondents)	Paediatrician N (% of respondents)	GP N (% of respondents)	Other N (% of respondents)
Quite a lot	59(16.50)	437(54.30)	15(48.40)	6(37.5)
Some	158(44.30)	279(34.70)	13(41.90)	5(31.3)
A little	140(39.20)	89(11.10)	3(9.70)	5(31.3)

agreed with the statement. Figure 5 displays the probiotic formulation that HCPs participating to the study prefer to recommend.

Regarding whether probiotic yogurts contain additional bacteria with proven health benefits, 40.4% ($n = 167$) of dietitians and 40.7% ($n = 257$) of paediatricians agreed, as opposed to 33.3% ($n = 10$) GPs. Dietitians and paediatricians agreed that a tablet/powder would be as effective as a food (31.7% ($n = 131$) and 28.3% ($n = 179$), respectively).

Areas of concern raised by HCPs

As dietitians responded more cautiously to whether they would recommend probiotics, it was worth further investigating their concerns. Their concerns were captured as free text and were then grouped into 5 areas. Table 4 shows the number of dietitians that raised these concerns. The most frequently cited concerns were of immunosuppressed patients and knowledge/education, followed closely by evidence/efficacy. Cost was also a concern raised by HCPs, although in a limited number of respondents. A chi-squared test showed how these concerns impact recommendation habits: the more concerns an HCP has, the less likely they are to regularly recommend a probiotic ($p < 0.005$) (Fig. 6).

Preferred mean for continuing education

HCPs prefer to obtain information at conferences ($n = 995$, 86.8%), workshops ($n = 945$, 82.6%), courses ($n = 926$, 81.3%) and study days ($n = 795$, 73%) rather than from social media sites, where 20.2% ($n = 215$) selected Facebook, 14.5% ($n = 152$) selected Twitter, 14% ($n = 115$) selected Linked In, 6.8% ($n = 71$) selected Instagram, and 5.2% ($n = 54$) selected Pinterest.

Discussion

There is an increasing demand from the general population for credible information about probiotics and their use in clinical practice. In particular, HCPs are considered by children's families and caregivers as the gatekeepers of dependable probiotic information. This questionnaire aimed at providing useful data able to better assist the development of proper responses to the request for viable information. The study investigated the attitudes towards probiotics of HCPs working in different European countries. The purpose of this study was

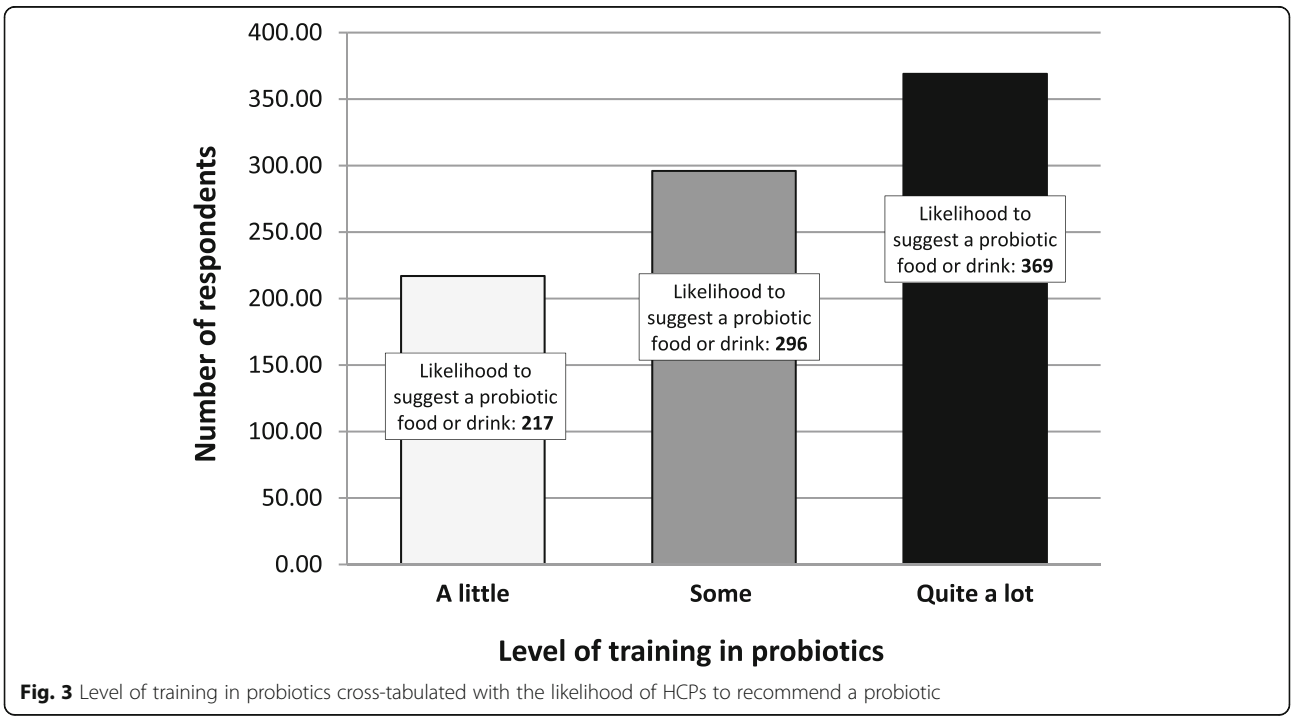

Fig. 3 Level of training in probiotics cross-tabulated with the likelihood of HCPs to recommend a probiotic

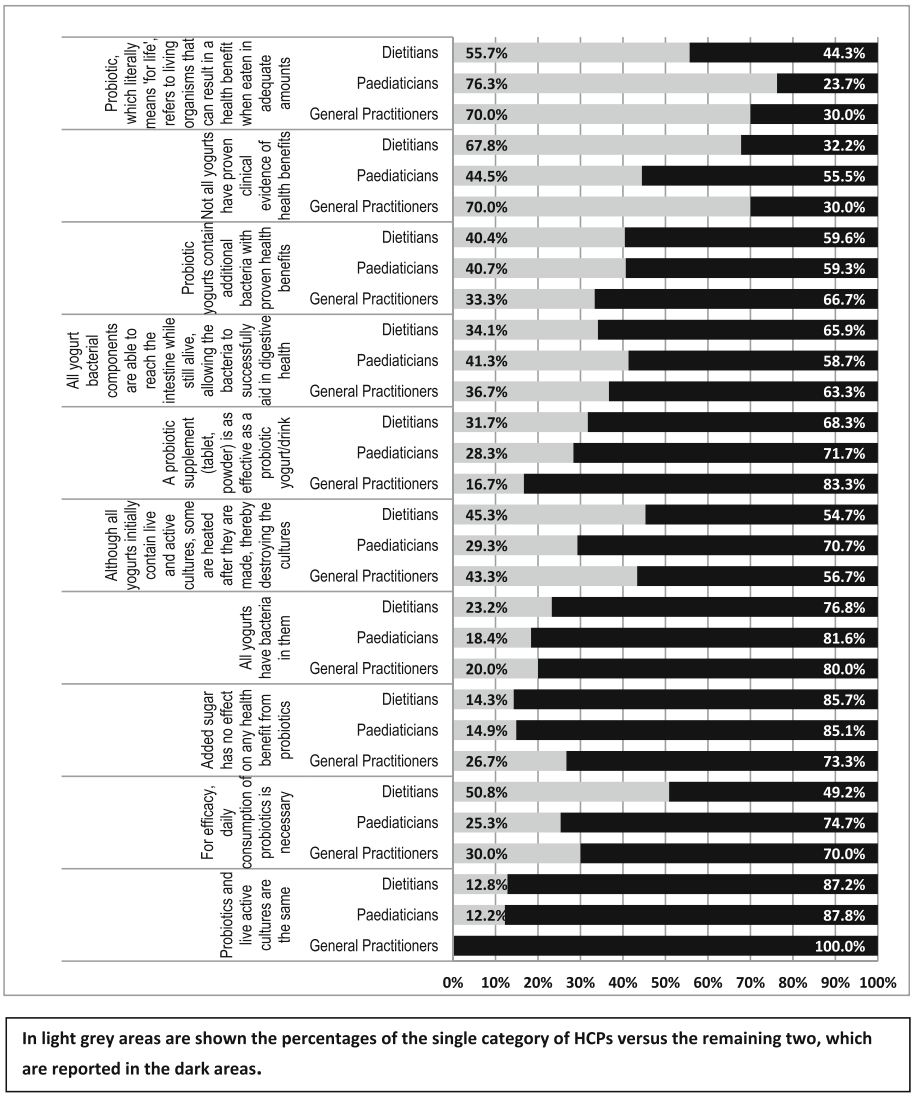

Fig. 4 Statements about the use of probiotics. Percentage of statements that HCPs have agreed with

to explore HCPs' prescribing attitudes, counselling habits and knowledge of probiotics to obtain data that would be useful for developing proper, although generalized, recommendations for education on this topic, regardless of possible existing differences among the countries where the HCPs practice.

In general, the results of this study confirm that the knowledge and interest about the role of gut microbiota in health and disease has significantly increased in recent years, most likely due to the considerable number of high-quality studies and meta-analyses published in the scientific literature [24–26]. In fact, the majority of all HCPs in the study (86.3%) agreed that probiotics have a place in clinical medicine, and a significantly large number of them (72%) are likely to recommend a probiotic. These results were similar, with no significant differences in percentage of answers between the UK dietitians and the four groups of paediatricians working in the different countries (Croatia, Italy, Russia and Turkey), who are characterized by a diverse medical background and training in paediatrics [16].

However, data from the group of 409 dietitians working in UK indicate that this group of professionals do not agree to the same degree that probiotics are an evidence-based intervention for health. In fact, on further investigation, the data showed that only 55.3% of dietitians were likely to recommend a probiotic, although they believed probiotics have a place in clinical medicine (78.2%), and only 37% percent of dietitians reported being unsure or not convinced of the evidence. These findings show a lower percentage than those found in a previously published UK survey that was

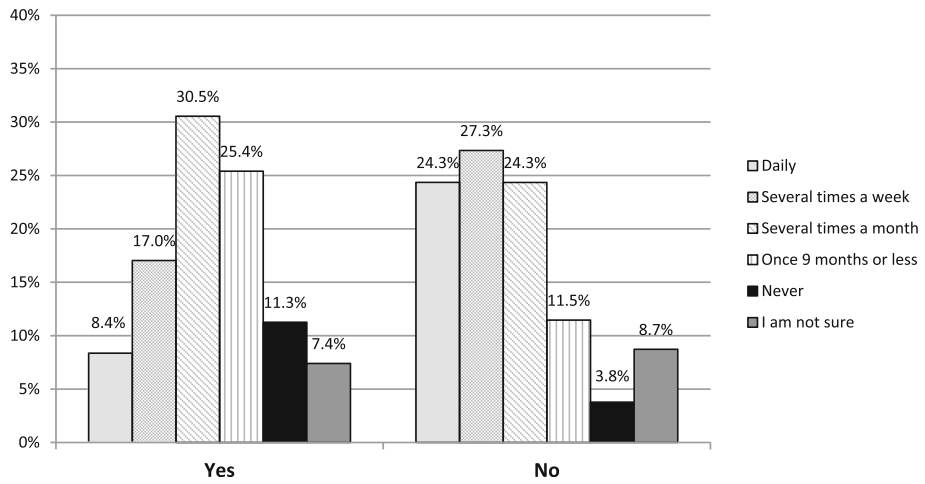

Fig. 6 The cross-tabulation of recommendation of probiotics in practice according to concerns about their use

carried out predominantly amongst clinical practice nurses and among GPs and dietitians, where 91.2% of dietitians were likely to recommend a probiotic [13].

The questionnaire showed that among the three categories of HCPs participating in this study, paediatricians appeared to be more confident in their knowledge of probiotics and their ability to recommend a specific product, regardless of the country in which they practised. However, it is not possible to conclude whether this finding could be generalized or is related to local factors, such as medical background, practising habits or commercial information that could influence the prescription habits of the paediatricians working in the four participating countries. Furthermore, when asked to choose the statements they agreed with (out of a list of 10 statements), the group of dietitians working in the UK had a low level of awareness of the WHO definition of a probiotic, although it has been widely publicized. In contrast, paediatricians working in Croatia, Italy, Russia and Turkey and GPs practising in different European countries had a higher level of agreement on the definition of a probiotic (see Fig. 4).

The majority of HCPs were unaware that EU legislation prohibits manufacturers of probiotic-containing products from labelling their products and communicating about probiotics with consumers [27]. The results of this study emphasize the importance of HCPs to be properly educated [28] and updated on probiotics, as patients and families would like their HCPs to be informed and knowledgeable about using probiotics as a treatment option and need to feel comfortable in talking about the use of probiotics as part of complementary treatments [29]. The results of this survey also suggest that, in general, increased knowledge about probiotics leads HCPs to have increased confidence regarding these products [30]. Professionals who rated their knowledge as high were also more likely to recommend a probiotic. Finally, to acquire further information on probiotics, the majority of HCPs favoured more traditional forums, such as courses, workshops, conferences and study sessions.

Table 4 Areas of concerns for dietitians recommending probiotics

Concern	n (%)
Immunosuppressed patients	50 (28%)
Education	49 (28%)
Evidence/Efficacy	46 (26%)
Cost	19 (11%)
Other	12 (7%)
Total concerns raised	176

Conclusions

The purpose of this study was to contribute to a better understanding of probiotics in the clinical practice of European professionals who are involved in paediatric healthcare. However, the existing diversity in paediatric healthcare systems and the diverse medical context between European countries are limiting factors for studies aiming at developing standardized clinical practice or medical education programmes. Indeed, there are huge variations in Europe in the delivery of healthcare services, prescribing habits and medical counselling for children and families [16]. For instance, there are significant differences among European countries in the organization of paediatric hospital and nonhospital first-contact services. These services are provided in various forms among the 53 European countries, and they depend on whether primary care GPs, primary care paediatricians or a combination are primarily responsible for care and whether other HCPs, such as nurses or

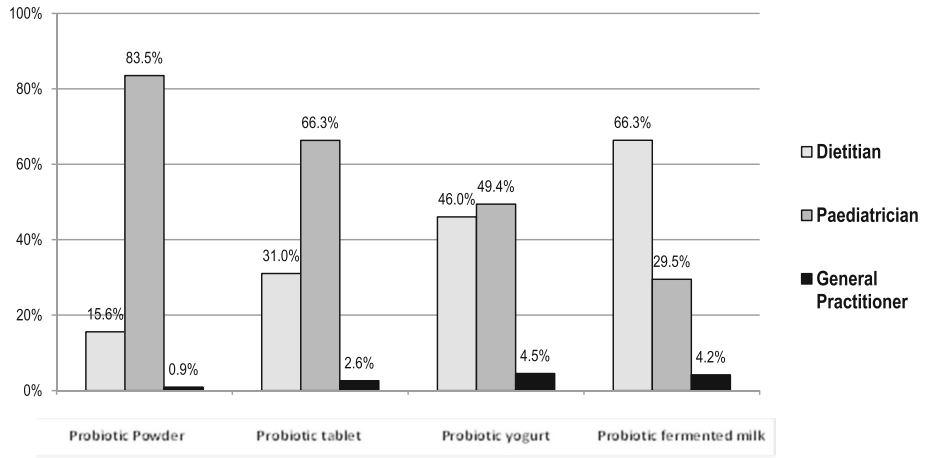

Fig. 5 Formulation of probiotic HCPs prefer to recommend

dieticians, are involved instead of paediatricians in certain areas of clinical care, including nutrition.

These factors have a general impact on studies involving different European medical contexts and may account for the intrinsic limitations of this study, such as the development of comparable conclusions between the data obtained from different countries. However, although it is not possible to draw conclusive evidence or develop generalized guidelines or protocols based on the results of this study, the data generated here offer practical, helpful information that may contribute to the development of useful recommendations for local European contexts.

In particular, the results of this study suggest that educational institutions, scientific organizations and policymakers should develop programmes to provide HCPs and their professional bodies with up-to-date, validated scientific content as training materials. Training programmes need to address basic and targeted health concerns, including information on what a probiotic is, which strains are present in commercial products, which health disorders could benefit from the use of probiotics, and finally, what the appropriate dosages are.

Educational institutions, scientific organizations and policymakers could play key roles to develop scientifically accurate and evidence-based educational content on probiotics. As probiotics are often commercially produced, industry could provide effective information platforms to better circulate correct and scientifically validated information to the public.

Finally, the findings of this pilot study suggest that this type of investigation should be expanded, and specific comparisons between groups of HCPs based on the country of work, the area of expertise and the clinical field should be carefully explored. Further studies would enable the acquisition of valuable information to help develop recommendations for the use of probiotics in paediatric clinical practice.

Abbreviations

AAD: Antibiotic Associated Diarrhoea; BDA: British Dietetic Association; EPA/UNEPSA: Union of National European Paediatric Societies and Associations/European Paediatric Association; ESPCG: European Society for Primary Care in Gastroenterology; ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; EU: European Union; GPs: General Practictioners; HCPs: Healthcare Professionals; IBS: Irritable Bowel Syndrome; UK:: United Kingdom; WHO: World Health Organization

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

The following Authors: MPM, FCC, MV, JM, LN, RP, IG, MC, LNB have made substantial contributions to the conception and design of the work; they have also all contributed to the acquisition, analysis and interpretation of data. All listed Authors have approved the submitted version of the manuscript and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Ethics approval and consent to participate
Ethical approval was received from the School of Biosciences Research Ethics Committee (SBREC150106A, 12/10/2015). The survey was anonymous with no personal or identifiable data being collected.
The Study was ethically approved by the Ethics Committee of the European Paediatric Association/Union of National European Paediatric Societies, Office of Presidency.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett C, Knight R, Jeffrey I, Gordon I. The human microbiome project: exploring the microbial part of ourselves in a changing world. Nature. 2007;449(7164):804–10.
2. Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the human microbiome. Nutr Rev. 2012;70(Suppl 1):S38–44.
3. Dahiya DK, Renuka PM, Shandilya UK, Dhewa T, Kumar N, Kumar S, Puniya AK, Shukla P. Gut microbiota modulation and its relationship with obesity using prebiotic fibers and probiotics: a review. Front Microbiol. 2017;8(563):1–17.
4. King S, Glanville J, Sanders ME, Fitzgerald A, Varley D. Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and metaanalysis. Br J Nutr. 2014;112:41–54.
5. Hojsak I, Fabiano V, Pop TL, Goulet O, Zuccotti GV, Çokuğraş FC, Pettoello-Mantovani M, Kolaček S. Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups. Acta Paediatr. 2018;107(6):927–37.
6. Prodeus A, Niborski V, Schrezenmeir J, Gorelov A, Shcherbina A, Rumyantsev A. Fermented Milk consumption and common infections in children attending day-care centers: a randomized trial. J Pediatr Gastroenterol Nutr. 2016;63:534–43.
7. Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, Krabshuis J, Lemair T, Aufmann P, Paula JA. World gastroenterology organisation global guidelines: probiotics and prebiotics october 2011. J Clin Gastroenterol. 2012;46:468–81.
8. Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, Vandenplas Y, Weizman Z, on behalf of the ESPGHAN working Group for Probiotics and Prebiotics. Use of probiotics for Management of Acute Gastroenteritis: a position paper by the ESPGHAN working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2014;58:531–9.
9. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European society for pediatric gastroenterology, hepatology, and nutrition/european society for pediatric infectious diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr. 2014;59:132–52.
10. Szajewska H, Berni Canani R, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z, on behalf of the ESPGHAN working Group for Probiotics/prebiotics. Probiotics for the prevention of antibiotic-associated diarrhea in children. J Pediatr Gastroenterol Nutr. 2016;62(3):495–506.
11. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev. 2015;(2):CD006895.
12. Kang E-J, Kim SY, Hwang I-H, et al. The effect of probiotics on prevention of common cold: a meta-analysis of randomized controlled trial studies. Korean J Fam Med. 2013;34:2–10.
13. Jordan D, Johnson N, Thomas L. Probiotics in primary care: a survey of health professionals. Pract Nurs. 2015;26:402–5.
14. Schultz M, Baranchi A, Thurston L, Ching Yu Y, Wang L, Chen J, Sapsford M, Chung J, Binsadiq M, Craig L, Wilkin B, Mcbride D, Herbison P. Consumer demographics and expectations of probiotic therapy in New Zealand: results of a large telephone survey. N Z J Math. 2011;2124:36–43.
15. Bruhn C, Bruhn J, Cotter A, Garrett C, Klenk M, Powell C, Stanford G, Steinbring Y, West E. Consumer attitudes toward use of probiotic cultures. J Food Sci. 2002;67:1969–72.
16. Ehrich J, Namazova-Baranova L, Pettoello-Mantovani M. Introduction to "diversity of child health Care in Europe: a study of the European Paediatric association/Union of National European Paediatric Societies and Associations". J Pediatr. 2016;177S:S1–10.
17. GNU Operating System. GNU GENERAL PUBLIC LICENSE Version 3, 29 June 2007. https://www.gnu.org/licenses/gpl-3.0.en.html. Accessed 18 June 2018.
18. Pealer LN, Weiler RM, Pigg RM Jr, Miller D, Dorman SM. The feasibility of a web-based surveillance system to collect health risk behavior data from college students. Health Educ Behav. 2001;28:547–59.
19. Nichols JAA, Paul R, Roche N. A web questionnaire to determine the advice general practitioners give on probiotics. J Nutr Environ Med. 2005;15(4):212–22.
20. Draper K, Ley C, Parsonnet J. Probiotic guidelines and physician practice: a cross-sectional survey and overview of the literature. Benefic Microbes. 2017;8(4):507–19.
21. Galesic M, Bosnjak M. Effects of questionnaire length on participation and indicators of response quality in a web survey. Public Opin Q. 2009;73:349–60.
22. De Vaus D. Surveys in social research. 5th ed. London: Routledge; 2002.
23. Etikan I, Musa SA, Alkassim RS. Comparison of convenience sampling and purposive sampling. Am J Theor Appl Stat. 2016;5:1–4.
24. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The international scientific Association for Probiotics and Prebiotics Consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11:506–14.
25. Johnston BC, Goldenberg JZ, Vandvik PO, Sun X, Guyatt GH. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev. 2011;(11):CD004827.
26. Leyer GJ, Li S, Mubasher ME, Reifer C, Ouwehand AC. Probiotic effects on cold and influenza-like symptom incidence and duration in children. Pediatrics. 2009;124:e172–9.
27. EFSA finalises the assessment of 'general function' health claims. European Food Safety Authority. https://www.efsa.europa.eu/en/press/news/110728. Accessed 18 June 2018.
28. Pettoello-Mantovani M, Campanozzi A, Maiuri L, Giardino I. Family-oriented and family-centered care in pediatrics. Ital J Pediatr. 2009;35(1):12.
29. Chin-Lee B, Curry WJ, Fetterman J, Graybill MA, arpa K. Patient experience and use of probiotics in community-based health care settings. Patient Prefer Adherence. 2014;8:1513–20.
30. Macdonald-Wicks LK, Gallagher LM, Snodgrass SJ, Guest M, Kable A, James C, Ashby S, Plotnikoff RC, Collins CE. Difference in perceived knowledge, confidence and attitudes between dietitians and other health professionals in the provision of weight management advice. Nutr Diet. 2015;72:114–21.

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REVIEW ARTICLE

Paediatricians play a key role in preventing early harmful events that could permanently influence the development of the gut microbiota in childhood

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Keywords
Dysbiosis, Gut microbiota, Prebiotics, Probiotics, Synbiotics

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ABSTRACT

Aim: The development of the gut microbiota occurs primarily during infancy, and growing evidence has emphasised its positive role and implications for human health. The aim of this review was to provide essential knowledge about the gut microbiota and to describe and highlight the importance of the factors that influence the gut microbiota in early life and their potential harmful effects later in life.

Methods: The European Paediatric Association, the Union of the National European Paediatric Societies and Associations, convened a panel of independent European experts to summarise the research on microbiota for general paediatricians. They used PubMed and the Cochrane Library to identify studies published in English up to June 2018.

Results: A number of clinical conditions can disrupt the development of a stable gut microbiota. Changes in the microbiome have been documented in many chronic diseases, mainly immune-mediated gastrointestinal and liver diseases, and distinct patterns have been associated with each specific disease. The gut microbiota can be positively modulated with probiotics, prebiotics, synbiotics, paraprobiotics and postbiotics.

Conclusion: Paediatricians can play a key role in preventing harmful events that could permanently influence the composition and/or function of the gut microbiota. Various treatment strategies can be used.

INTRODUCTION

The microbial communities hosted by the human gut have been forged over millions of years of co-evolution with humans, to achieve a symbiotic relationship leading to physiological homoeostasis. The gut microbiota has become a new, fascinating and promising area of research, which enables us to understand the development of gut functions and some health disorders and diseases, as well as their treatment or prevention.

The development of the gut microbiota occurs primarily during infancy. Evidence regarding the implications of the gut microbiota in children is increasing, and new insights have been reported about the development of the microbiome during early life. For example, advances in genome sequencing technology and metagenomic analysis are increasing our broader understanding of the gut microbiota and highlighting differences between healthy and diseased states. Healthcare professionals involved in paediatric care may find it difficult to interpret the complex data published in specialised literature. However, this information is of considerable importance in paediatric practice. Different definitions have also caused confusion. These include the interchangeable use of the basic terms microbiome and

Key notes

- The aim of this review was to describe what is already known about the gut microbiota, by focusing on the factors that influence its early development and potential harmful effects later in life.
- Our review showed that changes in the microbiome have been documented in many chronic diseases, mainly immune-mediated gastrointestinal and liver diseases.
- Paediatricians can positively modulate the gut microbiota by using probiotics, prebiotics, synbiotics, paraprobiotics and postbiotics.

microbiota by the medical community and the general public when they are talking about the local mini-ecosystem of a collection of microorganisms in the gut.

METHODS

The European Paediatric Association, the Union of the National European Paediatric Societies and Associations, convened a panel of eight independent European experts from five countries to outline the essential elements of the current knowledge on the gut microbiota that may be useful for general paediatricians in their practice. The panel was chosen based on the experts' scientific profiles and publication history, and all members were active participants in the work and activities of the association. The panel held their first meeting with regard to this review at the 8th Europaediatrics Congress in Bucharest in June 2017, where they discussed relevant issues about the definition and function of the gut microbiota. They decided that a particular focus of this review would be to highlight the factors that influence the gut microbiota in early life, as well as their potential harmful effects in later life, for the benefit of general paediatricians. Each panel member was responsible for reviewing the literature on a given topic, according to their specific expertise. They searched for papers published in English up to June 2018 by using PubMed and the Cochrane Library. The members then summarised the relevant findings on their given topic, and the panel discussed the findings discussed in a series of meetings until they reached a final consensus.

RESULTS

A microbiological approach to understanding the gut microbiota

Previously called the gut microflora, the microbial communities are composed of approximately 10^{14} bacteria, which is approximately 10 times the number of cells in the human body (1). The term gut microbiota refers to the organisms that comprise the microbial community, while the term microbiome refers to the collective genomes of the microbes, including bacteria, bacteriophages, fungi, protozoa and viruses that live inside and on the human body. The gut microbiota may be considered a human organ that can be transplanted, and it has its own functions, such as modulating the expression of genes involved in mucosal barrier fortification, angiogenesis and postnatal intestinal maturation of several gut-associated systems (2).

The gut microbiota comprises more than 2000 microbial species. Its diversity has been revealed by the application of metagenomics: 16S ribosomal ribonucleic acid gene or deoxyribonucleic acid (2). *Firmicutes* and *Bacteroidetes* are the two dominant bacterial phyla in most individuals. Other phyla include *Proteobacteria, Actinobacteria*, *Fusobacteria* and *Verrucomicrobia* (2). Groups of bacterial families have been classified into enterotypes on the basis of their functions. The term enterotype and its definition remain debated. For example, the classification may be based on the metabolism of dietary components and the ability to metabolise drugs. The aim of this classification is to help us to understand the role of the gut microbiota in health and disease. Ageing is associated with changes in the diversity of noncultured species that current laboratory culturing techniques are unable to grow in the laboratory. These are a greater proportion of *Bacteroides*, a distinct abundance of *Clostridium* clusters, an increased enterobacteria population and a lower number of bifidobacteria. The taxonomic alterations may be due to changes in diets, such as less fibre, and/or, the increased use of antibiotics with advancing age (3).

There is no definition of a normal microbiota, since the bacterial species vary in different groups of individuals. The vast majority of microbial species give rise to symbiotic host–bacterial interactions that are fundamental for human health. Disrupting the development of a stable gut microbiota, which is known as dysbiosis, may be associated with several clinical conditions. These include nosocomial infections, necrotising enterocolitis in premature infants, inflammatory bowel disease, obesity, autoimmune diseases, allergies or even functional bowel disorders or behavioural problems.

Factors influencing neonatal intestinal colonisation

Foetal colonisation and prematurity

The sterility of the gut of the foetus *in utero* has been challenged by studies that have identified bacteria, bacterial deoxyribonucleic acid or bacterial products in the meconium, amniotic fluid and placenta. These indicate the initiation of microbial colonisation from the mother to offspring (4,5). Therefore, during developmental phases, the foetus could encounter bacteria *in utero* that might contribute to establishing the microbiota before delivery. This prenatal bacterial colonisation of the foetal gut might be a source of microbial stimulation, providing a primary signal for the maturation of a balanced postnatal innate and adaptive immune system. However, studies stating the existence of this *in utero* microbiota remain controversial (3,4). Importantly it has been shown that meconium with low bacterial diversity has been associated with a more frequent onset of sepsis in very low birth weight babies (6).

The first and most important phase of normal colonisation occurs when the newborn foetus passes through the birth canal and ingests maternal vaginal and faecal microorganisms. These bacteria proliferate further when oral feeding is initiated. After 48 hours, the number of bacteria is already as high as around10^4–10^6 colony-forming units per millilitre of intestinal content. However, many factors can influence this process and they may potentially impair the establishment of what is known as symbiosis (7) (Fig. 1).

The pattern of bacterial colonisation in preterm infants differs from the pattern observed in the healthy gut of full-term infants during the neonatal period (7). This abnormal colonisation, which is mostly due to the routine use of sterile formula and antibiotics in neonatal intensive care units, could play a central role in feeding intolerance. It

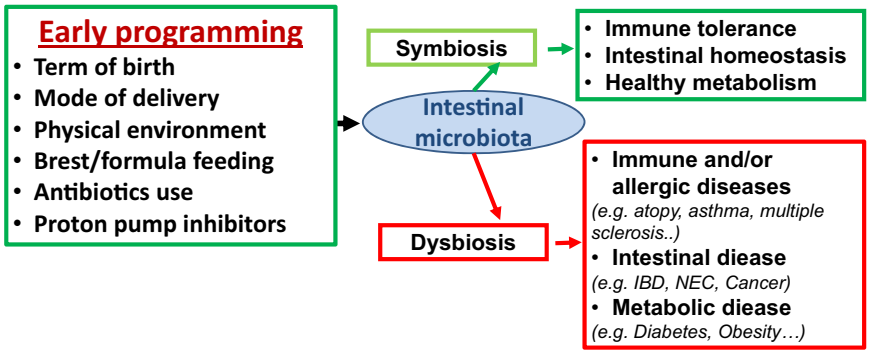

Figure 1 Role of neonatal bacterial colonization in establishing symbiosis.

could also be indicated in the development of necrotising enterocolitis, which is a severe disease primarily that affects premature infants and often leads to death or short bowel syndrome, which requires an extensive bowel resection (6).

Mode of delivery

The microbiota of vaginally delivered infants mirrors the vaginal and gut microbiota of the mother. Infants delivered by Caesarean section have reduced bacterial biodiversity, and colonisation by *Bifidobacteria* can be delayed by up to six months, in contrast to vaginally delivered infants (7,8). Infants delivered by Caesarean section exhibit bacterial communities composed of prominent genera, such as *Lactobacillus*, *Prevotella*, *Escherichia*, *Bacteroides* and *Bifidobacterium*. After a Caesarean section, the gut microbiota is characterised by a reduced number of *Bifidobacteria* species. Although vaginally delivered neonates exhibit individual microbial profiles, these are characterised by predominant groups, such as *Bifidobacterium longum* and *Bifidobacterium catenulatum*. Dominguez-Bello et al. used multiplex 16S ribosomal ribonucleic acid gene pyrosequencing to characterise the bacterial communities of mothers and their neonates. Interestingly, they reported that vaginally delivered infants acquired bacterial communities that resembled their own mothers' vaginal microbiota and that these were dominated by *Lactobacillus*, *Prevotella* or *Sneathia* spp. In contrast, infants delivered by Caesarean section harboured bacterial communities similar to those found on the skin surface and these were dominated by *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp. (8).

Influence of feeding

The mode of oral feeding may influence the composition of the gut microbiota in infants. Breastfeeding has been associated with higher diversity, as assessed using the Shannon index (9). Human milk contains beneficial factors for the gut microbiota, such as oligosaccharides (10). Oligosaccharides function as prebiotics, by stimulating the growth of *Bifidobacterium* and *Lactobacillus* species, thereby selectively altering the microbial composition of the intestine (10). It is likely that evolutionary selective pressure has equipped *Bifidobacterium longum* subsp. *infantis* with multiple enzymes to deconstruct human milk glycans. As a result, this subspecies is able to outcompete other *Bifidobacteria* as well as other commensals and pathogens in the gut lumen of healthy breastfed infants (10). In formula-fed infants, *Enterococci*, *Bacteroides* and *Clostridia* predominate. When breastfed infants are one month of age, there is a direct association between the levels of secretory immunoglobulin A in intestinal secretions and the number of *Bifidobacteria* in the gut. Furthermore, the level of the proinflammatory cytokine interleukin-6 in intestinal secretions is inversely related to the number of *Bifidobacterium fragilis* organisms in the gut at one month of age. It has been suggested that human milk oligosaccharides do not just stimulate *Bifidobacterium longum* subsp. *infantis* proliferation, they also activate important genes involved in the proinflammatory and anti-inflammatory balance in the intestinal mucosa (11). These observations provide additional evidence of the beneficial effects of breastfeeding for the newborn infant (Fig. 2). In addition to human milk oligosaccharides, human milk contains other glycans with antimicrobial and prebiotic activity that are thought to have beneficial effects on the infant (12). On the other hand, there is accumulating evidence that human milk is not sterile, but contains maternally derived bacterial molecular motifs that are thought to influence the development of the newborn infant's immune system (13). This mechanism, which has been called bacterial imprinting, requires further research (13). However, comparative studies with formula-fed infants have not carefully documented the effects of formula feeding on the gut microbiota or health-promoting bacteria. There is growing evidence that the microbiota does not reach its adult composition until two to three years of age (14). Finally, host defences can be improved by breastfeeding, which helps the immature intestinal mucosal immune system to develop and respond appropriately to highly variable bacterial colonisation and food antigen loads. Later in life, the type of food consumed influences the profile of the gut microbiota (15) and short-chain fatty acids play a central role (16). Short-chain fatty acids are organic fatty acids that are produced in the distal gut by the bacterial fermentation of macro-fibrous material that

escapes digestion in the upper gastrointestinal tract and enters the colon. They are central to the physiology and metabolism of the colon. Resident bacteria can also metabolise dietary carcinogens, synthesise vitamins and assist in the absorption of various molecules. Research has shown that 90-95% the short-chain fatty acids present in the colon are made up of acetate (60%), propionate (25%) and butyrate (15%). Butyrate is a major energy source for the colonic epithelium. Short-chain fatty acids have been associated with improved metabolic functions in individuals with type 2 diabetes mellitus, as they help to control blood glucose levels, insulin resistance and glucagon-like peptide-1 secretion (16).

Gut microbiota predators

The use of broad-spectrum antibiotics significantly reduces the relative abundance of *Bacteroidetes* and increases the abundance of *Firmicutes* at the same time. A reduction in microbial diversity is often observed in infants under one year of age who have received oral antibiotics. Complete recovery of the initial bacterial composition is not always achieved. The response depends on the type of antibiotics, the duration of administration and the baseline microbiome. Studies have reported that antibiotics that target specific pathogenic infections and diseases may alter the gut microbiota ecology, and interactions with the host metabolism, to a much greater degree than previously assumed (17).

The prolonged use of antibiotics, which is common in preterm infants, profoundly decreases microbial diversity and promotes the growth of predominant pathogens, such as *Clostridium*, *Klebsiella* and *Veillonella*, which have been associated with neonatal sepsis. It has been suggested that there may be healthy microbiota present in extremely premature neonates that may ameliorate the risk of sepsis (6). More research is needed to determine whether different antibiotics, probiotics or other novel therapies could re-establish a healthy microbiome in neonates. It has also been reported that when low-dose antibiotic exposure disrupted the microbiota during maturation, this altered the host metabolism and adiposity in mice (18). A study that gave mice low-dose penicillin immediately after birth demonstrated that metabolic alterations and changes in the ileal expression of genes were involved in immunity (18). Administering low-dose penicillin sufficiently perturbs the microbiota to modify body composition, even when these drugs are limited to early life. This indicates that microbiota interactions in infancy may be critical determinants of long-term host metabolic effects.

Other xenobiotics, such as proton pump inhibitors, may alter the gut microbiota. Meta-analyses have shown that the use of proton pump inhibitors potentially increased the risk of enteric infections caused by *Clostridium difficile*. They have also led to small intestinal bacterial overgrowth, spontaneous bacterial peritonitis, community-acquired pneumonia, hepatic encephalopathy and adverse outcomes of inflammatory bowel disease (19).

The role the gut microbiota plays in gut maturation

A study by Hooper et al, published in 2001, reported that a single bacterial species, *Bacteroides thetaiotaomicron*, which is a prominent component of normal mouse and human intestinal microbiomes, modulated the expression of genes involved in several important intestinal functions. These included nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, angiogenesis and postnatal intestinal maturation (20). Another study that covered gastrointestinal motility, found that bacterial metabolites, such as short-chain fatty acids and deconjugated bile salts, generated potent motor responses (21). Colonised mice have been shown to have a faster intestinal transit time than germ-free mice (20). Collectively, the gut microbiota influences tissue regeneration, the permeability of the epithelium, the vascularisation of the gut and tissue homoeostasis.

Role of the gut microbiota in the development of the gut immune system

The intestine is an important immune organ that harbours approximately 60% of the total immunoglobulins and more than 10^6 lymphocytes per gram of tissue. The largest pool of

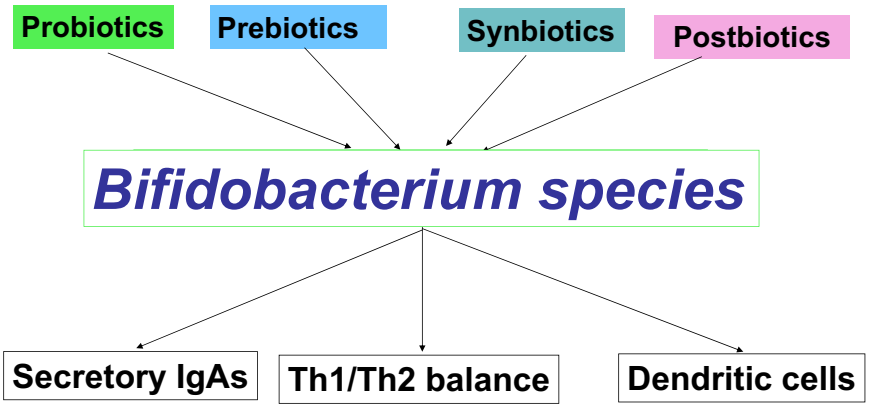

Figure 2 The central role played by Bifidobacterium species in the development of the gut associated immune system.

immune-competent cells in the body is housed in the intestinal mucosa. The number of T lymphocytes and plasmocytes within the intestinal lamina propria increases markedly in response to intestinal colonisation. Although immunoglobulin A producing cells are virtually absent in germ-free mice, high levels are detectable in the mucosa when bacterial colonisation occurs (22). The gut microbiota exerts positive stimulatory effects on the intestinal innate and adaptive immune systems, by modulating the development of the intestinal mucous layer and lymphoid structures, immune-cell differentiation and the production of immune mediators (23,24). The innate immune system must discriminate between pathogens and the harmless commensal bacteria of the gut microbiota. Pathogen recognition receptors, such as Toll-like receptors and nucleotide-binding oligomerisation domain receptors, enable us to recognise a restricted number of bacterial motifs. These can be either microbe-associated molecular patterns or, in the case of pathogens, pathogen-associated molecular patterns (24). Both types of pathogen recognition receptors are naturally expressed by the intestinal epithelial and antigen-presenting cells, such as dendritic cells or macrophages, and this enables them to sense any bacterial motifs easily. The intestinal epithelial barrier is protected by a highly viscous microfilm to avoid permanent and unwanted stimulation of the innate immune system. This prevents close contact between the commensal bacteria and intestinal epithelial cells.

The intestinal mucosal barrier function can be defined as the capacity of the intestine to host commensal bacteria and molecules, while preserving the ability to absorb nutrients and prevent the invasion of host tissues by resident bacteria. The dense communities of bacteria in the intestine are separated from body tissues by a monolayer of intestinal epithelial cells. The assembly of the multiple components of the intestinal barrier is initiated during foetal development and continues during early postnatal life. This means that the intestinal barrier is not completely developed soon after birth, particularly in preterm infants. The secretion of mucus-forming mucins, secretory immunoglobulin A and antimicrobial peptides reinforces the mucosal barrier on the extra-epithelial side, while a variety of immune cells contribute to mucosal defence on the inner side. Thus, the mucosal barrier is physical, biochemical and immune in nature. In addition, the microbiota may be viewed as part of this system because of the mutual influence of the host and the luminal microorganisms.

Altered mucosal barrier function, accompanied by increased permeability and/or bacterial translocation, has been linked to a variety of conditions. These have included metabolic disorders, such as type 2 diabetes mellitus, insulin resistance, obesity and inflammatory bowel diseases (25). Genetic and environmental factors may converge to evoke defective functioning of the barrier, which, in turn, may lead to overt inflammation of the intestine as a result of an exacerbated immune reaction towards the microbiota. Inflammatory bowel diseases may be both precipitated and treated by either stimulation or downregulation of the different elements of the mucosal barrier, and the outcome depends on the timing, the types of cells affected and other factors. Fermentation products of commensal bacteria have been shown to enhance the intestinal barrier's function, by facilitating the assembly of tight junctions through the activation of adenosine monophosphate-activated protein kinases (26). On the other hand, removing the entire detectable commensal gut microbiota by using a four-week course of four orally administered antibiotics – vancomycin, neomycin, metronidazole and ampicillin – led to more severe intestinal mucosal injury in a mouse colitis model induced by dextran sulphate sodium (27). Early treatments with broad-spectrum antibiotics have been shown to alter the gastrointestinal tract's gene expression profile and intestinal barrier development (28). This finding underlines the importance of normal bacterial colonisation in the development and maintenance of the intestinal barrier. Antibiotic therapy between birth and five years of age might increase the risk of Crohn disease by disrupting the pattern of gut colonisation (29). A meta-analysis confirmed that antibiotic use was associated with an increased risk of new-onset Crohn disease, but not of ulcerative colitis (30).

In summary, the gut microbiota protects against pathogens, influences the development of the intestinal barrier and its functions and plays many roles in the development of the gut immune system. It acts by competing for nutrients and receptors, by producing antimicrobial compounds and by stimulating a multiple-cell signalling process that can limit the release of virulence factors.

Role of the gut microbiota in health and disease

As emphasised above, microorganisms colonise the human gut from birth, and even before that, and stimulate the development of the local and systemic immune systems. In addition, the newly developed immune system shapes the gut flora, which means that it is unique for every individual. An imbalance or alteration in the composition and/or function of the microbiota, which is usually called dysbiosis, has been found to be associated with many chronic diseases (31). However, in this relationship, it is almost impossible to delineate the causes from the consequences, as few studies have shown that changes in the microbiota precede inflammation (31).

Inflammatory bowel disease

The current hypothesis of the aetiology of inflammatory bowel disease suggests that the inflammation is a consequence of an unrestrained or aberrant immune response to the gut flora, which is shaped by different environmental factors in a genetically predisposed individual (32).

The most consistent changes that have been described have been a reduction in the diversity of the gut microbiota, increased abundance of *Bacteroidetes* and *Proteobacteria* and the loss of *Firmicutes* (32). Furthermore, the loss of certain specific beneficial microbes, such as *Faecalibacterium prausnitzii* and members of *Clostridium* clusters XIVa and IV, has previously been described (33). The importance of these specific microorganisms has been

further demonstrated by their ability to inhibit inflammation and affect the differentiation of regulatory T cells. More precisely, *Faecalibacterium prausnitzii* has the ability to stimulate the production of interleukin-10 and inhibit proinflammatory cytokines such as interleukin-12 and interferon-gamma. Other mechanisms could also be involved, such as decreased production of short-chain fatty acids, which then affects the differentiation and expansion of regulatory T cells and the growth of epithelial cells.

Another well-described feature of patients with inflammatory bowel diseases is altered intestinal barrier function, and this has mainly been increased permeability and decreased mucus production. Both of these factors can be influenced by the microbiota, but they can also give bacteria easier access to the mucosa, allowing them get closer to immunocompetent cells. Patients with inflammatory bowel diseases exhibit increased colonisation by bacteria that are able to adhere to the intestinal epithelium, causing altered permeability of the intestine (34). This adherence can be further promoted by the increased number of mucolytic bacteria, such *Ruminococcus gnavus* and *Ruminococcus torques* (35). In addition, the number of sulphate-reducing bacteria, such as *Desulfovibrio*, is increased in patients with inflammatory bowel disease. This has been shown to result in the production of hydrogen sulphate, which damages intestinal epithelial cells and induces mucosal inflammation (36).

Functional gastrointestinal disorders

The pathogenesis of functional gastrointestinal disorders has not yet been fully explained, but the proposed mechanisms include mild gastrointestinal inflammation, visceral hypersensitivity, an altered brain–gut axis and altered gut microflora (37).

The most notable changes in microbial intestinal colonisation during the first weeks and months of life have been described in infants with infant colic (38). These infants were reported to have decreased faecal-bacterial diversity, increased gram-negative bacterial colonisation and a lack of *Actinobacteria* and *Firmicutes*, which appears to have a protective effect. More specifically, infants with colic have been shown to have more *Proteobacteria* and less *Bifidobacteria* and *Lactobacillus* (39). Although a cause versus effect phenomenon has not been fully described, there is evidence that changes in the gut microbiota precede the development of infantile colic (40).

Similar changes in the microbiome have been reported in older children with functional gastrointestinal disorders. One meta-analysis, published in 2017, identified downregulated colonisation of *Lactobacillus*, *Bifidobacterium* and *Faecalibacterium prausnitzii* in patients with irritable bowel syndrome, particularly in irritable bowel syndrome where diarrhoea predominated (41). Furthermore, a greater proportion of the *Proteobacteria* phylum and of genera, such as *Dorea, Haemophilus*, *Ruminococcus* and *Clostridium* species, were found in the same group of patients, (42). These changes might have altered or influenced visceral perception, gut motility, gut permeability and intestinal gas production, which can lead to functional gastrointestinal disorders where pain is the predominant complaint.

Allergies

The immune system of the gastrointestinal tract is in close proximity to many antigens that originate mainly from food and the gut microbiota, both of which can affect immune tolerance. The normal commensal microflora play an essential role in inflammatory homoeostasis and appropriate immune regulation and may therefore influence the development of allergic diseases. It has been suggested that alterations in the microbiota can disrupt mucosal immune tolerance, leading to allergic diseases, such as food allergies, atopic dermatitis and even asthma (43). The early microbiota of children who later developed allergies has been characterised by lower bacterial diversity, with predominant *Firmicutes*, higher counts of the *Bacteroidaceae*, increased numbers of the anaerobic *Bacteroides fragilis*, *Escherichia coli*, *Clostridium difficile*, *Bifidobacterium catenulatum*, *Bifidobacterium bifidum* and *Bifidobacterium longum.* In contrast and decreased numbers of *Bifidobacterium adolescentis*, *Bifidobacterium bifidum* and *Lactobacillus* have been reported (44). When the microbiota of children with allergies was assessed at the onset of allergic symptoms in one study, it showed a different pattern, with higher counts of *Bacteroides*, lower counts of *Akkermansia muciniphila, Faecalibacterium prausnitzii* and *Clostridium* and overall lower bacterial diversity (45).

The potential mechanisms underlying an increased risk of sensitisation and allergy development, detected as a consequence of dysbiosis in animal models, have been related to various alterations in mucosal regulatory T cells. Other reported effects were defects in the epithelial barrier function, as evidenced by increased mucosal permeability, diminished secretory immunoglobulin A production and excretion and altered dendritic and B-cell function (44).

Obesity and liver disease

Studies have shown that gut microbiota could also play an important role in the etiopathogenesis of obesity and other prevalent chronic liver diseases, such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

Nonalcoholic fatty liver disease has become one of the most frequent causes of liver disease and represents a spectrum of pathologies, varying from steatosis to nonalcoholic steatohepatitis, with or without cirrhosis, and possible evolution to hepatocellular carcinoma. Nonalcoholic fatty liver disease is a multifactorial disease that is affected by genetic, metabolic, dietary and environmental factors. The most commonly proposed theory is the multiple hit hypothesis, which also involves changes to the gut microbiota (46).

The gut microbiota plays an important role in obesity, and this is primarily based on its influence on energy balance. Dysbiosis affects short-chain fatty acid production and metabolism and adipocyte lipid deposition, with a decrease in mitochondrial fatty acid oxidation. Human studies have reported that the balance between

Bacteroidetes and *Firmicutes* has been related to obesity. Lean subjects have more *Bacteroidetes* in their gut microbiota, and diet that restricted fats and carbohydrates was shown to increase the ratio in favour of *Bacteroidetes* (47).

With regard to chronic liver disease, the proposed mechanisms for the negative effects of dysbiosis include small intestine bacterial overgrowth, altered release of inflammatory cytokines, alteration of the intestinal barrier, choline metabolism, endogenous ethanol production, regulation of hepatic toll-like receptors expression in patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis and an alteration in bile acid metabolism (48).

Furthermore, there is evidence that gut dysbiosis promotes the progression of nonalcoholic steatohepatitis to cirrhosis and hepatocellular carcinoma via an increase in tumour necrosis factor alpha and interleukin-8, the activation of toll-like receptor-4 and toll-like receptor-9 and the production of interleukin-1beta in Kupffer cells, favouring lipid accumulation, hepatocyte death, steatosis, inflammation and fibrosis (49).

There have been many animal studies that have evaluated the gut microbiota differences associated with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, but few studies have been performed in humans and they have produced inconsistent results. Patients with nonalcoholic steatohepatitis, including children, have been reported to have lower levels of *Bacteroidetes* than patients with liver steatosis or healthy individuals (50). *Firmicutes* have been found in higher levels in individuals with nonalcoholic fatty liver disease than in healthy subjects (51), but the results have not been consistent (52).

Modulation of the gut microbiota

The gut microbiota can be modulated to achieve health-promoting effects (53). The beneficial manipulation of the composition and metabolic footprint of the gut microbiota can be achieved by using probiotics. These can be defined as a preparation of, or a product containing, viable microorganisms in an adequate number to enable such dietary preparations to favourably modulate the gut microbiota (53,54). The ability to exert a beneficial modulation on the gut microbiota may be enhanced by combining probiotics with other ingredients (64), namely prebiotics, which are capable of favouring the growth and/or activity of microorganisms. Prebiotics appear to be poorly understood by the general public in this regard (55). It is important to correctly define, and understand, prebiotics and their potential when they are combined with probiotics. This information needs to be disseminated beyond the scientific community, so that regulatory agencies, the food industry and healthcare professionals can correctly describe them and suggest how they should be used. The combined use of prebiotics and probiotics may be described as synbiotic if the net health benefit is synergistic and scientifically validated (56). Finally, the terms paraprobiotic and postbiotic describe nonviable bacterial cells and soluble factors that are secreted as metabolic by-products by live bacteria. Such products, which could also be released after bacterial lysis, can provide additional physiological benefits to the host organism. That is why they have received increasing attention from scientific researchers and industry, due to their potential food and pharmaceutical applications (Table 1).

Probiotics

Probiotics have been defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (53,57). The term probiotics is used widely, but not always properly, in the scientific literature and by the industry. Their fundamental characteristics have been described extensively in the literature (53), including their microbial origin, their viability and their benefit to the health of the host (Table 2). The microbial origin of a probiotic product must be guaranteed by identifying a taxonomically defined microbe or combination of microbes. A probiotic must therefore be properly identified by strain-genotypically and phenotypically characterised. An essential characteristic of a probiotic is its viability (57), as it must be a live microorganism that is able to survive the acidity of the stomach in order to reach and colonise the intestinal tract. Moreover, a probiotic must be guaranteed to remain viable and stable throughout the technical procedures, during its production, use and storage.

A consensus statement was issued by the International Scientific Association for Probiotics and Prebiotics in 2013 with regard to the possible benefits of probiotics to human health. The statement sought to further clarify the appropriate use and scope of the term probiotic and stated that probiotics should exert specific general benefits, which it defined as core benefits (58). These benefits include contributing to establishing and sustaining a healthy gut microbiota. They are expected to be obtained by creating a favourable intestinal environment through nonstrain-specific beneficial actions that are shared by most probiotics, which sustain a healthy digestive tract and immune

Table 1 Probiotics, prebiotics, synbiotics, paraprobiotics and postbiotics in clinical practice. Definitions

- Probiotics: Food or food supplements containing viable microrganisms, able to modify the microflora of their hosts, with potential beneficial outcomes on their health
- Prebiotics: Food or food supplements containing nondigestible components, able to selectively stimulate the activity and, or, growth of autochthonous bacteria
- Synbiotics: Products containing a combination of probiotics and prebiotics
- Paraprobiotics: Nonviable, inactivated microbial cells containing products that have shown dose-related beneficial effects in selected groups of patients
- Postbiotics: Products containing inactivated (nonviable) bacterial products or metabolic by-products from probiotic microorganisms, able to exert potentially beneficial biological activity on their hosts

Table 2 Attributes of probiotics

- Human origin
- Not a pathogen
- Resistant to technical procedures
- Resistant to gastric acidity
- Capable of adhering to intestinal epithelium
- Capable of colonising the intestinal tract
- Capable of producing antimicrobial substances
- Acts as immunomodulator
- Influences human metabolic activities

system. In fact, some effects of probiotics can be observed across taxonomic groups and are achieved through general mechanisms, such as the inhibition of pathogens and the production of beneficial metabolites. These effects should be distinguished from other benefits, such as neurological or endocrinological effects, which are strain specific.

An important aspect of probiotic activity is identifying the adequate amount that is able to confer health benefits on the host and a specific accepted definition of this is not currently available. Nevertheless, some regulatory approaches in Canada and Italy (59,60) have suggested that a probiotic product should contain at least $1^{\wedge}10^{9}$ colony-forming units per serving to be able to exert the claimed beneficial effects.

The 2013 Statement also describes the different categories of live microorganisms for human use, in order to distinguish what can and cannot be considered a probiotic, according to health claims (58). Products claiming to contain live and active cultures should not be considered probiotics, because the simple use of the terms live and active does not imply any probiotic activity. Foods or supplements that state they contain probiotics have no specific health claims, and their expected effects are those related to the core benefits, as demonstrated by well-conducted human studies. Products containing probiotics that make specific health claims are those that claim to have any beneficial health effects, according to documented evidence from well-designed observational studies. Products containing probiotics that claim they can prevent or treat a specific disease need to be backed up by appropriate trials to meet the regulatory standards for drugs.

Probiotics are commonly used in paediatric practice, and a summary of the indications and limitations is reported in Table 3. Their use includes preventing common and nosocomial infections, allergies and antibiotic-associated diarrhoea, treating acute gastroenteritis and functional abdominal pain disorders and preventing and treating infantile colic. Guidelines by Hojsak et al. on using probiotics in clinical practice for children were published in 2018 (53), and the study reported that they seemed to be safe in general, even when provided in high doses. The authors provided a detailed description of the correct conditions for their use, together with specific positive instructions (53) for the use of strictly defined strains for various clinical conditions. These conditions include preventing upper respiratory tract infections in children attending day care centres, nosocomial diarrhoea and antibiotic-associated diarrhoea and treating acute gastroenteritis and infantile colic in breastfed infants.

Prebiotics

The definition of prebiotics has undergone an important evolution over time. They were initially referred to as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already residing in the colon (S61). Several studies have focused on the nondigestible oligosaccharides fructans, namely fructooligosaccharides and inulin, and galactans, namely galactooligosaccharides, and how they exert their effects through the enrichment of *Lactobacillus* and/or *Bifidobacterium* spp. (S62).

Prebiotics have been described as nondigestible compounds that confer a beneficial physiological effect on the host (S63). They do this by metabolising microorganisms in the gut, which then modulate the composition and/or activity of the gut microbiota. In 2017, the International Scientific Association for Probiotics and Prebiotics Consensus Statement proposed a new definition for prebiotics (S64). The document discussed the concept of selectivity with respect to fermentation by bacteria and suggested that prebiotics were defined as substrates that are selectively utilised by host microorganisms and confer a health benefit on the host (51) (Table 4). Incorporating the concept of selectivity in the definition is important, as it distinguishes between prebiotics and other substances. The term selective does not mean that only lactobacilli and bifidobacteria are affected by prebiotics. It means that a broader range of microorganisms, but not all, can be affected. Substances that can affect the composition of the microbiota, but are not selectively used by microorganisms, are not prebiotics.

The use of prebiotics in paediatric clinical practice is currently limited. Human milk oligosaccharides are a group of prebiotics that can influence a newborn infant's gastrointestinal health by favouring the development of a healthy gut microbiota through some metabolic and immunological activities. It has been demonstrated that an infant's consumption of human milk oligosaccharides increases the proportion of human milk oligosaccharide-consuming *Bifidobacteriaceae*, particularly *Bifidobacterium longum* subsp. *infantis* and *Bacteroidaceae* (S65). The mechanisms of action in the newborn infant's intestine include immune regulation and preventing the adhesion of pathogens to the intestinal epithelium, which protects the infant from infections (S66). Some compounds that are equivalent to human milk oligosaccharides or bovine milk oligosaccharides are obtained by enzymatic synthesis. It is still a matter of debate whether these are able to exert beneficial effects on human health by selectively stimulating the microbiota and thus acting as prebiotics. The existing literature does not provide definitive conclusions, but some human milk oligosaccharides may be considered candidate prebiotics. Studies have reported that prebiotics containing

Table 3 Use of probiotics in children

Preventing common infections	Preventing nosocomial infections	Preventing allergies	Preventing antibiotic associated diarrhoea (AAD)
• Children attending day care centres during winter months: if probiotics are considered for preventing upper respiratory tract infections, only lactobacillus rhamnosus (LGG) could be considered. However, evidence is limited and meta-analyses confirming its efficacy are lacking. • Preventing gastrointestinal infections in day care centres: the use of probiotics is not supported by convincing evidence.	• Preventing nosocomial diarrhoea: if the use of probiotic is considered, only LGG can be recommended (at least 109 CFU/day for the duration of their hospital stay). • Preventing nosocomial respiratory tract infections: insufficient evidence to recommend probiotics in these conditions.	• Preventing atopic diseases: based on the currently available evidence, probiotics cannot be recommended	• Preventing AAD: LGG or *S. boulardii* should be considered. • Preventing C difficile-associated diarrhoea: evidence indicates that *S. boulardii* can be considered *Notes:* • Other strains of probiotics, on their own or in combination, are currently not recommended. • No safety data are available on the use of probiotics for preventing AAD in severely ill children. Their use in these patients should undergo special evaluation.
Treating acute gastroenteritis (age)	**Treating functional abdominal pain disorders**	**Preventing and treating infantile colic**	**Safe probiotic use**
• LGG and *S. boulardii* may be considered as an adjunct to the oral rehydration therapy. (LGG should be administered for 5–7 days, at a dose of ≥1010 CFU/day, while *S. boulardii* should be administered for 5–7 days, at a dose of 250–750 mg/day) • No recommendation are currently available for the use of other strains or products containing single or multiple strains of probiotics *Note:* • Probiotic administration initiated early in the course of diarrhoea is recommended to maximise results. Spell out terms in yellow in full please.	• Recommendations for the use of probiotics in these conditions are limited by the scarcity of the available evidence and the lack of current guidelines.	• A probiotic treatment can be considered. However, L. reuteri DSM 17938 is the only strain that has proved to be effective treating infantile colic in breastfed infants. (It should be used at a dose of at least 108 CFU/day for 21–30 days). *Notes:* • Limited evidence on the use of L. reuteri DSM 17938 in preventing infantile colic precludes specific recommendations. • Insufficient evidence is currently available for the use of other strains of probiotics or products containing probiotic mixtures	• The use of probiotics in children seems to be safe in general, even when provided in high doses. • Probiotics should be used with caution in special situations, such as prematurity, immunocompromised patients, critically ill patients, central venous catheters, cardiac valvular disease and short-gut syndrome. • Some probiotic strains are not recommended for children (namely Enterococcus faecium SF68), due to the possible transfer of vanomycin-resistance genes. • *S. boulardii* has been effective in children with C. difficile infections. However due to the potential for infections spread, special caution is required in critically ill patients.

Table 4 Prebiotics selectively used by host microorganisms

- CLA, conjugated linoleic acid
- PUFA, polyunsaturated fatty acid
- FOS, fructooligosaccharides
- GOS, galactooligosaccharides
- MOS, mannanoligosaccharide
- XOS, xylooligosaccharide
- HMOs, human milk oligosaccharides
- Phenolics and phytochemicals
- Readily fermentable dietary fibres

immunoactive oligosaccharides could effectively prevent atopic dermatitis in low-atopy risk infants and that they could potentially be used to prevent adolescents becoming overweight. However, the clinical significance and efficacy of prebiotics and their possible widespread use in paediatric practice still needs to be clarified (S67-69).

Synbiotics

Synbiotics are commonly described as a combination of probiotics and prebiotics in functional food compounds. Functional food is a food that has been modified and claims to improve a person's health or well-being by providing benefits that extend beyond the traditional nutrients it contains. Examples of functional foods include bread, cereals and drinks that are fortified with vitamins or selected herbs. They can also contain nutraceuticals, which have physiological benefits or provide protection against chronic disease.

Studies have reported that their combined use has facilitated the survival of live microbial dietary supplements and their implantation in the gastrointestinal tract (S66–68). This mechanism has been reported to generate a

beneficial effect in the host organism, by the metabolic activation of a restricted type of bacteria, which is considered to be health promoting, and the selective stimulation of its growth (S69). It has been suggested that these combined conditions have improved the host's welfare (S70).

Single products containing an appropriate combination of probiotics and prebiotics have been reported to guarantee a greater effect than when they have been used separately. In fact, the synbiotic activity of foods containing a combination of prebiotics and probiotics is based on their elective action in two different areas of the gut. Probiotics are mainly active in the small and large intestine, while prebiotics are mainly active in the large intestine (S69). Synbiotics act in combination in two main ways: by improving the viability of probiotic microorganisms and by providing specific benefits for the host's health.

The rationale of using a synbiotic formulation of prebiotics is because they function as a selective medium, favouring the growth of certain probiotic strains, their fermentation and their intestinal passage. Furthermore, several studies have reported that prebiotics have positively influenced the ability of probiotic microorganisms to develop higher tolerance to particular situations caused by the presence of possibly challenging conditions. These include oxygenation and the pH and temperature of the intestines (S71). In brief, the main reason for using synbiotics is that the survival of probiotics in the digestive system is challenging in normal conditions and when an appropriate prebiotic is not present.

Therefore, using prebiotics to stimulate the effectiveness of probiotics appears to be a good way of inducing the beneficial modulation of the metabolic activity of probiotics in the intestine. At the same time, this preserves the intestinal biostructure, favours the development and maintenance of a beneficial microbiota and inhibits the growth of potential pathogens in the gut.

In general, the beneficial outcomes of synbiotics for the host's health have been related to significant increases in short-chain fatty acid levels, ketones, carbon disulphides and methyl acetates. In particular, the potential beneficial activity of synbiotics in clinical practice has been described in different clinical conditions (Table 5). The reported potential therapeutic properties of synbiotics include anticarcinogenic, anti-allergic and antibacterial effects (S67). A few studies, which need to be confirmed or validated, have also suggested that synbiotics could be used to prevent constipation, diarrhoea and osteoporosis and in treating brain diseases associated with altered hepatic function (S72).

Studies suggest that the synbiotic activity exerted by a combination of prebiotics and probiotics in functional food products is mainly due to their ability to modulate the host's immune system. This means that they can be used in clinical practice for selected conditions. It has been reported that healthcare professionals have used synbiotics in clinical practice before using antibiotics and surgery interventions and that their use may be related to cost-effectiveness and safety considerations. Finally, the availability of synbiotic-based commercial products is rapidly increasing, due to the large number of possible existing combinations of prebiotics and probiotics. This may offer increased therapeutic options in the near future (S72).

Table 5 Activity of synbiotics in humans

- Improving the viability of probiotics
- Expanding Lactobacillus and *Bifidobacterium* genus counts
- Sustaining immune system modulation abilities in hosting organisms
- Increasing hepatic functions in patients affected by cirrhotic dysfunctions
- Preventing bacterial translocation in individuals in restricted communities
- Preventing hospital-acquired infections in patients receiving surgery and/or postoperational procedures
- Reducing risk factors for colon cancer
- Providing preventive effects in selected clinical conditions (namely osteoporosis, allergic disorders, constipation and diarrhoea)

Paraprobiotics and postbiotics

In addition to the factors provided by the host organisms, further regulatory elements are able to support the maintenance and growth of the gut microbiota by favouring bacterial development, reproduction, protection from external insults and intercellular communication (S73). Data from the literature have emphasised that bacterial viability, which characterises probiotic activity, is not the exclusive factor involved in exerting health-promoting effects (S74). In this regard, the term paraprobiotics is used to identify nonviable, inactivated microbial cells that have shown dose-related beneficial effects for consumers. It has been suggested that paraprobiotics are safer than viable bacterial products for selected groups of patients, such as individuals with impaired immune systems, because they pose a reduced risk of infection, microbial translocation or potential inflammatory responses. Inactivated bacterial cells are typically obtained artificially, through chemical or physical methods such as heating, acid deactivation, freeze-drying, sonication and ultraviolet treatment. This means that they are able to modify the cell structure and/or the physiological functions of the bacteria while preserving the beneficial properties of their viable forms (S74).

The term postbiotics describes soluble factors that may be secreted by viable bacteria or by-products resulting from bacterial lysis (S73, S74) (Table 6). Several bacterial strains have shown the ability to express a wide range of soluble factors of different natures, including cell surface proteins, vitamins, enzymes, peptides, teichoic acids, plasmalogens and organic and short-chain fatty acids. These cell-free supernatant metabolites have been reported to possess antimicrobial, antioxidant and immunomodulatory properties. These can positively influence microbiotal homoeostasis as well as the metabolic and/or signalling pathways of the host organism. The active structure and mechanism of action that enable postbiotics to produce a beneficial effect in the context of physiological, immunological, neuro-

Table 6 Composition and function-based distinction of postbiotics

Composition element based	
• Lipids (butyrate, dimethylacetyl-derived plasmalogen, propionate)	• Organic acids (propionic acid, 3-phenyllactic acid)
• Carbohydrates (galactose-rich polysaccharides, teichoic acids)	• Various complex molecules (cell wall associated peptidoglycans, lipoteichoic acids)
• Proteins (lactocepin, p40 molecules)	
Physiological function based	
• Immunomodulation (*Lactobacillus* sp., *Bifidobacterium* sp., Fecali bacterium sp.)	• Hypocholestrolemic (*Bifidobacterium* sp.)
• Anti-inflammatory (*Lactobacillus* sp.)	• Antihypertensive (*Lactobacillus* sp.)
• Antiproliferative (*Lactobacillus* sp.)	• Anti-obesogenic (*Lactobacillus* sp.)
• Antioxidant (*Lactobacillus* sp., *Bifidobacterium* sp., *Strep salivarius* ssp.)	• Hepatoprotective (*Lactobacillus* sp., Enterococcus lactis)
	• Antimicrobial (*Lactobacillus* sp.)

hormone biological and metabolic reactions in the host have not yet been clarified. Investigations are currently in progress to explain the beneficial health effects of postbiotic products reported in the literature. These health effects have been previously been related to their possible anti-inflammatory, antiproliferative, antioxidant, hypocholesterolaemic, antihypertensive, anti-obesogenic, hepatoprotective and antimicrobial activities (S74).

The definitions of probiotics and prebiotics have a long history, particularly with regard to the standing of probiotics in international regulations, but there is still no consensus on their definitions. It is unclear whether these terms will be maintained or changed in future.

Specific commercial products use fermentation technology, such as fermented milk-based infant formulas, and these can be used in clinical practice to beneficially modulate the gut microbiota and gut immunity. Selected lactic acid bacterial strains are used in industrial processes to ferment cows' milk, and these are combined with heat treatment. The end products are formulas that contain no viable bacteria or prebiotic components, but do contain specific active factors resulting from the fermentation process (S75). Metabolites produced through fermentation processes are used as raw materials for pharmaceutical products, healthcare supplements and functional foods. Experimental *in vitro* and *in vivo* studies have indicated that specific fermentation products are involved in establishing immune balance and oral tolerance, although the mechanism of action underlying these functions has not yet been fully explained (S75).

Changes in the microbiome have been documented in many chronic, mainly immune-mediated, gastrointestinal and liver diseases and distinct patterns have been associated with each specific disease. However, causality and the mechanisms by which the gut microflora influences the aetiopathogenesis of a disease have not been fully explained, so they may be considered limiting factors of this review. Paediatricians are on the frontline when it comes to caring for children's health and well-being. The strength of this review was that we have emphasised the key roles that paediatricians' play in minimising preventable early harmful events that could permanently influence the composition and/or function of the gut microbiota.

CONCLUSION

The basic science relating to the gut microbiota is changing rapidly, as clinical data provide evidence of the importance of diversity in the microbial community and point to the general accepted role of so-called protective bacteria. Gut microbes are moving rapidly from being considered potentially dangerous to being considered as a positive influence on health when they are properly implemented. In clinical practice, modulation of the gut microbiota may be achieved by using several approaches, including probiotics, prebiotics, synbiotics, paraprobiotics and postbiotics.

A better understanding of the potential impacts of the gut microbiota on human health, and of the use of related commercially available products, would lead to more appropriate use of these products in clinical practice by healthcare professionals.

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CONFLICT OF INTEREST

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References

1. Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. *Nature* 2012; 486: 207–14.
2. Arrieta MC, Stiemsma LT, Amenyogbe N, Brown EM, Finlay B. The intestinal microbiome in early life: health and disease. *Front Immunol* 2014; 5: 427.
3. Rodríguez JM, Murphy K, Stanton C, Ross RP, Kober OI, Juge N, et al. The composition of the gut microbiota throughout life, with an emphasis on early life. *Microb Ecol Health Dis* 2015; 26: 26050.
4. Collado MC, Rautava S, Aakko J, Isolauri E, Salminen S. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Sci Rep* 2016; 6: 23129.
5. Efrem S, Lim ES, Rodriguez C, Holtz LR. Amniotic fluid from healthy termpregnancies does not harbor a detectable microbial community. *Microbiome* 2018; 11: 87.
6. Neu J, Walker WA. Necrotizing enterocolitis. *N Engl J Med* 2011; 364: 255–64.

7. Biasucci G, Benenati B, Morelli L, Bessi E, Boehm G. Cesarean delivery may affect the early biodiversity of intestinal bacteria. *J Nutr* 2008; 138: 1796S–1800S.
8. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA* 2010; 107: 11971–75.
9. Schwartz S, Friedberg I, Ivanov IV, Davidson LA, Goldsby JS, Dahl DB, et al. A metagenomic study of diet-dependent interaction between gut microbiota and host in infants reveals differences in immune response. *Genome Biol* 2012; 13: r32.
10. Underwood MA, German JB, Lebrilla CB, Mills DA. Bifidobacterium longum subspecies infantis: champion colonizer of the infant gut. *Pediatr Res* 2015; 77: 229–35.
11. Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. *Front Microbiol* 2014; 5: 494.
12. Chichlowski M, De Lartigue G, German JB, Raybould HE, Mills DA. Bifidobacteria isolated from infants and cultured on human milk oligosaccharides affect intestinal epithelial function. *J Pediatr Gastroenterol Nutr* 2012; 55: 321–27.
13. Garrido D, Kim JH, German JB, Raybould HE, Mills DA. Oligosaccharide binding proteins from *Bifidobacterium longum* subsp. infantis reveal a preference for host glycans. *PLoS ONE* 2011; 6: e17315.
14. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. *Nature* 2012; 486: 222–7.
15. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014; 505: 559–63.
16. Puddu A, Sanguineti R, Montecucco F, Viviani GL. Evidence for the gut microbiota short-chain fatty acids as key pathophysiological molecules improving diabetes. *Mediators Inflamm* 2014; 2014: 162021.
17. Faa G, Gerosa C, Fanni D, Nemolato S, van Eyken P, Fanos V. Factors influencing the development of a personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy. *J Matern Fetal Neonatal Med* 2013; 26 (Suppl 2): 35–43.
18. Ferrer M, Martins dos Santos VA, Ott SJ, Moya A. Gut microbiota disturbance during antibiotic therapy: a multi-omic approach. *Gut Microbes* 2014; 5: 64–70.
19. Naito Y, Kashiwagi K, Takagi T, Andoh A, Inoue R. Intestinal dysbiosis secondary to proton-pump inhibitor use. *Digestion* 2018; 97: n195–204.
20. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 2001; 291: 881–4.
21. Kashyap PC, Marcobal A, Ursell LK, Larauche M, Duboc H, Earle KA, et al. Complex interactions among diet, gastrointestinal transit, and gut microbiota in humanized mice. *Gastroenterology* 2013; 144: 967–77.
22. Sommer F, Backhed F. The gut microbiota–masters of host development and physiology. *Nat Rev Microbiol* 2013; 11: 227–38.
23. Ruemmele FM, Bier D, Marteau P, Rechkemmer G, Bourdet-Sicard R, Walker WA, et al. Clinical evidence for immunomodulatory effects of probiotic bacteria. *J Pediatr Gastroenterol Nutr* 2009; 48: 126–41.
24. Chung H, Pamp SJ, Hill JA, Surana NK, Edelman SM, Troy E, et al. Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* 2012; 149: 1578–93.
25. Sanchez de Medina F, Romero-Calvo I, Mascaraque C, Martinez-Augustin O. Intestinal inflammation and mucosal barrier function. *Inflamm Bowel Dis* 2014; 20: 2394–404.
26. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J Nutr* 2009; 139: 1619–25.
27. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell* 2004; 118: 229–41.
28. Schumann A, Nutten S, Donnicola D, Comelli EM, Mansourian M, Cherbut C, et al. Neonatal antibiotic treatment alters gastrointestinal tract developmental gene expression and intestinal barrier transcriptome. *Physiol Genomics* 2005; 23: 235–45.
29. Hildebrand H, Malmborg P, Askling J, Ekbom A, Montgomery SM. Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. *Scand J Gastroenterol* 2008; 43: 961–66.
30. Ungaro R, Bernstein CN, Gearry R, Hviid A, Kolho KL, Kronman MP, et al. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. *Am J Gastroenterol* 2014; 109: 1728–38.
31. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. *Clin J Gastroenterol* 2018; 11: 1–10.
32. Oyri SF, Muzes G, Sipos F. Dysbiotic gut microbiome: A key element of Crohn's disease. *Comp Immunol Microbiol Infect Dis* 2015; 43: 36–49.
33. Varela E, Manichanh C, Gallart M, Torrejon A, Borruel N, Casellas F, et al. Colonisation by *Faecalibacterium prausnitzii* and maintenance of clinical remission in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2013; 38: 151–61.
34. Ahmed I, Roy BC, Khan SA, Septer S, Microbiome Umar S. Metabolome and inflammatory bowel disease. *Microorganisms* 2016; 4: 20.
35. Png CW, Linden SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI, et al. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *Am J Gastroenterol* 2010; 105: 2420–8.
36. Loubinoux J, Bronowicki JP, Pereira IA, Mougenel JL, Faou AE. Sulfate-reducing bacteria in human feces and their association with inflammatory bowel diseases. *FEMS Microbiol Ecol* 2002; 40: 107–12.
37. Schreck Bird A, Gregory PJ, Jalloh MA, Risoldi Cochrane Z, Hein DJ. Probiotics for the treatment of infantile colic: a systematic review. *J Pharm Pract* 2017; 30: 366–74.
38. Partty A, Kalliomaki M. Infant colic is still a mysterious disorder of the microbiota-gut-brain axis. *Acta Paediatr* 2017; 106: 528–29.
39. Dubois NE, Gregory KE. Characterizing the intestinal microbiome in infantile colic: findings based on an integrative review of the literature. *Biol Res Nurs* 2016; 18: 307–15.
40. Partty A, Kalliomaki M, Endo A, Salminen S, Isolauri E. Compositional development of Bifidobacterium and Lactobacillus microbiota is linked with crying and fussing in early infancy. *PLoS ONE* 2012; 7: e32495.
41. Liu HN, Wu H, Chen YZ, Chen YJ, Shen XZ, Liu TT. Altered molecular signature of intestinal microbiota in irritable bowel syndrome patients compared with healthy controls: a systematic review and meta-analysis. *Dig Liver Dis* 2017; 49: 331–37.
42. Rajilic-Stojanovic M, Biagi E, Heilig HG, Kajander K, Kekkonen RA, Tims S, et al. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology* 2011; 141: 1792–801.

43. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy* 2014; 44: 842–50.
44. Ipci K, Altintoprak N, Muluk NB, Senturk M, Cingi C. The possible mechanisms of the human microbiome in allergic diseases. *Eur Arch Otorhinolaryngol* 2017; 274: 617–26.
45. Melli LCFL, do Carmo-Rodrigues MS, Araújo-Filho HB, Solé D, de Morais MB. Intestinal microbiota and allergic diseases: A systematic review. *Allergol Immunopathol (Madr)* 2016; 44: 177–88.
46. Frasinariu OE, Ceccarelli S, Alisi A, Moraru E, Nobili V. Gut-liver axis and fibrosis in nonalcoholic fatty liver disease: an input for novel therapies. *Dig Liver Dis* 2013; 45: 543–51.
47. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; 444: 1022–3.
48. Chu H, Williams B, Schnabl B. Gut microbiota, fatty liver disease, and hepatocellular carcinoma. *Liver Res* 2018; 2: 43–51.
49. Rivera CA, Gaskin L, Allman M, Pang J, Brady K, Adegboyega P, et al. Toll-like receptor-2 deficiency enhances non-alcoholic steatohepatitis. *BMC Gastroenterol* 2010; 10: 52.
50. Del Chierico F, Nobili V, Vernocchi P, Russo A, Stefanis C, Gnani D, et al. Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. *Hepatology* 2017; 65: 451–64.
51. Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009; 49: 1877–87.
52. Raman M, Ahmed I, Gillevet PM, Probert CS, Ratcliffe NM, Smith S, et al. Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2013; 11: 868–875.e3.
53. Hojsak I, Fabiano V, Pop TL, Goulet O, Zuccotti GV, Çokuğraş FC, et al. Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups. *Acta Paediatr* 2018; 107: 927–37.
54. Prodeus A, Niborski V, Schrezenmeir J, Gorelov A, Shcherbina A, Rumyantsev A. Fermented milk consumption and common infections in children attending day-care centers: a randomized trial. *J Pediatr Gastroenterol Nutr* 2016; 63: 534–43.
55. Hutkins RW, Krumbeck JA, Bindels LB, Cani PD, Fahey G, Goh YJ, et al. Prebiotics: why definitions matter. *Curr Opin Biotechnol* 2016; 37: 1–7.
56. Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, et al. World gastroenterology organisation global guidelines: probiotics and prebiotics October 2011. *J Clin Gastroenterol* 2012; 46: 468–81.
57. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr* 1995; 125: 1401–12.
58. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014; 11: 506–14.
59. Health Canada. Claims about the Nature of Probiotic Microorganisms in Food. Health Canada [online]. Available at: http://www.hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/probiotics_claims-allegations_probiotiques-eng.php%20 (2009) (accessed November 2018).
60. Ministero della Salute, Commissione unica per la nutrizione e la dietetica. Guidelines on probiotics and prebiotics. Ministero della Salute [online]. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1016_allegato.pdf (2013) (accessed on November 2018).

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1 References.