EPA-UNEPSA SCIENTIFIC ACTIVITY (2021-2023)

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

EPA-UNEPSA SCIENTIFIC ACTIVITY (2021-23)

A collection of scientific articles dedicated to child health, child health promotion and care published by EPA-UNEPSA during the years 2021-2023.

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INTRODUCTION

The European Paediatric Association, Union of National Paediatric Societies and Associations (EPA-UNEPSA), is committed to fostering connections among medical and non-medical experts. The overarching goal of EPA-UNEPSA is to provide education that transcends geographical boundaries, while respecting national nuances.

In recent years, EPA-UNEPSA has united over 50 European national paediatric associations and societies. Their collaborative efforts have given rise to a shared "learning across borders" initiative, sparking discussions on diverse aspects of child healthcare – spanning psychological, medical, legal, and economic domains. Additionally, EPA-UNEPSA has actively engaged in planning, conducting, and disseminating studies on child health services across Europe. Notably, EPA has attracted not only paediatricians but also experts in various facets of child healthcare, eager to contribute to projects aimed at enhancing child health on a European scale.

In 2019, EPA-UNEPSA forged an alliance with the European Confederation of Primary Care Paediatricians (ECPCP). Through a strategic agreement, the two scientific societies collaborate to advocate for European children. They encourage other European paediatric societies to unite in pursuing the common objective of presenting a unified voice for European Paediatrics.

The European Paediatric Association aspires to enhance the well-being of children and youth in Europe, elevating the quality of healthcare services provided to them and their families. This e-book encompasses a wide array of topics that mirror ongoing discussions, controversies, standards, gaps, bridges, challenges, and achievements. Recognizing the immense value of effective professional communication, we have made our previous publications widely accessible to paediatricians.

EPA-UNEPSA has broadened its intellectual foundation by establishing a multidisciplinary society, addressing the need to prevent the fragmentation of paediatrics. This approach enables tackling legal, economic, and organizational challenges in child healthcare across Europe. Importantly, EPA-UNEPSA remains steadfast in placing children and young people at the heart of its endeavours.

We invite you to enjoy reading the articles and encourage you to reach out to the EPA-UNEPSA Editorial Board with any questions or comments regarding the content.

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

EUROPEAN PAEDIATRIC ASSOCIATION

The Dark Side of the Web—A Risk for Children and Adolescents Challenged by Isolation during the Novel Coronavirus 2019 Pandemic

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In response to the global novel coronavirus disease 2019 (COVID-19) pandemic, many countries around the world adopted social isolation measures to contain the spread of the virus.[1] For children and adolescents, limitations in face-to-face activities and interactions with their traditional peer groups has been a frustrating experience. After disease containment measures, which included school closures, social distancing, and home quarantine, children and adolescents faced a prolonged state of physical isolation from their peers, teachers, extended family, and community networks that affects their emotional and behavioral health.[2] Parents and pediatricians are reporting signs of mental distress in children of all ages within the context of the pandemic.[3] In several cases, this unexpected social isolation has paradoxically improved the psychosocial state of fearful children, and the mental health of those who have been victims of bullying.[4] School function improved with distance learning and socialization may have increased using virtual connections to create a larger social group.[5]

However, children and adolescents who experience a prolonged state of physical isolation may look for alternative, somehow attractive or unconventional forms of socialization, available on the internet. Children may be exposed to the risks of unsupervised cyberspace exploration beyond the open web, which may lead them to areas that are usually not available to visitors. They may pass the gates of the "open" and "deep web" sections and enter into the dangerous "dark web" zones, which predominantly host unethical and criminal activities. In those shadowy corners of the world-wide web, there exist dangers ranging from identity theft and the drug trade to suicide chat rooms and child pornography.[6]

This commentary, authored by European Paediatric Association/Union of National European Paediatric Societies and Associations members of the working group on social pediatrics, briefly discusses the features of the dark web and its implications for children and adolescents. Our aim is to raise awareness of pediatricians and families on the growing risk of child exploitation through the web at a time when vulnerable young people face home lockdowns with potential abusers intruding on their privacy.

COVID-19 Novel coronavirus disease 2019

Definition of Open, Deep, and Dark Web

The open or surface web is the portion of the world wide web (www.) that is readily accessible to the public and searchable with conventional web search engines that includes the network of indexed websites. The surface web is estimated to include between 1% and 5% of the entire web, and the standard search engines are able to reach approximately 0.03% of the information that is available; much of the rest remains submerged in areas of the web not openly accessible.[7,8] These areas are identified as the deep web and the dark web, terms that are frequently abused and confused and usually associated with criminal activities. The term *deep web* describes the series of largely legitimate contents present on the web that are not indexed by common search engines and include pages on the internet that cannot be found by performing a search using the available internet platforms (eg, Google, Yahoo, Bing). Users need to know the exact address of the site to gain access. Another way to access a deep web site is to click on a link available after entering the deep web or by using an access code. This is true of private sections developed by public and private organizations, including banks, government, and academic institutions, which typically grant their members access to confidential databases, archives, or professional private chats.

The term *dark web* indicates the set of publicly accessible contents that are hosted on websites whose IP address is hidden, but can be accessed by using dedicated software, as long as they know the address (**Table I**; available at www.jpeds.com). Elements belonging to the dark web are private content exchanged between users within closed computer networks, which are internal structures defined as darknets. Although not all content in the dark web is illegal, more than 60% of the sites on the dark web host illicit material.[9]

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The Accessibility to the Dark Web and Its Risks for Children

The most popular way to access the dark web is via dedicated browsers, such as The Onion Router, which has more than 2.5 million users each day.[10] Other browsers enabling access to the dark web exist, such as I2P and Tails.[11]

The Onion Router, launched in 2002, uses the principle of onion routing, developed at the United States Naval Research Laboratory in the 1990s, in which the user data are first encrypted and then transferred through different relays present in the network.[12] Thus, it creates multilayered encryption (like layers of an onion) and keeps the identity of the user safe. A single encryption layer is decrypted at each successive Onion Router relay, and the remaining data are forwarded to any random relay until it reaches its destination server. Therefore, the last Onion Router node-exit relay appears to the destination server as the origin of the data, making it difficult to trace the identity of the user or the server by any surveillance system.

It is technically not illegal to access the dark web through the Onion Router browser. The US government and military use these types of shielded communication to share information and protect their agents and informants. It is also perceived as a right to privacy and encryption, as well as a safe space for journalists and whistleblowers. However, the danger of the dark web comes when users are technically naive and/or not careful with the contents. Children and adolescents in particular may be unprepared and easily fall victim to hackers, give away personal information without intention, or slip into illegal activity. There is also the potential for psychological damage because the large number of illegal activities available in the dark web includes a considerable amount of disturbing material.[13]

During the months of the COVID-19 pandemic, education and other important socializing activities for children and adolescents have been productively supported by the use of the web. However, at the same time, this has exposed them to clandestine groups, such as pedophile and other illegal networks, that have seen the increased use of the web as an opportunity to intensify their activities to approach unsupervised minors. Increased risks for children and adolescents reaching the dark web during the COVID-19 pandemic are multiple[14] and include online grooming for various purposes, introduction to suicide, and child pornography.[7] Child pornographic content is shared among offenders who redistribute them online through the dark web, causing lifelong harm to the victims.[7]

Protecting Children from Dark Web Hazards during COVID-19

Staying confined as a family should be perceived as an important opportunity for parents to turn a negative occurrence into a positive experience.[15] This situation offers an opportunity for parents and families to interact constructively with their children, stay positive, manage stress, and support them in filling their time with meaningful and healthy activities. The majority of school activities, free time, and social interactions, as well as time with friends and family outside the typical "nuclear family" have moved online during the COVID-19 crisis. Parents and caregivers shift their expectations and plan around screen time to modulate what is necessary for schoolwork. They can expand the time schedules of children to include additional online time for educational leisure activities, like virtual tours of zoos or museums or connecting with classmates via online educational activities, including games and networks. Children could spend their time on the web with positive activities and learn about cooperation and kindness. A large number of educational resources, platforms, and technologies have been created that provide parents and educators with a considerable selection that must be supported by an increased competence and familiarity with the technology.[16,17] In this new social context, pediatricians can play a central role in advising families on how to best manage the time of their children and protect them from the risks of an uncontrolled increased usage of web resources during the pandemic.[18,19]

Conclusions

The current global health crisis has brought unprecedented changes in people's interactions and routines owing to social distancing and confinement. In several countries, only essential businesses were functioning normally, and many adults in institutions and companies worked from home and children followed their school lessons online. Families, communities, businesses, and governments were forced to become familiar and progressively depend on the internet, digital technology, and social media to retain a semblance of normalcy, continue their daily activities, and expand their use for entertainment. This new social setting has created unique challenges and opportunities but has also exposed the most vulnerable part of the population—children and adolescents—to the unprecedented risks of the infosphere, which include uncontrolled access in dark areas of the web.[20] Governments are working to develop measures that aim at strengthening national prevention, response, and support services[21,22] (**Table II**; available at www.jpeds.com). Pediatricians and educational institutions can and should play a central role in directly supervising and managing the social side effects of the COVID-19 pandemic in their communities.[23,24] ■

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Table I. Different areas of the web

Areas	Description
Open web	The publicly visible part of the internet that can be access through standard search engines; includes indexed websites. Accessible by using conventional legal search engines: Google, Yahoo, Reddit, CNN.com, and others
Deep web	The internet that is generally hidden from public view. The deep web is not accessed via standard search engines. Much of its content is ordinary and legitimate. Organizations have websites that can only be read by authorized employees or clients, with their information password protected. One example is the medical history of an individual, which can be accessed by authorized persons. Type of contents accessible: Academic databases, medical records, financial records, legal documents, selected scientific reports, selected government reports, subscription only information, organizations-specific repositories.
Dark web	Generally accessible using dedicated software. This includes The Onion Router, I2P, and other software programs including Subgraph OS, Tails, Opera, Whonix, Firefox, and Waterfox. The Onion Router provides anonymizing software that can be accessed via a Google search and then downloaded free of charge. The Onion Router itself is not the dark web, but is a way to browse both the open and dark web, without being able to identify the user or track its activity. Type of contents accessible: Drug trafficking, pornography, sexual soliciting and abuse activities, assassination market, unlicensed guns traffic, fake IDs, terrorism, gambling, hacking tools, stolen credit cards, political protest and violence instigation and other illegal activities.

Table II. Prevention, response, and social support services needed during the COVID-19 pandemic

Monitor how restricted movement and lockdowns may exacerbate offline and online forms of violence and advise legislators based on latest data and existing models.
Enforce existing regulations and strengthen law enforcement to help monitor activities and respond to increased online risks.
Allot sufficient resources to bolster, train, and equip core child protection workers qualified to keep children safe throughout the pandemic. Activate center-based supports and home visits for those severely affected or adapt and deliver social services virtually.
Train health, education, and social service workers on the impact that COVID-19 may have on child well-being, including increased online risks. Providing front line mental health/psychosocial support with skills to talk to children about COVID-19 and address their anxiety and insecurity. Identify vulnerable children, including those separated, disabled, or in conflict settings, and those who may have lost parents or primary caregivers to the pandemic.
Raise awareness among government departments of the potential increased online risks to children during the pandemic. Develop a coordinated institutional approach.
Ensure that social service providers, schools, parents, caregivers, and children are aware of local reporting mechanisms, including the support numbers of local helplines and hotlines. In the absence of these services, local helplines and hotlines should be developed to support children in distress. Nationally based Child Helpline should be also developed. Families and carers should be instructed to contact the police when imminent danger is perceived. (Major international reporting networks include INHOPE Hotlines and IWF portals).
Promote educational initiatives on child online safety, to complement efforts to connect children to resources for online learning, socialization, and play. This should include raising awareness about online risks and resources, using media and other communications channels to spread key messages.

Ensuring Safe Food for Infants: The Importance of an Integrated Approach to Monitor and Reduce the Risks of Biological, Chemical, and Physical Hazards

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Despite a decrease in biological, chemical, and physical hazards in infant food owing to national and international control programs, the risks of hazards in infant food remain a global concern.[1] Raising consumer awareness on the consequences of unhealthy food consumption, and a growth of consciousness by the food industry of the importance of ensuring protection against contaminants in commercially available products, have limited the risk of food contaminants.[2,3] However, interventions applied across the food supply chain to inspect the presence of food contaminants and help to ensure a sustainable supply of nutritious safe food, are insufficient to provide an extensive and comprehensive protection.[3] Infant food safety in the economically advanced Western world is currently monitored by increasingly strict legal regulations; however, some countries still use banned substances in industrial food production owing to their poor economy and insufficient regulation.[4] The export and import exchange of commercial, often low-cost, infant food products, may raise serious risks for children's health despite the presence of standard control procedures and techniques, which may be insufficient or inadequate to detect a large variety of contaminants in food products.[3,4]

This commentary aims to increase awareness of the necessity to further decrease the risks of hazards of different nature in infants and children's food and to emphasize the importance of developing and constantly update integrated and effective systems for monitoring the presence of contaminants in infant food.[5]

Food Safety in a Globalized World

Food safety and protection of consumer's health are a major concern for many governments. Policies aim to prevent, mitigate, or eliminate risks at different stages of the food chain, while maintaining, providing, and supplying high-quality food to meet consumer demands.[2,4] Globalization involves trade liberalization, integration of production, and consumption and lifestyle patterns; this implies a widespread import, export, and distribution of a great variety of foodstuffs, including food for infants and children. Owing to increasing consumer demand for quality and transparency, larger scale food production, intensive food trade, and growing urbanization influencing production patterns of food, food safety has become a major priority in public health. Food safety and quality assurance involve trust, transparency, and harmonization of practices, which is a prerequisite for the development of efficient and reliable domestic and international trade. However, implementing efficient food safety control is a complex task owing to several factors, including the variety of products resulting from the diversity of raw materials, processing, packaging, and storage and to the different regulatory contexts and health surveillance systems between countries. Furthermore, the diversity and changes in consumer practices favor a constant evolution of products facilitated by agri-food innovations and advances in human health knowledge, which also contribute to the regulatory changes.[6]

Potential Hazards in Food

Biological, chemical, or physical hazards may be introduced into the food supply at any time during harvesting, processing, transporting, preparing, storing, and serving food. Understanding the risks associated with each of these steps can significantly decrease the potential of foodborne illnesses. All can be avoided through an effective food safety management system.

Biological hazard occurs when food becomes contaminated by micro-organisms. Many micro-organisms are beneficial; however, in the right conditions, some may cause a foodborne illness.[7] Foodborne diseases can be caused by consuming food or water contaminated by pathogenic micro-organisms, which include bacteria and their toxins, fungi, viruses, and parasites.[8,9] Food can be contaminated

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both at the source as raw material and during food processing, storage, and distribution. Infected individuals or carriers of pathogens and the environment, through food contact surfaces and facilities, can spread micro-organisms to raw or processed food.

Food contaminants include environmental contaminants, food processing contaminants, unapproved adulterants, food additives, and migrants from packaging materials.[10] Typically, chemicals used for pest control or for cleaning and sanitizing food contact surfaces and food preparation equipment may contaminate food. Persistent organic pollutants are a common and dangerous group of chemical contaminants that persist in the environment, bioaccumulate through the food web, and pose a risk of causing adverse effects to human health and the environment (**Table I**; available at www.jpeds.com).[1]

A variety of extraneous materials in foodstuffs are hazardous to individuals, causing illness or injury. Foreign items can be unintentionally introduced to food products, or naturally occurring objects may fail to be separated along a food processing line and excluded from consumption (**Table II**; available at www.jpeds.com). Materials normally absent in food products include metal fragments in ground meat, bone chips, pieces of product packaging, stones, glass or wood fragments, insects or other filth, and personal items.[11] Furthermore, individuals may be exposed to metals and metal compounds as environmental pollutants from industrial or other human activities.[11] Heavy metals such as lead, arsenic, mercury, or cadmium, may be considered a potential contaminant. These substances are of concern owing to their toxicity, particularly in the case of a long-term intake, because they may accumulate in the body and cause organ damage, especially in susceptible groups, including young children.[11]

The Importance of Developing an Integrated Approach to Food Safety Monitoring

Improving risk assessment and monitoring of food safety, including the use of big data, is important. Effective control programs are required to plan integrated approaches along the entire food chain for detecting, assessing, and mitigating relevant pathogens and other contaminant hazards.[12] That implies the development of efficient food safety control systems, supported by reliable authentication and traceability approaches. Effective control systems should be implemented across the entire food chain, focusing on the combination of hazard monitoring and control options. To overcome the complexity and the diversity of food chains, tools, databases, procedures, and operating models, need to be integrated in a user-friendly and upgradable decision support system for identification, detection, ranking, and control of hazards and risk assessment. A reliable and effective integrated approach is based on the involvement and contribution of different disciplines competent but not limited to risk assessment, food technology, predictive toxicology, residue chemistry, predictive microbiology, child health, data science, and knowledge engineering. The integrated approaches should collect and combine pertinent knowledge and data from the entire food chain, taking into account the diversity of biological, chemical, and physical hazards. Finally, the different criteria contributing to risk ranking should consider and include the public health impact, community perception of the risks, diversity of local cultures, and a rigorous selection of the different sources of information.[12]

In 2020, the European Paediatric Association, Union of National European Paediatric Societies and Associations working group on nutrition joined forces with a consortium of 19 European research centers, coordinated by the French National Research Institute for Agriculture, Food and the Environment, to develop a research program called safe food for infants, supported by the European Union (EU).[13,14] This EU-funded project aims to improve risk-based food safety management of biohazards. To achieve these goals, the consortium is developing procedures to enhance top-down and bottom-up hazard control by combining management options within the frame of the EU Horizon 2020 research and innovation program.[14] In view of the food safety challenges in the monitoring and detecting of contamination in food supplies, whether by accident or fraud, the consortium is developing decision support systems to enhance safety controls along the food chain. Focusing on the potential risks raised by the major international channels of infant food trade, the program is also establishing educational and knowledge transfer activities to foster harmonization of good practices. Global collaboration in the area of food safety and control is of great strategic importance, and the EU program includes cooperation with public health authorities of governments around the world.[15]

Conclusions

Owing to increasing populations and global threats, the integrity and safety of global food chains are at risk. In many countries, simply getting enough to eat can be an issue, with poor quality food often contaminated with hazardous agents, whereas in developed countries the pressure to deliver cheap, affordable food may affect quality and safety.[16]

The fate of nations is determined by what they eat, and pediatricians are on the front line to contain the risks of food hazards.[7,17] They can play a key role if they will actively cooperate and integrate their efforts with governments and local, state, federal, and global public health institutions and agencies, to ensure that infants and children have access to good and safe food. *EPA-UNEPSA thanks the European Commission for its support in the area of child safety. EPA-UNEPSA is a partner of the European Union's Horizon 2020 research and innovation program n.861917.* ■

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Table I. Summary of most common persistent organic pollutants: Associated contaminated food and health hazards

Persistent organic pollutants	Contaminated food	Possible hazards
Polyaromatic hydrocarbons	Dairy products, grain, flour and bran, rice, fruit and vegetables, oyster, water	Mutagenicity/carcinogenicity, DNA damage, oxidative stress, impaired male fertility, respiratory diseases, cognitive dysfunction among children and cancer (breast cancer)
Organochlorine pesticide	Eggs, dairy products, meat and meat products, rice, fruit and vegetables, honey, oil, fish, mussel, water	Neurologic symptoms, endocrine disruption, infertility and fetal malformation, diabetes, cancer (breast cancer, testicular, prostate and kidney cancer), reproductive problems, cardiovascular problems, high blood pressure, glucose intolerance and obesity
Polychlorinated biphenyls	Eggs, dairy products, meat and meat products, rice, fruit and vegetables, oil, fish, mussel, water	Endocrine disruption, neurologic disorders, liver injury, diabetes, cancer (breast, prostate, testicular, kidney, ovarian and uterine), cardiovascular problems and obesity
Polybrominated diphenyl ethers	Fish, mussels	Reproductive problems, cancer (testicular), diabetes, obesity and cardiovascular problems
Perfluorinated compounds	Eggs, fish, water	Breast cancer
Hexabromocyclododecanes	Eggs, oil, fish	Endocrine disruption, reproductive problems and behavioral disorders
Polychlorinated naphthalenes	Meat and meat products	Cancers
Dioxins/furans	Eggs, dairy products, meat and meat products, oil, fish,	Language delay, disturbances in mental and motor development, cancer, diabetes, endocrine disruption, high blood pressure, glucose intolerance, and cardiovascular problems

Table II. Common sources of physical hazards in food

Glass	Light bulbs, glass containers and glass food containers
Metal	Fragments from equipment such as splinters, blades, needles, utensils, staples, etc
Plastic	Material used for packaging, fragments of utensils used for cleaning equipment
Stones	Incorporated in field crops, such as peas and beans, during harvesting
Wood	Splinters from wood structures and wooden pallets used to store or transport ingredients or food products
Natural components of food	Hard or sharp parts of a food (eg, shells in nut products)
Metallic contaminants	Natural and anthropogenic sources of heavy metal contamination include agricultural activities, such as pesticide and herbicide application, contaminated irrigation water, municipal waste used for fertilization and mineral fertilizer containing traces of heavy metals

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Research Letter | Public Health

Comparison of COVID-19 Incidence Rates Before and After School Reopening in Israel

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Introduction

Schools reopened in Israel on September 1, 2020, following summer vacation during active SARS-CoV-2 spread when the incidence of new cases of COVID-19 in Israel was one of the highest in the world. During September 2020, COVID-19 cases further surged in Israel, resulting in school closure (September 14), and a countrywide lockdown. Schools were reopened on November 1. We examined the dynamics in infection rates in children and youths aged 0 to 19 years compared with other age groups, with the goal of understanding whether school reopening was associated with SARS-CoV-2 infection in those aged 0 to 9 years.

Methods

Because deidentified data from public sources were used, this cohort study was considered exempt from institutional review board approval and informed patient consent was not required. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Daily data were obtained from public national sources of the Ministry of Health,[1,2] of COVID-19 incidence, SARS-CoV-2 polymerase chain reaction (PCR) tests performed, and the rate of positive samples. SARS-CoV-2 age group–specific weekly incidence rates were calculated and adjusted for the number of tests performed for the following age groups: 0 to 9 years, 10 to 19 years, 20 to 39 years, 40 to 59 years, and 60 years and older. For each age group, incidence rate (weekly number of new cases per 100 000 population of the specific age group) was multiplied by the proportion of this age group in the general population and divided by the proportion of the samples taken from individuals of this age group out of all samples obtained.

Adjusted incidence rate ratios (IRRs) and test positivity rate ratios (RRs) were calculated by comparing mean weekly adjusted incidences and positivity rates in: (1) the first 3 weeks of September, and (2) the weeks during November and December with the last week of August and the last week of October, respectively (weeks that preceded school reopenings) (eAppendix in the Supplement).

We also examined the dynamics of curves of weekly adjusted incidence during the first 3 weeks of September and their slopes. Differences in the incidence, and positivity rates of SARS-CoV-2 PCR tests were analyzed, and *P* values and 95% CIs were determined using 2-proportion *z* tests. $P < .01$ was considered statistically significant. Linear regression was used to generate the slopes statistics. Data analysis was performed using Social Science Statistics software and Excel spreadsheet software version 2019 (Microsoft) from January 2021 to February 2021.

Results

Data were analyzed from 47 620 children aged 0 to 9 years, 101 304 youths aged 10 to 19 years, 151 295 adults aged 20 to 39 years, 103 056 adults aged 40 to 59 years, and 63 438 adults aged 60 years and older with SARS-CoV-2 infection. Children aged 0 to 9 years had the lowest increase in IRRs

+ Supplemental content

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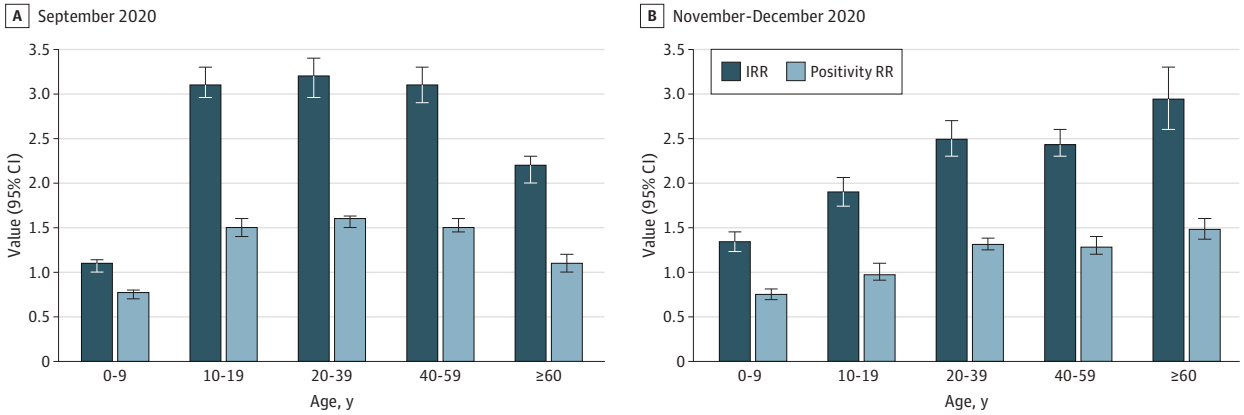
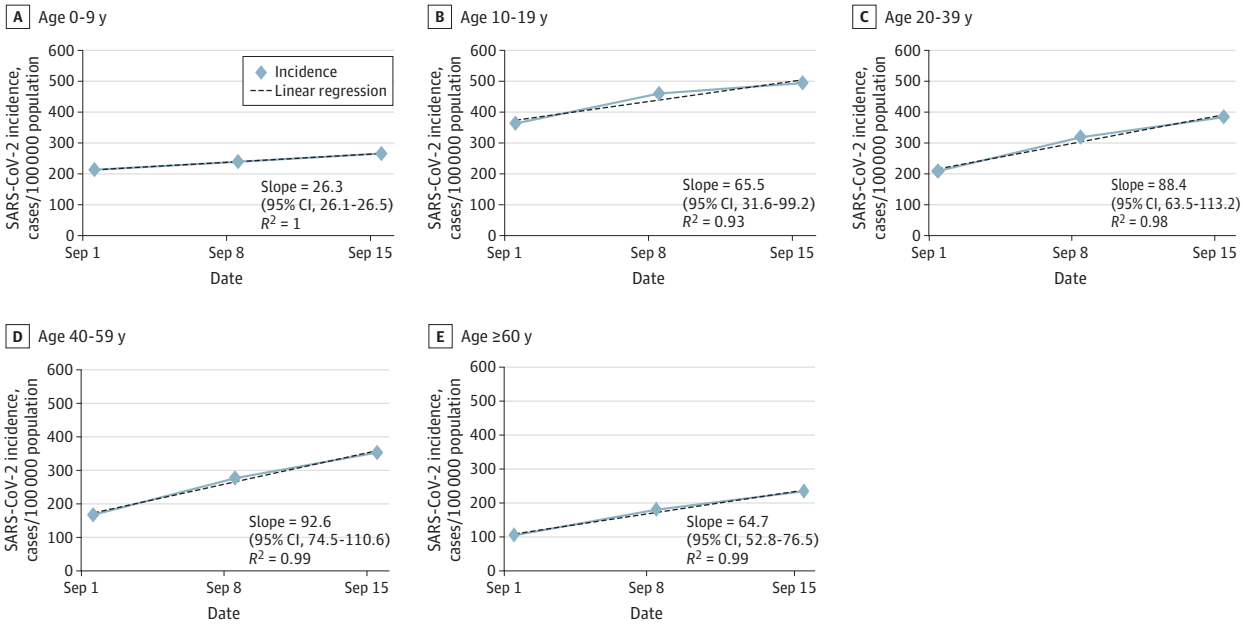
($P < .001$) and in positivity RRs of tests ($P < .001$) during both September (**Figure 1**A) and November to December (Figure 1B) school attendance periods. For September, the IRRs for the different age groups were 1.1 (95% CI, 1.0-1.14) for those aged 0 to 9 years, 3.1 (95% CI, 2.96-3.3) for those aged 10 to 19 years, 3.2 (95% CI, 2.96-3.4) for those ages 20 to 39 years, 3.1 (95% CI, 2.9-3.3) for those aged 40 to 59 years, and 2.2 (95% CI, 2.0-2.3) for those aged 60 years and older; and the positivity of test RRs were 0.77 (95% CI, 0.7-0.8) for those aged 0 to 9 years, 1.5 (95% CI, 1.4-1.6) for those aged 10 to 19 years, 1.6 (95% CI, 1.5-1.66) for those aged 20 to 39 years, 1.5 (95% CI, 1.45-1.6) for those aged 40 to 59 years, and 1.1 (95% CI, 1.0-1.2) for those aged 60 years and older. For the November to December periods the IRRs for the different age groups were 1.34 (95% CI, 1.23-1.45) for those aged 0 to 9 years, 1.9 (95% CI, 1.74-2.06) for those aged 10 to 19 years, 2.5 (95% CI, 2.3-2.7) for those aged

Figure 1. Mean Weekly Increases in Incidence Rate Ratios (IRRs) and Positivity Rate Ratios (RRs)



Mean weekly adjusted IRRs and positivity RRs of SARS-CoV-2 tests were calculated by comparing the mean weekly incidence and positivity rates during the following time periods: A, September 1 to September 21, 2020, with those of the week prior to school reopening (August 24-31); and B, November 1 to December 31, 2020, with those of the week prior to school reopening (October 22-29). Error bars indicate 95% CIs.

Figure 2. Weekly Adjusted Incidence Curves in Studied Age Groups



Weekly adjusted incidence (new SARS-CoV-2 cases per 100 000 population of the specific age group) during September 1 to September 21, 2020. Dates outlined represent day 1 of the studied week. R^2 denotes the R^2 value of the regression line. The slope (with 95% CIs) is for the linear regression line.

20 to 39 years, 2.43 (95% CI, 2.3-2.6) for those aged 40 to 59 years, and 2.95 (95% CI, 2.6-3.3) for those aged 60 years and older; and the positivity of test RRs were 0.75 (95% CI, 0.7-0.8) for those aged 0 to 9 years, 0.97 (95% CI, 0.95-1.1) for those aged 10 to 19 years, 1.3 (95% CI, 1.25-1.4) for those aged 20 to 39 years, 1.28 (95% CI, 1.2-1.4) for those aged 40 to 59 years, and 1.48 (95% CI, 1.35-1.6) for those aged 60 years and older.

Children aged 0 to 9 years had also significantly lower slopes of adjusted incidence of new cases than any other age group during the first 3 weeks of September (**Figure 2**). The respective slopes were 26.3 (95% CI, 26.1-26.5) for ages 0 to 9 years, 65.5 (95% CI, 31.6-99.2) for ages 10 to 19 years, 88.4 (95% CI, 63.5-113.2) for ages 20 to 39 years, 92.6 (95% CI, 74.5-110.6) for ages 40 to 59 years, and 64.7 (95% CI, 52.8-76.5) for ages 60 years and older.

Discussion

Children aged 0 to 9 years had the lowest increases in IRRs and in positivity RRs of tests during the 2 school attendance time periods. They also had lower slopes of adjusted incidence curves related to the first 3 weeks of September. These analyses suggest that children in this age group do not have substantial rates of SARS-CoV-2 infection during school attendance and are supported by previous data that demonstrated lower infection rates and lower transmission potential of this age group.[3-6]

The main limitation of the study is its observational design that cannot inform causal relationships. It is difficult to assess the accurate role of youths aged 10 to 19 because the differences in terms of IRRs and positivity RRs from adults aged 20 to 59 years were insignificantly small. Although it appears that youths aged 10 to 19 years could have actively participated in the spread of infection following school reopening similar to adults aged 20 to 59 years, they could also have been secondary contacts of other sources of infection.

In conclusion, our study's findings suggest that children aged 0 to 9 years did not have substantial rates of SARS-CoV-2 infection during school attendance periods, and it may be assumed that they did not have a substantial role in COVID-19 spread either during this period. Therefore, resuming school for this age group when lockdown was released appears to have been safe for them. It is probably safer to resume school attendance for youths aged 10 to 19 years only when the epidemic is under control and after implementation of steps to decrease spread in schools.

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SUPPLEMENT.

eAppendix. Supplemental Methods

The Role of Pediatricians in Providing Greater-Quality Care for Children: An Ongoing Debate

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More than 40 years have passed since the first International Conference on Primary Health Care, held in Alma-Ata, Kazakhstan in 1978; 134 countries and 67 international organizations met and established the strategic prominence of primary healthcare, emphasizing its role in maternal and child healthcare.[1] Twenty years later, in 1998, the United Nations Convention on the Rights of the Child was signed by 140 nations and later ratified by a total of 196 nations.[2] Although accepted with various reservations or interpretations by the parties, this international treaty is regarded as an event of major historical significance for human rights, as it set out the civil, political, economic, social, health, and cultural rights of children.[3] However, in 2021, children's health may not be a main concern for public authorities in Europe.[3] Child healthcare frequently is regarded as a secondary objective in the development of public health policies and not as a central issue. Cost-containment policies instead of quality of healthcare frequently have inspired strategic decisions in public health investments for pediatric structures and workforce.[4] The negative implications of this decisional approach have been shown by the substantial unpreparedness of virtually all European health systems during the coronavirus disease 2019 (COVID-19) pandemic,[5] particularly in the area of primary care.[6] The debate on the negative effects of cost-containment policies in the area of primary care in not new.[7,8] In recent years, the role of pediatricians within the several European healthcare systems was variously reformed by governments,[9] with an eye more to the budget than to the quality of care and its structural components, including staffing adequacy, training, and consistency as well as facility environment and size.[10]

As a result, the number of general pediatricians in Europe has decreased during the past 20 years.[11,12] Data from the World Health Organization show that the average number of general pediatricians per 100 000 population in Europe declined 30.1% from 26.5% in 1998 to 18.5% in 2013.[13] A further reduction in the pediatric workforce was reported in 2018 by the European Paediatric Association, the Union of National European Paediatric Societies and Associations (EPA-UNEPSA).[14] During the past 20 years, due to different factors, including socioeconomic and political reasons, several European countries decided to reform their public health systems and the responsibility of pediatric healthcare delivery was moved from pediatricians to general and family practitioners.[11] The aim of this commentary by the Spanish Primary Care Pediatrics Association (AEPap), in collaboration with the European Confederation of Primary Care Pediatricians and EPA-UNEPSA, is to discuss data supporting the essential role played in Europe by well-trained pediatricians vs other providers in delivering quality healthcare for children.

High-Quality Care Provided by Pediatricians in Economically Advanced Countries

The controversy over healthcare delivered to children by doctors trained in pediatrics vs general practitioners (GPs) dates back at least a century in the western world.[15] Children's hospitals and pediatric pavilions were established in both continents during the 18th and 19th centuries.[16,17] However, pediatrics was later distinguished as a separate specialty.[18] The field of pediatrics as we know it today developed as a separate specialty in the first half of the past century, bringing with it the longstanding debate around who to entrust with the healthcare of children—pediatricians or GPs?[19] As a result, parents often were confronted with the important question of whether to choose a pediatrician or a family doctor for the care of their children, and authorities established their public health strategies for child healthcare and family services based on economic factors rather than on the importance of providing quality care. However, conclusions and decisions were often founded on unclear or insufficient elements. A 2011 systematic review by AEPap compared the work of pediatricians in primary care with that of other

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EPA-UNEPSA	European Paediatric Association, Union of National European Paediatric Societies and Associations
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professionals, showing that pediatricians provide better-quality healthcare.[20] By monitoring the scientific literature listed in PubMed MEDLINE, Embase, Cochrane Central Register of Controlled Trials, TRIP Database, and Google Scholar, AEPap selected 1150 articles discussing clinical practice in primary care pediatrics. Their analysis contributed useful information to the debate over the adequacy of child healthcare provided by different professional figures.[21]

Implementation of Vaccine Policies and Protocols by Pediatricians

Child immunization is a crucial preventive activity in child healthcare.[22] The AEPap review reports that during the past 10 years, most published articles that compared the quality of healthcare provided to children by different professional figures were related to vaccination. Pediatricians recommended vaccinations 2.6 to 11.10 times more frequently than family doctors (lower OR 2.6 [1.9-3.7]; higher OR 11.10 [1.57-78.54]). Studies performed in France, where there is an active network of pediatric primary care dedicated to vaccination programs,[23] showed that pediatricians ensure that families comply with their children's immunization schedules for pneumococcus, MMR, pertussis, meningitis B, and hepatitis B more frequently than family doctors.[24-26]

Appropriateness of Antibiotic Prescription

The rational use of antibiotics in childhood is a worldwide objective, as it is essential to prevent bacterial resistance and to avoid iatrogenic harm, while contributing to the cost containment in public health. One-fifth of the papers selected for review by AEPap discussed antibiotic therapy in pediatrics and the prescriptive attitudes of clinicians. Although the heterogeneity of the studies did not allow for a rigorous meta-analysis, the data showed that in 62.5% of the studies antibiotic prescription by pediatricians was reported to be more appropriate and in line with official clinical practice guidelines.[21,27]

The Contribution of Pediatricians to Prevention Programs and Laboratory Testing Adequacy

Overweight and obesity have become increasingly prevalent worldwide and chronic noncommunicable diseases, including type 2 diabetes, primary hypertension, and coronary heart disease are strongly associated with obesity. The systematic AEPap review indicates that pediatricians were more accurate than generalists in assessing the nutritional status of children and adolescents and in following the guidelines for diagnostic procedures and preventive programs for these conditions.[21,27,28] Finally, the review reports that pediatricians were more diligent than GPs or other specialists in areas of clinical practice, such as the use of laboratory tests in the diagnosis and management of different conditions (streptococcal, celiac disease, diabetes mellitus, and early diagnosis of acute lymphoblastic leukemia), and referring to specialists for the pharmacologic treatment of psychiatric disorders.[27]

Conclusions

The AEPap review offers useful data, which further emphasizes the fact that clinicians caring for children and adolescents must be adequately trained in pediatrics. The average training period of a pediatrician in Europe is 4-6 years.[10,11] The training in pediatrics of family doctors differs between countries,[29] varying from a few weeks in the United Kingdom to an average of 4 months in the rest of the countries, with a range of 3-6 months. An appropriate pediatric workforce is essential to attain the optimal physical, mental, and social health and well-being for all infants, children, and adolescents.[30] The partner societies EPA-UNEPSA and European Confederation of Primary Care Pediatricians are actively engaged in emphasizing to the European governments and legislators the importance of well-trained pediatricians in charge of the health of children and adolescents and that pediatrician-based healthcare systems are not replaced by family doctor-based systems. To prolong the dispute between different professional figures about the primacy of their role in child healthcare is ultimately of little benefit to children. The key point of the debate is that children should be cared for by doctors adequately trained in pediatrics. ■

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EUROPEAN PAEDIATRIC ASSOCIATION

Plan for the Worst, but Hope for the Best: Investing in Pediatric Services

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Millions of young children throughout the world are not reaching their full potential owing to poor economic conditions, causing a variety of social disadvantages, including inadequate nutrition, lack of early stimulation and education, and major exposure to communicable and noncommunicable diseases.[1] Adverse socioeconomic circumstances in childhood are not isolated experiences[2,3] but rather cofactors predisposing children to a state of general disadvantage, resulting in various detrimental health consequences associated with increased morbidity and mortality later in life.[3]

The World Health Organization, the World Bank, and several individual countries have made global investments to reduce socioeconomic gaps in childhood, establishing intervention programs in different settings, particularly in economically disadvantaged countries. Their strategic approach is based on the principle that investing in the early years is one of the smartest investments the global community can make to break the cycle of poverty and address inequality while promoting health and well-being and boosting productivity later in life.[4]

In low- and middle-income countries, approximately 250 million children aged <5 years (43% of this population) will fail to attain their potential because of adversities and deficient socioeconomic conditions that they face during their early years.[4,5] However, the risk of poverty or social exclusion is also a real threat in many areas traditionally considered economically privileged.[6] Currently, approximately 30 million European children living in the Eurozone are facing poverty, a dramatic decline in opportunities, and denial of their rights.[7] The current economic, financial, and social crisis resulting from the COVID-19 pandemic is increasing these risks. Projection data indicate that the pandemic will take its toll on society, particularly on younger people, for some time to come, undermining social welfare, including healthcare systems, in low-, medium-, and high-income countries alike.[8] The aim of this commentary written by the Working Group on Social Pediatrics of the European Paediatric Association and the Union of National European Paediatric Societies and Associations is to emphasize the importance of investing in pediatric health and services, calling for early action to limit the impact of the COVID-19 pandemic-related global economic recession on young people.

A Decade of Declining Welfare Affecting Children's Health and Well-Being in the Western World

After the Second World War, the state of children's health and well-being in economically advanced countries has steady improved.[9] However, more recent events have slowed this positive trend. The global financial crisis of 2009 inaugurated a decade of general socioeconomic decline, which seriously affected the living conditions of people in many Western countries, especially fragile families and their children.[10] Following the 2009 economic depression, approximately 30% of children living in European Union (EU) countries and increasing numbers of US households experienced poverty and social exclusion, resulting in unequal access to resources and opportunities for a healthy and happy childhood, including good nutrition and fair quality education.[11,12] The 2012 United Nations Children's Fund Report[13] shows that following the 2007-2009 Great Recession, the United States ranked 34th out of 35 member nations of the Organization for Economic Cooperation and Development.[14] However, income support and direct benefits provided by government programs have mitigated the recessive social effects of economic depression, as the family poverty rate was reduced from an estimated 31% to approximately 16% in 2014.[15,16] In Europe, modest yet encouraging early signs of recovery from a state of social uncertainty were severely hampered by the unexpected 2020 COVID-19 pandemic, which further distressed the socioeconomic conditions of the European population. In an effort to react to the negative situation, the EU released a recovery plan with a total cost of $2 trillion,[17] funded by a mix of grant funding and loans to states. The largest long-term budget in the EU's history should be used to confront today's realities and in planning to prevent tomorrow's uncertainties. However,

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despite the commitments made by EU decision makers, the national European pediatric societies raised strong concerns, as marginalized communities and vulnerable group populations, including children and elderly persons, are currently at risk for becoming even more vulnerable owing to a prolonged state of emergency caused by the pandemic.[12,18] Their health and well-being may suffer a long-term decline that could be difficult to reverse owing to further worsening of their socioeconomic conditions, already compromised by the recessive effects of the 2009 financial crisis.[19]

Childhood Poverty and Social Exclusion in Europe

Children are generally socioeconomically disadvantaged compared with persons of working age.[20] The child poverty count is typically multidimensional and based on the analysis of several standard indicators.[21] The average child poverty rate in the EU countries, which is formally monitored by the EU statistical database (Eurostat), showed significant variations during the past decade. More than 20% of those age <24 years in the EU were living at risk of poverty in 2010; thus, 1 in 5 young people were living in a household with an income <60% of the national median income.[22] In 2016, the proportion of children at risk of poverty or social exclusion in the EU was 26.4%. data released by Eurostat for the year 2019 show that 92.4 million people in the EU countries, equivalent to 21.1% of the population, were at risk of poverty or social exclusion.[23] Eurostat reported that in 2019, approximately two-fifths of the population living in single adult households with dependent children were at risk of poverty or social exclusion, and the risk of poverty or social exclusion was also relatively high among households composed of 2 adults with more than 2 children.[7] These data are of great concern to the European pediatric societies.[12] The data analysis indicates an important cross-country variation in dimensional child poverty rates. However, in every European country there are children living in poverty, including the well-developed northern European countries Germany, Holland, and the Czech Republi, and the Scandinavian model welfare states Norway, Sweden, Denmark, Finland and Iceland.[7,23] Eurostat reports that in these countries, 11.9%-19.4% children were at risk of poverty or social exclusion during the past decade. In Greece, Italy, Hungary, and Latvia, this figure is 33%-41%, and in Romania and Bulgaria, it is more than one-half (52%).[24,25]

Social and Economic Return of Investing in Children

During the years following the 2009 global crisis, the European members of the G8, including Italy and France, which have a GDP per capita of between €24 000 and €29 000, had from one-fifth to one-third of their children at risk of poverty or social exclusion.[26] Owing to the economic effects of the COVID-19 pandemic, these negative trends will not soon be reversed. Correlations between the economy and the health of children are complex, and establishing causative links is difficult.[27] The return of investment on children's services is measurable only over the long term.[28] However, several studies have demonstrated that an integrated approach including health, nutrition, education, and income supplementation programs may trigger significant increases in future wages in adulthood for children involved.[28-31]

Conclusions

The health and well-being of children is in decline.[12] The Union of the European Societies of Pediatrics is actively engaged in raising the awareness of governments and legislators of the importance of planning for the worst but hoping for the best[32] by investing in children. Investments in services useful for improving the physical, mental, and emotional development of children during their developmental years are critical for promoting and preserving their well-being throughout their lifetime.[33,34] Social mobility in European societies is currently uneven and not improving; well-planned investments in children may help ameliorate this disadvantage and may be passed from one generation to the next.[34] Providing individuals with the proper constructive conditions to build a balanced healthy physical and mental state will contribute not only to the quality of life of single individuals or of groups of people, but also to the welfare of nations.[4,35,36] ■

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Prevention and contrast of child abuse and neglect in the practice of European paediatricians: a multi-national pilot study

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Abstract

Background: Child abuse and neglect, or maltreatment, is a serious public health problem, which may cause long-term effects on children's health and wellbeing and expose them to further adulthood vulnerabilities. Studies on child maltreatment performed in Europe are scarce, and the number of participants enrolled relatively small. The aim of this multi-national European pilot study, was to evaluate the level of understanding and perception of the concepts of child abuse and neglect by European paediatricians working in different medical settings, and the attitude toward these forms of maltreatment in their practice.

Methods: The study was performed by a cross-sectional, descriptive, online survey, made available online to European paediatricians members of 50 national paediatric, who belonged to four different medical settings: hospital, family care, university centres and private practice.
The questionnaire, designed as a multiple choice questions survey, with a single answer option consisted of 22 questions/statements. Frequency analyses were applied. Most of the data were described using univariate analysis and Chi-squared tests were used to compare the respondents and answers and a significance level of $p \leq 0.05$ applied.

Results: Findings show that European paediatricians consider the training on child maltreatment currently provided by medical school curricula and paediatric residency courses to be largely insufficient and continuing education courses were considered of great importance to cover educational gaps. Physical violence was recognized by paediatricians mostly during occasional visits with a significant correlation between detecting abuse during an occasional visit and being a primary care paediatrician. Results also showed a reluctance by paediatricians to report cases of maltreatment to the competent judicial authorities.

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Conclusions: Data of this study may provide useful contribution to the current limited knowledge about the familiarity of European paediatricians with child maltreatment and their skills to recognize, manage and contrast abusive childhood experiences in their practice. Finally, they could provide local legislators and health authorities with information useful to further improve public health approaches and rules able to effectively address shared risk and protective factors, which could prevent child abuse and neglect from ever occurring.

Keywords: Maltreatment, Child, Violence, Abuse, Neglect

Background

Child abuse and neglect (CAN), or maltreatment [1], is a serious public health problem, which may cause long-term effects on children's health and wellbeing and expose them to further adulthood vulnerabilities [2, 3]. According to recent reports, in the United States about 1 in 7 children experience CAN each year and in 2018 nearly 1770 children died of abuse and neglect [4]. In Europe, the 2018 World Health Organization status report on child maltreatment prevention, estimates that this phenomenon involves at least 55 million children living in the Region [5]. Poor socio-economic conditions are recognized to be important causative factors [6]. Children living in poverty are particularly exposed to abuse and neglect, and the rates of these type of abusive experiences are 5 times higher for children living in families with low socio-economic status compared to children from families with higher socio-economic status [7]. Child maltreatment is also costly [3]. In 2015, the total lifetime economic burden associated with child abuse and neglect the United States was approximately $428 billion, causing an economic burden comparable to the cost of other high profile public health problems, such as type 2 diabetes and stroke [4, 6].

Child abuse and neglect are part of the adverse childhood experiences (ACE's) suffered by individuals under the age of 18 and usually caused by a parent, caregiver, or different person in a custodial role, which results in harm, potential for harm, or threat of harm to a child [8, 9]. In general, abuse refers to usually deliberate acts of commission, while neglect refers to acts of omission [10, 11]. The most common forms of maltreatment (Table 1) are related to other forms of violence through shared risk and protective factors [12]. Therefore, prevention of child abuse and neglect greatly contributes to prevent other forms of violence. However, preventive programs addressing ACE's are largely based on the knowledge and capability to recognize abusive childhood experiences by healthcare professionals, particularly paediatricians [13], whose ability to recognize these events needs to be regularly updated and implemented [2].

Recent studies have explored child abuse and neglect in various contexts, particularly families and professionals practicing different types of job, including police officers, lawyers and teachers [14–16]. However, limited data are available about the experience of paediatricians regarding child maltreatment in their practice [2, 3]. The aim of this pilot study, promoted by the Italian Federation of Paediatricians in collaboration with the European Working Group on social paediatrics, was to evaluate both the level of understanding and perception of the concepts of child abuse and neglect by European paediatricians working in different medical settings, and the attitude toward these forms of maltreatment in their practice.

Methods

This study, performed during February–May 2020, was planned by the Italian Federation of Paediatricians (Federazione Italiana Medici Pediatri, FIMP) in collaboration with the working group on social paediatrics of the European Paediatric Association, the Union of National European Paediatric Societies and Associations/ (EPA/UNEPSA) and the European Confederation of Primary Care Paediatricians (ECPCP). A questionnaire focusing on the knowledge, understanding, and attitude towards child abuse and neglect in their practice was made available online to European paediatricians members of the 50 national societies affiliated to EPA-UNEPSA and ECPCP, who were informed on the aims of the study and requested to voluntarily participate in the survey. The participants solicited belonged to four different medical settings: hospital (secondary and tertiary care), family care (community and primary care), university centres and private practice.

Design of the questionnaire

A cross-sectional, descriptive, online survey, modelled on the ISPCAN Child Abuse Screening Tool Children's Version (ICAST-C) [17], was developed in 2019 using web-based standard guidelines [18] and validated by the department of information technology of EPA-UNEPSA, in Berlin, Germany. The principles of iCAST – Intelligence Led Cyber Security Testing, introduced by the Hong Kong Monetary Authority (HKMA) in response to the ever changing cyber security landscape, were applied to its development [19]. The questionnaire was hosted on the Survio international platform [20].

Table 1 Common forms of Adverse Childhood Experiences (ACE) in minors

MOST COMMON FORMS OF CHILD MALTREATMENT
Physical Abuse Legal definitions vary from country to country. However, physical abuse is broadly defined as any non-accidental physical act inflicted upon a child by a parent, caregiver, or other person who has responsibility for the child, which can result in physical injury. Examples include hitting, kicking, shaking, burning, or other shows of force against a child.
Sexual Abuse Sexual abuse occurs when an adult or another child asks or pressures, or force a child for sexual contact. The abuser may use physical abuse, bribery, threats, tricks, or take advantage of the child's limited knowledge of sexual matters. Most cases are perpetrated by a person familiar to the child. Sexual abuse can also include taking photos of the child, or showing them pornography through pictures, magazines, movies, online.
Emotional Abuse Emotional abuse refers to behaviors that harm a child's self-worth or emotional well-being. It is characterized by inattention to a child's emotional needs, failure to provide psychological care, permitting a child to use alcohol or other drugs. In addition, children who witness domestic violence or who live with a sex offender in their homes can fall under the umbrella of emotional abuse. Examples include name calling, shaming, rejection, withholding love, and threatening
Neglect The failure of a parent, guardian, or other caregiver to provide for a child's basic physical and emotional needs. These needs include housing, food, clothing, education, and access to medical care. It can be in the form of physical, medical, education and emotional neglect.
Child Trafficking / Commercial Sexual Exploitation of Children (CSEC) A commercially sexually exploited child is one under the age of 18 who engages, agrees to engage in, or offers to engage in sexual conduct in exchange for money, clothing, food, shelter, education, goods or care. Exploited youth are not "child prostitutes," they are child victims.
Abusive Head Trauma Infants, babies or small children who suffer injuries or death from severe shaking, jerking, pushing or pulling may have been victims of Abusive Head Trauma (AHT), formerly Shaken Baby Syndrome. The act of shaking a baby is considered physical abuse, as spinal, head and neck injuries often result from violently shaking young children.
Institutional Abuse or Neglect Abuse or neglect which occurs in any facility for children, including, but not limited to, group homes, residential or public or private schools, hospitals, detention and treatment facilities, family foster care homes, group day care centers and family day care homes.

The questionnaire consisted of 22 questions/statements divided into four sections [21]: *Demographic data (n.4), Awareness and attitude of about CAN (n.7), Education and competence about CAN (n.5), Practice and formal procedures about CAN (n.6).* The questionnaire was designed as a multiple choice questions survey, with a single answer option. In accordance to standard guidelines indicators of response quality in web surveys, the average time needed to fill out the questionnaire was 10 min [22].

Ethics

The study was performed in accordance with the Declaration of Helsinki's principles and ethical approval was received by the Ethics Committee of the European Paediatric Association/Union of National European Paediatric Societies (EC.UNEPSA.002A,12/12/2019). The study was anonymous, voluntary, with no personal or identifiable data being collected. All respondents approved their participation by informed consent and had access to the pretested forms for their final validation.

Statistics

Frequency analyses were applied to check for data errors, and any values outside of this range were easily identified and recoded to fit into existing categories [23]. Most of the data were described using univariate analysis. Chi-squared tests were used to compare the respondents and answers and a significance level of $p \leq 0.05$ applied. SPSS software (version 23. 2015, IBM, USA) was used for statistical analysis. The statistical analysis was elaborated by the statistical analysis unit of the European Association of Paediatrics in Berlin, Germany and further validated by the statistic unit of the Pediatric research center of the University of Foggia in collaboration with the statistical unit of the local health district of Bari, Italy.

Results

A total of 1083 e-forms were collected. Participants (respondents) belonged to 22 European countries (Albania, Armenia, Austria, Belgium, Bosnia and Herzegovina, Croatia, France, Germany, Hungary, Ireland, Israel, Italy, Kazakhstan, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Spain, Turkey, and Slovenia), thus providing a balanced geographic distribution throughout the continent, also representative of different socio-economic local realities [24, 25]. Of those who declared their gender, more women ($n = 716$, 66.1%) than men ($n = 368$, 33.98%) contributed to the study. Greater group of respondents belong to age group 51–60 (31, 3%), followed by age groups > 61 (25,7%), 41–50 (21,9%) and < 40 (21.1%). The majority of respondents were family care paediatricians working in community or primary care settings (51,6%), while hospital paediatricians working in secondary and tertiary care were 34,3%, paediatricians working in university centres 10,1% and private care paediatricians 4,0%.

Awareness and attitude about CAN

Most of the times (49,4%), child abuse, neglect and in general violence against children, were identified by paediatricians as occasional finding during routine checks and in about one out of four cases (23,1%) during visits directly related to the matter. In 17,4% of the cases maltreatments were unreported and could be identified during emergency visits, while 10,1% of paediatricians recognized cases of child abuse and neglect in different circumstances.

In the majority of cases in which CAN was identified by respondents, paediatricians were requested to visit children by one of the parents (41,7%) or by a different family member (21,6%). While the intervention of a paediatrician to recognize possible cases of child maltreatment was solicited by teachers or school officers in 7,9% of the cases and by family friends in 4,2%. In about one fourth of the cases (24,6%), the suspect of CAN was raised by other unspecified types of figures. Eighty per cent of respondents have encountered at least a case of emotional or psychological child abuse in their practice and 76.3% have faced at least a case of physical or sexual child abuse (Fig. 1). In the majority of these cases, paediatricians' respondents have activated legal procedures in order to protect the victims (Fig. 2).

Education and competence about CAN

One fourth (25,9%) of respondents rated their knowledge and competence about CAN to be good although improvable, and 2,6% to be excellent, while the majority of participants assessed their education on CAN as adequate (42,1%) and a minority not adequate (2,6%). During the three years preceding the study, about half of the respondents (47,8%) did not attend any continuing education course on CAN, versus 40,2% who attended educational programs addressing CAN, which in 39,2% of the cases were specialized courses held in person and 1.0% on line, while 12,0% attended generic in presence courses on domestic violence.

Knowledge about CAN provided in Europe by medical school curricula and paediatric residency programs was rated to be largely unsatisfactory, particularly due to the insufficient number of training hours dedicated to CAN (Fig. 3a and b). To this regard, the majority of paediatricians participants to the study indicated that educational programs on CAN should be made mandatory and included in the curricula of medical schools and residency courses in paediatrics, rating this option as useful (33.1) and necessary (65,5%), while only 1,4% consider that unnecessary.

Practice and formal procedures about CAN

Local child protective services, including social services, were the first institutional point of reference in case of CAN for 64,1% of participants in the study, while for 22, 4% of them local judicial authorities were their first choice to report a maltreatment. Contacting specialized hospital centers was the first option for 8,0% of respondents, 2,9% of them reported episodes of CAN to different institutions and 2,6% did not make any report.

83,6% of the paediatricians reported the existence of specific laws protecting victims of CAN in their countries, and two third (66,1%) confirmed the presence of standardized formal procedures that can be activated if cases of CAN are detected by doctors. However, 15,5% stated the absence of any formal procedure for the contrast of child maltreatment, while 18,5% of respondents were unaware of any form of procedure that could be activated in cases of CAN in their country. Although the large majority of respondents reported the existence of laws for the contrast of CAN in their countries (83,6%), only 52% rated these laws as adequate.

The most important obstacles to an effective protection of CAN victims recognized by the paediatricians

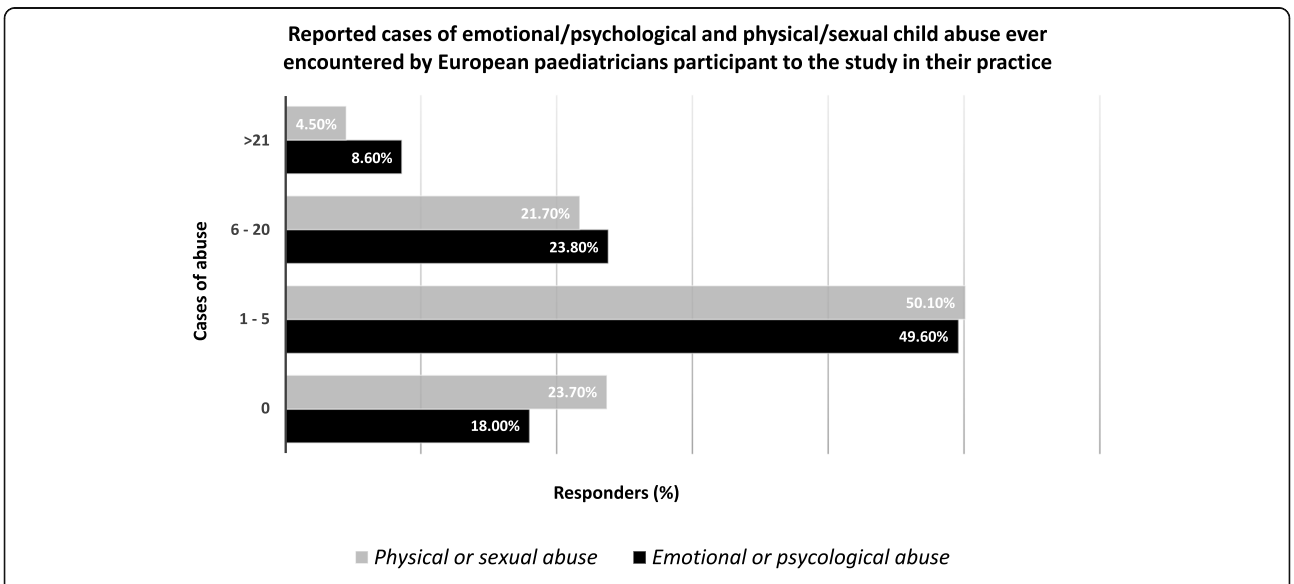

Fig. 1 Reported cases of emotional/psychological and physical/sexual child abuse ever encountered by European paediatricians participant to the study in their practice. Percent of paediatricians who reported cases of physical/sexual and emotional/psychological child abuse, and number of cases ever observed in their practice

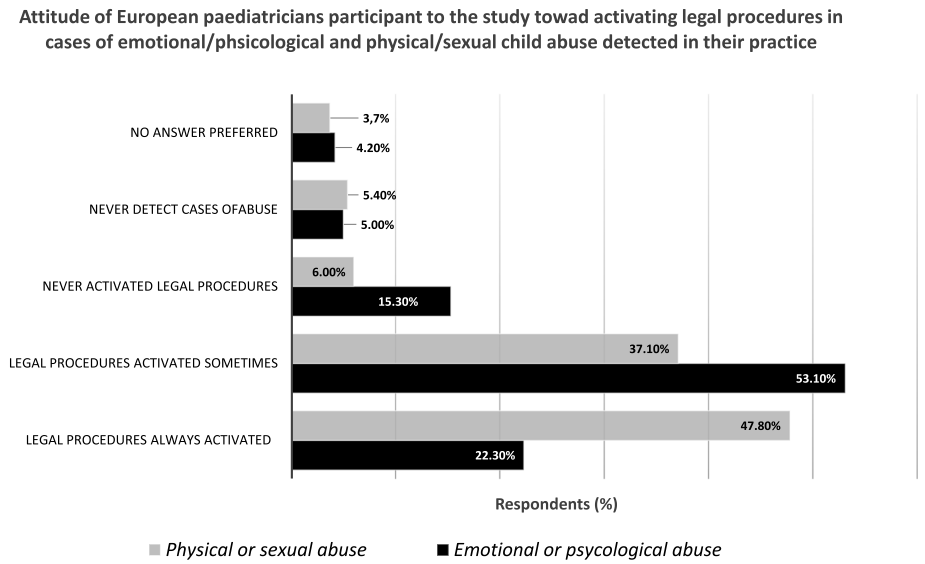

Fig. 2 Attitude of European paediatricians participant to the study toward activating legal procedures in cases of emotional/psychological and physical/sexual child abuse detected in their practice. Percent of paediatricians who activated or did not activate legal procedures in presence of detected cases of emotional/psychological and physical/sexual child abuse in their practice

enrolled in the study are reported in Fig. 4. Finally, the large majority of respondents (88,0%) endorsed the statement that only a join action by child healthcare professionals at multi-national level, would provide an important lever to stimulate legislators to issue more effective laws and procedures to protect the victims of CAN.

Discussion

Child maltreatment is a critical public health issue, with lifelong health consequences for victims and their families [26]. Detecting suspicious injuries may provide an important opportunity for early recognition and intervention to protect vulnerable children [2]. However, the identification ad report of suspected cases of CAN may be one of the most challenging and difficult tasks for pediatrician [26]. To identify initial revealing signs of abuse and manifestations of neglect requires professional competence acquired by adequate training, which cannot be improvised [27]. Maltreatment is usually recognized in clinical settings [26]. However, indicators of the various forms of child abuse are often nebulous and may be detected in different settings by various figures, including family friends, teachers and other members of the community related to the victims. Raising social awareness about maltreatment and close collaboration

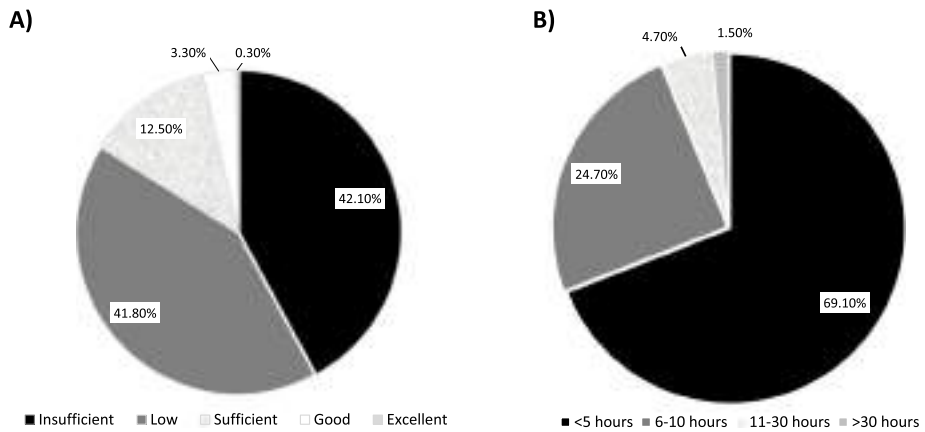

Fig. 3 Knowledge about child abuse and neglect (CAN) provided in Europe by medical school curricula and paediatric residency programs, rated by European paedatricians participant to the study. A) Quality of educational programs on CAN provided in European medical schools and residency courses in paediatrics rated by paedatricians participant to the study (%). B) Reported number of training hours on CAN offered by European medical schools and paediatric residency courses, as reported by paediatricians participant to the study (%)

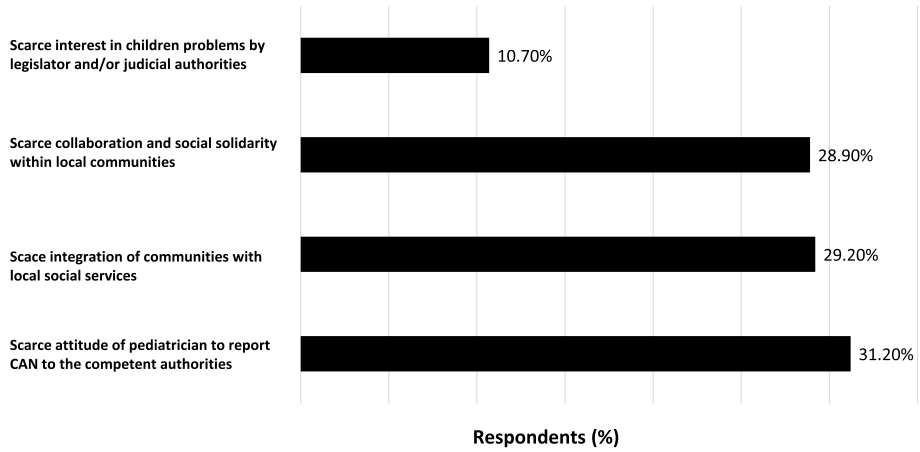

Fig. 4 Most important obstacles to an effective protection of Child Abuse and Neglect (CAN) victims recognized by paediatricians enrolled in the study. List of major impediments to an effective management of CAN identified by paediatricians participant to the study (%)

between members of local communities and paediatricians [28] are key factors to limit CAN and the phenomenon of domestic violence in general [29, 30]. During the past twenty years, a few previous studies have investigated attitudes and experiences of paediatricians on child maltreatment, however providing useful data regarding the progress and level of competence and awareness developed by paediatricians toward CAN worldwide [15, 31–33]. A recent study performed in Italy, about the competence of family paediatricians in Italy to identify child abuse, emphasized the scarce knowledge and ability of paediatricians and general practitioners to deal with child abuse and the importance of proper training programs [34]. However, studies on CAN performed in Europe are scarce, and the relatively small number of participants enrolled, somehow limited the importance of the information provided by the data analysis of these reports. The present study involved a number of participants significantly larger than previous studies. Furthermore, to our knowledge, no previous multi-national studies on attitudes and experiences of paediatricians on child maltreatment were performed in Europe, which could provide an updated overview at continental level.

Child abuse and neglect cases can be difficult to evaluate, and input from a trusted colleague, senior clinician, or medical specialists can be helpful [35]. The data of this study show a correlation between the number of reported cases of physical violence (> 5) and the age of paediatricians, as the higher the age of those enrolled in the questionnaire, the greater the number of findings they carried out, with a statistically significant difference (p 0.002; RR equal to 1.1).

Child maltreatment was recognized by the paediatricians participant to the study mostly during occasional visits (49,4%), and data analysis showed a significant correlation between detecting abuse during an occasional visit and being a primary care paediatrician (p 0.0034). In most of the European countries, if medical history or physical examination reveal suspicious signs and/or injuries, and in presence of a reasonable suspicion that a child has been abused, paediatricians are mandatorily required by law to report to child protective services or judicial authorities for further investigation. This study, showed a reluctance by paediatricians to report cases of CAN to the competent judicial authorities, while they mainly turn to child protection centres, which attitude correlated significantly with the reported finding of abuse ($p > 0,05$). There is a correlation between thinking that the laws in one's country are adequate and having encountered physical and psychological abuse (p 0.002).

With proper education and training, most abuse can be prevented or interrupted [13]. Data of this study showed a statistically significant correlation between the number of training hours completed by respondents during their medical school and residency courses and those who believe they have sufficient education on CAN (p 0.002). The hours of academic training dedicated to this topic were also found to be statistically significant with respect to the cases of CAN identified, since paediatricians who recognized more than 5 cases had received a greater number of training hours on CAN (> 5), (p 0.2; RR 1.8) during their university studies. Cases of physical violence were detected in a greater percentage by paediatricians who had received a higher number of training hours during university studies (p

0.2). Furthermore, a large number of respondents reported to have acquired sufficient competence on CAN due to continuing education courses attended during the past three years (RR 1.8).

Conclusions

Timely identification and intervention to protect violated children have the potential to stop the abuse, secure the child's safety and prevent further stress in victims [36]. Paediatricians play an important role in the contrast of child maltreatment [37]. Data of this study particularly emphasize the importance to strengthen the knowledge on CAN through updating university curricula and specialist paediatric training, which for years have remained at levels that are currently not adequate to effectively contrast this phenomenon [38].

Our study was purposely limited to paediatricians and did not include family physicians, emergency physicians, advanced practice nurses or other medical personnel who care for children. In this regard, it captures the experience of those individuals considered most trained in the medical care and advocacy of children [32]. A further possible limitation of the study may be its cross-sectional design, based on analysing data of variables collected at one given point in time across a sample population or a pre-defined subset, and therefore any associations between educational and professional experiences and attitudes could not be considered causal. Limitations of survey studies due to various multiple factors cumulatively affecting their design, including number of questions and sample size are often unavoidable [39]. However, the data collected by this pilot study and their analysis may provide a useful contribution to the current limited knowledge about the familiarity of European paediatricians with child maltreatment and their skills to recognize, manage and contrast abusive childhood experiences in their practice. Finally, they could provide local legislators and health authorities with information useful to further improve public health approaches and rules able to effectively address shared risk and protective factors, which could prevent child abuse and neglect from ever occurring. Further multi-national studies focusing prevention and contrast of child abuse and neglect in the practice of European pediatricians would be useful to provide a better knowledge on CAN and its prevention.

Abbreviations

CAN: Child abuse and neglect; EPA/UNEPSA: European Paediatric Association/Union of National European Paediatric Societies and Associations; ECPCP: European Confederation of Primary Care Paediatricians; HKMA: Hong Kong Monetary Authority

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Authors' contributions

All authors (NP; GC; NL; BD; KLG; PD; PTL, CSA; NBL; MJ; VM; GI; LL; BMT; PMM; FP) have made substantial contributions to the conception, design and acquisition of data of the work. BMT; PMM, NL; NP; GI; PF have made substantial contributions to data analysis and interpretation. PMM; PN; PF gave a major contributions in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki's principles and ethical approval was received by the Ethics Committee of the European Paediatric Association/Union of National European Paediatric Societies (EC.UNEPSA.002A,12/12/2019). The manuscript does not report on or involve the use of any animal or human data or tissue.

Consent for publication

Not applicable: the manuscript does not contain any individual person's data in any form (including any individual details, images or videos).

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Implications of the COVID-19 Pandemic for Pediatric Primary Care Practice in Europe

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The COVID-19 pandemic has taken a heavy toll on the adult population.[1] In the US, out of 1.4 million diagnosed with COVID-19, 154 children have died.[2] In a large cohort study of 135 794 children tested for COVID-19, the infection rate was low (4%), many positive children remained asymptomatic, and if signs of illness were present, disease symptoms were typically mild. The case fatality rate in this group was 0.2%.[3] In Europe, early studies showed a low fatality rate of 0.69% in children who tested positive for COVID-19, and 4% developed severe illness.[4] Low mortality and morbidity rates due to COVID-19 in European children during the pandemic were confirmed by the statistical office of the European Union.[5]

However, despite the available evidence suggesting that the direct impact of COVID-19 on child and adolescent mortality and morbidity is somehow limited, child services suffered important indirect effects, owing mainly to discontinuities seen throughout Europe by many local health systems strained by the pandemic.[6] The disruptions to care-seeking and preventive interventions in the majority of European countries, including checks for healthy children, vaccination plans, and mental disorders programs, were extensive and concerned the European pediatric societies.[7] The aim of this commentary, jointly authored by the European Confederation of Primary Care Pediatricians (ECPCP) and EPA-UNEPSA, is to raise awareness of the indirect consequences caused by the pandemic on pediatric primary care practice in Europe and the risks for child health and well-being.

Indirect Impact of COVID-19 on Pediatric Primary Care Practice in Europe

European countries have seen a two-wave pattern in reported cases of COVID-19 in 2020, with a first wave during the months of March to July, followed by a second wave in late summer and autumn of the same year. The first wave caused a pronounced indirect impact on health services for children and changes in the daily practice of pediatric primary care. Considerable disruption of essential health services occurred in many countries.[7-9] The measures taken by governments to contain the crisis often raised criticism from the European pediatric societies because of their frequent changes and the overall negative impact on children's physical and mental health and their education.[10-12]

In summer 2020, the ECPCP performed a study involving the majority of its member societies. Data from primary care pediatricians working in 17 European countries during the first wave of the COVID-19 pandemic were collected by a questionnaire, with the aim of obtaining information about the consequences of the pandemic on pediatric primary care practices in different locales and the risks for child health.[13,14] The study showed that significant adjustments in daily pediatric practice took place during the generalized lockdown accompanying the first pandemic wave of COVID-19. Several changes in routine clinical practice were made by pediatricians to minimize the transmission of COVID-19 from patient to patient and among office staff. At the beginning of the pandemic, a serious shortage of protective equipment endangered health workers worldwide,[15] particularly in ambulatory settings.[16,17] However, 95% of European primary care pediatricians reported systematic use of personal protective clothing and face masks within a short time from the onset of the pandemic, and 92% expressed their commitment to maintaining this practice beyond its end.[13]

With the intent to compensate for potentially infectious encounters, in-person visits were significantly reduced and replaced with phone and, to a lesser extent, video consultations. Slightly more than one-half (55%) of primary care pediatricians reported that during the pandemic period March-August 2020, in-person consultations rates dropped by 40% to >80% compared to previous periods. However, an effort was made to continue to offer the option of pediatrician–patient encounters by applying the "ECPCP empty waiting room policy" characterized by well-planned appointment schedules, which helped minimize waiting times and discouraged unscheduled walk-in visits.[13] In most European countries, primary care pediatricians followed the directions recommended by local public health departments and World Health Organization health officials and limited the number of accompanying persons during visits in private settings, such that children could be accompanied by only 1 caretaker.[18,19] As a result, crowding of patients in waiting rooms was significantly reduced.[13] Providing separate rooms and separate consulting hours for infectious and noninfectious patients was another

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important safety measure, although it was not possible in all circumstances.

However, the changes applied to routine practice because of the pandemic and fearful attitudes by parents caused unintended and sometimes negative consequences.[13] As reported by 40% of pediatricians participating in the ECPCP study, at the beginning of the epidemic, a considerable number of patients with minor illnesses were discouraged to come to doctor's offices, which had the unintended effect of some delays in recognizing serious conditions, thereby increasing the risk of complications.[13] A large proportion of the pediatricians involved in the study (86%) reported that due to the restricted access to emergency services, in many cases, family members of their patients admitted failing to report or delaying reporting to local health authorities serious health conditions or life-threatening diseases besides COVID-19 involving their children. The most commonly unreported conditions included diabetic ketoacidosis, hematologic and oncologic diseases, appendicitis, peritonitis, child abuse, severe bacterial infections (eg, urinary tract infection), meningitis, pneumonia, and acute cardiac problems.[13] Similar data were reported in the US[20] and Israel.[21] A study involving 53 Italian diabetes centers revealed that COVID-19 significantly worsened the presentation of type 1 diabetes in children.[8]

Decline in Vaccinations During COVID 19

In the summer of 2020, the World Health Organization and UNICEF warned of an alarming decline in the number of children receiving life-saving vaccines worldwide.[22] According to data collected in collaboration with the US Centers for Disease Control, the Sabin Vaccine Institute, and Johns Hopkins Bloomberg School of Public Health, three- quarters of the 82 countries involved in a preliminary study reported significant COVID-19–related disruptions in their immunization programs by May 2020.[22]

Similar alarming data were recorded by the ECPCP study, as primary care pediatricians reported a decrease in vaccination coverage in the various European countries, which ranged from 11% to >50%, in children <2 years and >2 years of age. A major obstacle to the implementation of vaccination programs reported by European pediatricians is families' fear of leaving home during lockdown and the hesitation to vaccinate their children during the pandemic.[22,23]

Negative limpact of COVID 19 Lockdown on Children's Social Interactions and Well-Being

Social distancing during COVID-19 has caused a drastic upheaval in how people work and socialize. Many children have been uprooted from their places of education and care, and it may be difficult for them to understand why their routine has been disrupted. Not much is known about the long-term mental health effects of large-scale disease outbreaks on children and adolescents.[24] However, monitoring young people's mental health status over the long term, and studying how prolonged school closures, strict social distancing measures, and the changes in lifestyle caused by the pandemic affect the well-being of children and adolescents would be greatly useful.[24] Although during school closure parents had the chance to dedicate more valuable time to their children, in many cases COVID-19 has contributed to increased external stressors and lowered the quality of social relationships and family cohesion.[25] In families that spend longer periods together, COVID-19 may exacerbate preexisting vulnerabilities, including depression and anxiety, which can harm the stability of relationships and increase the risks of abuse and violence.[25,26] The European societies of primary care pediatrics have advised the EU public health authorities about these risks and stressed the importance of a coordinated approach by pediatricians and mental health service providers to properly manage the whole range of conditions affecting the mental well-being of children caused by the pandemic.[9]

The lockdown due to COVID 19 has also exacerbated socioeconomic inequalities, including worsened educational performance of children from poor socioeconomic backgrounds, who could not be adequately supported by their parents during home schooling (**Figure**; available at www.jpeds.com). In Europe, 76% of ECPCP members interviewed endorsed the statement that children should go back to school to further their social development, as the benefits may outweigh the risks if all official public health requirements are observed and under the condition that adequate personal protection for the school staff could be guaranteed.

Conclusions

Coordinated efforts among healthcare professionals[27] will help ensure optimum health care for both sick and healthy children during the future course of the pandemic. To maintain a high quality level of pediatric primary care practice in Europe, legislators, health authorities and professional pediatric societies should collaborate closely.[28] In view of the challenges posed by the pandemic, the data provided by the ECPCP suggest that it will be essential to implement a strategy aimed at preserving the continuity of preventive services and vaccination programs and focusing on the free, fearless access of all children to health services. ■

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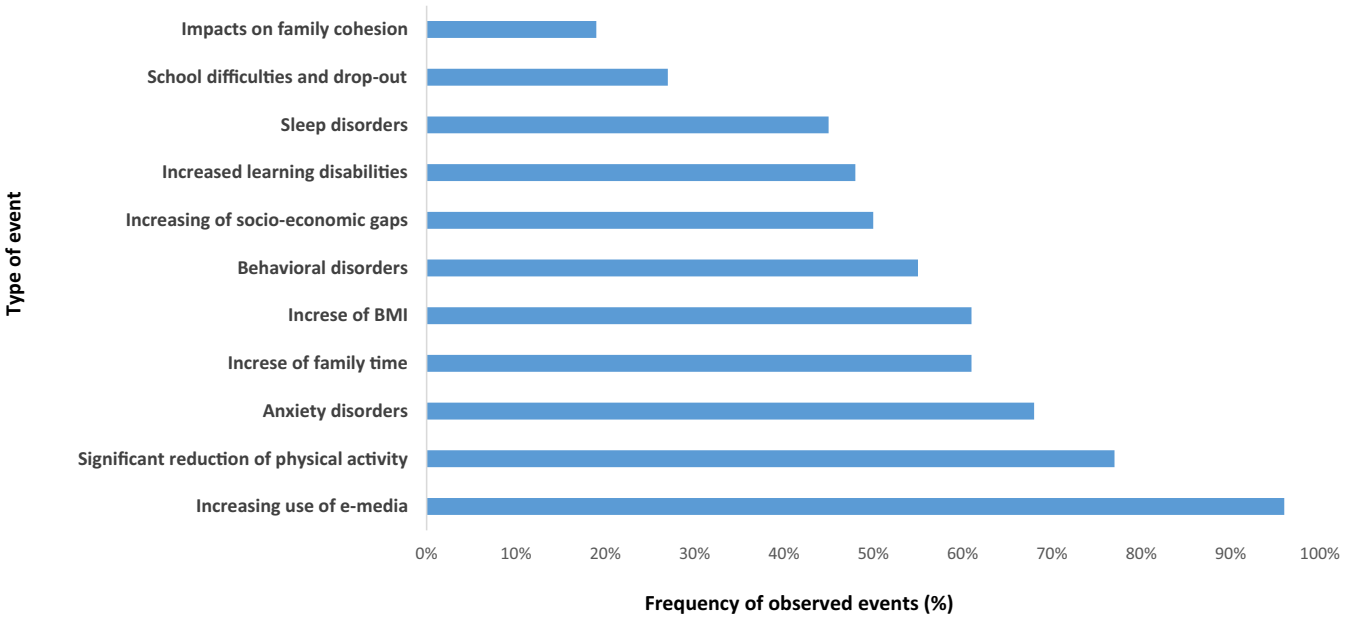

Figure. Most frequent events observed in children and their families by European primary care pediatricians in their practices during the COVID-19 pandemic (year 2020).

French Pediatric Societies Call for School to Stay Open amid the Coronavirus Disease 2019 Pandemic

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With the onset of the coronavirus disease 2019 (COVID-19) pandemic in February 2020, the majority of European countries experienced 2 national lockdowns, which involved school closing, imposed by governments to control spread of the virus. In September 2020, on the reopening of the schools after the first lockdown, serious concerns were raised in Europe by scientific societies and governments on the possible role of schools in facilitating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) circulation in the population. In response, European countries produced technical documents and guidelines on COVID-19, which included guidance for a safe reopening of schools and children's educational services. Different preventive strategies were adopted by European governments to control suspected and confirmed cases of infection in the school environment.[1,2] In February 2021, based on available epidemiologic data, public authorities in Europe considered establishment of a third general lockdown of the population, as a preventive measure to combat a resurgence of the infection, mainly caused by variants of the original virus.[3] An extended school closing was also considered by many European countries as a part of their third lockdown strategy.

The European Center for Disease Prevention and Control reported that during 2020 in the European Union countries and the United Kingdom, <5% of COVID-19 cases involved subjects under the age of 18 years and concluded that the role of children in viral transmission and its impact in epidemic expansion remains unclear.[4,5] A systematic review on school closures for COVID-19 control found no conclusive evidence for a convincing effect of this measure in reducing viral transmission at population level.[6] The evidence available to date suggests that children are more likely to contract COVID-19 from infected family members rather than from other children in school settings.[2,6,7]

The aim of this commentary, authored by major French pediatric societies, in collaboration with the European Paediatric Association and other European pediatric centers, is to bring awareness to the importance of European children's health and well-being and to recommend keeping schools and other educational facilities open amid the COVID-19 pandemic. Child health is a state of physical, mental, intellectual, social, and emotional well-being and not merely the absence of disease or infirmity.[8,9] Prolonged school closing exposes children to serious mental and social distress, possibly leading to serious long-term effects later in life. These consolidated notions prompted the authors to emphasize that indiscriminate school closing policies established by European countries during the COVID-19 pandemic is a questionable preventive measure not supported by sufficient evidence.[4]

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Indirect Impact of COVID-19 on Children's Mental and Emotional Well-Being

Since February 2020, general pediatricians, child psychiatrists, and pediatric emergency departments in many European countries have observed a significant increase in outpatient and inpatient consultations and hospitalizations related to a variety of mental disorders including anxiety, depression, dark thoughts, and suicidal acts.[10] They also report a significant increase of violence and abuse against children,[11,12] especially among families that were abusive prior to the pandemic and in those experiencing stress and economic instability because of pandemic-related economic downturns.[13,14] The epidemiologic profile of patients changed, as subjects who typically needed care for infectious illness were replaced by a large number of abused, depressed, anxious, and suicidal children.[13,15]

COVID-19 infection rates in children are lower compared with adults, and mortality rates are significantly lower.[16] In the US as of March 2021, children were 13.2% of the infected

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population, 0.00%-0.19% of all COVID-19 deaths, and 10 states reported zero child deaths.[17] Similar rates are reported in Europe by the European Center for Disease Prevention and Control.[18] However, 1 year after the onset of the pandemic, although the infection and mortality rate caused by COVID-19 in children is contained, a large number of subjects <18 years old need medical assistance because of pandemic-related mental disorders and many of them report serious death wishes.[19-21] Based on increasing epidemiologic data on mental distress caused by COVID-19 early in 2020, the United Kingdom Royal Society for Public Health raised concern about the negative effects of the pandemic on the mental and social health of children. The Royal Society for Public Health also expressed fear of a correlated parallel pandemic of domestic maltreatment seriously involving children, just as the first wave of COVID-19 pandemic was for adults.[22] The persistence of the COVID-19 pandemic in Europe suggest an important role for schools, daycare centers, kindergartens, and socio-educational settings in maintaining adequate levels of well-being in the younger population.

French Pediatric Societies Call for Closing Schools as a Measure of Last Resort

Since May 2020, French pediatric societies rallied to keep schools, daycares, and kindergartens open, despite a persistent general uncertainty and political disagreement on how to combat the pandemic.[5,7] The difficult task for the French societies was to dispute the general idea, based on the influenza model, that children could play an important role in SARS-CoV-2 dissemination. However, in support of the French societies' position, studies performed worldwide during school time reported that children <11 years old showed low rates of infection and that symptomatic forms were much less severe and contagious than in adults.[5,6,23,24] In France, during the period between September 2020 and March 2021, the Ministry of Education closed a limited number of the total 61 500 public schools (range of school closing/week 0.01%-0.25%) and 528 400 classes (range of class closing/week 0.001%-0.17%) because of infection episodes. During this period, 1 162 850 teachers and 12 400 000 students (6-18 years old) who were periodically tested at school showed lower rates of infection compared with the general population. COVID-19 mean positivity rate for teachers and students was 0.05% ± 0.06% and 0.10% ± 0.09%, respectively.[25]

Pediatric societies in many European countries have called for schools to stay open based on local national data. In Sweden, where daycare centers and schools remained open without children wearing masks, teachers and children aged 7-16 years showed one-half the risk of severe COVID-19 compared with adults in other occupations[26] (0.43; 95% CI 0.28-0.68). A comparative study performed between March and May 2020 in Finland, where schools were closed, and Sweden, where schools remained open, showed no difference in incidence of infection and hospitalizations or deaths in <20 years old subjects.[27] In Italy, reports indicate that schools do not act as an amplifier for transmission of SARS-CoV-2 and other settings where young people typically congregate were identified as a greater carrier of transmission.[2,28]

Security fails without usability.[29] A study performed by the Italian society of pediatrics in schools, which involved a large number of students, teachers, and school employees, showed that in presence of clear and consistent preventive measures, including physical distancing, frequent hand hygiene, adequate ventilation, cleaning and disinfection, the infection rate was as low as 0.09% in the month of September, 1.11% in October, and 0.23% in November. In Israel, where schools closed between March and April 2020 and reopened gradually in May, analysis of national data showed that school reopening had a limited effect on viral infection rates in children and adults and that it was not a major contributor to the SARS-CoV-2-related mortality.[29,30] The incidence of SARS-CoV-2 infections gradually increased in Israel following school reopening in all age groups, with a significant increase in incidence of infection in the population, particularly in adults testing positive for COVID-19 compared with children.[29,30] Following summer vacation, in September 2020 the spread of SARS-CoV-2 escalated and the incidence rate of infection grew significantly causing a new countrywide lockdown including school closing. Schools reopened in Israel in November 2020 and current data show that as of March 2021, children age 0-9 years had the lowest increase in mean incidence rates and positivity rates of tests during school attendance periods. Particularly, subjects age 10-19 years showed no increase in incidence rates during September through November compared with adults.[31] Reports also suggest that German children contract COVID-19 infections mainly outside school[32] and similar data are reported in the US by the Centers for Disease Control and Prevention in the Morbidity and Mortality Weekly Report series.[33] The United Kingdom Scientific Advisory Group for Emergencies, which in July 2020 reported that few clusters of disease had been linked to school and that preventive measures needed to vary between primary and high school settings,[34] stated that schools have a moderate impact on transmission, with primary age children being at lower risk of infection than older children. The Scientific Advisory Group for Emergencies also reported that differences in school settings and structures and the type of mitigations adopted influenced the potential for transmission.[35] The debate about whether and how the virus spreads in schools and what conditions may allow for schools to safely and successfully reopen for in-person learning remains open in Europe and in the US. The views and rules established by the 50 European governments and their expert committees during the pandemic are different and uncoordinated.

Uncommon Sense: to Enable Schools to Open Safely and Remain Open by Adopting Consistent COVID-19 Prevention and Control Measures

Common sense is often uncommon.[36] To properly pursue their present and future life achievements, children must have full access to the benefits of in-person learning and key support school services. To keep schools open as safely and as soon as possible, and ensure that they stay open, is an important social challenge posed by COVID-19. Governments worldwide are engaged to safeguard the health and well-being of their future generations and avoid further social differences and disadvantages children from low-resourced communities may experience in the absence of in-person educational options. The emergence of more contagious SARS-CoV-2 variants is a matter of concern. However, children were found no more susceptible to these lineages than are adults,[23] thus, closing schools on the basis of incomplete information could have serious repercussions.[23] The French experience, similarly to that reported by the Centers for Disease Control and Prevention in the US, shows that schools that have consistently implemented preventive and mitigation strategies have been able to safely open for in-person education and remain open.[23,37,38]

Conclusions

On March 19, 2021, the French government declared a new lockdown in large areas of the country until late April. However, based on available data and a careful cost-benefits analysis, schools were excluded from the measure and remained opened. The European Paediatric Association[39] supported the call of French pediatric societies for schools to stay open amid the COVID-19 pandemic by careful development, planning, and adopting of adequate safety measures to be observed by teachers and students during school time.[38,40] However, despite careful planning and vigilant implementation of essential elements of safe in-person procedures, under particular epidemiologic circumstances, school officials in consultation with the local public health departments may consider temporarily closing schools or parts of a school and limit in-person instruction. In such circumstances, schools should provide continuity of education through remote learning or at-home activities.

To follow stringent safety guidelines, based on careful considerations of a variety of factors and established with an emphasis on ensuring the health and wellness of students, their families, teachers, and staff, may be complicated. However, it is possible to have convenience if insecurity is tolerated, but if security is considered a relevant objective to pursue, a community must be prepared for inconvenience.[41]

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Children Witnessing Domestic and Family Violence: A Widespread Occurrence during the Coronavirus Disease 2019 (COVID-19) Pandemic

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Across the world, children and adolescents are exposed daily to toxic levels of violent behaviors, including domestic and family violence. Violence increasingly has permeated and profoundly affected the lives of children, who are the most vulnerable members of society.[1] Pediatric societies in Europe and North America have raised great concern over the effect that abusive experiences will have on present and future generations.[1-4] The global spread of coronavirus disease 2019 (COVID-19) during the past year has dramatically worsened the situation, contributing to a further increase in violence and aggression within households. Reports of domestic abuse and family violence have increased around the world with social isolation and quarantine measures, and national health and social care systems worldwide have faced serious challenges posed by the rising rates of domestic and family abuse.[5] Children are typically the primary victims of family violence[2]; however, children who live in homes in which partner abuse occurs are described as secondary victims.[6] Minors increasingly are witnessing various forms of unprecedented emotional and physical domestic abuse, often resulting in femicide, and exposed to the emotional, behavioral, physical, social, and cognitive effects.[2]

There are documented gendered patterns in violence perpetration and victimization.[7] This commentary, authored by the working group on social pediatrics of the European Paediatric Association/Union of National European Paediatric Societies and Associations, discusses children witnessing family violence and domestic abuse, including femicide as the most extreme and irreversible expression of domestic violence involving parents or household members. Our aim is to raise awareness regarding this phenomenon, which is rapidly expanding during the COVID-19 pandemic, and on the serious long-term effects on the well-being of children.

The Hidden Pandemic of Children Witnessing Family and Domestic Violence

The broad term of family violence refers to abusive behaviors and violence occurring between family members, which can include violence between current or former intimate partners, as well as acts of violence between parents and children, siblings, and kinship relationships in general. Domestic violence describes violent behavior between current or former intimate partners, where one partner tries to impose power and control over the other through fear and threats. This includes physical, sexual, psychological, social, verbal, spiritual, and economic abuse[8] (**Table**; available at www.jpeds.com). Consequent detectable physical injuries may involve the head and neck, musculoskeletal system, chest, abdomen, and skin, which are important indicators of an abusive condition.[8]

Although the devastating consequences of domestic violence on women are well described, much less is documented about their impact on children who witness a parent or caregiver who is being abused and a victim of violence. Concern has been expressed by the European pediatric societies over the effects these experiences will have on present and future generations.[9] Data collected during the first year of the COVID-19 pandemic show a widespread spike in domestic violence as a result of social distancing and quarantine, including a rise in the number of women experiencing intimate partner violence and escalation into femicide.[10] A report from the Canadian Minister for Women and Gender Equality emphasized that the COVID-19 crisis had empowered perpetrators of domestic violence, which resulted in a 20%-30% increase in rates of gender-based violence in some regions of the country, compared with the same period of the previous year.[11] Similarly, in France and Argentina, the cases of intimate partner violence also increased by 30% and 25%, respectively, after the onset of the pandemic. In China, family violence tripled in Hubei province, and in Italy the number of homicides of women in cohabiting relationships increased by 10% during the first 10 months of 2020

COVID-19 Coronavirus disease 2019

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compared with 2019.[12,13] In the US, during the pandemic, domestic violence increased 12% on average and 20% during working hours[14,15]; 18 law enforcement agencies reported a sharp increase of 6%-20% in major US cities.[16]

Domestic violence is likely to involve children, who often become secondary victims. Growing up in a violent home may be a terrifying and traumatic experience that can impact every aspect of a child's life, growth, and development and cause long-term health effects.[17] Witnessed violence has a significant impact on youth mental health and on the likelihood of engaging in aggressive and antisocial behavior later in life.[18] These children are at a greater risk to externalize destructive behaviors such as fighting, bullying, lying, or cheating and to internalize negative behaviors such as anxiety and depression.[19]

The important reality of a child's close tie to their mother or female role model or custodian is a consolidated notion,[20] and an increasing number of children witnessing family and domestic violence to the extreme outcome of femicide suffer severe symptoms of post-traumatic stress disorder.[21] Typically, child witnesses are predisposed to an inappropriate use of violence as a means of resolving conflicts and show a greater willingness to use violence themselves.[21] They are also at greater risk than their peers of developing an array of age-dependent negative effects, including several clinical disorders such as allergies, asthma, gastrointestinal problems, bed-wetting or nightmares, and headaches.[22] However, the definition should not be restricted to children who witness abuse visually but expanded to include children who also hear violence, such as yelling or other forms of nonphysical violence.[23]

Prevention, Screening, and Resilience

Physicians and pediatricians should be trained to recognize indicators of domestic and family violence and to address this issue on multiple levels.[24] Educational programs about domestic violence have focused particularly on the primary victims, and important progress has been made in this area.[25] However, medical schools also should include in their educational programs on child abuse and neglect the potential negative effects on children who witness domestic violence, and existing programs must be broadened to include effects on silent witnesses and to encourage physicians to screen for and help prevent violence.

Violence-prevention measures can begin in the clinic. Physicians may raise the issue of family and domestic violence with couples planning to have a child or during prenatal examinations, and pediatricians should be able to assess the parents' methods of resolving conflict and their responses to anger. It is important that pediatricians are trained to discuss nonviolent forms of discipline, such as time-outs and removal of privileges, and couples should be educated about the negative effects that arguments and fights have on children. Parents and household members also must be informed of the negative consequences of watching violence on television or any other media. Of particular importance is exploring the presence of guns and other weapons in the home, as it increases the risk of negative events, including a disempowering and demoralizing effect on women, psychological and/or sexual coercion, and women being killed by intimate partners. Children should be told that if they see a gun, they must not touch it and should leave the area immediately and tell an adult. Screening for family violence should be routinely and preferably privately performed with mothers by asking open, nonjudgmental questions.

Finally, helping children to develop resilience is of importance, as children may mitigate the effects of witnessing violence due to their ability to build resilience.[26] Pediatricians, schoolteachers, and social workers can have a key role in identifying potential protective factors that mediate the negative effects of witnessing domestic violence and assist children in developing their resilience skills.[26]

Conclusions

The impact of COVID-19 upon domestic violence is well documented.[27-29] However, insufficient attention has been given to children who witnessed family and domestic violence during the current pandemic, particularly on those children whose mothers were murdered by a family member. Studies will provide a better understanding of this phenomenon, as well a way as to develop strategies useful to intercept risk factors and to plan for prevention programs,[30] including the promotion of healthy, respectful, nonviolent relationships.[31] Pediatricians should be professionally trained to recognize family and domestic violence and the risks for children to be victims of witnessed violence.[24] ■

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Table. Abusive behaviors and common warning indicators suggesting domestic violence

Physical abuse: a person using physical force on the partner, which causes, or could cause, harm. It includes direct assaults on the body, use of weapons, driving dangerously, destruction of property, abuse of pets in front of family members, assault of children, and forced sleep deprivation.

Indicators: slapping, shaking, beating with one's fist or with an object, strangulation, burning, kicking, and threats with a knife. Various cutaneous signs may include bruises, lacerations, abrasions, burns, oral trauma, bite marks, and traumatic alopecia.

Psychological/emotional abuse: a person's attempts to frighten, control, or isolate the partner. Frequently due to excessive jealousy, the intent is to control the partner's activities. It is in the abuser's words and actions, as well as their persistence in these behaviors. It includes name calling, derogatory pet naming, character assassination, yelling, patronizing, public embarrassment, dismissiveness, jokes that might have a grain of truth or be a complete fabrication with the intent to make the partner look foolish, sarcasm, insults and derision about the partner's appearance, belittling the partner's accomplishments, and putting-down partner's interests.

Indicators: isolation from others, weeks of silence, difficulty identifying and processing emotions (alexithymia), being unconfident or lacking self-assurance, struggling to control emotions, difficulty making or maintaining relationships, acting inappropriately.

Sexual abuse: any form of sexual activity without consent, coerced sex through threats or intimidation or through physical force, forcing unwanted sexual acts, forcing sex in front of others, and forcing sex with others. Causing pain during sex, assaulting the genitals, coercive sex without protection against pregnancy or sexually transmitted disease, criticizing, or using sexually degrading insults.

Indicators: unusual anger, sudden anxiety, negative self-talk, declining physical health, drug and alcohol abuse

Social abuse: a behavior that seeks to cut the partner off from family, friends, or community and in general to harm partner's relationships with others. It also could include the attempt at systematic isolation from family and friends through techniques, such as ongoing rudeness to family and friends, moving to locations where the victim knows nobody, and forbidding or physically preventing the victim from going out and meeting people.

Indicators: partner encourages friends who are abusive, gossips or spread rumors about the victim, monitors social activities, treats the victim disrespectfully in front of others, reports secrets or embarrassing stories, refuses to socialize with the victim's family or friends, prohibits the partner from working outside the home, demands the partner to account for all social contacts, selects visitors, alienates them from family and friends, and forces the victim to move away from friends and a supportive environment

Verbal abuse: the act of forcefully criticizing, insulting, or denouncing another person. Usually perpetrated through continual put downs and humiliation, either privately or publicly, with attacks following clear themes that focus on intelligence, sexuality, body image, and capacity as a family member, parent, or spouse.

Indicators: verbal assault, constant disagreement, sarcastic jokes, controlling conversations, blaming, dismissal of partner's feelings, threatening and intimidation, victim-blaming for loss of temper, gaslighting, abusive anger and rage, use of words of shame, name calling, yelling, gender privilege, racism (religious, cultural, skin-related).

Spiritual abuse: any attempt to exert power and control over someone using religion, faith, or beliefs. It can be exerted by denying access to ceremonies, land or family, preventing religious observance, forcing victims to do things against their beliefs, denigration of cultural background, or using religious teachings or cultural tradition as a reason for violence.

Indicators: shame, make fun of, or ridicule the religious beliefs or practices of the victim. Use beliefs with manipulating or bullying intents, demand that children are raised with/without a certain religion. Using scriptures or religious beliefs to control clothing, behavior, sexuality, decision making, choice to have children or not, finances.

Economic abuse: Economic abuse occurs when one partner gains full or partial control of the other's finances or employment opportunities. Victims have incomplete or no control on money and provided only an inadequate allowance. Subjects abused may be unable to manage their checking accounts or income without the interference of their abusive spouse, who forces them to be dependent on others. It can impact victim's ability to care for children, meet their financial obligations, and obtain education or employment.

Indicators: victims prohibited from working, forced to turn over paychecks, imposed to take an allowance. Partners refuse to share financial information and/or takes credit cards out or opens accounts in the victim's name. Victims forced to add the partner's name on their accounts or property.

Increased Exposure to Violence and Risk of Neurodevelopmental Disorders in Children

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Exposure of children and adolescents to violence has significant short and long-term consequences in terms of academic, social, physical, and psychological functioning.[1,2] The relationship of exposure to traumatic events, including various forms of violence, with depression, anger, anxiety, dissociation, posttraumatic stress, and total trauma symptoms has been widely debated.[1-3] It is largely accepted that adverse early life experiences and abusive events suffered during childhood can cause profound effects on the development and function of the nervous system and increase the risk of neurodevelopmental disorders.[4] Studies investigating the relationship between various types of neurodevelopmental disorders and exposure to violence and their consequences have been inconclusive.[3]

The alarming phenomenon of family and domestic violence has increased significantly during the COVID-19 pandemic.[5] Several studies have documented a surge in abuse-related physical and nonphysical trauma in children during this period.[6] Similar observations have been made after periods of economic decline or turbulence.[7]

This commentary, authored by the Working Group on Social Pediatrics of the European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA/UNEPSA), briefly discusses the important relationship between the occurrence of traumatic events, particularly violence, and neurodevelopmental disorders in children. Our aim is to raise awareness of these circumstances, which may occur during or following periods of social turmoil, as in the case of the 2009 economic crisis[8,9] and the COVID-19 pandemic,[10] and expose children to the risks of serious immediate and long-term effects on their health and well-being.

Physical and Emotional Traumatic Events in Children

Children experiencing frightening, dangerous, or violent distressing events may feel physically endangered or extremely alarmed as a result.[11] Witnessing a traumatic event that endangers the life or physical security of a loved one also can be traumatic for minors. In early life, these circumstances can be particularly important, as young children's sense of safety depends on the perceived safety of their attachment figures.[12] Traumatic events are referred to as indirect trauma in cases where participants witness the event and as direct trauma in cases where participants themselves experience the event.[13] In recent years, minors are increasingly witnessing violent events[14] or experiencing a combination of direct and indirect violence.[6,15] It also is not unusual for children to experience an overlap between maltreatment and witnessed family and domestic violence, which often takes place in the context of a violent community environment.[3,16]

A significant number of children worldwide are exposed to traumatic life events. Exposure to at least one trauma is a common experience in more than two-thirds of children by age 16 years, and >30% of children have been exposed to multiple traumatic events by this age.[17] However, estimates of trauma exposure rates and subsequent psychological sequelae among children and youth vary depending on the type of sample, type of measure, informant source, and other factors, including geography.[17,18] Harmful events for children can come from outside of the family, as in the case of natural disasters, car accidents, school shootings, or community violence, or from within the family, as in the event of domestic violence, physical or sexual abuse, or the unexpected death of a loved one.

Traumatic events include various forms of violence (**Table**; available at www.jpeds.com). Strong emotions and physical reactions in children may be triggered by violent events irrespective of whether they are witnessed or sustained directly and may persist long after the events. These conditions may cause children to feel terror, helplessness, or fear and may induce physiological reactions, including palpitations, nausea, vomiting, and impaired urinary and bowel control.[1,4] The intensity of such physical and emotional responses may increase progressively in children who feel overburdened owing to a lack of protection by custodians or their inability to react to traumatic events.[19]

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Common Neurodevelopmental Disorders in Children

Neurodevelopmental disorders are traditionally considered to include physical as well as functional abnormalities related to a group of heterogeneous conditions characterized by difficulties or delays in the acquisition of skills in a variety of developmental domains, including social, motor, language, and cognition in general.[3] These conditions result from abnormal brain maturation that normally precedes clinical impairment, and revealing symptoms may arise at various points in childhood. Recent studies have concentrated on recognizing predictive biological and behavioral markers with the aim of initiating treatments that may either alter developmental trajectories or lessen the clinical severity of these conditions.[20,21] Neurodevelopmental disorders may be triggered by various causes, such as early exposure to dangerous substances, perinatal immune activation due to prenatal and postnatal infections[20] and exposure to traumatic events, including violence.[3] In economically advanced countries, as many as 15% of children are considered to have a neurodevelopmental disorder characterized by behavioral alterations.[21]

Traumatic Events Associated with Neurodevelopmental Disorders in Childhood

An increasing number of studies have addressed the issue of children's exposure to violence and its relationship with neurodevelopmental disorders, particularly when these events are experienced during sensitive developmental periods.[3] Alterations in brain structures, including the amygdala, hippocampus, basal ganglia, and prefrontal cortex, have been linked to violence exposure, and deficits in executive functioning, self-regulation and externalizing behaviors have been associated with impairments in these areas.[22,23]

A direct relationship between attention deficit hyperactivity disorder (ADHD) and violent criminality has been extensively documented, and the long-term effects of autism spectrum disorders, tic disorders, and obsessive-compulsive disorder on criminality are recognized.[24] The neurobiological effects of violence exposure in children and adolescents are unclear, and studies investigating the association between exposure to violence and clinical conditions related to neurodevelopmental disorders, including ADHD, autism spectrum disorders, and learning and tic disorders, are relatively limited.[3]

Although a few studies have reported that witnessing violence associated with direct victimization may result in poorer outcomes compared with only one type of violence exposure, others have shown show no significantly different outcomes between children who were both witnesses and victims and those who experienced only one mode of violence exposure.[25] Other studies have reported higher rates of psychiatric disorders, including ADHD, in children with a higher number of victimization experiences, suggesting that the higher rate of psychiatric diagnosis and poorer outcomes among polyvictims may be the result of more frequent experiences of violence.[26] However, whether the experience of polyvictimization suffered by children is more closely associated with poorer outcomes compared with frequent chronic victimization of one type remains unclear.[3,27,28]

Conclusions

Behavioral disturbances related to neurodevelopmental disorders have increased owing to numerous factors, including social, economic and health-related factors,[6] which have engaged various professional figures involved in the care of children, including educators, social workers, psychologists, and pediatricians.[29] A useful approach to violence-associated neurodevelopmental disorders requires interdisciplinary collaboration and expertise in order to effectively challenge this phenomenon and to promote an advancement of knowledge in this field. The EPA-UNEPSA Working Group on Social Pediatrics is currently developing a network of experts among its member societies with the aim of promoting educational initiatives to increase the general understanding of violence associated neurodevelopmental disorders and help pediatricians to effectively limit their impact on physical, intellectual, and social-emotional development of children. ■

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Table. Major traumatic events during childhood

- **Natural or artificially caused Disasters:** Major catastrophes, disasters or events that are results of natural events or consequences of intentional or unintentional manmade actions.
- **Extreme Personal or Interpersonal Violence (as a Victim and/or Witness)**: Includes intense violence by or between individuals including exposure to homicide, suicide and other similar extreme events.
- **Witnessing Domestic Violence:** Exposure to emotional abuse, including actual or attempted physical or sexual assault. Witnessing aggressive control perpetrated by a parent/caretaker against another adult in the child victim's home environment or perpetrated by an adolescent against one or more adults in the child victim's home environment.
- **Victim and/or Witness to Community Violence:** Extreme violence in the community, including exposure to gang-related violence.
- **School Violence:** Violence occurring in a school setting, including, but not limited to school shootings, bullying, interpersonal violence among classmates, and classmate suicide.
- **Physical Abuse or Assaults:** The use of physical force, inflicted with or without the use of an object, with the intention of causing the child to experience bodily pain or discomfort. This includes spanking, hitting, pinching, paddling, whipping, slapping, and may involve the infliction of severe corporeal punishment.
- **Sexual Abuses or Attempts:** unsolicited real or attempted sexual contacts, exposure to age-inappropriate sexual material or social contexts, sexual exploitation, unwanted or coercive sexual actions or contacts.
- **Emotional Abuse and Psychological Maltreatment:** Acts or omissions committed against children, other than physical or sexual abuse, that cause conduct, cognitive, affective or other mental disturbance. Such acts include verbal abuse, emotional abuse, excessive demands on a child's performance that may lead to negative self-image and disturbed behavior. Perpetrators reject, criticize, threaten, demean, engage in name-calling, insult and berate the children, who may be also humiliated.
- **Neglect:** The ongoing failure to meet a child's basic needs. Omission to provide the necessary, age-appropriate care to children. Caretakers, although financially able, fail to support children financially or by other means. It includes physical neglect, medical neglect and educational neglect. Leaving children hungry or dirty, or without proper clothing, shelter, supervision or health care.
- **Serious Accident or Illness:** Suffering an injury or accident. Having a physical illness or experiencing medical procedures that are highly painful and/or life threatening.
- **War/Terrorism/Political Violence:** Exposure to acts of war/terrorism/political violence including incidents such bombing, shooting, looting, or accidents that are a result of terrorist activity
- **Forced Relocation:** Forced relocation/displacement to a new home due to family needs or war or political reasons, generally including political asylees or immigrants fleeing political persecution.
- **Traumatic Distress due to Separation:** Death of a parent, primary caretaker or sibling, abrupt and/or unexpected, accidental or premature death or homicide of a close friend, family member, or other close relative. Unexplained, sudden separation from a parent, primary caretaker or sibling due to circumstances beyond the will of children.
- **System-Induced Trauma:** Traumatic removal from the home, traumatic foster placement, sibling separation, or multiple placements in a short amount of time.

EUROPEAN PAEDIATRIC ASSOCIATION

Effects of Coronavirus Disease 2019 (COVID-19) on Family Functioning

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More than a year and a half after the first clinical manifestations of coronavirus disease 2019 (COVID-19) were reported in Wuhan, China,[1,2] the magnitude of the pandemic across the globe and its related clinical and social effects[3] remain unclear.[4] The pandemic has affected lives and sparked concerns about everything from health to job security. In high–Gross Domestic Product (GDP) countries, despite trillions in coronavirus aid released by governments, many families still struggle to pay for basic necessities like food and rent, and these difficulties worsened during the pandemic.[5,6] The general social uncertainty caused by the pandemic seems to have also affected family resilience, weakening the ability of individuals to confront challenges, survive difficulties, and thrive in adversities as a group.[7,8]

To reduce community spread of the virus, many countries adopted unprecedented confining measures, including the restriction of populations in their homes and reduction of interpersonal contacts. Confinement, quarantine measures for suspected COVID-19 cases, and social distancing were prolonged, and their effectiveness was debated at social, scientific, and political levels.[9] However, although their prevention value in limiting viral spread is generally recognized,[6] it is also widely accepted that social isolation measures have upended family lives.[4] In particular, they have affected family functioning and parenting, which are significantly associated with the physical and psychosocial functioning of children and adolescents.[10]

This commentary, authored by the Working Group on Social Pediatrics of the European Paediatric Association/Union of National European Paediatric Societies and Associations, briefly discusses the effects of the confinement measures taken to combat the COVID-19 pandemic on family functioning. Our aim is to raise the awareness of pediatricians, social work professionals, and policy makers, as knowledge of the effects of social restrictions on family functioning may contribute to the efforts of national health systems to be effectively prepared to handle the social effects of future public health crises. Adopting a more mindful and coordinated approach may help overcome divergences across countries, particularly in terms of complex sociopolitical realities.

Family Functioning: a Social and Structural Asset of Global Family Environment

The physical and psychosocial performance of children and adolescents challenged by adversities is significantly related to a number of family factors, including family functioning and parenting, which are typically embedded within the context of a family.[10] Specific variables that characterize parent–child relations in each family also may play a role in maintaining balanced physical and psychosocial functioning in children struggling with external events affecting their families. Parent–child dyadic rigidity, together with the presence or absence and the magnitude of such variables as unstable family income, broken home, family mobility, parent mental health, number of children in the family, single-parent family, and parental past, may accelerate a deterioration of intrafamily relationships.[10] In contrast, parent–child interaction processes of dyadic positive affect and flexibility may help prevent possible negative impacts on children's daily life and contribute to an effective parent–child coregulation.[10-12]

Family functioning is a multidimensional concept that refers to the dynamics and quality of family members' relationships. This is based on the organization and level of conflict and cohesion internal to families and in large part on their adaptability and communication skills. In general, a family environment characterized by cohesion, clear communication ability, well-defined roles, and good emotional balance and regulation describes a positive family functioning.[11,12] Inadequate or defective family functioning refers to families showing disorganization characterized by unclear family roles, high levels of inner conflict situations, and poor affective and behavioral control.[11,12] Family structure also plays an important role in achieving balanced family functioning.[13]

Family functioning is widely used as an evaluation criteria for parents, caregivers, and families.[14] A variety of measures are available to assess functioning in families challenged by negative events and to evaluate family factors useful for identifying families most at risk for poor family functioning. It is important to properly assess family functioning for

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caregivers to provide informed support, tailor interventions, evaluate outcomes for individuals and the entire family,[14,15] and ultimately develop programs and interventions that aim to improve family relationships and the overall family functioning. Five major theoretical models commonly used to assess family functioning are reported in **Table** (available at www.jpeds.com), which can be suitably selected and adopted as an assessment tool depending on the family context in which they are used.

Effects of COVID-19 Pandemic on Family Functioning

A variety of natural, economic, and public health crisis have affected families throughout the world, causing distress to family members, including mental health problems, interparental conflict, and relational instability, generating an increase in rough and abusive parenting.[16,17] During the COVID-19 pandemic, families have suffered severe financial and psychological hardships, which were particularly problematic in complex sociopolitical contexts[18] characterized by important socioeconomic diversities, such as in Europe, making it difficult to establish coherent and consistent decision processes. In addition to the usual consequences of a public health crisis, including job instability and financial disruptions, families have experienced stress caused by social isolation, confinement within the household, rupture in the nature of school settings, concern for the future, and the need to make unprecedented health-related decisions for family members in a context of uncertainty.[19]

Understanding the influence of the pandemic on family functioning is therefore essential to plan effective support interventions and preventive measures and allocate adequate resources to properly assist families during and after the pandemic. Recent studies in Europe and the US have provided evidence of a significant increase in overall mental distress in people tested before and during the pandemic[20] and have shown a consistent deterioration in parent and child mental and behavioral health during the first months of the pandemic.[21,22] In particular, increases in parent depression and children's internalizing and externalizing problems from before the pandemic were significant findings that normally are observed only infrequently in developmental and family studies.[21,22] During the pandemic, these 2 factors increased by 2-fold and were more likely to score in the clinical range.[21]

Preliminary reports on the social consequences of COVID-19 suggest that mental health problems and family conflicts generated by the pandemic may negatively impact family functioning, including the ability to develop resilience.[7,8] The ongoing COVID-19 pandemic offers an important opportunity to further investigate the implications of deterioration in parent and child psychological well-being during extraordinary public health events. They may in fact amplify intrafamily conflicts and compromise the capability of parents to implement and sustain protective health behaviors of family members, including social distancing, handwashing, mask-wearing, and preventive plans recommended by public health authorities.[23] Assessment of family functioning during a pandemic, as in the case of COVID-19, is important to maintain an adequate dynamic and quality of family members' relationships.

Conclusions

It is currently unclear whether and to what extent family instabilities due to the COVID-19 pandemic may recover during the months following the end of this public health emergency, and for how long the negative effects of this event will persist and affect parent and child well-being. However, experience from past crises suggests the strategic importance of establishing or potentiating preventive measures based on the promotion of individual and family resilience before a crisis[8,17] and to plan for providing support to families after the onset of a crisis.[24] Family support plans should include the promotion of coping skills, family relationship quality, and attitude management.[25] Assisting families in recovering from pandemic periods and from crises in general requires a multidimensional and interdisciplinary approach including schools, pediatricians, social work professionals, mental health clinicians, counselors, family service agencies, and sport organizations.[26,27] ■

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Table. Five major theoretical models of family functioning

Stress and Coping Theory

Developed in the 1960s, this model is based on the notion that person and environment are in a dynamic, mutually reciprocal, and bidirectional relationship. Key elements are:

a. Stress, defined as the relationship between the person and the environment that is appraised by individuals as exhausting, draining, or exceeding personal resources and as compromising their well-being
b. Coping, identified as the thoughts and acts used by people to manage the demands of stressful circumstances.

The functioning of individuals is indissolubly related to their life context factors, and family functioning is viewed as the family's ability to adapt to stress and reduce the family and its members' overall vulnerability and susceptibility to stress.

Beavers System Model

Developed over the past 30-year period, this model is based on clinical observations of both dysfunctional and healthy families involved in treatment and research programs. Families are typified using 2 dimensions:

a. Family competence: indicates the structure of the family, available information, and flexibility of the group to adapt to new circumstances. The ability of a family system to negotiate, function and deal effectively with stressful situations is directly related to its capability to intercept and use energy from the outside world to assist in maintaining its structure and flexibility.
b. Family style: indicates the quality and style of family interaction and evaluate whether the families acquire most of their satisfaction by a centripetal way, from within the family, or, in a centrifugal way, from the outside world. According to these dimensions, family health is related to a curvilinear relationship, with optimal families falling in the middle of the continuum, experiencing satisfaction from both within the family and the outside world. In contrast, dysfunctional families are associated with both centripetal and centrifugal ends of the continuum. In this model, families are rated in these dimensions based on the structure and flexibility they display in such areas as autonomy, power, parental coalitions, family mythology, goal-directed behaviors, social intermediation ability, and family affect.

Circumplex Model of Family Functioning

Developed over the past 30 years, this model is based on clinical and research work with families and marital couples. Families are typified using 3 dimensions:

a. Cohesion, defined as the emotional bonding that family members have toward one another. It encompasses the factors of emotional bonding, family boundaries, coalitions, time, space, friends, decision making, interests, and recreation.
b. Flexibility: includes the quality and expression of leadership and organization, role relationships, and relationship rules and negotiations.
c. Communication: indicates the positive communication skills utilized within a couple or a family system. It is considered a factor able to facilitate a positive modulation within the primary dimensions of cohesion and flexibility.

In a system of curvilinear continuum, optimal functioning is considered to be characterized by a balanced level of cohesion and flexibility, and is expected to fall in the middle of each continuum and dysfunction at the end of each continuum.

McMaster Model of Family Functioning (MMFF)

Thus systems-based model regards the family as an open system, characterized by a complex interaction between intrafamily subsystems, such as individual, marital and dyad, and the various external systems, such as extended family, schools, religion, or work. Instead of characterizing families through single dimensions, this model takes a whole-systems approach by evaluating the complex of family structure, organization, and transactional patterns. The assessment of family health or dysfunction is based on the ongoing articulated interplay between the individual relationships and the family system.

The approach to family functioning using this model implies the following guiding principles: parts of the family are related to each other; one part of the family cannot be understood in isolation from the rest of the system; family functioning is more than just the sum of its parts; a family's structure and organization are important in determining the behavior of family members; and transactional patterns of the family system are involved in shaping the behavior of family members. Family functioning is related to the accomplishment of essential functions and tasks grouped in 3 areas:

a. Basic tasks
b. Developmental tasks
c. Hazardous tasks.

This model identifies 6 core areas that impact a family's ability to meet these functions and tasks: problem solving, communication, roles, affective responsiveness, affective involvement, and behavioral control.

Process Model of Family Functioning

This systems-based model investigates family functioning in the context of the ability of a family and its members to accomplish a multiplicity of tasks. The model distinguishes 7 basic dimensions to evaluate how successful a family is in confronting basic developmental and crisis tasks that can be recognized as central objectives to family life: task accomplishment, role performance, communication, affective expression, involvement, control, values, and norms.

The Process Model recognizes the importance of the larger social system and family history, as well as the intrapsychic interpersonal factors typical of the McMaster Model of Family Functioning. However, beyond these important factors of family system, the Process Model emphasizes the existence of a variety of additional influential factors. This model may be regarded not as a model of family therapy, but rather as a model for understanding families.

nutrients

MDPI

Review

Term Infant Formulas Influencing Gut Microbiota: An Overview

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Abstract: Intestinal colonization of the neonate is highly dependent on the term of pregnancy, the mode of delivery, the type of feeding [breast feeding or formula feeding]. Postnatal immune maturation is dependent on the intestinal microbiome implementation and composition and type of feeding is a key issue in the human gut development, the diversity of microbiome, and the intestinal function. It is well established that exclusive breastfeeding for 6 months or more has several benefits with respect to formula feeding. The composition of the new generation of infant formulas aims in mimicking HM by reproducing its beneficial effects on intestinal microbiome and on the gut associated immune system (GAIS). Several approaches have been developed currently for designing new infant formulas by the addition of bioactive ingredients such as human milk oligosaccharides (HMOs), probiotics, prebiotics [fructo-oligosaccharides (FOSs) and galacto-oligosaccharides (GOSs)], or by obtaining the so-called post-biotics also known as milk fermentation products. The aim of this article is to guide the practitioner in the understanding of these different types of Microbiota Influencing Formulas by listing and summarizing the main concepts and characteristics of these different models of enriched IFs with bioactive ingredients.

Keywords: microbiome modifying formula; probiotics; prebiotics; synbiotics; postbiotics; human milk oligosaccharides; diarrhea; gastrointestinal infections

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1. Introduction

Intestinal colonization takes place immediately after birth [1]. It is highly dependent on the term of pregnancy, the mode of delivery, the type of feeding [breast feeding (BF) or formula feeding (FF)] and the use of antibiotics or proton pump inhibitors [1,2]. Postnatal immune maturation is, as well, highly dependent on the intestinal microbiome implementation and composition [1–3]. Type of feeding is a key issue in the human gut development, the diversity of microbiome, and the intestinal function at any age in life [4,5]. By providing bioactive components, human milk (HM) protects the infant against pathogenic infections.

It promotes barrier function, stimulates the immune system and facilitates immune tolerance [6,7]. In the past, infant mortality rate in Europe was very high (≥20%) especially in non-breastfed infants [8]. Compared to formula-fed infants, studies of the "intestinal flora" of BF infants showed differences, especially regarding *Bifidobacteria* species [9,10]. Later on, oligosaccharides were identified as the most important bifidogenic factor in HM [10]. Nowadays, it is well established that exclusive BF for 6 months or more, relative to FF, decreases the incidence and/or the severity of a number of infectious diseases [7,11].

As a matter of fact, the composition of the new generation of infant formulas (IFs) aims in mimicking HM by reproducing similar or close beneficial effects on intestinal microbiome and, in turn, on the gut associated immune system (GAIS). Reproducing the beneficial effects of breast milk remains a considerable challenge. Several approaches have been developed currently for designing new IFs by the addition of bioactive ingredients such as HM oligosaccharides (HMOs), probiotics, prebiotics [fructo-oligosaccharides (FOSs) and galacto-oligosaccharides (GOSs)], or by adding the so-called post-biotics also known as milk fermentation products. The aim of this article, the third of a trilogy [12,13], is to assist the practitioner in the understanding of these different types of Microbiota Influencing Formulas (MIFs). Our aim is to help them in the prescription of an IF by listing and summarizing the main concepts and characteristics of these different models of enriched Ifs with bioactive ingredients influencing gut microbiota.

2. Methods

This is a literature review of narrative nature [14]. We performed a search in MEDLINE and EMBASE using the search terms infant formula, fermented infant formula, intestinal microbiota influencing formula, HM oligosaccharides (HMOs), prebiotics, probiotics, synbiotics, postbiotics, considering most relevant literature, including clinical trials, review, systematic review and metanalysis published from 2000 onwards, focusing on gastrointestinal clinical and nonclinical outcomes, and excluding allergy, respiratory infections and other non-gastrointestinal outcomes, in line with the topic of the Special Issue.

Authors reviewed relevant literature on a specific topic, with the purpose of identifying what has been accomplished previously, allowing for consolidation, for building on previous work, for avoiding duplication and for identifying omissions or gaps [14], and summarized the content of their paragraph in a short conclusion statement on which there was consent [14].

2.1. Probiotics Supplemented IFs

The long-lasting debate on the safety and clinical effects of adding probiotic preparations to IFs, follow-on formulas, and special medical foods has not reached a final consensus and large number of studies are currently ongoing to provide further useful information in this area [15]. During recent years, research has focused particularly on the modifications induced by a probiotic supplementation on infant microbiome and on probiotics' efficacy and safety on a different number of pathologies [16]. However, IFs are increasingly being supplemented with probiotics and probiotics' market has expanded globally during recent years [13,16]. Since over two decades the definition of probiotics proposed by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO), that describes them as "live microorganisms which when administered in adequate amounts confer a health benefit on the host", has become the most widely accepted and adopted version worldwide [12,13]. It has proven valuable throughout the years by researchers, legislators, industry and consumers, as it includes a broad range of microbes and applications, while at the same time well it summarizes the fundamental nature of probiotics, characterized for being microbial, viable and beneficial to health [17].

Probiotics are identified by their specific strain, which includes the genus, the species, the subspecies, and an alphanumeric strain designation, as shown in the example in Table 1. The seven core genera of microbial organisms most often used in probiotic commercial products are *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, *Escherichia*, and *Bacillus* [18].

Table 1. Example of nomenclature used to identify commercial strains of probiotics.

Genus	Species	Subspecies	Strain Designation	Strain Abbreviation
Lactobacillus	*rhamnosus*	*NA*	GG	LGG
Bifidobacterium	*animalis*	lactis	DN-173010	*Bifidus regularis*
Bifidobacterium	*longum*	longum	36624	*Bifantis*

2.1.1. Rational for the Use of Probiotics in Infant Formula

A rapid colonization of the immature neonatal gut with microbes takes place at birth, further supported by enteral diet and milk [19]. This process starts the organization of a complex ecosystem signals that lead post-natal gut maturation [1,12] towards appropriate digestive and immunological functions [20,21], which further develop through the subsequent and progressive introduction and establishment of different bacteria in infancy and early childhood [22]. Facultative and aerobic bacteria establish first, followed by progressively more strict anaerobes and finally, in adult individuals, the intestinal microbiota includes several hundred, mostly anaerobic, bacterial species [23]. The intestinal microbiota variously contributes to many functions of the gut, which in addition to its primary function of nutrient digestion and absorption, plays an important immunologic role as a protective barrier against the pathogenic microorganisms and the passage of potential harmful macromolecules into the body. Commensal microbes provide the major drive for maturation of the immune system [20]. The bacteria derive from different sources and the colonization pattern, together with several aspects of the gut immune maturation. They are influenced by delivery mode and environmental factors [23] and depend on the interaction with the host-specific gut microbiota. To this regard, early gut colonization takes place through vertical mother-neonate transfer of maternal bacteria, which reach breast milk via an entero-mammary pathway and recent reports emphasized the importance of assessing early host–microbe interactions due to the impact that early gut colonization may have on later health [24]. It is therefore conceivable the potential and important role, played by probiotic supplemented formulas, in influencing and possibly determining the microbiota profile of infant and its positive effect on gut maturation [25].

2.1.2. Microbiota and Gut Development

Gut development is effectively promoted by HM through a direct or indirect activity on gut microbiota [26]. For instance, gut microbiota maturation may be directly influenced by lactoferrin which controls microbes colonization by its anti-microbial function, or indirectly by commensal bacteria [22]. The contribution of other factors may further influence the gut maturation, as in the case of the intake of essential fatty acids and fatty acid desaturase genotype which contribute to the infant immune system maturation [27,28]. Gut microbiota development and gut maturation of formula-fed infants may therefore depend on different functional milk components such as probiotics added to formula. However, still insufficient studies have adequately investigated the relationship between gut microbiota development and gut maturation in early infant life in the same group of subjects, and information on host-microbe crosstalk are currently also still insufficient [22], particularly in reference to probiotic supplemented IFs.

2.1.3. Probiotics Supplemented IFs Tolerability and Safety

The ability to manipulate the composition and metabolic footprints of gut microbiota is longtime well known [12] and IFs supplementation with probiotics has the purpose of modulating the activity of the intestinal microbiota of infants through modifying its balance [29]. Introducing probiotics in formulas in addition to the purpose of conferring health-promoting properties, has an impact on the functional characteristics of the product, including the improvement of taste and other variables known as texture and mouthfeel characteristics/properties, which can make food appealing or not. Probiotic-supplemented IFs do not raise any health concern regarding growth, as stated by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [16]. However, few recent cases of *Lactobacillus* or *Bifidobacterium* sepsis in infants receiving probiotics have been reported and there are still many challenges related to the stability and functionality of probiotics in dairy products [29,30]. In neonatology, supplementation with *Bifidobacterium* spp. and *Lactobacillus* spp. is most common. In particular, *B. bifidum* and *L. acidophilus* added to infant formula seem to remain more stable if compared to expressed breast milk and sterile water following storage at 4 °C for 6 h [31].

2.1.4. Probiotics Supplemented IFs in Gastrointestinal Disorders

As reported by a large number of studies [32], the effects on different health conditions elicited by probiotics activities are highly strains specific, although it is somehow difficult to perform an effective comparative analysis of the growing available data, due to continuous changes of probiotics' taxonomy [30]. A number of recent critical reviews of the literature have evaluated the use, effectiveness and safety of various specific probiotic strains and many different guidelines, position papers and evidence-based recommendations for various clinical indications have been developed in relation to several health conditions affecting children including prevention of nosocomial infections, allergy and gastrointestinal (GI) disorders [16,33,34]. In reference to the latter, various reports have indicated that supplementation of infant formula with probiotics may be useful in certain conditions [34]. A systematic review conducted by ESPGHAN reported the existing evidence related to the safety and health effects of the administration of probiotics supplemented compared with probiotics unsupplemented formula [16]. In general, previous randomized clinical trials (RCTs) report a modest benefit when giving probiotics with the aim to prevent acute gastrointestinal tract infections in healthy infants and children, while meta-analyses and Cochrane reviews have shown that probiotics reduce the number of diarrheal stools and the duration of diarrhea [35–39]. Recent studies have suggested the usefulness of probiotics in preventing infections. Strains of probiotics including *Lactobacillus rhamnosus* GG (LGG), *Streptococcus thermophilus*, *Lactobacillus. casei*, *Bifidobacterium lactis*, or *Lactobacillus reuteri* have been used to supplement infant formula [39], and a reduced incidence rates of gastrointestinal infections were observed in infants receiving formula supplemented with *L. fermentum* [40,41]. Studies on the use of probiotics in the prevention of antibiotic-associated diarrhea have shown that the use of a probiotic-supplemented formula, particularly with *B. lactis* and *S. thermophilus*, reduces the incidence of antibiotic-associated diarrhea [42,43]. The effectiveness of probiotic supplemented formula to reduce colic frequency, crying and irritability in children younger than six months, is debated [44]. For instance, the use of formula with *B. lactis* BL999 and LPR, *L. reuteri* or LGG was not associated to a reduction of these symptoms in children younger than six months, while several studies show a reduced frequency of colic in children older than six months [16,39,45].

2.1.5. Conclusion on Probiotics Supplemented IFs

The increasing worldwide use of commercial probiotic supplemented formulas, and the growth of the related literature have raised the attention of law makers, healthcare professionals and consumers on the advantages and risks related to the use of these products in children and very young infants. The major issues related to the use of probiotics to supplement dietetic products for infants have been well emphasized by many

authors. In particular, the ESPGHAN Committee on Nutrition [16] expressed its concern on the important factor of timing, as supplemented formulas are most often initiated early in infancy, if not at birth. Therefore, introducing external factors, such as probiotics, at a time when gut microbiota is developing may influence and permanently affect the development of the ecosystem, leading to currently unclear changes. Finally, the length of administration represents a further element of concern, as the supplemented products may be sometimes administered for prolonged periods, which outcomes have not been sufficiently studied.

Clinical research has shown that probiotic supplementation of newborns and infants with specific bacterial strains through formula is safe. However, specific structured clinical questions supported by well designed, prospective and randomized double-blind studies on adequately selected population will contribute to clarify the health benefits of specific bacterial strains for infants and the usefulness of probiotic supplemented IFs as a mean for their administration (Table 2).

Table 2. Summary of beneficial effect of MIFs enriched with Probiotics.

MIFs Enriched with Probiotics—Key Points
• The intestinal microbiota (IM) contributes to the early and healthy development of gut functions
• Commensal microbes are essential for maturation of the immune system
• IFs supplementation with probiotics has the purpose to modulate the activity of the intestinal microbiota of infants by modifying its balance
• Probiotics enriched IFs have modest benefit in preventing acute gastrointestinal tract infections in healthy infants
• Probiotics reduce the incidence of antibiotic-associated diarrhea
• The effectiveness of probiotic supplemented IFs to reduce colic frequency, crying and irritability is debated
• Major issues related to the use of probiotics: timing, duration of treatment

2.2. Prebiotics Supplemented IFs

A dietary prebiotic was defined by The International Scientific Association for Probiotics and Prebiotics (ISAPP), in 2010, as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health". Later in 2017, ISAPP redefined a prebiotic as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" [46], giving relevance to prebiotics conferring health benefits to the whole body, and not only to the gastrointestinal tract. In the context of increasing interest for the potential health benefits of prebiotics added to food products, they are also frequently presenting IFs with the aim to stimulate the establishment and maintenance of a healthy gut environment, more faithfully resembling that of breastfed infants. The most commonly used and studied prebiotics ingredients include galactooligosaccharides (GOS), polydextrose (PDX), fructooligosaccharides (FOS), 2′-fucosyllactose, lacto-N-neo-tetraose, inulin, oligofructose and galactofructose; with GOS, FOS, and/or PDX, and mixtures of GOS/FOS (the most studied is a 9:1 mixture of short-chain (sc)GOS and long-chain (lc)FOS) being the prebiotics most frequently use and largely studied.

2.2.1. Rational for the Use of Prebiotics in IFs

Contrary to HM, cow's milk does not contain prebiotic oligosaccharides, that are added to IFs to indirectly act, through selective fermentation that stimulates the growth of *Bifidobacteria* and *Lactobacilli*, for improving intestinal barrier function, protecting against pathogens and enhancing local and systemic immune function [47], with all the health consequences that have been extensively described in the probiotics section.

2.2.2. Prebiotics Supplemented IFs and Intestinal Parameters

Different type of prebiotics substrates may act differently on the growth of intestinal bacteria as, for example, inulin, maltodextrin and PDX have been associated with relatively poor *Lactobacillus* and *Bifidobacterium* growth with respect to GOS and lactulose [48]. A RCT evaluating oligofructose/FOS (50:50, 4 or 8 g/L) or GOS/FOS (8 g/L) supplemented

formulas showed that the total number of fecal bacteria increase in all prebiotic groups and more closely resembled that of the breastfed infants [49]. Moreover, other RCTs evaluating GOS/FOS [50–53] as well as only-GOS enriched formulas [54,55] have demonstrated a selective stimulating effect on the growth of *Bifidobacteria* and/or *Lactobacilli*, resembling the way in which HM acts on microbiome of breastfed infants. Moreover, it has been shown that the beneficial effects on the growth of *Bifidobacteria* and *Lactobacilli* in infants fed with a scGOS/lcFOS (9:1) supplemented formula were maintained even for months after ceasing the prebiotic formula [52]. Studies also showed that FOS-supplemented formulas are associated with increased bifidobacteria [56]; however, one study [57] reported a significant effect only after 1 month of prebiotic-supplemented formula feeding, whereas the effect was no longer significant after 2 months, and another study [58] did not show any statistically significant difference between the infants fed with a prebiotic-enriched formula and those fed an unsupplemented formula. In association with the stimulation of growth of *Bifidobacteria* and *Lactobacilli* [59], some RCTs have also demonstrated that infants fed with prebiotics-supplemented formula (GOS/FOS mixture, PDX and GOS) had shown reduced faecal clostridia [53,54,60]. Similarly, infants fed with a prebiotic-enriched formula (0.4% GOS/lcFOS) showed significantly decreased clostridia percentage in stools after 6 weeks of intervention with respect to infants fed with regular formula (0% vs. 3.29%, respectively); this observation being potentially associated with a reduced risk of intestinal infection [61].

The healthier composition of microbiota in infants fed with prebiotics-added formulas with respect to standard ones may also be associated with other intestinal parameters, such as the faecal pH. The faecal pH has proven to modulate the intestinal environment, and lower faecal pH results in decreased amounts of pathogenic bacteria [62]. Infants fed with a GOS/FOS (90:10, 6 g/L) supplemented formula showed a lower faecal pH after 16 weeks compared to infants fed with a probiotic-enriched formula or with a regular formula [63]; a similar result was also shown in another RCT comparing gastrointestinal parameters, including faecal pH, in infants fed with a GOS/FOS mixture (90:10, 4 g/L) supplemented formula with respect to a standard one [64]. In another study, infants fed with a scGOS/lcFOS-enriched formula showed lower faecal pH after 8 weeks of intervention but not after 26 weeks [53]. The same lower faecal pH was also demonstrated after 4 months of an only-GOS (0.44 g/dl) enriched-formula [54]. The same authors have also demonstrated, in the faeces of infants fed with the GOS-supplemented formula, that the percentage of acid acetic was higher than in the control group; whereas the percentages of propionic and butyric acids were lower, more closely resembling the Short Chain Fatty Acids (SCFAs) pattern that is observed in breastfed infants. SCFAs can improve insulin sensitivity and glucose tolerance, modify lipid metabolism, upregulate the antioxidant glutathione, and affect oxidative stress beneficially in the colon of healthy humans [65]. Recently published review [66] found some differences in microbiota composition and immune parameters in infants fed prebiotic-supplemented formulas compared to those fed standard formulas; however, these findings have been considered inconsistent.

2.2.3. Prebiotics Supplemented IFs and Growth

Growth parameters and other clinical outcomes have been evaluated in various studies in infants being fed with prebiotic-supplemented formulas. A systematic review published in 2011 [67], including 12 RCTs mainly using GOS and mixture of GOS and FOS-enriched formulas, showed significantly increased weight gain in full term infants receiving the prebiotic formula, without any significant impact on length and head circumference. More recently, an updated systematic review [66] showed no significant difference in growth parameters (weight, height and head circumference) in infants fed with GOS/FOS enriched formulas with respect to those fed with standard formulas. A transient increased in body weight was demonstrated at 3 and 6 moths follow-up ($p < 0.01$) in the study by Bruzzese et al. [68] in the group of infants receiving a GOS/FOS-supplemented IF compared to the control group. However, the effect was no longer statistically significant at 9 and 12-months follow-up; head circumference did not show any statistically significant increase

in supplemented with respect to unsupplemented group at any time-point. On the contrary, length was significantly increased in the infants receiving the GOS/FOS-enriched IF at all time-intervals ($p < 0.05$). A PDX/GOS-supplemented formula resulted in no differences in anthropometric measures with respect to infants receiving a control formula or a formula supplemented with 0.4 g/100 mL of a prebiotic blend of PDX and GOS from 14 to 60 days of age [60] or from 14 to 120 days of age [69].

2.2.4. Prebiotics Supplemented IFs in Gastrointestinal Disorders

The systematic review by Skorka A, et al. [66] also reported on other clinical outcomes including stool frequency and consistency. In only 4 trials, a higher stool frequency was reported in the supplemented infants with respect to unsupplemented ones. Prebiotics added to IFs included GOS/FOS mixture [70], oligofructose enriched-inulin [71], GOS [54], and PDX/GOS mixture [69]. On the contrary, the previously cited review [66] showed that at least 8 RCTs, published from 2009 onwards, failed to demostrate any significant effects on stool frequency in infants fed with prebiotic-enriched formulas. A number of trials evaluating stool consistency in GOS, FOS/GOS, FOS/GOS/AOS, PDX/GOS and oligofructose-enriched inulin supplemented formulas reported softer stools in infants receiving the prebiotic-supplemented formulas [66], more closely resemblig the stool consistency pattern seen in infants receiving HM.

More specific clinical gastrointestinal (GI) outcomes also include frequency of abdominal pain with crying; several studies found no statistically significant difference between infants fed with a prebiotic-supplemented formula with respect to those fed with a regular formula. A RCT by Vandenplas at al, comparing the GI tolerance of a specific fermented formula (FERM) with scGOS/lcFOS mixture (9:1 ratio and concentration of 0.8 g/100 mL) showed a lower incidence of infantile colic, based on the adapted Roma III criteria, and a lower overall crying time, respectively at 8 and 17 weeks follow-up [72].

The frequency of spitting up/regurgitation, constipation, flatulence, abdominal distention was not significantly different between groups [66,73]. Studies have evaluated different prebiotic supplementations (different ingredients and doses) with treatment durations ranging from 2 weeks to 12 months. Conflicting results were demonstrated for vomiting, with a trial reporting a significantly reduced number of days with vomiting in infants fed with a FOS-enriched IF with respect to infants fed unsuppplemented formula [57], and another showing no difference in either the duration or the frequency of episodes of vomiting in infants receiving the prebiotic formula with respect to those fed with the standard one [74]. Incidence of diarrhea and GI infections was reduced in infants fed with a GOS/FOS-supplemented IF with respect to infants in the control group in the study by Bruzzese et al. [68] and by Ivakhnenko & Nyankovskyy [51], respectively. However, in the already cited systematic review [66] no significant benefits in the reduction of incidence of diarrheal episodes and/or GI infections were found. On the contrary, a RCT showed, at 10 months of age, that the duration of diarrhea was significantly shorter in the group of infants fed with a GOS/FOS enriched formula compared to the control group ($p = 0.03$) [75]. More recently, a double-blind controlled trial showed no difference in the incidence of GI infections in the first year of life in infants fed with a 0.5 g GOS/100 mL supplemented formula compared to those who had received a regular formula [76].

2.2.5. Conclusion on Probiotics Supplemented IF

The ESPGHAN Committee on Nutrition [16] concluded that, due to the limited numbers and heterogeneity of the different included studies, no robust conclusions may be drawn, and prebiotic-supplemented formulas should not be routinely recommended in infants. However, the ESPGHAN Committee on Nutrition has also recognized some potential benefits of prebiotics added to IFs. More already cited studies have shown that adding prebiotics to IFs may be associated with a favorable modulation of microbiome composition and metabolic activity, that promotes the development of an intestinal environment more similar to that of BF infants. These non-clinical effects may be considered in the context

of the general action of prebiotics in maintenance of health. Nevertheless, the possible impact of feeding infants with a prebiotic-supplemented IF on most clinical outcomes is still unclear and remains to be more properly clarified in terms of real clinical benefits, potentially durable for infants' health. However, considering the well-established benefits of HM and the unquestionable recommendation to breastfeed whenever possible, and keeping in mind the central role peadiatricinans play in preventing early harmful events on the infants' intestinal microbiome [13], prebiotic-enriched formulas, giving their human-milk-mimicking modulation of gut microbiome may be considered as a safe alternative to standard IFs for some, selected, non-breastfed infants, as those with hard stools (Table 3).

Table 3. Summary of beneficial effect of MIFs enriched with Prebiotics.

MIFs Enriched with Prebiotics—Key Points
• Prebiotics stimulate the establishment and maintenance of a healthy gut environment
• Commensal microbes are essential for maturation of the immune system
• Prebiotics act through selective fermentation in the GI tract, which stimulates the growth of bifidobacteria and *Lactobacilli*
• Different types of prebiotics substrates act differently on the growth of intestinal bacteria
• Prebiotics enriched IFs are associated with lower intestinal pH, with a SCFAs pattern more similar to breastfed infants
• Prebiotics enriched IFs are not associated with increased frequency of stool
• Prebiotic supplemented formulas may be considered in infants with hard stool

2.3. HM Oligosaccharides (HMOs) Supplemented IFs

The benefits of HM might be due to bioactive components considered to play a key role in neonatal microbiome implementation and in turn, immune defense and intestinal maturation. HMOs are non-digestible carbohydrates present in high concentrations in HM, existing in a tremendous structural diversity [9,77–79]. Over 200 free oligosaccharide structures have been identified from HM [9,77–79], which is very much higher than in any mammalian milk [9]. However, only 50 structures are assumed to represent 99% of HMO abundance in HM. The wide variability found in the concentration of HMOs between different women, and even in the same woman, during lactation, is due to polymorphism in the Lewis and Secretor genes [10]. These factors determine both the quantity and pattern of HMOs in milk. Other factors such as maternal age, parity, body weight, body mass index, urban or rural residency, season and lactation may influence the HMOs content of HM [77,80–82]. Therefore, HMOs content of HM varies over the course of lactation: 20–25 g/L in colostrum and 10–15 g/L in mature milk. According to the energy content HM (64 kcal/100 mL), HMOs represent 1.5–2.3 g/100 kcal [83]. As a matter of fact, a term infant with a daily consumption of approximately 800 mL of HM would intake approximately 10 g/d of HMOs.

HMOs from HM fall into 3 main categories according to their structure: (i) fucosylated neutral (35–50%); (ii) sialylated acidic (12–14%), and (iii) non-fucosylated neutral (42–55%) [9,78,79]. Today, industry is able to produce oligosaccharides structurally identical to those in HM [82,84]. Some IFs have been enriched with two different HMOs: 20-fucosyllactose (20FL) and lacto-N-neotetraose (LNnT).

Recent and updated reviews have summarized the beneficial effects of HMOs. They are thought to have various mechanisms of action based on the specific structures of these HMOs. As prebiotics, they play a key role in promoting microbiome composition and diversity. They prevent pathogen adhesion and could act as antiviral components and prevention of NEC. HMOs contribute to the maturation of intestinal mucosa and GAIS development. They modulate cell receptor signaling, intestinal barrier functions and production of SCFAs.

2.3.1. Rational for the Use of HMOs in Infant Formula

HMOs are resistant to the gastric acidity and to GI enzymes and reach the colon without being hydrolyzed; just 1% of HMOs is absorbed and join to the systemic circulation. HMOs are "prebiotics" that selectively induce the growth of beneficial (probiotic) organisms such as *Bifidobacterium*, a dominant species in the intestine of breastfed infants [10,85]. *Bifidobacterium longum* subsp. *Bifidobacterium infantis* colonizes efficiently on medium supplemented with HMOs, including 2′-FL, as the sole source of carbohydrate [86–88]. *B. infantis* produces short-chain fatty acids (SCFAs), which favor the growth of commensal bacteria instead of pathogenic bacteria [89]. At 3 months of age, infants fed with an IF supplemented with 2′-FL and LNnT are more colonized with beneficial *bifidobacteria* while they experience a decrease colonization with pathogenic bacteria [90]. A study demonstrated that among the 24 probiotic strains, only *Bifidobacterium. longum* subsp., *B. infantis* ATCC 15697 and *B. infantis* M-63 were able to ferment 3′-sialyllactose, 6′-sialyllactose, 2′-FL, and 3′-FL [91]. All these data demonstrate the selective presence of HMO. On the intestinal mucosa, HMOs mimic the glycans, preventing gut epithelial adhesion leading to competition with pathogens (virus bacteria, toxins and/or eukaryotes) and also constituting a biofilm to inhibit the passage of pathogens [92–94]. Moreover, they have the ability of being fermented by commensal bacteria (i.e., *Bifidobacteria*) which promote their growth, inhibiting also the colonization by pathogens [95]. A prospective study in infants, demonstrated the beneficial effect of 2′-FL in decreasing in the number of episodes of *C. jejuni*-associated diarrhea [96].

HMOs promote gut maturation increasing growth of *Bifidobacterium*, also inducing the production of SCFAs after the fermentation of *Bifidobacterium* and *Lactobacillus*. SCFAs such as butyrate and propionate can stimulate mucin release, increase mucosal blood flow and modulate intestinal epithelial cell and Goblet cells [97].

HMOs can also directly alter epithelial cell gene expression and the binding ability of certain pathogens to the cell surfaces via changing the expression of cell surface glycocalyx [98–100].

2.3.2. HMOs and Immune Modulation

In neonatal period immune system is immature and the balance between TH1/TH2 is not well established, Th2 response is predominant [10,101]. HMOs affect the expression of several cytokines including IL-8, IL-1β, colony-stimulating factor 2 (CSF2), platelet factor 4 (PF4) and IL-17C. They also influence the expression of certain chemokines and cell surface receptors including intercellular adhesion molecule-1 (ICAM-1), intercellular adhesion molecule-2 (ICAM-2), interferon γ receptor 1 (IFNGR1), and IL-10 receptor a (IL10RA) [102]. They modulate the intrinsic expression of cell trafficking-related inflammatory markers, the lymphoid tissue-related signaling pathways and the cytokine and chemokine networks responsible for Th1/Th2 balance [6,93,103]. HMOs may either act locally on cells of the mucosa-associated lymphoid tissues or on a systemic level since 1% of the HMOs are absorbed and reach the systemic circulation [104,105].

Dentritic cells (DCs) are important in the regulation of T cell differentiation and of development of innate and adaptive immune responses during infections and inflammatory diseases. Proper activation of innate immune cells is essential for immune education in early life. Therefore activation of DCs by HMOS is very important for immune development in neonates [102,103]. HMOs are considered to target expression of receptors involved in pathogen recognition, such as toll-like receptors (TLRs), to interact with dendritic cells (DCs) in close proximity to the intestinal epithelial barrier; one sub-population, tolerogenic DC (tDC), which are are functional regulatory T cell (Treg) inducers. tDCs are important for the production of regulatory cytokine (i.e., TGF-β IL-10, IL-27) and reduction of inflammatory cytokine production (i.e., IL-4, IL-12, IL-6, and TNF-α) [103,106].

It was demonstrated that number of interferon-γ-producing CD3+CD4+ and CD3+CD8+ lymphocytes as well as interleukin-13 (IL-13)-producing CD3+CD8+ lymphocytes increases when cord blood T-cells are exposed to acidic HMOs [107]. It was shown also that acidic HMOs also reduce IL-4 production in a subset of lymphocytes and induce IFN-g and IL-10

in human cord blood; indicating that HMOs may downregulate Th2 response in neonatal period and could establish T1/Th2 balance [108].

Goehring et al. demonstrated that the plasma concentration of inflammatory cytokines in the breastfed infants and infants fed with experimental formula supplemented with 2′-FL was markedly lower than that in the infants fed with control formula supplemented with galacto-oligosaccharides [109]. This study indicates that infants fed with a formula supplemented with 2′-FL have lower plasma inflammatory cytokine profile for TNFα, IL1-β, IL1- α and IL 6, which resembles those of a breastfed infant group [109].

2.3.3. HMOs Supplemented IFs, Growth and Gastrointestinal Disorders

Nowadays, some clinical studies involving HMO supplemented IFs are available. As mostly focused on infant growth and tolerance, they showed normal growth and the absence of deleterious effects [90,110]. Marriage et al. studied growth and tolerance of HMO supplemented formula [111]. Formula-fed infants were randomized to 1 of 3 formula with a caloric density of 64.3 kcal/dL. Each formula contained galactooligosaccharides (2.2 g/L or 1.4 g/L), and the 2 experimental formulas contained varying levels (0.2 or 1.0 g/L) of 2′-fucosyllactose (2′FL). The 3 formula groups were compared with a breastfed reference group. There were no significant differences among any groups for weight, length, or head circumference growth during the 4-month study period.

A RCT using HMOs supplemented IFs with 20-FL found immune outcomes similar to that of infants fed HM, while the group receiving an IF supplemented with only GOS showed a different result [109].

A multicenter RCT involved 14 days of age healthy infants fed to 6 months of age: with an IF supplemented with 1.0 g/L 2′fucosyllactose (2′FL) and 0.5 g/L lacto-N-neotetraose (LNnT) as compared to a control IF [90]. It reported the absence of difference in body weight gain, length, head circumference, and BMI as well as in the incidence of GI symptoms, including flatulence, spitting up, and vomiting.

Parschat et al. in a randomized controlled study gave to infants aged $\leq$ 14 days a mixture of five HMOs (5HMO-Mix) (5.75 g/L total, comprising 52% 2′-fucosyllactose, 13% 3-fucosyllactose, 26% lacto-N-tetraose, 4% 30 -sialyllactose, and 5% 60 -sialyllactose) or an IF without HMOs for 4 months, with the others exclusively breastfed [112]. There were no differences in weight, length, or head circumference gain between the two formula groups. The 5HMO-Mix was well tolerated, with 5HMO-Mix and breastfed infants producing softer stools at a higher stool frequency than the control IF group. A study compared the intestinal microbiome of infants fed HMOs supplemented IF [20FL (1 g/L) and LNnT (0.5 g/L)] and those fed without milk. The HMOs group had intestinal microbiome more similar to those breastfed at 3 months of age, with *Bifidobacterium* being more abundant, while *Escherichia coli* and *Peptostreptococcaceae* were less abundant. Fecal concentrations of SCFAs in infants fed the HMOs supplemented formula, were more similar to those in breastfed infants [87,89].

2.3.4. Conclusion on HMOs Supplemented IFs

According to these clinical data, IF enriched with 2 HMOs, 2o FL and LNnT, are considered as safe by the European Union as well as by the US and approved for use as food [113]. They are already available in several countries. However, the number of RCTs that evaluated the effect of these HMOs supplemented IFs on infant health are scarce, generating relatively limited evidence of the potential preventive effects of supplemented IFs with one or both of these HMOs. Therefore, more controlled clinical trials are needed for promoting routine supplementation of IFs. (Table 4)

Table 4. Summary of beneficial effect of MIFs enriched with HMOs.

MIFs Enriched with HMOs—Key Points
• HMOs are non-digestible carbohydrates present in high concentrations in human milk
• HMOs play a key role in promoting intestinal microbiome composition and diversity
• HMOs prevent pathogen adhesion and could act as antiviral components
• HMOs-enriched IFs result from the addition of industrially produced HMOs of two types 2o FL and LNnT
• HMOs-enriched IFs are associated with normal infants' growth
• Incidence of GI symptoms, including flatulence, spitting up, and vomiting did not differ between HMOs-supplemented and unsupplemented IFs
• IF enriched with 2 HMOs, 2o FL and LNnT, are considered as safe and approved for use as food
• There is limited evidence regarding the potential preventive effects of supplemented IFs with one or both the above-mentioned HMOs

2.4. Synbiotics Supplemented IFs

As knowledge about microbiota evolves, new therapies arise with the aim of preventing the dysfunction or restoring homeostasis. Synbiotics supplementation is an evolving and advancing field which was initially thought as a mix of prebiotics and probiotics [65]. This was actually inconclusive as there were no indications on which should be the interaction between the synbiotic and the microbiota. Indeed, a recent consensus panel by ISAPP gave a newer, more specific definition: "a mixture, comprising live microorganisms and substrate(s) selectively utilized by host microorganisms, that confers a health benefit on the host". In fact, this statement was made more inclusive by creating subcategories: "synergistic", where the substrates do not need to be prebiotics but to be metabolized only by the co-administered microorganism with a synergistic beneficial effect on the host; "complementary", where each of the component must fulfill the requirements for prebiotic or probiotic [114].

2.4.1. Rational for the Use of Synbiotics in Infant Formula

In the past 20 years, synbiotics have been studied to achieve a formula milk that resembles the mothers' one, in order to recreate a gut microbiota that is similar to breastfed infants. Synbiotics should be more beneficial than prebiotics or probiotics alone due to synergistic effects. As a combination, these mixtures might offer an added effect on the microbiota homeostasis. Mechanisms of action include resistance to colonization by pathogens through blockage of adhesion sites, production of inhibitory substances, degradation of toxin receptors, stimulation of immunity, and competition for nutrients [115]. *Lactobacilli* and *Bifidobacteria* are commonly used in these synbiotics because, generally, they can adhere to the intestinal wall and produce nutrients such as butyrate, hinder the adhesion and inhibit the growth of pathogens, as well as stimulating the immune system and enrich the normal flora [116]. Prebiotics enhance *Bifidobacteria* and *Lactobacilli's* survival and proliferation. Moreover, they have been shown to dampen the growth of pathogenic genera such as *Clostridium* [117]. It is now recognized that prebiotics in the synbiotic mixture enhance the survival of probiotic bacteria and stimulate the host's endogenous bacteria [118]. However, the superiority of synbiotics over probiotics or prebiotics has not been well established.

2.4.2. Synbiotics Supplemented IFs and Growth

Consumption of synbiotic-enriched IF has increased in the past decades, although, to date, clinical data regarding their use are limited. Puccio et al. [119] conducted one of the first studies to evaluate the tolerability and safety of combined administration of probiotics and prebiotics in formula milk. In this trial, 138 non-breastfed infants after day 14 of life were enrolled to receive either an experimental formula containing 2×10^7 colony forming unit (CFU) of *Bifidobacterium longum* BL999 and a mixture of prebiotics (90% GOS and 10% FOS) or a standard infant formula until 112 days of age. The investigators demon-

strated equivalent weight gain between the two groups, whereas no significant difference was found in length, head circumference, or incidence of adverse events between the two groups. Infants in the intervention group had a lower incidence of constipation ($p = 0.03$) and significantly higher stool frequency (2.2 ± 0.7 versus 1.8 ± 0.9 occurrences/day, $p = 0.018$) underscoring better tolerability of the formula.

One of the first trials on the long-term safety of synbiotic-containing formulas was conducted in Finland by Kukkonen et al. [120]. It included 925 mothers with children at high risk for allergy were randomized to receive a mixture of *Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* subsp. *shermanii* JS at a dose of 8–9 × 10^9 CFU, or a placebo, twice daily for 4 weeks before delivery. Infants received the same probiotics and 0.8 g of GOS or a placebo, daily, for 6 months after birth. At the end of the 2-year follow-up, no difference was detected in the growth of infants in the two groups, neonatal morbidity, and functional disorders such as infantile colic.

In another trial [121] including 284 infants randomized to receive, from 2 to 16 weeks of age, a control formula or one of the following 3 different study formulas containing the first *Bifidobacterium longum* BL999 (BL999), *Lactobacillus rhamnosus* LPR (LPR), the second BL999, LPR and 4 g/L of 90% GOS/10% short-chain-FOS, and the third BL999, *Lactobacillus paracasei* ST11 (ST11) and 4 g/L GOS/short-chain-FOS. Weight gain was demonstrated in all groups; in contrast, there were no significant differences between study groups in recumbent length, head circumference, digestive tolerance, and frequency of adverse events. Vlieger et al. [122] conducted another RCT randomizing a total of 126 infants into 2 groups: the first received a formula containing *Lactobacillus paracasei* subsp. *paracasei*, *Bifidobacterium animalis* subsp. *lactis* and GOS (0.24 g/100 mL) (synbiotic group); the second received the same prebiotic-containing formula without probiotics (prebiotic only group). The duration of the intervention was 3 months. No significant difference was observed for gain in weight, length, and head circumference between the two groups. In an additional RCT, 146 infants were randomized to receive for 6 months either a formula enriched with GOS and FOS, or another formula with synbiotics (FOS/GOS and *Lactobacillus paracasei* subsp. *paracasei* strain F19 at a dose of 10(9) CFU) [15]. In both groups, growth parameters were similar. In a more recent trial conducted on healthy term infants a 30% fermented infant formula (FIF) (using *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065) with a specific prebiotic mixture (short-chain GOS and long-chain FOS (9:1, 0.8 g/L)) was compared to a standard formula and a group of breastfed infants [73]. Again, the experimental formula was well tolerated, daily weight gain and growth outcomes were equivalent and close to those of breastfed infants. A tendency in increased stool frequency has been also observed.

A recent meta-analysis concluded that the use of synbiotics have not any significant effect on growth parameters [123].

2.4.3. Synbiotics Supplemented IFs and Intestinal Parameters

In a multicenter RCT conducted in South Africa, the effect of a formula supplemented with *Bifidobacterium animalis* subsp. *lactis* strain CNCM I-3446 (10(7) CFU)/g and a mixture of bovine milk-derived oligosaccharides (BMOS) generated from permeated whey (containing GOS and milk oligosaccharides such as 3′- and 6′-sialylactose) on intestinal *Bifidobacteria* levels of infants born to human immunodeficiency virus (HIV)-positive mothers has been studied [124]. A total of 421 infants were randomized into 4 parallel groups: the first two groups were infants born by cesarean section (CS) assigned to the study formula ($n = 92$) or a control formula ($n = 102$); the other two groups consisted of infants born vaginally randomized to the study ($n = 115$) or control ($n = 113$) fomula. The intervention period was 6 months. The tested formula induced a strong bifidogenic effect in both modes of delivery compared with the control formula, succeeding in correcting the low level of *Bifidobacteria* found in infants born by CS. Faecal pH was significantly lower in infants fed with the tested formula compared with control at 10 days and 4 weeks regardless of the type of

delivery, while, at 3 months, this acidification effect persisted only among infants born by CS.

The same bifidogenic effect was also observed in a trial involving an IF supplemented with a mixture of GOS and FOS [50] but also in another trial using synbiotics-enriched infant formula [125]. In particular, the latter is a trial conducted in Germany in healthy infants randomized to receive an extensively hydrolysed formula with the prebiotic short-chain-FOS/long-chain-FOS (9:1) mixture with *Bifidobacterium breve* M-16V (n = 45) or the same formula without this synbiotic (n = 57) for a 13-week intervention period [125]. A statistically significant higher percentage of fecal *Bifidobacteria* was found at 13 weeks in the synbiotic group compared to the control group (60% vs. 48%, p = 0.014). In addition, a lower level of potential pathogens such as *Clostridium lituseburense/Clostridium histolyticum* was observed in the synbiotic group compared with the control group at both baseline and at the end of the intervention time (p = 0.003 and p = 0.013, respectively).

The doses of probiotics and synbiotics used in the various trials in infants and children range from 10(8) to 10(11) CFU/day [126]; on the other hand, in HM the number of bacteria is quite lower (10(3) to 10(5) CFU/mL, about 10(6)–10(8) CFU/day) [127]. Therefore, it is critical to identify the effects of different doses of synbiotics on the infant's gut microbiota.

In a recent trial conducted by Phavichitr et al. a synbiotic mixture (0.8 g/100 mL short-chain GOS/long-chain FOS (9: 1) and *Bifidobacterium breve* M-16V at 10(4) CFU/mL or 10(6) CFU/mL) similar in doses to that found in HM on 290 healthy infants aged 6 to 19 weeks [128]. After 6 weeks of intervention, a significant increase in the proportions of *Bifidobacteria* and a reduction in the abundance of *Clostridium difficile* have been observed. Even though a lot of studies showed the role of synbiotic in modifying gut microbiota composition, a lack of well-designed studies does not allow final conclusions.

2.4.4. Synbiotics Supplemented IFs in Gastrointestinal Disorders

Stool pattern (frequency and consistency) have been evaluated in infants receiving synbiotic-enriched IF. In the trial by Chouraqui et al. stool frequency was significantly higher in infants who received formula containing BL999, LPR, and GOS/short-chain-FOS compared with the control group (2.1 vs. 1.6 per day, p = 0.03) [121]. Similarly, in another trial, infants in the synbiotic group had a higher frequency of stools during the first 3 months than the prebiotic-only group (1.52 vs. 1.29 times/day, respectively; p = 0.04) and the stools had a greater consistency (2.57 vs. 2.36, respectively, p = 0.05) [122]. No significant differences between groups were observed in crying and sleeping hours, antibiotic use, number of parent-diagnosed infections, number of adverse events and visits to the general practitioner [122]. In the study by Meli et al., infants fed BMOS-containing formula had more frequent (p < 0.0001) and less hard stools (p = 0.0003) also in the study by Meli et al. [129]. A higher stool frequency was reported in the groups supplemented with BMOS and this effect is similar to that described in previous studies on oligosaccharides added to the formula [119] and to that seen in breastfed infants. The partially fermented formulas with prebiotics made stool consistency lower than that of those fed the control formula and more similar to that of breastfed infants [73,130].

Among the beneficial effects of synbiotic-enriched formulas, it has also been hypothesized that these formulas could reduce the incidence of infectious diseases [68,118,131]. Based on the assumption that infectious diseases are a major public health issue, it is likely that synbiotic IFs could be able to mimic the preventive and beneficial effects of maternal breastfeeding on infectious diseases.

In the londitudinal study by Picaud et al. [132] infants fed with a follow-on IF enriched with FOS (28 mg/g of powder) and two probiotic strains (*Bifidobacterium longum* at 10(7) CFU/g of powder and *Streptococcus thermophilus* at 10(6) CFU/g of powder) for three months had less infectious diseases than infants fed standard formula (31. 0% vs. 40.6%; p = 0.005) and, specifically, significantly less GI infectious diseases (3.5% vs. 6.8%; p = 0.03). Similar results were also demonstrated in another Spanish RCT conducted in children 1–6 months of age fed a formula supplemented with *Lactobacillus fermentum* CECT5716

at a concentration dose of 10(7) CFU/g of formula and GOS (0.3 g/100 mL) or a control formula containing only the same concentration of GOS for 5 months [40]. In this study, the incidence rate of GI infections in infants in the synbiotic formula-fed group was 3 times lower than in the control group (p = 0.018). This is the same result obtained in another study in which a reduction of 46% in the incidence of GI infections using the same strain of *Lactobacillus fermentum* was observed [41], and in other RCTs in which other synbiotic formulas were effective in preventing community-acquired GI infections and diarrhea episodes [41,132,133].

In the already cited RCT conducted by Meli et al., there were no statistically significant differences in the frequency of flatulence, fussing, vomiting, crying and spitting up. On the contrary, a higher incidence of colic in the BMOS formula group was observed compared to the control group and the authors hypothesized that it could be due to a higher level of oligosaccharides added to the formula, compared to the levels used previously [119,134]. However, the risk of colic was not significantly different between the control group and the group fed formula with BMOS and probiotics, which suggests the hypothesis that the addition of probiotics may favorably modulate the risk of colic attributable to oligosaccharides.

2.4.5. Conclusion on Synbiotics Supplemented IFs

At present, there are too limited data available in the literature on IFs supplemented with synbiotics to provide specific therapeutic indications. Back in 2011, in the systematic review on the use of synbiotics of the ESPGHAN Committee on Nutrition [11] caution was required in their use given the paucity of data, although no adverse effects were reported and their use was considered as safe.

IFs enriched with synbiotics have shown positive effects on modulation of microbiome composition and metabolic activity, leading to a beneficial impact on gut immune functioning, GI symptoms and creating an intestinal environment that is more similar to that of breastfed infants. In a scientific world increasingly oriented towards the search for personalized target therapies, further investigations should be encouraged to evaluate the possible impact of synbiotic-enriched IF on gut microbiota, growth and infectious diseases. This is a large field for more well-designed long term clinical trials needed to establish which types of prebiotic and probiotic species and strains, single-strain, or multi-strain, the optimal doses, the duration of intake and of course the safety of synbiotics. For these reasons, to date, there are no recommendations on the routine use of formula supplemented with synbiotics in infants. (Table 5)

Table 5. Summary of beneficial effect of MIFs enriched with Synbiotic.

MIFs Enriched with Synbiotics—Key Points
• The substrates do not need to be prebiotics but should be metabolized only by the co-administered microorganism with a synergistic beneficial effect on the host
• Each component must fulfill the requirements for prebiotic or probiotic
• Synbiotics might offer an added effect on the intestinal microbiota homeostasis
• Infants' growth parameters did not differ between synbotics-supplemented and unsupplemented IFs
• Synbiotics enriched IFs seem to be associated with reduced incidence of GI infections
• Frequency of flatulence, fussing, vomiting, crying and spitting up is not reduced in infants fed with synbiotics-enriched IFs
• No specific therapeutic indications may be provided for synbiotics-enriched IFs

2.5. Postbiotics Supplemented IFs

In the last 20 years, different terms referring to inactivated or killed microorganisms as paraprobiotics, non-viable probiotics, heat-killed probiotics, tyndallized probiotics [135] have been used. In 2019 The ISAPP consensus statement [135] defined postbiotics as "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host". The adjective 'inanimate' has been specifically chosen to refer to microorganisms that are no longer viable but still retain their functions.

The currently defined classes of postbiotics [136], including both metabolites and fragments of microorganisms that may exert a beneficial effect in the host include cell-free supernatants (derived from *L. rhamnosus* GG, *L. acidophilus*, *L. casei*, *L. plantarum* and from yeast: *S. cervisiae*, *S. boulardii*), exopolysaccharides (derived from *L. plantarum*. *L. helveticus*, *L. kefiranofaciens*, *β-glucans*), antioxidant enzymes such as glutathione peroxidase, peroxide dismutase, catalase, NADH-oxidase (derived from *L. fermentum*, *L. plantarum*, *L. delbruekii* subsp. *lactis*), cell wall fragments as bacterial lipoteichoic acid (derived from *Lactobacillus* and *Bifidobacteria*), SCFAs: acetic, propionic and butyric acids (from the fermentation of plant polysaccharides in gut microbiota), bacterial lysates (obtained by chemical or mechanical degradation of Gram-positive and Gram-negative bacteria), postbiotics derived from dietary polyphenols (urolithin A, equol and 8-prenylnarigenin). They have a heterogeneous composition and there are several techniques (chemical or mechanical) by which postbiotics can be obtained.

2.5.1. Rational for the Use of Postbiotics in Infant Formula

There are some specific indications about the formulation of postbiotics as reported in ISAPP Consensus Statement [135]: the progenitor microorganism must be characterized at the molecular level to identify the corresponding product and trace of any potentially 'unsafe' genes, must provide a detailed description of the inactivation process and matrix, must confirm successful inactivation, must demonstrate the ability to bring benefit with quality clinical studies, must provide a detailed description of preparation's composition and assessment of safety in the final host and context of use.

2.5.2. Postbiotic, Microbiota and Metabolic Activity

Data collected until now can partially explain the complex effects of postbiotics, but it seems that they can act with pleiotropic properties on gut epithelium and microbiota, immune system, systemic metabolism, and the nervous system [135]. Although the effect may be temporary, molecules such as lactic acid and bacteriocins (still present despite inactivation) may have direct antimicrobial activity. They may also act indirectly by modulating intracellular cross talk (quorum sensing) or by providing valuable substrates for certain strains by supporting their proliferation. Postbiotics can then compete with resident microorganisms for adhesion sites in the presence of fimbriae or lectins [135].

SCFAs in postbiotic preparations have been shown to influence the function of the intestinal barrier by acting on tight junctions and, also, to protect it from the negative action of lipopolysaccharides if present at sufficient levels. Moreover, some proteins (Msp1/p75 and Msp1/p40 or HM0539) enhance epithelial barrier function and exopolysaccharides can reduce the inflammation promoting barrier function [135].

Numerous bacterial interaction structures can stimulate an immune response. Among these, peptidoglycans and derivatives have been shown to interact with NOD2, lipoteichoic acid with Tool Like Receptor 2 (TLR2) and TLR6, lipopolysaccharides from certain Gram- (E. coli Nissle for example) with TLR4, beta-glucans and lipoproteins with TLR2. Other immunomodulatory metabolites such as histamine, SCFAs or branched-chain fatty acids have shown a role in various immune responses, such as suppressing Nf-KB. Metabolites as lactic acid may mediate immune effects through GPR31-dependent dendrite protrusion of intestinal CX3CR1+ cells [135,136].

As with the microbiota, the effects on the metabolism of metabolites or enzymes expressed by postbiotics can be direct or indirect. Succinate, for example, a substrate of intestinal gluconeogenesis, improves glycaemic control in vivo; acetate, on the other hand, has been shown to regulate appetite centrally. SCFAs can improve insulin sensitivity and glucose tolerance, modify lipid metabolism, upregulate the antioxidant glutathione, and affect oxidative stress beneficially in the colon of healthy humans [135].

Microorganisms can produce various neuroactive compounds (serotonin, dopamine, acetylcholine and GABA) that can act on both the enteric and central nervous systems with the potential to modulate behavior and cognitive function and others that bind receptors expressed in the brain (indoles and bile acids). Microbial enzymes can also metabolize dietary precursors for host neurotransmitter synthesis, such as tryptophan (for serotonin) and tyrosine (for dopamine) [135]. In addition, microbial metabolites, such as SCFAs, if present in a sufficient quantity in the postbiotic preparation, could stimulate enterochromaffin cells to produce serotonin, which can subsequently enter the bloodstream. In addition, it appears that serotonin can also be produced by enterochromaffin cells, which in turn are stimulated by SCFAs if present in sufficient quantity in the postbiotic. In clinical studies, SCFAs have also been shown to play a role in eating habits by stimulating the release of anorexigenic hormones, such as peptide 1 and peptide YY, to promote satiety.

Finally, although some B vitamins may also be present in postbiotics and have an important role in central nervous system function, it is still unclear how much of these substances are present in postbiotics [135] (Figure 1).

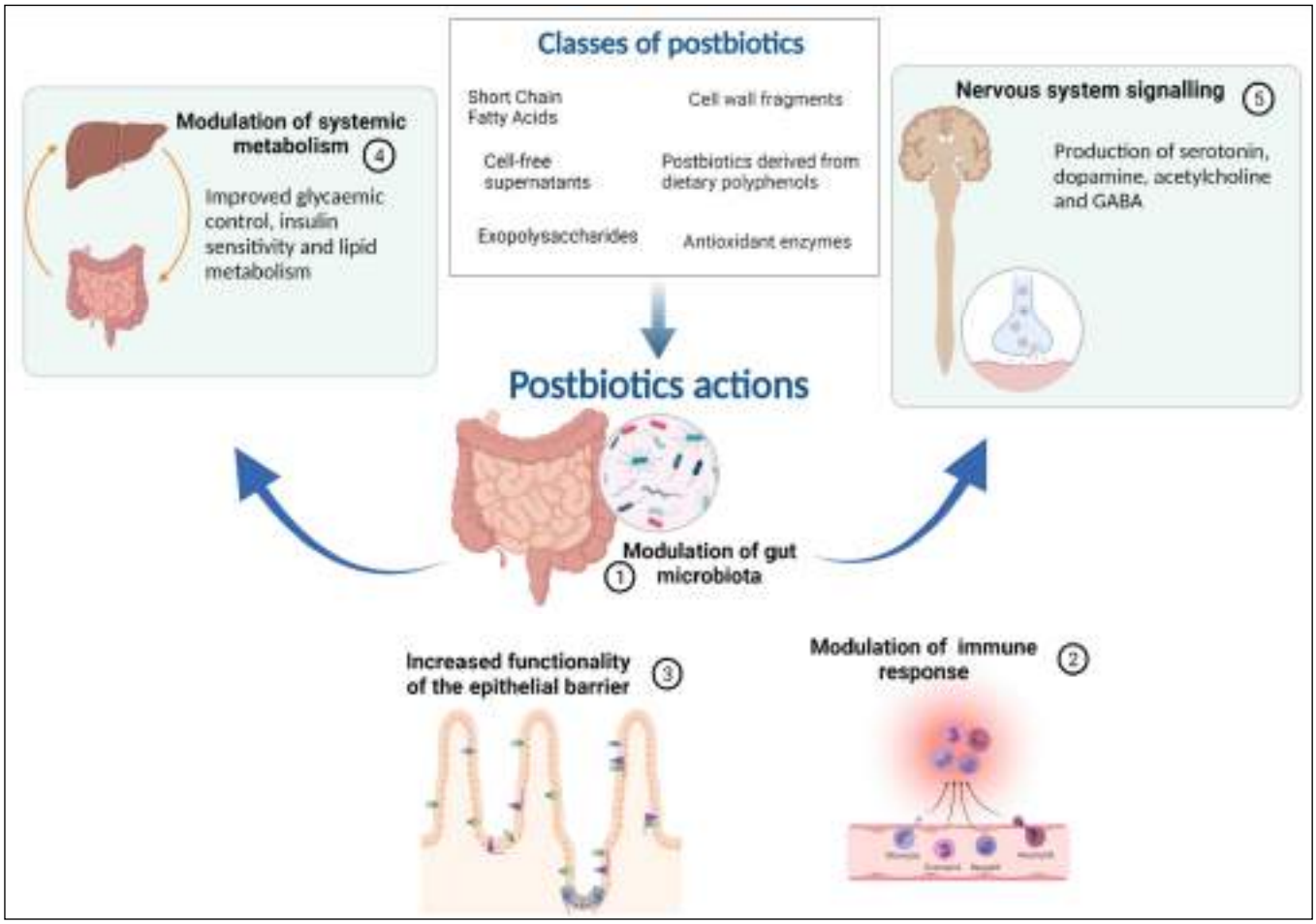

Figure 1. The five mechanisms of action of postbiotics: modulation of the resident microbiota, enhancement of epithelial barrier functions, modulation of local and systemic immune responses, modulation of systemic metabolic responses, and systemic signalling via the nervous system.

2.5.3. Postbiotics Supplemented IFs in Gastrointestinal Disorders

Most of the RCTs on postbiotics studied the benefits of FIF compared to breast milk or standard formula and the clinical use in GI and allergic diseases. Among the most investigated are the postbiotics derived from *Bifidobacterium breve* C50, *Streptococcus thermophilus* 065, *Lactobacillus acidophilus* LB, *Lactobacillus paracasei* CBA L74 or 33.

In healthy infants, a meta-analysis [137] based on studies from Italy and France showed that fermented infant formula (FIF) *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 do not offer clear additional benefits compared to standard IF, although there are GI benefits that cannot be excluded and no adverse effects [138–144].

FIF using *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 combined with prebiotics (scGOS/lcFOS) are safe to use and well-tolerated [72,73,145]. Studies performed in healthy term infants proved that there are effects in colics, reducing overall crying time [72], with no difference on weight gain [130,145] and softer stool consistency than standard formula and closer microbiome composition and metabolic activity towards breastfed infants [73,130].

Also, the thymus index (as a marker of the immune competence level) was similar with breastfed infants and effects were comparable to those of the bacteria composing the intestinal microbiota [138]. After its use, higher bifidobacterial levels and *Bifidobacterium longum*/*Bifidobacterium infantis* ratio compared to standard formula were proved [140]. Using FIF with heat-inactivated *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 in premature infants during the hospital stay for 2–5 weeks showed good clinical tolerance, lower abdominal distension, benefits in inflammatory markers (lower faecal calprotectin), no significant changes in bacterial colonization [146]. In a previous prospective study in healthy neonates, after a 3-month intervention, there was no difference in calprotectin level [147]. Heat-killed *Lactobacillus acidophilus* LB was used in infants or children with acute diarrhea [148–150] with a reduction of the duration of diarrhea in hospital, in non-rotaviral infection by one day [148], but not in outpatient [151]. The same reduction of the severity of episodes with fewer cases of dehydration, fewer medical consultations, fewer ORS prescriptions, fewer switchers to another formula (milder course of the disease) was also proved for heat-inactivated FIF with *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 in healthy term infants [141]. Contrary to these results, a double-blind RCT from Pakistan, including healthy infants with high risk for diarrhea-related mortality, demonstrated that heat-inactivated *Lactobacillus acidophilus* had no difference in diarrhea prevalence compared to placebo [152]. Another randomized study showed that in healthy infants under 5 months of age, the use of heat-inactivated *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 had a good rate of acceptance, the infants presenting less diarrhea [153]. Three RCTs analyzed the adverse effects of postbiotics in infants and children and concluded that there was no significant difference between study and control groups [149,154,155] and many other studies reached the same conclusion [72,138–142,145,156].

2.5.4. Conclusion on Postbiotics Supplemented IFs

The use of postbiotics seems to bring a benefit for healthy term neonates in developing the microbiota or immunomodulation when used in functional foods. There is limited evidence to recommend using postbiotics in acute gastroenteritis. Studies showed that postbiotics are well tolerated and have no adverse effects in infants and children. As postbiotic signatures are dependent on bacterial strains and processes, the safety and suitability of specific postbiotics in infant formula remains to be confirmed. Also, future studies should be realized to establish the recommended dosage and their effects in children (Table 6).

Table 6. Summary of beneficial effect of MIFs enriched with Postbiotic.

MIFs Enriched with Postbiotics—Key Points
• Postbiotics are metabolites and fragments of microorganisms resulting from fermentation with live bacteria
• Postbiotics may exert a beneficial effect in the host by pleiotropic properties
• Postbiotics influence gut epithelium and microbiota, immune system, systemic metabolism, and the nervous system. Synbiotics might offer added beneficial effects on intestinal microbiota homeostasis
• Infants' growth parameters did not differ between postbiotics-supplemented and unsupplemented IFs
• Postbiotics-enriched IFs are associated with softer stool
• Contrasting results on the efficacy of postbiotics in reducing diarrhea episodes: there is limited evidence to recommend using postbiotics for prevention or treatment of acute gastroenteritis

2.6. MIFs and Allergy

Although the present review is aimed to consider main concepts and characteristics of MIFs specifically focusing on gastrointestinal outcomes, IFs enriched with different bioactive ingredients, including probiotics, prebiotics, HMOs, postbiotics and synbiotics, have also been studied in allergic infants. In fact, a healthy intestinal microbiota plays an important immunologic role and an altered patterns of early gut colonization may be associated with increased risk of developing allergic diseases, particularly food sensitization, and especially cow's milk allergy (CMA), and atopic eczema.

HMOs promote gut maturation, increasing growth of Bifidobacterium, inducing, also, the production of SCFAs after the fermentation of Bifidobacterium and Lactobacillus. SCFAs such as butyrate and propionate can stimulate mucin release, increase mucosal blood flow and modulate intestinal epithelial cells and Goblet cells [97]. The maturation of the intestinal barrier function is very important during the neonatal period as the first line of defense, this barrier being also important for the prevention of allergy. Moreover, proper activation of innate immune cells is essential for immune education in early life, and the capability of HMOs to activate dendritic cells (DCs), deeply involved in the regulation of T cell differentiation and in development of innate and adaptive immune responses, is very important for immune development in neonates [103].

Probiotics and prebiotics may modulate immune development throughout several different pathways, thus their role in allergy prevention and treatment have been extensively studied. The World Allergy Organization (WAO), in 2015, has recommended the use of probiotics in pregnant and lactating women and in non-exclusively breastfed infants at high risk of allergic disease [157]; nevertheless, recommendations of both probiotics and prebiotics were based on very low quality evidence. The WAO guideline panel, based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) in 2016, suggested the use of prebiotic supplementation in infants who were not exclusively breastfed. Again, recommendations were based on a very low certainty of evidence [158].

Conversely, the Academy of Allergy and Clinical Immunology [159] and ESPGHAN [16] did not recommend the use of probiotics and/or prebiotics for the prevention of allergic diseases. Beneficial effect of prebiotics in allergy, and specifically in CMA, is still inconclusive. Whey-based extensively hydrolyzed formula (EHF) containing two HMOs was tolerated and could be recommended to CMA patients [160]. In a recent meta-analysis considering studies comparing the use of amino acid-based formulas containing synbiotics in infants with CMA, versus amino acid-based control formulas, both formulas were shown to be effective in managing allergic symptoms [161].

However, considering that the maturation of the infant immune system occurs mainly in the first months of life, that are the ideal time for prevention of the development of allergic diseases [162] it can be assumed that the use of synbiotics IFs might be more effective in inducing tolerance as, individually, both prebiotics and probiotics have immunomodulatory effects. Postbiotics have also been studied with contrasting results, with studies showing a decrease in the positive skin-prick test responses, without any change in proportion of children with CMA [139] and others indicating that liveable, but not heat-inactivated bacteria may be beneficial on infants affected by CMA [163]. The use of bacterial lysates to influence the immune system was analyzed regarding allergic diseases; and published meta-analyses and systematic reviews showed a reduction of the incidence of allergic rhinitis episodes [164] and symptoms of atopic dermatitis [165].

Strong evidence is missing for recommending MIFs in the prevention of allergic diseases; however, bioactive ingredients, by balancing intestinal bacterial environment, favoring immune maturation, stimulating SCFAs production and enhancing intestinal barrier may favorably act in the modulation of those pathogenic mechanisms that have been associated with allergy development.

3. Conclusions

Type of feeding is a key issue in the human gut development, the diversity of microbiome, and the intestinal function at any age in life. Whereas breastfeeding is the reference, the increasing efforts industry is making in the production of IFs that may qualitatively resemble and act as close as possible to HM have led to the supplementation of different bioactive ingredients, including probiotics, prebiotics, synbiotics, postbiotics and HMOs. Concomitantly, scientific data on the benefits of MIF is continuously growing, with much evidence indicating overall positive effects on microbiome composition and metabolic activity. Some benefits are also emerging from RCTs evaluating the clinical impacts these enriched formulas may have on the health of FF infants. Nowadays, none of these IFs has demonstrated conclusive superiority, while clear evidence still lacks. For supporting the challenge of mimicking the benefits of breast milk, more RCTs are still needed. Their aims are to better clarify, if present, which benefits the supplementation of IFs with MIF may practically have on different clinical aspects, including prevention of GI disorders and infections, and their durability over time. So far, whereas no routine recommendations can be done, MIF have generally proven to be well-tolerated and safe in ensuring infants' normal growth.

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Climate Change and Environmental Pollution Induced Risks on Children's Health: Are Pediatricians Prepared to Meet the Challenge?

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Increasing research and scientific evidence have highlighted strong links between climate change, environmental pollution, and adverse health effects in humans. In 2009, the report by *The Lancet* and University College London Institute for Global Health Commission emphasized climate change as the biggest threat to the survival of humanity and warned that its effects on health will affect most populations during the following decades, putting the lives and wellbeing of billions at increased risk.[1] More recently, a policy statement by the American Academy of Pediatrics (AAP) and the AAP technical report on global climate change and children's health stressed that children, particularly those belonging to lower socioeconomic status, are at higher risk of developing diseases for which climate change may be directly or indirectly responsible.[2,3] The potential health effects of climate change and their related negative events, which plagued the world's population during recent years, have been extensively studied.[4] These include disasters because of extreme weather events[5] and heat waves,[6] the increase in zoonosis,[7] respiratory diseases due to air pollutants and aeroallergens,[8,9] water scarcity, and low nutritional quality of food.[10,11] Moreover, a recent review suggested that a link between climate change and mental health conditions cannot be ignored, as mental disorders represent one of the major common noncommunicable diseases.[12,13]

The European societies of pediatrics are highly concerned about the influence of climate change and environmental pollution on child health.[14,15] This commentary, authored by the working group on social pediatrics of the European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA/UNEPSA), briefly discusses the important health impacts of climate change and its relevance to children. Our aim is to further raise the awareness of pediatricians and public health authorities on this key issue for the future of children's health and propose key areas for action.

Effects of Climate Change and Environmental Pollution on Child Health and Well-Being

The profound demographic, socioeconomic, and industrial changes that characterize the current era of globalization have directly and indirectly progressively influenced the environment.[15,16] For thousands of years the Earth's climate has remained rather stable, being characterized by a consistent temperate central tendency and stable atmospheric levels of carbon dioxide.[17,18] However, since the beginning of the last century gas levels, including carbon dioxide, methane, and other greenhouse gases have increased in association with changes in climate and other earth systems. If global emission of different types of gas will progress with the same intensity shown during the past decades, models predict that in the turn of a century the climate will experience significant changes, including a profound weather variability, rise of world's mean temperature to 4.0°C, and a sea elevation of 0.58 ± 0.2 cm.[18] The impact of climate change on infectious diseases is well known, particularly for those that are spread by insect vectors and by contaminated water. In parallel, the intense industrialization of the past decades has brought negative effects, such as worsening air pollution, that remain uncontrolled[19] despite the efforts of several countries.[20] Environmental pollution events have been increasingly related to health conditions, including allergic diseases related to increased allergen production, infectious diseases, diabetes, respiratory, and cardiovascular diseases.[21,22] Research on climate change and health concentrated on studying how chemical substances can interfere with children's health.[23] A particular interest has focused on endocrine disruptors,[24,25] as experimental evidence of their possible damage on various endocrine and nonendocrine systems has accumulated over the years.[25] Several studies have reported innovative methodological approaches to better define the specific risk level, with the aim to clarify the different interpretations provided by toxicologists and endocrinologists.[26] Of particular concern are the reports that most of the chemicals studied are able to cross the placenta[27] and reach the fetus, causing possible damage to many organs and systems, including the central nervous system, and epigenetic alterations that can favor various pathologies later in life and in offspring.[28,29]

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The increasing evidence of the effects of climate change and air pollution on children's health has prompted several scientific societies in Europe and the US to adopt precautionary principles in the presence of raising threats of harm to human health or the environment, even if cause and effect relationships are not fully established scientifically.[30,31] Reports show that up to 90% of the consequences of climate change on health take place during the period between birth and adolescence.[32,33] For instance, 50% excess mortality among infants in the perinatal period was documented during extremely hot periods in Spain,[34] and moderate and severe stunting are projected in children age <5 years at the national level in 2030 in 44 countries under low and high climate change.[35] Therefore, scientific societies have drawn attention to the importance of establishing effective precautionary measures to safeguard health throughout the developmental, and in particular in the perinatal and postnatal periods.[36]

The Importance of Promoting Continuous Environmental Education in Pediatrics

As emphasized by the former president of the International Pediatric Association, pediatricians play an important role in protecting children from the risks of global adverse events.[37,38] They must become engaged in strategies that address climate change, environmental sustainability of health systems, and the promotion of resilience, which help children and their families to face health adversities because of environmental instability.[37,38] Promoting continuous environmental education dedicated to professional figures including pediatricians, healthcare professionals and schoolteachers is central to these strategies. Efforts should be made to develop basic training and continuing educational activities on environmental health, not only by educational institutions, but also by public or private organizations, including professional bodies and pediatric associations. For instance, climate change-related information and learning materials must be part of global child health teaching modules and open-access courses as well as residency training programs.[38] An example is provided by the Pediatric Environmental Health Specialty Units supported by the AAP, which provides pediatric and environmental health education to health care providers and health profession students.[39]

Despite the importance of climate change and environmental pollution for children and adolescent's health, there is currently no effectively coordinated preventive strategy at a global level.[15,40] A serious obstacle in raising awareness about these topics is the uncontrolled information often disseminated by social networks, which make it difficult to distinguish between true and false data. In Europe the profound diversity among the public health services of its 50 countries have also hampered the development of effective common policies and reduced the operational ability of private institutions devoted to environmental health.[15,41] A French survey, based on a questionnaires offered to midwives, gynecologists-obstetricians, general practitioners, and residents in gynecology-obstetrics and general medicine showed that the majority of health professionals did not provide information on endocrine disruptors to pregnant women.[42,43] This is similar to previous studies showing that, with the exception of tobacco smoke, there was little attention in common clinical practice to environmental health by various health professionals including nurses and pediatricians.[44] A review on the impact of climate change on health reports that only two previous studies have focused on how to change behaviors and habits of patients toward climate change.[44,45]

Conclusions

Management of the health effects of climate change and environmental pollution will require a collective coordinated effort involving stakeholders at all levels, including sectors of government and civil society and a close collaboration between many academic disciplines.[45,46] Approximately two-thirds of all preventable ill health due to the environment occurs in children, as they are an especially vulnerable subpopulation due to their developing physiology and anticipated long-term exposure.[47] Therefore, pediatricians well trained in environmental health[48] should have a central role in the collective effort of tackling one of the biggest global health threats of the 21st century, taking preventive action in the face of uncertainty, exploring a wide range of alternatives to possibly harmful actions and increasing public participation in decision-making. Finally, pediatricians must take an active role in recognizing illnesses associated with climate change, and develop early warning systems and improve prevention and mitigation strategies. Particularly in the case of diseases occurring in the immediate term such as diarrhea, asthma, heat stroke, sunburn, allergies, and communicable diseases such as malaria, dengue, encephalitis, Lyme disease, and other emergent infectious diseases.[47,49] ■

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EUROPEAN PAEDIATRIC ASSOCIATION

Viewpoint of the European Pediatric Societies over Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Children Younger Than Age 12 Years Amid Return to School and the Surging Virus Variants

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Since its first appearance in the Wuhan region of China in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide public health and socioeconomic crisis.[1] According to the World Health Organization Coronavirus (COVID-19) dashboard, as of September 2021, there have been more than 217 million confirmed cases and 4.5 million deaths reported.[2] Mass vaccination campaigns against SARS-CoV-2 are ongoing worldwide. Currently, 5.38 billion doses have been administered globally, 39.9% of the world population has received at least 1 dose of a COVID-19 vaccine, and approximately 40 million are administered each day. However, only 1.8% of people in low-income countries have received at least 1 dose,[3] and there will likely be increasing high demand for the limited supplies of vaccine against SARS-CoV-2 in many areas, raising important ethical issues and socioeconomic debates on how vaccine distribution should be prioritized.

Children are returning to class after long pandemic closures. As a new school year begins, local governments in low- and high-income countries are struggling over teacher vaccinations and mask mandates amid the surge of virus variants.[4] With the fast spread of the more contagious delta variant and SARS-CoV-2 vaccines not available for much of the global school-aged population, children's health risks have become a pressing public health issue. A global debate is underway on whether SARS-CoV-2 vaccination should be made available in children younger than age 12 years and be made mandatory for those attending schools.

This commentary, authored by the working group on social pediatrics of the European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA-UNEPSA), presents the viewpoint of EPA-UNEPSA and its partner society European Confederation of Primary Care Paediatricians (ECPCP), on SARS-CoV-2 vaccination in children younger than age 12 years. The aim is to raise awareness of pediatricians, lawmakers, public health officers, and school educators on the importance of extending vaccination after a careful risk assessment is made. We emphasize that proper and safe vaccination procedures should be initiated after satisfactory clinical trials are completed and following formal approval by public authorities.[5]

Increased Cases of COVID-19 in Children following the Emergence of Virus Variants

These changes may affect the virus's properties, including ability of spreading, severity of associated diseases, and resistance to preventive and therapeutic measures.[6] The emergence of SARS-CoV-2 variants rapidly spreading worldwide pose an increased risk to global public health. In Europe, the delta variant initially arose in the United Kingdom in April 2021[6] and later became the dominant strain in the majority of the European countries. Currently, the classification developed by the World Health Organization to identify specific variants of interest and variants of concern helps to prioritize an effective global monitoring and research, to elaborate the development of public health guidance to prevent the spread of COVID-19, and ultimately to inform the ongoing response to the COVID-19 pandemic[6] (**Table**; available at www.jpeds.com).

After the delta variant became the most dominant circulating strain, the number of children contracting COVID-19 has increased.[7] After the infection initially declined among children in early Summer 2021, the US and European

AAP	American Academy of Pediatrics
COVID-19	Coronavirus disease 2019
ECPCP	European Confederation of Primary Care Paediatricians
EPA-UNEPSA	European Paediatric Association/Union of National European Paediatric Societies and Associations
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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countries showed an impressive 5-fold increase of cases in this population. As reported by the American Academy of Pediatrics (AAP), during a 4-week period between July and August 2021, COVID-19 cases in children increased from 38 000 to nearly 204 000 and numerous states reported an increase, although moderate, in child hospitalizations amid the ongoing delta surge.[7] Similarly, a significant increase in COVID-19 cases is reported in Europe. In the United Kingdom, there has been a 5-fold greater rate of COVID-19 test positivity among children 5-12 years of age (0.35% prevalence) and adults ages 18-24 years (0.36% prevalence) than in those 65 years of age or older.[8] Furthermore, of great concern is the increase of pediatric multisystem inflammatory syndrome in children associated with COVID-19, which showed an incidence of about 100 affected children per week.[9] In Italy, the local National Institute of Health reports that after the emergence of the delta variant, the increase of COVID-19 cases involved the population 0-9 years old, whereas the older age groups showed a decline in cases.[10] In Israel, emerging data indicate a sharp rise in SARS-CoV-2 infections during the first months of 2021 in the population 0-9 and 10-19 years, with more than 50 000 children and teens testing positive.[11]

The Importance of Using COVID-19 Vaccine in Children Younger Than 12 Years after Rigorous Risk Assessment and Approval Procedures

The debate over the importance of COVID-19 vaccination in children younger than 12 years rapidly arose after the emergence of aggressive virus variants. In this population, the number of infections sharply grew in parallel with the number of severe cases, which led to the hospitalization of young children.[9] In particular, the delta variant showed to be more contagious to children and from children than the older variants. SARS-CoV-2 may spread in schools, homes, and gatherings where kids typically can get infected most and although the virus has been less aggressive in children than adults, not all children have been immune to some severe health risks associated to the infection, including multisystem inflammatory syndrome in children.[9]

Two main approaches may be considered in vaccine prioritization: directly vaccinate people at greatest risk for severe outcomes and indirectly protect the weakest part of the population by vaccinating those who do the most transmitting.[12] The experience provided by the influenza vaccination programs, which suggest that children are vaccinated due to their critical role in transmission,[13,14] shows that direct protection is superior when reproduction numbers are high, but indirect protection is greater when transmission is low.[15]

The rationale behind vaccinating children younger than 12 years would be not only to help the communities reach herd immunity, minimize viral transmission, and reduce the risk of development of virus variants but also to protect this age group from the SARS-CoV-2 infection and disease. Vaccines undergo rigorous regulatory approval procedures to ensure their safety, efficacy, and quality.[16] Clinical trials are currently underway for the COVID-19 vaccine in children younger than 12 years old and is strictly monitored in the US by the Food and Drug Administration and in Europe by the European Medicines Agency.[17,18] Currently, trials of the COVID-19 mRNA vaccines in younger children are under way.[19] The studies aim to assess safety and immune responses after 2 vaccinations with 3 different dose sizes.[19] A trial of AstraZeneca's COVID-19 vaccine in children aged 6-17 years started in March 2021 in the United Kingdom. However, this trial was paused as a precautionary measure following reports of blood clots in adults who received this vaccine.[19] A study compared rates of 25 adverse events between vaccinated and unvaccinated adult individuals.[20] Few adverse events were associated with the vaccine, including swelling of the lymph nodes, appendicitis, and herpes zoster. Myocarditis was associated with an excess of 2.7 cases per 100 000 vaccinated persons.[20]

Several pediatric organizations urge for an early emergency approval of the vaccine in children younger than age 12 years and a possible administration of the vaccine off-label in this age group, who currently have no available vaccine. However, the EPA-UNEPSA, ECPCP, and their member pediatric societies join AAP in strongly discouraging such practice.

Conclusions

SARS-CoV-2 vaccines proved their effectiveness to prevent severe illness and hospitalization in adults and adolescents. EPA-UNEPSA, ECPCP, and their member European pediatric societies urge national authorities to work intently toward the authorization of safe SARS-CoV-2 vaccine programs. The vaccination in children younger than age 12 years will allow a large number of children to attend school, spend time with friends, travel with their families, and enjoy their communities safely.[21-23] European pediatric societies join AAP recommendations against giving the vaccine to children younger than 12 years before rigorous clinical trials are completed, adverse events carefully assessed, and not until vaccines are authorized and adequate dosage established by the respective national agencies. This ensures that vaccines are safe and effective for this age group. ■

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Table. SARS-CoV-2 VOC and VOI (September 2021)

WHO labels	Pango lineage*	GISAID clade†	Nextstrain clade‡	Additional amino acid changes shown	Earliest documented samples	Date of designation
Currently designated VOC						
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K//+S:452R	United Kingdom, 09/2020	18/12/2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, 05/2020	12/18/2020
Gamma	P.1	GR/501Y.V3	20J (V3)	+S:681H	Brazil, 11/2020	11/01/2021
Delta	B.1.617.2	G/478K.V1	21A	+S:417N	India, 10/2020	VOI: 04/04/2021 VOC: 11/05/2021
Currently designated VOI						
Eta	B.1.525	G/484K.V3	21D	–	Multiple countries, 12/2020	3/17/2021
Iota	B.1.526	GH/253G.V1	21F	–	US, 11/2020	3/24/2021
Kappa	B.1.526	G/452R.V3	21B	–	India, 10/2020	4/4/2021
Lambda	B.1.526	GR/452Q.V1	21G	–	Peru, 12/2020	6/14/2021
Lambda	B.1.526	GH	21H	–	Colombia, 01/2021	8/30/2021

VOC, variants of concern; *VOI*, variants of interest; *WHO*, World Health Organization.
*Pango lineage: The Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN) is a software tool developed by members of the laboratory of Andrew Rambaut, with an associated web application developed by the Centre for Genomic Pathogen Surveillance in South.
†GISAID clade: Global initiative on sharing avian influenza data (GISAID) (https://www.gisaid.org/about-us/mission/).
‡Nextstrain clade: Nextstrain is an open-source project to harness the scientific and public health potential of pathogen genome data (https://nextstrain.org/).

European Pediatric Societies and severe acute respiratory syndrome coronavirus-2 vaccination in children under age 12 years: a different path in England?

To the Editor:

The European Pediatric Societies' viewpoint regarding 'Severe Acute Respiratory Syndrome Coronavirus-2 Vaccination of Children Under 12 Years Old Amid Return to School and the Surge in Virus Variants' presents an interesting contrast with the path taken in England and Wales in June to September 2021.[1-5]

On June 4, 2021, the Pfizer/BioNTech vaccine was approved for use in children aged 12-15 years.[2] By July 19, when all social controls related to coronavirus disease 2019 (COVID-19) precautions were relaxed in England, including within schools, guidance was issued against vaccination in healthy 12- to 15-year-olds.[3] Because of a greater risk of severe COVID-19, children under 18 years were vaccinated if they had underlying health conditions or were living with an at-risk family member.[3] By August 4, there was a recommendation for a first dose of vaccine for all 16- to 17-year-olds, whether or not they had underlying health conditions.[3] However, although there were concerns about the rare side effect of vaccine myocarditis, by September 13, a first dose of the vaccine was offered to all children aged 12-15 years.[4] As of September 19, weekly case rates have increased to 495 per 100 000 in 5- to 9-year-olds, and to 1021 per 100 000 in 10- to 14-year-olds.[5] In the 15- to 19-year-old age group in the same week, cases have decreased to 495 per 100 000; there was rapid vaccine uptake in 16- and 17-year-olds, with 65% having received a first dose.

The vaccine is yet to be approved in 5- to 11-year-olds, and we wonder about the implications on the state of child health in England and Wales in the coming months. With more than 80% of adults vaccinated against severe acute respiratory syndrome coronavirus-2, what is the European Pediatric Societies' view about the presence of low rates of severe COVID-19 disease amongst healthy children, and whether there are convincing health benefits of COVID-19 vaccination for children themselves?

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Reply

To the Editor:

We thank Dr Brown for her interest in our commentary regarding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in children under the age of 12 years and for sharing the epidemiological data relating to the coronavirus disease 2019 (COVID-19) pandemic in England and Wales. Dr Brown reported a contrast with the path taken by England and Wales in recent months compared with other European areas.

The European Centre for Disease Prevention and Control, an agency of the European Union, has reported increased transmissibility across all age groups for SARS-CoV-2 variants of concern, most notably for the Delta variant.[1] The European Centre for Disease Prevention and Control also reports that in areas where an increasing percentage of adults are fully vaccinated against COVID-19 but where children are not vaccinated, increasingly greater proportions of SARS-CoV-2 cases are expected among children in the coming months. The COVID-19 pandemic has aggressively affected the European continent, although affecting populations differently, and the ways SARS-CoV-2 spreads are still partly unclear. Comparing the spread of coronavirus in different countries may be difficult using the epidemiological data released by governments. However, alarming data observed in young populations have recently been reported by several countries. For instance, children aged 19 years or less accounted for more than 50% of all cases of COVID-19 in Israel during September 2021 (54%), compared with 26% in June 2020 In children aged 9 years or younger, COVID-19 cases were 31.4% of all COVID-19 cases recorded in Israel during the same period, compared with only 7.9% of cases observed in June 2020.

Children of all ages are susceptible to and can transmit SARS-CoV-2.[2] Children seem to be particularly susceptible to the newer variants, and predisposed to develop severe and even fatal cases, including the multisystem inflammatory syndrome.[3] Furthermore, the extent and severity of long-term effects, including the long-COVID syndrome, is unknown.[4] Children

tend to transmit the virus more efficiently than observed with the former variants and convincing data show that SARS-CoV-2 transmission in the community is correlated with the prevalence of infection rates in schools.[5] Decreasing SARS-CoV-2 transmission in schools with the aim of protecting both young and adult populations, can be achieved by effective prevention strategies, based on promoting COVID-19 vaccination for those eligible.[5]

In conclusion, one of the lessons learned from the Delta variant epidemic wave is that it is going to be difficult to control SARS-CoV-2 outbreaks without vaccination of children.[6] Ongoing international research and collaboration is essential and at present, the European Pediatric Association/Union of National European Pediatric Societies and Associations joins the American Academy of Pediatrics in recommendations against giving the vaccine to children under age 12 years before rigorous clinical trials are completed, adverse events carefully assessed, vaccines are authorized, and adequate dosage established by the respective national agencies.

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Global Emergencies in Child Health: Challenges and Solutions—Viewpoint and Recommendations from the European Paediatric Association and the International Pediatric Association

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Global emergencies, including natural disasters, epidemics, drought, armed conflicts, and the SARS-CoV-2 pandemic, have affected populations on five continents, causing devastating socioeconomic effects.[1] Children are a most vulnerable and defenseless group.[2] In tense situations, they feel overwhelmed and insecure and are often left to their own devices. Their rights to protection and integrity are threatened.[3]

The European Paediatric Association, Union of the National European Paediatrics Societies and Associations and the International Pediatric Association, representing the national pediatric societies from 149 countries, held a joint conference on October 9, 2021, in Zagreb, Croatia, to discuss the issue of global emergencies in pediatrics and their significant economic and social impact.[4,5] Delegates discussed the challenges posed by a wide variety of emergencies in the context of increasing global complexities, while also exploring possible solutions.

This commentary, prepared by the European Paediatric Association, Union of the National European Paediatrics societies and Associations–International Pediatric Association working group, includes the viewpoint and recommendations from the conference (**Table**; available at www.jpeds.com). The group strongly recommends that countries develop, reorganize, and strengthen their health systems to address the social and environmental issues caused by global emergencies to enable more efficient and effective allocation and use of available resources for disaster preparedness and emergency response resources in communities. The statement emphasizes the importance of active involvement of all stakeholders, including governments and healthcare professionals. Their joint effort should focus on developing strategic partnerships with key international constituencies, such as the diplomatic, nongovernmental, legal, and academic communities, and the media with the aim of providing adequate support to infants, children, and adolescents affected by adversities.[6] Pediatricians and their professional societies across the world must collaborate and share their experiences with new and emerging challenges in child health and together mitigate against inequalities within and between countries and between continents and together strongly and courageously advocate for the health and well-being of children.[7,8] ■

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Table. Global emergencies in child health: challenges and solutions. Viewpoint and recommendations from the 2021 joint conference of EPA/UNEPSA-ECPCP-IPA

Diversities, variations, and heterogeneities characterize healthcare services throughout the 5 continents. Cultural and economic complexity and a large disparity in availability, affordability, and accessibility of pediatric care has been shown by pediatric services and community care across the world. The adoption of international aims and objectives relating to services for children including standards of care, education, training, quality improvement projects, research programs, robust outcome measures and socioeconomic goals, are required in order to ensure the effective management of healthcare and the well-being of infants, children, adolescents and their families.

Child health and well-being challenged by emergencies

New emergencies, including the effects of a devastating global economic crisis, random cyberattacks and the SARS-CoV-2 pandemic, were added to the long list of issues that chronically afflict children and impact their health and well-being.

The consequences of such socioeconomic turbulence raise serious concerns regarding the sustainability of healthcare systems and their ability to provide effective childcare to ensure that essential and optimum medical attention and health care services are provided from infancy, through childhood and adolescence.

Turning crisis into opportunities

In a world of increasing economic interconnections the challenges are greater, but so too are the opportunities. Crisis may become an opportunity if interventions for recovery are well-planned and managed. It is of fundamental importance to carefully explore a number of possible solutions to counteract the negative effects of global emergencies and assist countries and their administrators in their efforts to develop cost-effective solutions, while ensuring that the goal of balancing budgets does not decrease the basic quality standards for public health.

Cultural heritage as a strength for cooperation

Cultural heritage is a fundamental category of tangible and intangible values characterizing all aspects of a community, which are continuously remodeled by the political, economic and social concerns. The concept of diversity, as a direct expression of cultural heritage, has become progressively perceived as a resource, helping societies to identify the best solutions to confront and respond to challenges encountered by the different communities throughout the world. The importance of dialogue within diversity and between diverse cultures has emerged as a strong element of cohesion between cultures, in addition to the contribution that diversity can provide for solutions of common problems.

Establishing effective cooperation platforms among countries

The presidents of the national pediatric societies, were convened by the EPA/UNEPSA, in collaboration with the IPA and the European Confederation of Primary Care Pediatricians (ECPCP) in Zagreb on October 9, 2021. One conclusion—effective cooperation between countries throughout—is based on the acknowledgement that diversity is a factor of strength and not of weakness. This key factor may create the basis of an effective cooperation in all fields of public interest. Contribution to the efforts of creating an effective platform for cooperation and a multidisciplinary approach to common issues in public health may reduce fragmentation of pediatrics and tackle the legal, economic, and organizational challenges of child healthcare throughout the world.

Natural, economic disasters and public health emergencies

Natural and economic adversities and public health crises have often revealed a low degree of self-sufficiency and a high degree of unpreparedness by nations. Natural, economic disasters and public health emergencies are interconnected phenomena.

Disasters and distressing natural events need to be met with rescue and recovery interventions, including adequate health approaches. 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.

Tackling emerging and re-emerging infections of major importance in child health

A complex interplay of environmental and human factors, including ecological, genetic, political and socioeconomic factors, interact to result in the emergence of infectious diseases with unique impacts on children as the most vulnerable members of our society These emerging infections can have unique impacts on younger populations in terms of both physical and mental health, as well as social well-being. In order to best protect them from the impact of emerging and re-emerging infectious diseases, it is imperative to understanding how factors that determine disease emergence and emerging diseases themselves can affect the young.

Mitigating harm to children directly and indirectly involved in armed conflicts and gun violence

All children should be guaranteed the right to live, learn and grow up safely—free from violence and fear. Each year, thousands of children are either killed or severely injured in armed conflicts around the world or involved in episodes of domestic and community violence characterized by the use of guns. Although concerns are raised worldwide about the use of explosives, the protection of children often lacks practical solutions. Focus on challenges and practical steps on how to strengthen the protection of children in such conflicts should be further implemented at national and international level.

Meeting minor refugees' basic needs

Around the world, millions of families and their children are fleeing their homes owing to adverse events. Protracted conflicts, persistent violence, extreme poverty, and disadvantage press for action to protect children from conflict and to address the root causes of violence and poverty that displace children from their homes. Unaccompanied minors traveling across the world seeking protection is a related increasing phenomenon, which poses a significant challenge to the authorities and the social and healthcare systems worldwide. Both short- and long-term solutions are essential in order for children to escape conflict, persecution and poverty. These must include increasing access to education, strengthening health and child protection systems and social safety nets, expanding opportunities for family income and youth employment, and facilitating peaceful conflict resolution and tolerance.

A multitude of children currently face danger, detention, deprivation, and discrimination. The global pediatric community must stand up for them, work collectively in order to identify issues of concern and strongly advocate with local and international stakeholders.

The importance of developing reliable and effective coordinated strategies

A nation's ability to prepare for, respond to, and recover from disaster/emergencies, especially in regard to children, should not depend on a single level or agency of government, and cannot be tackled with fragmented approaches, but by integrated strategic plans.

RECOMMENDATIONS

An effective system for disaster management should depend on well-planned, coordinated, interactive strategies and reliable methodologies, based on a shared responsibility, centered on each team member doing what it does best and leveraging the expertise and strengths of others. Most importantly, it must be relevant and applicable to the needs of the country and community.

The many threats posed to global health have 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 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.

Effective strategies established to tackle emergencies should include an integrated 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. Sharing knowledge, expertise and recourses will be key to success.

Caring for children after an emergency event should be a priority, as the amount of trauma/damage caused by a disaster can be overwhelming and affect children physically and mentally. Separation from school, family, and lack of peer support from friends can create additional stress and anxiety for children.

(*Continued*)

Table. Continued

Final statement

Investment in services for the health and well-being of children and adolescents will improve the physical, mental and emotional development of children and the subsequent health and well-being of adults. These services must have the ability to respond effectively to emergencies and to any form of challenge to preserving the health and well-being of all children.

It is now more important than ever that pediatricians and their professional societies across the world collaborate and share their experiences as new and emerging challenges in child health continue. Together they can mitigate against inequalities within child health, between countries, between continents and together strongly and courageously advocate for the health and well-being of children.

Zagreb, Croatia, October 9, 2021

Internaional Pediatric Associaion (IPA)

European Paediatric Association-Union of National European Paediatric Societies and Associations (EPA-UNEPSA)

European Confederation of Primary Care Pediatricians (ECPCP)

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EPA/UNEPSA, European Paediatric Association, Union of the National European Paediatrics societies and Associations; *IPA*, International Pediatric Association; European Confederation of Primary Care Pediatricians (ECPCP).

nutrients

MDPI

Review

Development of the Gastrointestinal Tract in Newborns as a Challenge for an Appropriate Nutrition: A Narrative Review

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Abstract: The second and third trimesters of pregnancy are crucial for the anatomical and functional development of the gastrointestinal (GI) tract. If premature birth occurs, the immaturity of the digestive and absorptive processes and of GI motility represent a critical challenge to meet adequate nutritional needs, leading to poor extrauterine growth and to other critical complications. Knowledge of the main developmental stages of the processes involved in the digestion and absorption of proteins, carbohydrates, and lipids, as well as of the maturational phases underlying the development of GI motility, may aid clinicians to optimize the nutritional management of preterm infants. The immaturity of these GI systems and functions may negatively influence the patterns of gut colonization, predisposing to an abnormal microbiome. This, in turn, further contributes to alter the functional, immune, and neural development of the GI tract and, especially in preterm infants, has been associated with an increased risk of severe GI complications, such as necrotizing enterocolitis. Deeper understanding of the physiological colonization patterns in term and preterm infants may support the promotion of these patterns and the avoidance of microbial perturbations associated with the development of several diseases throughout life. This review aims to provide a global overview on the maturational features of the main GI functions and on their implications following preterm birth. We will particularly focus on the developmental differences in intestinal digestion and absorption functionality, motility, gut–brain axis interaction, and microbiomes.

Keywords: gastrointestinal development; preterm infants; digestion; intestinal motility; enteric nervous system; microbiota; gut–brain axis; microbiota

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1. Introduction

The maturation of the gastrointestinal (GI) system in full-term and preterm human infants is an area of great interest from both a nutritional and medical practice standpoint. Particularly in preterm infants less than 28 gestational weeks (GW), delivery constitutes a nutritional emergency in which the infant has high and difficult-to-meet nutritional needs [1]. A contributing factor to the nutritional emergency is the relatively underdeveloped GI system of premature neonates, which limits their ability to utilize enteral nutrition. The GI system of preterm infants exhibits reduced digestive and absorption capacities,

prolonged gastric emptying times, and limited intestinal motility compared to term infants. [2,3]. These same limiting factors that lead to a nutritional crisis alter the preterm infant's response to orally administered therapeutic agents [4].

The disorders of GI ontogenesis, along with other factors such as early postnatal stress, microbiota alterations induced by infections, or early antimicrobial use in the Neonatal Intensive Care Unit (NICU), result in an impaired activation of intestinal peristalsis and of the gut–brain axis [5]. Disturbances of physiological inflammatory responses further contribute to this impairment. Abnormal development of bowel function is the main determinant of food intolerance, a major problem in the NICU.

Newborns need the structural and functional maturation of the GI tract for digestion and absorption of the nutrients from colostrum and breast milk. They also need a complete development of intestinal motor function which includes suck–swallow coordination, continence of the gastroesophageal sphincter tone, adequate gastric emptying, and intestinal peristalsis. Full-term babies can acquire adequate amounts of nutrients to promote the rapid growth that occurs shortly after birth. However, half of preterm infants are delayed in reaching full enteral feeding volumes and have gastroesophageal reflux, gastric residuals, and constipation due to delayed gastric emptying, prolonged bowel transit, abdominal distension, and delayed passage of meconium, all of which are GI functions describing immaturity [6]. There are few studies available on fetal ontogenesis and early neonatal adaptation of motility and barrier functions of the human intestinal mucosa [7–9]. The functional components of the human GI tract do not develop simultaneously: in fact, although the anatomical differentiation of the human intestine usually occurs within 20 GW, functional maturation is postponed over time and requires organized peristalsis and coordinated sucking and swallowing, which are not defined until 29–30 and 32–34 GW, respectively [10].

In this review we will provide a global view of the basic intestinal function present in the GI tract at birth in term and preterm infants. We will pay particular attention to developmental differences in intestinal digestion and absorption functionality, motility, gut–brain axis interaction, and microbiomes.

2. Development of Digestion and Absorption in the Neonate

The human GI tract is an organ with one of the largest surface areas of the body. The size of the intestine exhibits an estimated one-thousand-fold increase from 5 through 40 GW [11]. Autopsy data have shown the following intestinal prenatal lengths: 125 cm by 20 GW, 200 cm by 30 GW, and 275 cm at term. This growth continues, ultimately reaching a length of approximately 575 cm by 20 years of life [12]. When including villus and microvillus structures, the surface area in the adult is estimated to be 200 m^2. This surface is in contact with food, microbes, and other potentially antigenic components, and plays a key role in the digestive and absorptive processes [13]. The large intestine is approximately 60 cm in a full-term infant, which increases up to 150 cm by adulthood [11].

The GI tract is comprised of several structures that extend though the oropharynx, esophagus, stomach, duodenum, jejunum, ileum, cecum, and colon. Each one of these performs discrete functions critical to health. Thought to be primarily an organ of digestion, absorption, and excretion of waste, it contributes to overall health in a much broader sense [14]. In addition to digestion and absorption, the intestinal tract exerts neural, endocrine, exocrine, and immunologic functions [15,16]. The main developmental features of protein, carbohydrate, and lipid digestion are detailed in the following paragraphs and summarized in Figure 1.

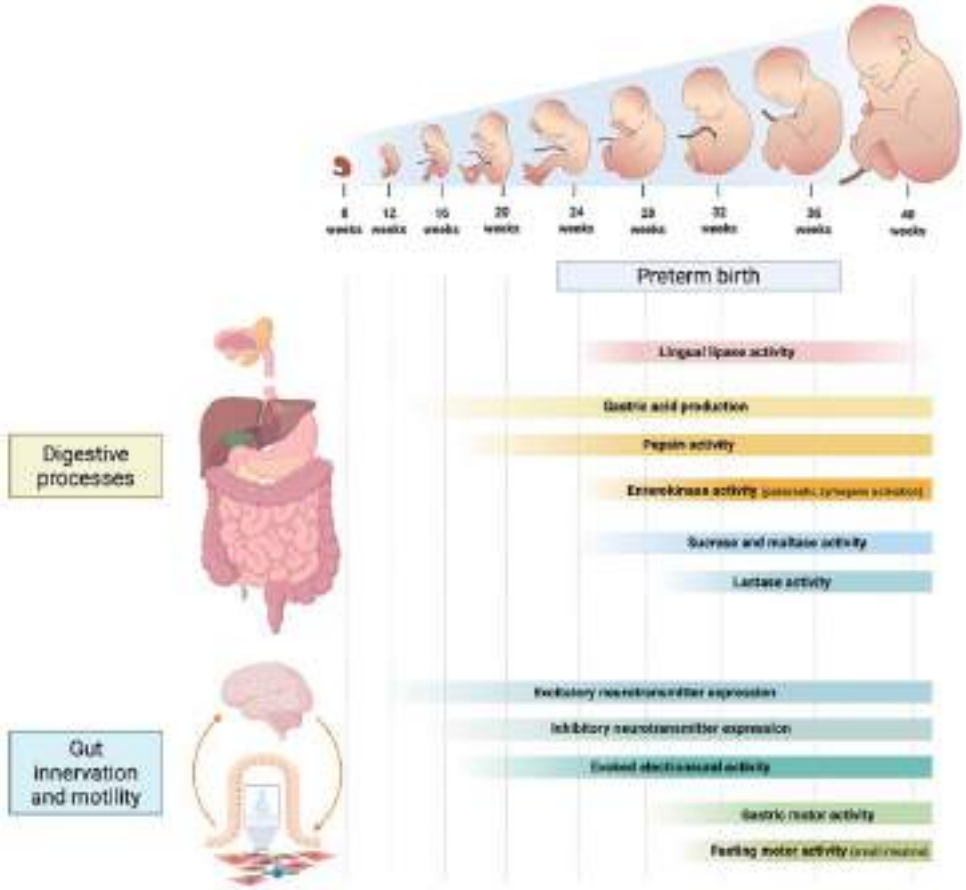

Figure 1. Developmental phases of the main digestive processes, gastrointestinal innervation and motility patterns throughout different gestational weeks.

2.1. Proteins

Protein sources for term and preterm infants are comprised of two major components, whey and casein. Digestion of these proteins is initiated in the stomach, where parietal cells secrete hydrochloric acid which, in combination with activation of the proenzyme pepsinogen, denatures some of these proteins. Parietal cells are present by the late first trimester of pregnancy, and they actively secrete gastric acid by the second trimester. [17,18]. After preterm birth, gastric acid production is limited in comparison to infants born at 40 GW. During the first two months after birth, gastric acid production doubles [19]. The proenzyme pepsinogen can be detected in the fetal stomach by 17–18 GW. After birth, pepsin activity is in line with the infant's maturity [20].

Other major enzymes are produced by the pancreas during this time. These include trypsinogen, chymotrypsinogen, and carboxypeptidase, all of which are zymogens that require activation by enterokinase, which is produced by the upper intestinal epithelial cells. By 24 GW, enterokinase is active at 25% of the level found in older infants [21]. These enzymes break large protein molecules into oligopeptides, dipeptides and single amino acids. As these molecules move distally, the absorptive process into the small intestinal epithelial cells occurs. This is accomplished by several transporter mechanisms. There are limitations of these processes in preterm infants. [22].

This leads to the question of whether hydrolyzed protein formulas are better tolerated, thereby providing enhanced nutrition for these preterm infants. One study demonstrated that, when compared to infants receiving standard formula, infants fed hydrolyzed protein formula had better feeding tolerance and a shorter time in achieving full feeds [23].

2.2. Carbohydrates

Salivary and pancreatic amylases are involved in the luminal digestion of complex sugars. Digestion into oligosaccharides is then complemented by absorptive hydrolysis into monosaccharides at the epithelial brush border by enzymes that include lactase, sucrase, maltase, isomaltase, and glucoamylase. Sucrase, maltase, and isomaltase have been shown to be fully active in preterm infants. Lactase activity, which hydrolyzes lactose, which is the most abundant disaccharide, into glucose and galactose, is low in preterm infants. [21].

Salivary amylase, which digests complex carbohydrates of 18–29 glucose units, is an initiator of carbohydrate digestion [24]. Pancreatic amylase, the secretion of which is limited, not reaching adult levels until about 2 years of age, is responsible for most initial carbohydrate hydrolysis. [25,26]. Due to suck–swallow incoordination, enteral feeding in many preterm infants necessitates the use of feeding tubes. These bypass the oral cavity, hence also bypassing the activity of salivary amylase.

Undigested carbohydrates pass into the distal intestine. Here, microbial fermentation results in the production of short chain fatty acids (SCFAs), which subsequently are absorbed. These can be utilized as energy sources, but butyrate has been also shown to serve as an important fuel for colonocytes as well as having properties that alter proliferation, differentiation, and turnover of colonic cells. [27,28].

Lactose is especially interesting from this perspective. Being the primary carbohydrate source in milk, lactose intolerance rarely occurs in the preterm population. Unabsorbed lactose conversion to SCFAs provides an efficient salvage pathway. One study suggests that lactase activity can be induced in preterm infants with enteral feedings of human milk [29].

Most lactase activity is found at the middle to the top of the villus, while sucrase, maltase and glucoamylase are found at the mid-villus [30]. During time of intestinal mucosal injury, the lactase-rich cells at the villus tip are the first to be injured and the last to be fully restored through the process of cell migration from crypt to the villus tip.

Insulin plays an important role in intestinal maturation and may also contribute to improve lactase activity following preterm birth. Amniotic fluid contains carbohydrates, protein, fat, electrolytes, immunoglobulins, and growth factors. Insulin is present in the amniotic fluid (up to 20 μU/mL) and after skin keratinization completed (around 26 weeks' gestation), amniotic fluid is the main source of insulin exposure to the GI tract and plays a role in development. Preterm birth abruptly interrupts these important fetal life processes and the local insulin exposure of the GI tract with detrimental consequences [31].

Oral insulin administration in preterm infants up to 28 days after delivery has proved effective in doubling the lactase activity [32].

2.3. Lipids

Triglycerides constitute half of the non-protein energy content in human milk and formula [16]. The digestion of triglycerides is initiated by bile acid micellar emulsification, which produces smaller droplets of triglycerides. This results in greater surface area for interaction with lipases, which hydrolyze long chain triglyceride into monoglycerides and free fatty acids, which in turn are absorbed into the small intestinal epithelium. Pancreatic lipase is one of the most important of these lipases.

The absorbed free fatty acids and 2-monoglycerides are re-esterified within the epithelial cell and subsequently converted to chylomicrons, which are transported from the basal region of the epithelial cell via the thoracic duct, from which they enter the blood circulation.

The digestion and absorption of medium chain triglycerides (MCTs) is less complex than that of long chain triglycerides. They do not require bile acid emulsification, are absorbed into the enterocyte without re-esterification and travel directly into the portal venous system. MCTs are frequently recommended for patients with lymphatic obstructions [33].

Different sources of lipase include lingual, gastric, pancreatic, and epithelial cells. Human milk contains a lipase termed bile-salt stimulated lipase. After activation in the small intestine in the presence of bile acids, it facilitates long-chain triglyceride digestion. Lingual lipase is secreted from glands at the base of the tongue; its activity is lower at birth

in infants at 26 weeks' gestation, peaks at 30–32 weeks, and declines near term [34,35]. Pancreatic lipase insufficiency is more prevalent in preterm infants when compared to older children. Adult levels are often not reached until 6 months after birth [36].

Another limitation of fat digestion relates to bile acids, which are synthesized and excreted from the liver via the biliary system at relatively low levels in very low birth weight (VLBW) preterm infants when compared to term infants. Bile ileal reabsorption is also lower in preterm infants, which results in less efficient lipid digestion when compared to term infants [37,38].

Essential fatty acids cannot be produced by the body and become deficient when not supplied in adequate quantities in the diet. To prevent deficiency, adequate dietary intake of linoleic and linolenic fatty acids can prevent deficiency. Furthermore, linoleic, and linolenic acids (18-carbons chain length) undergo desaturation and elongation enzymatic processes into long-chain polyunsaturated fatty acids (LCPUFAs) with more than 20-carbons. Required for formation of eicosanoids and central nervous system structures [39], it is concerning that preterm infants may not have the enzymatic capability to undergo these conversions. Many very preterm infants are provided formula that are not supplemented with these LCPUFAs, and even those receiving human milk may not receive adequate quantities of these important lipids [40].

3. The Development of Intestinal Motility

Intestinal motility includes coordinated movements of the GI tract such as mixing, propagation of motor activities, and receptive relaxation. These movements are regulated by multiple control systems including extrinsic neurons, intrinsic neurons (the enteric nervous system, ENS), interstitial cells of Cajal (ICCs), cells expressing platelet-derived growth factor receptor alpha (PDGFRα), and myogenic mechanisms, which can all operate simultaneously [41,42]. The principal maturational features of intestinal motility are detailed in the following paragraphs and summarized in Figure 1.

3.1. Anatomy and Physiology of Gastrointestinal Motility

The movements of the GI tract are different for each region. They also show marked differences in relation to prematurity [43,44].

In the literature there are several studies on GI motility in the preterm newborns compared to full term newborns, characterized by impaired gastric electrical activity and gastric emptying. Gastric motility is poorly organized in preterm infants and fundal and antral pressure waves increase with increasing gestational age (GA) [9,45,46]. In particular, this is relevant for preterm newborns of 28–32 weeks GA, while preterm infants of 32 to 36 weeks GA show a pattern of gastric electrical activity and emptying much closer to that of full-term newborns.

Gastric motility is ruled by myoelectrical activity that consists of rhythmically occurring transmembrane potential variations, called slow waves, that are independent of the presence of motor activity [47]. These waves that slowly travel through the GI tract are defined motor migratory complexes (MMCs) and occur every 2–4 h with the purpose of clearing the tract of undigested material, mucus, and debris [48]. MMCs initially occur due to vagal input and the release of motilin in the duodenum. Their propagation, on the other hand, is coordinated by enteric neurons. MMCs occur in humans only during periods of fasting and in the small intestine as opposed to other species. Phasic contraction is related to a different kind of electrical activity, called electrical response activity, characterized by spikes superimposed on gastric slow waves. The origin of electrical activity is found on the greater curve, approximately in the proximal corpus, from where the slow waves propagate towards the pylorus [48,49].

Different motor patterns occur in the proximal and distal stomach. In the proximal stomach, receptive relaxation and accommodation occur, which are both mediated by neurons in the brainstem via vagal reflexes. The distal stomach exhibits different motor patterns during feeding and fasting. In the feeding state, the distal stomach grinds and

mixes. Extrinsic neurons are not essential for this contractile activity, but it can be modulated by vagal pathways.

Intestinal motor activity is also correlated with gestational age and motor development, which is defined by phases I, II, and III of the migration of the motor complex between 37 GW and term age [50]. In particular, the frequency of duodenal contractions, the number of duodenal contractions per impulse, and the peak intraluminal pressure of duodenal motility in preterm versus full-term infants are different [46]. Clustered phasic contractions are more frequent but of shorter duration and lower amplitude; duodenal clusters are less common and antro-duodenal coordination is more immature in preterm infants [51].

A role of insulin on gut motility has also been supported by Shulman et al., who demonstrated significantly reduced gastric residuals within the first month in preterm infants treated with oral insulin compared to untreated peers [32].

3.2. The Enteric Nervous System

By 12 GW, the fetal colon has a dense neuronal network in the myenteric plexus with expression of excitatory neurotransmitter and synaptic markers. Instead, the markers of inhibitory neurotransmitters appear no earlier than 14 GW. However, electrical train stimulation of internodal strands did not evoke activity in the ENS of 12- or 14-GW tissues [52].

Onset of evoked electrical activity in the human fetal ENS appears at approximately 16 GW. Such activity appears to coincide with increases in gene expression of various ion channels known to modulate enteric action potentials. The temporal development of several neural subtypes and enteric glia occurs between 12 and 16 GW [53,54]. The ENS consists of three parts: enteric neurons, enteric glial cells (EGCs), and ICCs. They form two major ganglionated structures and functional subunits—submucosal plexus (or Meissner's plexus) and myenteric plexus (or Auerbach's plexus). Meissner's plexus is located in the connective tissue of submucosa, and innervates muscularis mucosae, intestinal neuroendocrine cells, glandular epithelium and submucosal blood vessels, while Auerbach's plexus is located between the circular and longitudinal muscle layers and is associated with the contractility of the circular and longitudinal muscles [55,56].

Studies carried out on intestinal samples of mice show that ENS originates mainly from the cells of the vagal neural crest called neural crest precursor cells (NCC) that enter the foregut at 9 embryonic days and then migrate rostro caudally and colonize the entire intestine by 14 embryonic days [57–59].

Cdh19 is a direct target of Sox10 during early sacral NCC migration towards the hindgut and forms cadherin–catenin complexes which interact with the cytoskeleton in migrating cells [60]. The migration phase is followed by the proliferation of NCCs which will form millions of ENS cells. The NCCs then assemble into groups (myenteric ganglia or submucosal ganglia) and then differentiate into a range of enteric neurons and glia cells and form complex neuronal networks necessary for controlled intestinal activity [61–63].

Diverse populations of fibroblast-like interstitial cells are present in the adult gut. Loss or dysfunction of these cells has been linked to a wide variety of GI disorders. This broad group of cells comprises various subpopulations of Kit-positive ICCs and fibroblast-like cells expressing PDGFRα. ICCs located at the level of the myenteric plexus (ICC-MY) mediate slow waves, the electrical events that time the occurrence of phasic contractions [64,65], while evidence is accumulating that ICC and PDGFRα-expressing cells located within and surrounding GI muscle bundles serve as intermediaries in both excitatory and inhibitory neuromuscular transmission.

Unlike enteric neurons and glial cells, ICCs do not arise from the neural crest, but have an embryonic development prior to the arrival of neural crest cells in the intestine. Several studies suggest that smooth muscle cells and ICCs are derived from a common mesenchymal precursor following an epithelial–mesenchymal transition process (EMT). Both ICC and CD34+ fibroblast-like cells derive from the coelomic epithelium, most likely from a common ancestor expressing the chlorine channel anoctamin-1 and smooth muscle

actin alpha. Differentiation to the ICC phenotype during embryogenesis depends on cell signaling via the receptor tyrosine kinase, Kit [66–69]. In recent studies on ontogeny of gastric electrical activity, myogenic control was found to be immature at birth and suggested a process of development from 1 week to 6 months.

3.3. The Microbiota-Gut–Brain Axis

During the early postnatal period, infants undergo consistent gut development, which is parallel and interdependent, even if not always synchronous, with brain development. In the first years of life, the gut experiences huge changes of the resident microbiota and a substantial maturation of both the enterocytes and of the ENS. Meanwhile, the brain and the central nervous system (CNS) grow rapidly, both in terms of brain volume and neural function.

The interdependency of the two developmental processes is mediated through the so-called gut–brain axis, which constitutes a bidirectional communication between the gut and the brain, made of several interrelated components [70]. In recent years, the role of microbiota in the gut–brain axis has been studied extensively, so that the GBA is now commonly referred to as the microbiota-GBA (MGBA) [71]. In this context, gut microbiota alterations have been directly linked to physical and mental health through a series of mechanisms which are yet to be fully elucidated [72].

The connection between gut and brain during early development involves both top-down and bottom-up mechanisms, with signals from the brain modulating GI functions, and GI-derived molecules influencing brain processes through different pathways. Even if the features of the MGBA in health and disease have been thoroughly described, the knowledge of the exact mechanisms through which the gut and the brain communicate in young infants is, at present, limited.

The mechanisms involved in the interplay between the brain and the gut include neural, endocrine, immune, and metabolic mediators [73].

Neural connections include the CNS, the ENS, and the autonomic nervous system (ANS). The ENS receives inputs from the brain and, in turn, provides ascending information through neural circuits. The ANS comprises sympathetic and parasympathetic nerves: the sympathetic system exerts mainly an inhibitory influence on the gut, while the vagus nerve (VN) appears to be able to sense hormones, cytokines, and metabolites from the GI tract, leading to afferent signals to the brain. The development and myelination of the VN is not complete at birth and continues until adolescence, with a peak in the myelination rate observed in the first months of life, when consumption of human milk, and human-milk-derived bioactive components, is the highest [74]. The ANS is connected to the limbic system of the brain, whose main components are the hippocampus, the amygdala, and the limbic cortex, and which is responsible for a variety of brain processes in health and disease [73].

As for humoral components of the MGBA, they mainly consist in the hypothalamic–pituitary–adrenal axis (HPA), the enteroendocrine system and the immune system. Stress responses are modulated through the HPA, via the release of corticosterone, adrenaline, and noradrenaline. The enteroendocrine cells (EECs) in the gut produce GI hormones such as ghrelin, glucagon-like peptide (GLP-1), cholecystokinin, and peptide YY (PYY); these hormones regulate food intake and satiety and are also involved in the regulation of emotions and mood [70].

The resident immune cells in the brain, known as the microglia, act as a neuroimmune component of the MGBA, by finely tuning neurogenesis and synaptogenesis. The maturation and function of the microglia appear to be related to changes in the gut microbiota, and also influenced by SCFAs [75], which are end-products of bacterial fermentation of dietary fibers and resistant starch in the colon. Furthermore, immune signaling molecules, whose production is also driven by gut microbiota, can play a role in the MGBA, by binding to VN receptors or by crossing the blood–brain barrier. In this respect, recent studies have suggested a potential role of bacterial peptidoglycans (PGNs), which are components of

the bacterial cell wall, released not only by exogenous bacteria, but also by the resident gut microbiota. It has been proposed that PGNs could enter the systemic circulation and reach the developing brain, where PGN sensing molecules are expressed abundantly during specific time windows of perinatal development, thus potentially exerting a direct effect on brain function and development [76].

Finally, a central role in the MGBA is played by metabolic mediators, including tryptophan metabolites such as serotonin (5-hydroxytryptamine, 5-HT), melatonin, SCFAs, and other neurotransmitters. 5-HT is involved in most branches of the MGBA; for instance, it acts as a neurotransmitter both in the CNS and ENS, and 5-HT receptors have a critical function in the HPA [77]. The production of host 5-HT in the gut is regulated by microbiota, as indigenous spore-forming bacteria, derived from mouse and human microbiota, have been shown to promote 5-HT biosynthesis from enterochromaffin cells in the colon, thus impacting GI motility and homeostasis [78]. SCFAs (acetate, propionate, and butyrate) are thought to influence gut–brain communication through different potential pathways, either directly or indirectly. Once produced by colonic fermentation, SCFAs can exert a direct effect on the intestinal mucosal immunity and can modulate the integrity and function of the gut barrier. Furthermore, by interacting with the EECs, SCFAs promote a direct gut–brain signaling through the secretion of gut hormones, such as GLP-1 and PYY, and other metabolic mediators such as γ-aminobutyric acid and 5-HT. In addition, they can induce systemic inflammation through differentiation of T regulatory cells and secretion of interleukins and can probably also act centrally in the CNS by modulating neuroinflammation [79].

There are several factors which could have a specific impact on the MGBA development in early life; one of the most relevant might be prematurity, as preterm birth interrupts the physiological growth and development of both the GI tract and the nervous system and leads to a certain degree of microbial dysbiosis. Despite that, at present there are no studies specifically designed to describe the unique features of the MGBA in preterm infants [80]. In addition, nutrition during sensitive developmental time windows is thought to have a major impact on the microbiota-gut–brain crosstalk [81,82], either through an effect of single nutrients (e.g., milk fat globule membranes [83], human milk oligosaccharides [84], or through the well-known benefits of exclusive human milk feeding compared to other feeding sources [85].

Most studies aimed at describing the developmental-related characteristics of the MGBA have been carried out using rodent models, even if gut and brain development in rodents do not exactly reproduce human developmental patterns [86]. For this reason, future preclinical research in the field of MGBA should be hopefully directed towards the use of animal models with more similar anatomy and physiology to that of humans (e.g., piglets). These models would allow a better understanding of the MGBA during early development and would pave the way for translating preclinical research into clinically relevant observations.

Beyond the contribution of studies based on animal models, the plausibility of the microbiota-gut–brain interplay also during early development is supported by clinical observations: so far, a limited number of studies has shown a correlation between specific microbial features in the gut during the early postnatal period and neurodevelopment, either in term or preterm infants [87–91].

The potential link between microbiota and neurodevelopment is particularly intriguing for preterm infants, as prematurity itself exposes them to both early dysbiosis and intrinsic risk of altered development. It has been suggested that the interplay between early dysbiosis and the gut–brain axis might lay the foundations for the altered neurodevelopment which is often observed in preterm infants experiencing necrotizing enterocolitis (NEC) [92]. Furthermore, a potential role of early alterations of the GMBA in later neurodevelopment has also been proposed for preterm infants not necessarily experiencing major neonatal complications such as NEC. For instance, in the French EPIFLORE population study, gut microbiota features in the first month of life in very preterm infants were

associated with 2 year outcomes, even after adjustment for confounders [88]. Similarly, in a small cohort of very low birth weight infants, a relationship between specific microbial characteristics during the first months of life (i.e., relative abundance of Bifidobacteria) and impaired neurodevelopment at 24 months corrected age was suggested [91].

4. Development of the Gut Microbiome

The intestinal microbiota is important in human growth and development. The human gut is home to trillions of microbial cells that bind in a symbiotic relationship to the host playing a vital role in both health and disease [93,94].

The relationship between microbiome and host is dynamic and many factors (such as genetic background, maternal diet prior to and during pregnancy, maternal microbiome, mode of delivery, gestational age, perinatal stress, infections during pregnancy and during the perinatal or neonatal period, feed type of neonates and especially of preterm infants, and other environmental factors such as temperature, humidity, pH, and oxygen levels in the tissues type) modulate the infants' microbiome constitution and its dynamic relationship with the host, which can be transformed from 'synbiotic' to 'dysbiotic' and life-threatening [95,96].

Of note, as illustrated in a recent narrative review, over the past decade several studies conducted on meconium have supported the fact that the fetus could be exposed to microbiota in utero, though previously the amniotic fluid and the placenta had been thought to be sterile [97]. Placental colonization through a hematic route has been hypothesized as possibly responsible for the fetal colonization before birth [98].

Advances in high-throughput nucleotide sequencing technologies have enhanced gut microbiota research by investigating how bacterial communities develop over time, what factors affect them, and how they affect health and disease [99].

4.1. Gut Microbiome in Term Infants

The microbiota performs fundamental functions in human health, especially in childhood. The first year of life is considered a crucial window for any manipulation of the intestinal microbiota in order to promote proper development of the immune system and human well-being [100]. Human first exposure to these microorganisms occurs at birth: once the baby is out of the womb, the microorganisms enter and settle in the intestine.

The TEDDY study, which describes the importance of the intestinal microbiota in the first years of life, demonstrated how the development of the microbiota in a full-term infant is influenced by breastfeeding, the type of birth, the geographical location, and the presence of siblings or animals in the home [101].

Other studies, on the other hand, are focusing on the impact that maternal factors, antibiotic use, host genetics, ethnicity, and even COVID-19 infection can have on microbiota development [102–104]. Therefore, alterations of the intestinal ecosystem, known as dysbiosis, during this critical period of development are often associated with various kinds of pathologies.

4.2. Gut Microbiome in Preterm Infants

Prematurity at birth is a determining factor in the development of the intestinal microbiota [105]. The premature baby, after birth, is admitted to NICU and thus exposed more to hospital-acquired bacteria than to familiar bacteria [106]. Furthermore, the clinical practices to which these small patients are exposed, e.g., ventilation, artificial feeding, and antibiotic reception, alter the normal development of the microbiota. Moreover, pre-term infants have immature GI tracts and naïve immune systems [107].

Several studies have shown how this immaturity and diversity of the microbiota affects the development of intestinal function and anatomy of intestinal villi, crypts and of the intestinal barrier [108], causing several serious disorders in the premature newborn such as late-onset sepsis (LOS) and NEC [109]. Substantial efforts have been made over the

past few decades to define the microbial characteristics of NEC and LOS, and compelling data have associated both conditions with intestinal dysbiosis.

Human milk has a protective role against both NEC and LOS as it confers immunological benefits to the baby and provides nutrient-specialized microbes that likewise enrich the baby's immune system [110]. Specifically, human milk provides nutrients such as oligosaccharides, essential for the growth of bifidobacterial-type bacteria [111,112]. Bifidobacteria have been shown to possess immunomodulatory and anti-inflammatory properties by strengthening the intestinal barrier and reducing the risk of NEC [110]. Premature babies have low levels of these bacterial species and are more exposed to the risk of NEC. Safety and efficacy of probiotic administration to modulate early gut microbiome in preterm neonates is being investigated [113]. Gaining a deeper understanding of the microbiome using relevant methodology will enable the exploration of new targeted therapeutic strategies in preterm disease as well as in a range of other pathologies.

5. Conclusions

The intestine represents a vast interface between our internal and external environments. The second and third trimesters of pregnancy are crucial to the anatomical and functional development of the GI tract and the related digestive functions. Following premature birth, the immaturity of the digestive and absorptive processes and of the GI motility represent a critical challenge to the establishment of adequate enteral intakes in the preterm population and are often involved in the development of premature-related GI complications, ranging from food intolerance to NEC. In the context of gut immaturity, the choice of the optimal source of nutrition for preterm infants is fundamental: keeping mother's own milk in mind as the magic bullet for preterm infants' nutrition, future research should continue to address the potential role for mother's own milk substitutes, such as donor milk and formula, for preterm infants. Specifically, the potential effects of donor milk treatments such as freezing and pasteurization on milk bioactive properties should be further investigated, while infant formula research should be oriented at developing a milk substitute which would be nutritionally adequate and, at the same time, easy to tolerate and digest for these immature infants.

Moreover, there is much evidence that microbes residing in the intestinal tract play important roles in the ontogenesis of the immune system and interact with the gut and central nervous system. The interplay between GI development and microbial colonization is dual: while the immature anatomical and functional features of the preterm gut predispose to an abnormal intestinal microbial colonization, the latter may interfere with the functional, immune, and neuronal development of the GI tract. It should be constantly kept in mind that the perinatal period most likely corresponds to a critical moment in which the "set points" are impressed; it is therefore necessary to learn more about normal and healthy colonization patterns in infants to promote these patterns and avoid perturbations that result in disease throughout life.

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EUROPEAN PAEDIATRIC ASSOCIATION

European Pediatric Societies Call for an Implementation of Regular Vaccination Programs to Contrast the Immunity Debt Associated to Coronavirus Disease-2019 Pandemic in Children

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In the initial months of the coronavirus disease 2019 (COVID-19) pandemic because of the lack of effective treatments and unavailability of a vaccine, governments worldwide developed a variety of safety measures to control the spread of virus among their populations. Heterogeneous strategies variously implemented during the first year of the pandemic were often maintained after COVID-19 vaccines were made available.[1,2]

Public health and social measures of containment, and nonpharmaceutical interventions (NPIs) that were developed and enforced at local level worldwide proved to be effective in limiting the spread of the disease and reducing the number of deaths.[3] Safety measures adopted to minimize possible viral contamination included frequent hand washing, wearing facemasks, and social distancing policies taken on by communities to limit the spread of a disease. To further reduce person to person transmission of the virus, most countries have introduced a combination of school and workplace closures; public event cancellations, restrictions on public gatherings, closures of public transport, and stay-at-home orders.[4]

The implementation of strict public health NPIs targeting COVID-19 has been credited for a reduction of many viral and bacterial infectious diseases in children.[5,6] For instance, global rates of respiratory syncytial virus (RSV), the most common cause of admission to hospital for infants in high-income countries, accounting for 60%-80% of bronchiolitis hospitalizations, have been significantly low since early 2020.[6,7]

However, the substantial decrease of protective immunity because of the extended period of low exposure to pathogens seems to have left a large part of the pediatric population susceptible to infections.[6] For instance, the interseasonal circulation of RSV has been reported in different areas, including Australia during late 2020, South Africa in early 2021, southern US in June 2021, and in Europe after summer 2021.[8]

This commentary, authored by the working group on social pediatrics of the European Pediatric Association/Union of National European Pediatric Societies and Associations, briefly discusses the insurgence of infectious diseases because of the immune debt associated to the public health NPIs established to control the COVID-19 pandemic. Our aim is to raise awareness of pediatricians and public health authorities on the importance vaccination programs in children to contrast the immune debt associated to the pandemic.[6,9]

COVID-19	Coronavirus disease 2019
NPI	Nonpharmaceutical intervention
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Effect of COVID-19 NPIs on Pediatric Infectious Diseases

Since the beginning of the COVID-19 pandemic, children and adolescents have shown low rates of infection, as well as relatively low rates of severe or critical forms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[10,11] NPIs have limited the spread of COVID-19 in Europe.[6,12] NPIs imposed to reduce the SARS-CoV-2 spread are also credited for the decrease of viral and bacterial infections observed, particularly in pediatric population[5] (**Figure**; available at www.jpeds.com).

Studies performed in the European Union have shown that lockdown measures have led to a rapid decline in the infectious respiratory diseases, specifically, a sharper decrease in influenza and RSV infections in 2020 and 2021, compared with previous years.[12] However, the implementation of NPIs among the various European countries was different with a negative correlation between the severity of the NPI imposed and the decline of the infectious diseases. For instance, the decline of influenza and RSV was stronger in Italy, compared with other European countries such as Sweden and Germany, where the NPIs were less stringent and the population less compliant.[12] The efficacy of the measures established to control of COVID-19 transmission is a consolidated evidence,[13] and their effectiveness is also recognized as a key factor in containing the spread of other respiratory infectious diseases.[3] However, the long-term impact of an extensive adoption of useful NPI safety measures is currently

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unknown.[6] In particular, it is unclear whether and to what extent infectious diseases that significantly declined during the pandemic will re-emerge after COVID-19 mitigation measures are lifted. Data on increasing numbers of RSV cases after the summer 2021 seems to suggest an imminent risk for children's health.[6]

Immunity Debt following Extended Periods of COVID-19 Mitigation Measures

Because of the NPIs enforced during the pandemic, children have experienced extended periods of low exposure to pathogens.[7,14] Immune memory is a defining feature of the acquired immune system.[15] Concerns have been raised about the lack of exposure to common infections and the possibility that prolonged periods of reduced contacts with pathogens may reduce protective immunity[6,7,16] and influence the development of adaptive immunity against infectious agents.[6,16,17] Activation of the innate immune system can also result in enhanced responsiveness to triggers.[15] In the absence of exposure to seasonal infectious diseases, immunity may decrease while the susceptibility to infections increases.[6] Therefore, the immunity debt caused by the NPIs adopted during the pandemic (**Figure**) could expose children to a greater potential for an increase in outbreaks and possible epidemics because of new or re-emerging infectious agents.[6,7]

Unusual Surge of RSV Infections in Children Amid the Ongoing Pandemic

A significant decline in infection rates was reported for pneumococcal diseases,[18,19] *Neisseria meningitidis* infections,[19,20] pertussis,[21,22] varicella,[21,23] measles,[21] enterovirus infections,[23] influenza,[5,23-25] and RSV infections.[5,24,26-28]

In Australia, RSV infections[29] began to increase during the spring months and peaked in late September 2021 with the number of cases significantly greater than in previous years.[24,25] In Japan, a significant outbreak of RSV infections was reported starting in spring 2021,[30] while in the US, RSV started to rise in some areas of the southern states before summer 2021.[30,31] In Texas, where the trend began at the end of June, nearly one-half of pediatric patients hospitalized in local hospitals in August 2021 were diagnosed with RSV.[32,33] In Europe, respiratory infections in young children have begun to rise in England following low infection rates in response to COVID-19 restrictions and positivity of samples tested for RSV rapidly increased over 5 consecutive weeks by the end of July 2021, well before the typical winter season.[34] In France, a delayed bronchiolitis epidemic driven by RSV was reported in March 2021.[27] In autumn 2021, epidemiology indicators showed an earlier and more rapid onset of bronchiolitis virus circulation compared to previous years.[34-36]

Israel has experienced a large outbreak of RSV bronchiolitis during the summer of 2021 following the decline of the COVID-19 third wave and the lifting of NPI. This outbreak resulted in a significant increase of hospitalizations and overloaded pediatric wards and pediatric intensive care units throughout the country.[37] In response to the RSV outbreak, the Israeli Ministry of Health recommended routine prophylaxis programs from the month of November.[38] In Italy, the Italian Society of Pediatrics reports that RSV infection rose earlier than the usual peak observed in December-January.[39,40] In some areas of Southern Italy, in October 2021 there was a 30% increase of RSV cases compared to previous years[39] and similar data are reported from the Northern regions, where in Veneto, in the month of October 2021 alone, the hospitalizations related to RSV were one-half of those recorded throughout the entire 2020-2021 winter season.[39]

Conclusions

COVID-19 mitigation measures led to shifts in typical annual respiratory virus patterns.[6] It is unclear whether this global trend will continue and how co-infection of RSV and other respiratory viruses with SARS-CoV-2 will affect disease severity in children during the winter season. Appropriate monitoring of the ongoing RSV epidemic and adequate interventional measures[41,42] should be continued and regular vaccination programs for infectious diseases maintained to protect children against respiratory viruses and other infectious agents and to prevent community transmission of diseases.[32,43] ■

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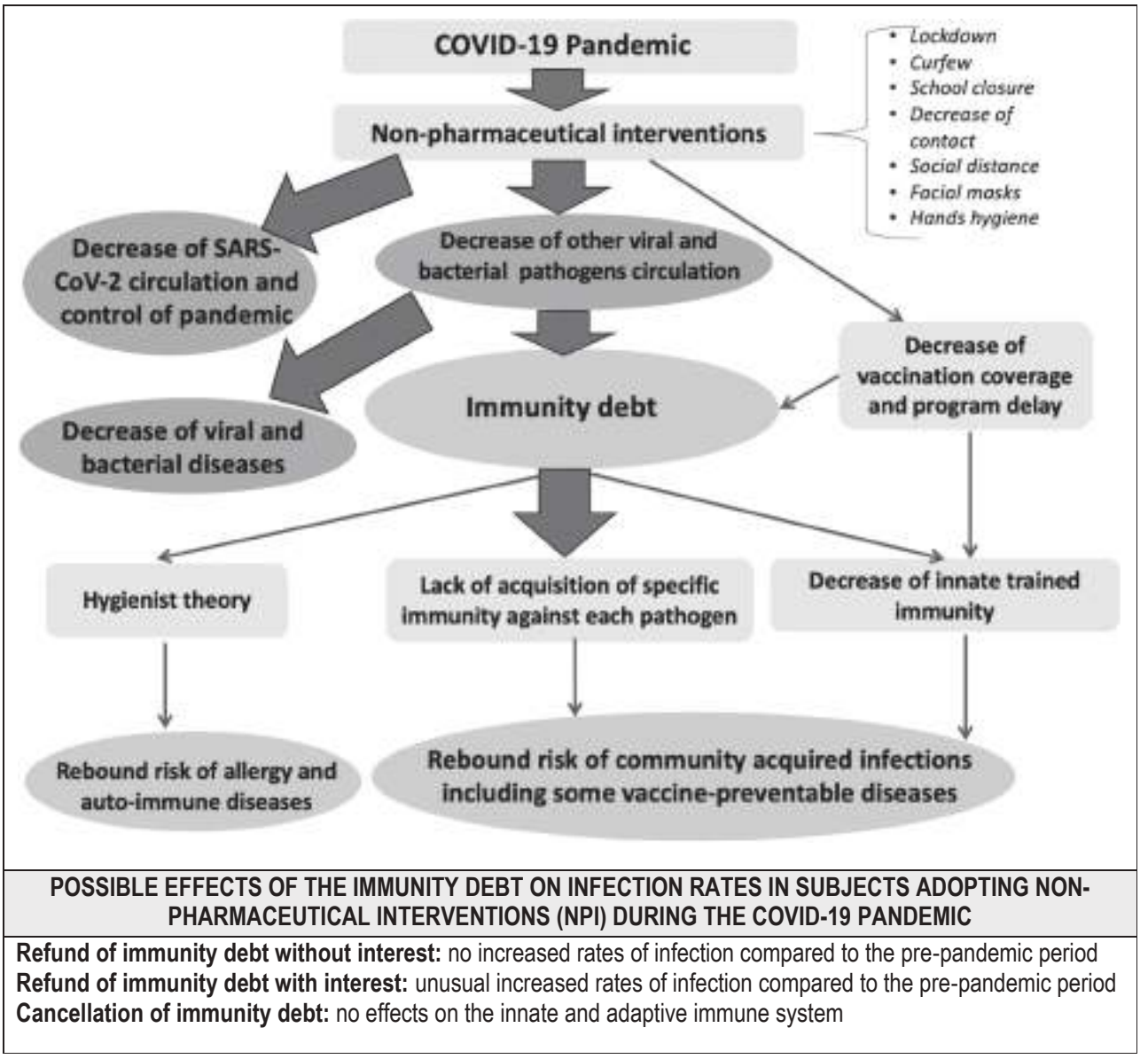

Figure. Immunity debt in children following the adoption of COVID-19 NPIs.

EUROPEAN PAEDIATRIC ASSOCIATION

Importance of Coronavirus Disease 2019 Vaccination in Children: Viewpoint and Recommendations of the Union of European National Societies of Pediatrics

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Coronavirus disease 2019 (COVID-19) vaccines, approved by the US Food and Drug Administration[1] (FDA) and the European Medicine Agency[2] (EMA), have been shown to be safe and effective[3,4] in the adult population at preventing severe disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide.[5,6] The use of COVID-19 vaccination in children aged 12-17 years has been the subject of extensive debate, as the assessment of risks and benefits was considered more complex than in adults.[7,8] Different circumstances were taken into account, including common reactions, infrequent serious side effects, possible impact on routine immunization programs, as well as vaccine supply and cost of vaccination.[9] However, COVID-19 vaccines for individuals of this age group were authorized initially for emergency use and later approved by the stringent regulatory authorities FDA and EMA and have since been adopted with widespread use in several countries worldwide.[10] In addition, both the FDA and EMA in October/November 2021 authorized the use of COVID-19 vaccines in children 5-11 years of age. Their approval followed a thorough evaluation process demonstrating the same high standards of quality, safety, immunogenicity, and efficacy observed in the older populations.[11,12] COVID data tracking indicates that in the US, 20.1% of the 5- to 11-year-old population have received at least 1 dose of COVID-19 vaccine by December 16. The percentage of fully vaccinated subjects in the 5- to 11-year-old group is 11.3%; 62.3% of adolescents in the 12- to 17-year-old age group have received at least 1 dose of COVID-19 vaccine.[4]

In Europe, the debate over the extension of the use of COVID-19 vaccine in children <17 years old is ongoing. The 27 member states of the European Union (EU) showed different views and adopted divergent policies. It is unclear whether a unitary position will eventually be taken by the EU and non-EU countries on the use of COVID-19 vaccination in individuals <17 years of age. In the meantime, the European Centre for Disease Prevention and Control reported that in the first week of December 2021, only 20.8% of the European population aged 12-17 years received at least 1 dose of vaccine, whereas no vaccinations were reported in children 5-11 years old.[13]

This commentary authored by the European Paediatric Association/Union of National European Paediatric Societies and Associations (EPA-UNEPSA), discusses the importance of implementing SARS-CoV-2 vaccination in children. The aim of this article is to advocate and raise awareness among pediatricians, lawmakers, public health officers, and school educators on the importance of COVID-19 vaccination in these 2 population groups. Vaccination of children and adolescents will protect them from the risks of SARS-CoV-2 infection and its short- and long-term complications.[14,15]

COVID-19	Coronavirus disease 2019
EMA	European Medicine Agency
EPA-UN-EPSA	The European Paediatric Association/Union of National European Paediatric Societies and Associations
EU	European Union
FDA	Food and Drug Administration
MIS-C	Multisystem inflammatory syndrome in children
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Importance of COVID-19 Vaccination in Children 12-17 Years Old

COVID-19 vaccination in children 12-17 years old is recommended by the US and European regulatory authorities.[1,2] Available studies on SARS-CoV-2 seroprevalence and viral shedding are unable to establish conclusively whether adolescents are infected at the same rate as adults.[16] Data on transmission from children to others are limited; some studies suggest similar infection rates, whereas others indicate lower infection rates among children. Early in the pandemic, some studies estimated that adults might have greater susceptibility to infection compared with individuals <20 years of age.[17] However, recent data in the US indicate that children have a greater seroprevalence than adults, and the infection to case ratio is greater in

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children. Children and adolescents are known to spread the virus to other age groups, and secondary transmission from children has been documented in both household and school settings.[18,19] In early studies, children and adolescents represented a smaller proportion of symptomatic subjects and showed a reduced number of cases of severe disease and deaths due to SARS-CoV-2 infection compared with older age groups.[20,21] However, the combination of mild and asymptomatic infection and reduced care-seeking in younger age groups are likely contributors to undertesting and underreporting of cases.[22] Deficient monitoring of SARS-CoV-2 in this age population[21] suggests that adolescents may remain largely undetected and therefore have a role in SARS-CoV-2 transmission. Intense social relations characterizing adolescence may be an additional factor contributing to the viral spread. Data from India reported the seropositivity rate for the Delta variant in children 6-18 years was comparable with that in older age groups.[16]

In the US, the proportion of cases in children has significantly increased from the 2.6% observed in the beginning of the pandemic to about 24% of all cases.[23] Recent data indicate a 38%-40% seroprevalence rate in children aged 5-17 years, which was greater compared with adults and older adults.[11,24] Similar data are reported in EU countries.[25] In addition, the median number of infections per reported case for children <17 years old was 6.2, compared with the general population, with a median of 2.4 infections per reported case. Data reported by the World Health Organization also suggest that SARS-CoV-2 infection rates in children, adolescents, and adults are similar,[16] and European Centre for Disease Prevention and Control reports that test positivity among the 10- to 19-year-old age group mirror those of most other age groups.[25] Collectively, these data indicate that children and adolescents are at least as likely as adults to be infected with SARS-CoV-2 but are less likely to be reported.

The risk of complications due to SARS-CoV-2 infection in the pediatric population supports COVID-19 vaccination in children and adolescents.[26] Multisystem inflammatory syndrome in children (MIS-C), long-COVID-19, and indirect effects on mental health and education are among the serious conditions that can be caused by even mild COVID-19, particularly in subjects with underlying medical conditions.[27,28] In the US, approximately one-third of those <17 years old who are hospitalized with COVID-19 require admission to the intensive care unit, and severity of illness for hospitalized cases is comparable with influenza. Although MIS-C is relatively infrequent in subjects affected by COVID-19, studies from Europe and North America have reported groups of adolescents requiring admission to intensive care units due to multisystem inflammatory conditions and toxic shock syndrome.[28] COVID-19 is currently among the top 10 causes of death for children in the US and Europe.[28,29]

Value of COVID-19 Vaccination in Children 5-11 Years Old

In the US, after the Centers for Disease Control and Prevention recommended COVID-19 vaccination for children aged 5-11 years in November 2021,[30] distribution of pediatric doses of the vaccine to pediatric offices, pharmacies, and health centers was scaled up rapidly toward full capacity. The COVID-19 vaccine in children in this age group also was approved by Health Canada, and in the first week of December 2021, 17.5% of individuals in this age range received at least 1 dose.[31] The European Medicines Agency approved the use of COVID-19 vaccine for children aged 5-11 years in November 2021, and the rollout in this age group started in Italy and France in December 2021.[32,33] It is important to ensure that all school-aged children <12 years are protected from COVID-19 infection.[34,35]

Approvals by regulatory authorities in the US and Europe were based on evidence that the efficacy and immunogenicity of these vaccines are as high as those in older individuals and show rare serious adverse effects.[30] Myocarditis associated with mRNA COVID-19 vaccines is a sporadic adverse event predominantly seen in male adolescents and young adults following the second vaccine dose, which has raised concern about this risk in younger children. However, based on available data from the years preceding COVID-19, the risk of vaccine-associated myocarditis in 5- to 11-year-old children is expected to be extremely low compared with adolescents and young adults, in whom such risk is already low.[36] We still do not have long-term outcome data on myocarditis following vaccination. However, preliminary survey data at three months following diagnosis showed that 52% reported no symptoms within the previous 2 weeks and 90% of cardiologists or health care providers felt their patient was fully or probably recovered.[37,38] The advantages of vaccination are considered to largely outweigh this risk, as the occasional cases of myocarditis associated with COVID-19 vaccination are predominantly mild and the risk of myocarditis following COVID-19 is greater than the risk of myocarditis after COVID-19 vaccination.[37-40]

The rare cases of MIS-C reported in adults following COVID-19 vaccination advised the importance of monitoring for this possible adverse event in children 5-11 years old. However, data from vaccine trials in children <12 years old have not identified any potential signal triggering this event.[39] It is also important to take into account that the number of children 5-11 years old who have died due to COVID-19 during the pandemic is greater than the mortality rates of the infections for which children were routinely vaccinated before COVID-19 vaccines were made available, including meningococcal disease, measles, varicella, and rotavirus.[36] The risk of severe disease in children with underlying medical conditions, and the importance of protecting children from any severe outcome related to COVID-19 infection, are all compelling reasons for vaccination of children 5-11 years old.[36,41]

Conclusions

Although children and adolescents with COVID-19 show generally less frequent and severe symptoms, they acquire and spread the coronavirus and present with clinical complications including hospitalization and death.[42-44] The

EPA-UNEPSA joins the American Academy of Pediatrics in welcoming the decision of the US and European regulatory authorities to authorize COVID-19 vaccination in children and adolescents who do not have contraindications using a COVID-19 vaccine authorized for use for their age.[45] The EPA-UNEPSA recommends the implementation of COVID-19 vaccination programs in these age groups[8] to protect children and adolescents' health and allow them to fully engage in all of the activities that are essential for their full development and wellbeing.[46,47] The recent authorization of COVID-19 vaccination for children from 5 to 11 years old in the US and Europe is anticipated to have an important impact in reducing the burden of COVID-19, through prevention of severe COVID-19 disease in the fully vaccinated in this age group, as well as through mitigation of transmission among close contacts. Vaccinated children and adolescents would not be exposed to the adverse mental and behavioral consequences associated with isolation, quarantine, and missing of school.[48]

In the EU, data from December 2021 show a 96% weekly increase of children hospitalized with laboratory-confirmed COVID-19, of whom 69% were <4 years old, strongly suggesting the importance of COVID-19 vaccination in younger children.[49] Vaccine trials in children aged 6 months to 5 years are underway in the US under careful supervision by the FDA, and key data are expected to be released in the coming months. ■

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Progress in immunization of children against coronavirus disease 2019: The role of pediatric societies

To the Editor:

The time has come to vaccinate children younger than 12 years of age against severe acute respiratory syndrome coronavirus 2.[1] Issues regarding the reliability, safety, and efficacy of the coronavirus disease 2019 (COVID-19) vaccines have complicated the process of immunizing children, in addition to the decision of parents to vaccinate their children.[2] Without international universal consensus, pediatric societies in various countries are establishing childhood COVID-19 vaccination positions.[3-7]

The American Academy of Pediatrics,[3] the Israel Pediatric Association,[4] the Canadian Paediatric Society,[5] and the Spanish Association of Pediatrics[6] have publicly recommended vaccination of children 5 years of age and older. The Indian Academy of Pediatrics[7] has declared itself in favor of vaccinating children between 2 and 18 years of age.

This growing consensus should serve to reassure the general population and parents about the logical fears about pediatric vaccinations serve as a valuable tool for health professionals but also for social communicators, scientific disseminators, social organizations, educators, managers, and politicians in charge of vaccination campaigns. In turn, the support of the different national pediatric societies, as authoritative opinions, should serve to improve public confidence and guide the actions of COVID-19 childhood vaccination.

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Reply

To the Editor:

As President of the European Pediatric Association/Union of National Pediatric Societies and Associations (EPA-UNEPSA), I would like to thank Dr Gallegos et al for their interest in the EPA-UNEPSA commentary on the importance of coronavirus disease 2019 vaccination in children. EPA-UNEPSA agrees with Gallegos et al that the hesitation and differing opinions about the reliability, safety, and efficacy of coronavirus disease 2019 vaccines may have complicated the process of immunization of children. Of importance has

been the position taken by many respected pediatric societies and their recommendation that children younger than 12 years of age be vaccinated.[1-4] The views and recommendations published by EPA-UNEPSA in *The Journal* to vaccinate children younger than 12 years of age align with those published by The American Academy of Pediatrics,[1] the Israel Pediatric Association,[2] the Canadian Pediatric Society,[3] and the Spanish Association of Pediatrics.[4]

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Child Malnutrition during the Coronavirus Disease 2019 Pandemic

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In the period before the onset of the coronavirus disease 2019 (COVID-19) pandemic, the number of people suffering from malnutrition had escalated worldwide, despite the efforts made by leading international organizations to mitigate this phenomenon.[1] During the prepandemic period, the World Health Organization (WHO) and the World Bank reported impressive data from Asia and Africa, where 381 and 250 million people were undernourished in 2019, respectively, followed by Latin America and the Caribbean (48 million).[2] In some areas of the world, the combined effect of conflict, climate crisis, and socioeconomic fragility threatens to have serious repercussions on the nutritional status of populations, particularly in children. From 2015 to 2019, malnutrition accounted for nearly one-half of the total number of child deaths worldwide (5.2 million in 2019) with significant costs in economic and human capital development terms.[3,4] This situation was further exacerbated by the onset of the COVID-19 pandemic. According to a European Pediatric Association/Union of National European Pediatric Societies and Association analysis, the COVID-19 pandemic is expected to cause major health and nutrition effects worldwide (**Table**; available at www.jpeds.com).[4-7] Before the pandemic, an estimated 144 million children under age 5 (21.3% of the total) had chronic malnutrition (stunting), 47 million (6.9%) had acute malnutrition (wasting), and 38 million (5.6%) were overweight, with the prevalence increasing in this group from 4.9% in 2000. Chronic malnutrition exacerbated by the pandemic threatens to seriously impair the mental, physical, and cognitive development of children, who may experience difficulty learning, entering the workforce, and poor social interaction within their communities.[8,9]

This commentary, prepared by the European Pediatric Association/Union of National European Pediatric Societies and Associations Social Pediatrics Working Group in collaboration with the International Pediatric Association, is designed to raise awareness among pediatricians, governments, decision-makers, and public health officials of the risks to childhood nutrition during and after the COVID-19 pandemic and to emphasize the importance of developing appropriate nutrition interventions and programs aimed to reduce the burden of COVID-19-related malnutrition in children.[10]

COVID-19	Coronavirus disease 2019
WHO	World Health Organization

Child Malnutrition and Its Socioeconomic Implications

The definition of childhood malnutrition has evolved in accordance with the principles, definition, and dimensions of New Nutrition Science and has progressively integrated the concepts of the 1978 Alma Ata Declaration.[11,12] Therefore, after being considered a biological deficiency of micronutrients and macronutrients, malnutrition is now viewed as a broad condition that includes social, environmental, and economic determinants. A consistent theoretical and research work now links social factors to children's nutritional status.[11] These factors include undernutrition-related conditions (protein-energy malnutrition) owing to insufficient intake of energy and other nutrients; deficiency diseases owing to insufficient intake of one or more specific nutrients, including vitamins or minerals; and overnutrition-related conditions (overweight and obesity) owing to excessive consumption of energy and other nutrients.

The burden of malnutrition is unacceptably high. As outlined by the World Bank, the costs of undernutrition must consider several socioeconomic determinants, including the significant impact of lost national productivity and economic growth. The cost to the global economy and society is calculated to be approximately $3 trillion per year in the form of lost productivity, ranging from 3% to 16% of GDP in low-income environments. The Consortium of Global Experts, estimated an economic productivity loss equivalent to $29 billion globally by the end of 2022 as a result of additional malnutrition burdens attributable to the COVID-19 pandemic.[13]

Sound programs supported by appropriate investments, however, can mitigate and prevent such losses, if strategic interventions focusing of child health will include malnutrition. For example, ensuring optimal nutrition in the critical

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1000-day window between the start of a woman's pregnancy and her child's second birthday.

Food quality plays an important role, and income is not the only determinant of stunting,; food insecurity, poorly diversified diets, high rates of infectious diseases, inadequate child nutrition, and other causal factors, including nursing practices and poor sanitation and hygiene, can also contribute. Poor food quality and financial crises, as well as conflict, natural disasters, and the COVID-19 pandemic, have worsened malnutrition in many regions.[2,3] Several changes had taken place during the prepandemic years, and significant transitions in global nutrition are now influencing the lifestyles of children and families in diverse social contexts globally. Rapid changes in food production systems and availability, environmental and living conditions are visible in many low- and middle-income countries. Although these changes could be seen as a positive socioeconomic factor, in many cases they have also stimulated a rapid increase in the burden of overweight and obesity, which were previously considered a disorder of wealthy countries.[5,13] Over the past 30 years, overweight rates have increased faster in low- and middle-income countries than in high-income countries, and many regions of the world have seen some increase in the prevalence of overweight children under age 5. In 2020, 38.9 million children under age 5 were affected by overweight and obesity, which are now insidiously pervasive conditions, even in countries where child undernutrition is endemic.[2,3,11] Overall, overweight and obesity are currently estimated to cost $2 trillion in economic and social expenditures globally and in the postpandemic years we may expect the causative conditions and costs to expand further.[2]

The Impact of the COVID-19 Pandemic on Global Child Nutrition

The COVID-19 pandemic has exacerbated already poor and malnourished situations, creating further impacts in children. The majority of the world's children—some 2.3 billion—live in 1 of the 186 countries that have adopted restrictive measures to contain the infection.[14] However, public and scientific attention has now focused almost exclusively on the health impacts of COVID-19, ignoring the economic and social costs that the restrictive measures imposed have on the most vulnerable population groups, including children. This point is especially true in economically fragile countries, where the mix of conflict, climate change disasters, and dramatic levels of food insecurity can have incalculable consequences. The pandemic threatens to undo decades of fighting extreme poverty, which globally had fallen from about 1.9 billion people in 1990 to 650 million in 2018.[15]

Experiences from previous outbreaks suggest that these phenomena have profound humanitarian effects, affecting the most vulnerable groups who are already exposed to various forms of frailty and malnutrition; this includes women, children, migrants, refugees, and people with disabilities. Data analysis from WHO and the World Bank show that globally by the end of 2022, at least 70 to 140 million people could be hungry owing to increased poverty as a result of the economic downturn triggered by COVID-19.[2,3,16] Nearly two-thirds of urban households (62%) have difficulty accessing meat, dairy products, fruits, vegetables, and cereals. In most cases (52%), this was linked to unsustainable price increases.[17]

In addition to the disruption of basic health services, the main factors through which COVID-19 is driving severe malnutrition for millions of people include loss of income owing to unemployment, wage retrenchment, and rising food prices. These factors are compounded by the growing impact of blockades and restrictions on food production and supply, weakening social safety nets, the suspension of school feeding programs, and the unfortunate general increase in political instability and conflict over the management of natural resources such as water.[17] A report by Save the Children shows that, in a sample of 37 countries, 9 out of 10 households lost more than one-half of their income during the pandemic and will have difficulty accessing health services, and that 8 in 10 households reported difficulty in purchasing food.[18] In addition, the economic impacts of the pandemic on households are expected to cause an increase in negative socioeconomic response mechanisms that will cause a general increase in child labor.

The impact on education during the pandemic period also contributed to a worsening of child feeding conditions.[19] The closure of school refectories puts at risk those children for whom eating at school represents the only opportunity to receive a full meal each day.

Conclusions

Poverty, climate change, and conflict continue to slow the fight against maternal and child malnutrition and the achievement of the WHO 2030 targets.[20] This pathway is now further compromised by the COVID-19 pandemic that exposes the most vulnerable sections of the world's population to a range of devastating health and socioeconomic consequences.[21,22] Although children account for a small proportion of COVID-19 deaths, it is estimated that decreasing levels of essential and routine health services by about one-half could result in 45% increase in child mortality.[23]

The choices that governments and all stakeholders are making in response to child malnutrition and to the COVID-19 emergency will have critical consequences for mothers and children.[24] Given the projected increase in maternal and child mortality, it is important to develop policies that respond to the immediate needs generated by the pandemic, but also look to future generations, to increase the resilience of communities, and to build better, sustainable, and inclusive societies for all children.[25-27] ■

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Table. Projected effects of the COVID-19 pandemic emergency on health, social issues and nutrition (2022 European Pediatric Association/Union of National European Pediatric Societies and Associations data analysis)

In 2022, owing to the emergencies caused by the pandemic, more than 130 million more people may suffer food deprivation compared with 2019.
An estimated 6.7 million more children under age 5 could be acutely malnourished by the end of the 2022, with more than one-half of the cases concentrated in Asia (59%) and 1 in 5 children (22%) in sub-Saharan Africa.
The number of children living in poor households could increase by an estimated 120 million by 2022, especially in certain economically and socially disadvantaged areas of the world.
After the onset of the pandemic an estimated 370 million children worldwide have not had access to school meals.
Although children account for a small percentage of deaths from COVID-19, decreases in essential and routine health services may be associated with an approximate 45% increase in infant mortality.
An estimated 80 million children are at risk of being excluded from standard vaccination programs owing to the pandemic.
It is estimated that a 6-month continuation of restrictive measures can result in up to 7 million unintended pregnancies.
Up to 31 million new cases of gender-based violence against women and girls are expected.

The Importance of Strengthening Mother and Child Health Services during the First 1000 Days of Life: The Foundation of Optimum Health, Growth and Development

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The first 1000 days of a child's life, spanning from the time of conception until 2 years of age, are a unique period of laying down the foundations of optimum health, growth, and development across the lifespan.[1,2] However, the first 1000 days are also a period of enormous vulnerability. How mothers and children are cared for during this crucial time has a profound influence on a child's ability to grow, learn, and thrive.[1]

The role of the first 1000 days of life is well-described.[1-3] However, investments in this key period are scarce and the provision of adequate health care services id insufficient. The aim of this report is to further raise the attention of decision-makers and health care officers and professionals, including pediatricians, pediatric surgeons, obstetricians, nurses, midwives, dieticians, and lactation consultants, on the importance of investing in health care services to support and empower parents and families during a most critical period of their children's life. In particular, we encourage the adoption of integrated strategies to establish adequate preventive efforts and a perspective shift to strengthen or develop where lacking, efficient health care services dedicated to the first 1000 days of life as the first line of prevention.

The Key Developmental Periods Characterizing the First 1000 Days

Three distinct periods can be identified during the first 1000 days (preconception, pregnancy and infancy), which are fundamental in promoting better outcomes in children's life.[3] Studies have highlighted the impact of poor parental health and well-being on the conceptus, before and from the moment of conception.[3-5] Specific programs and strategies have been developed to ensure that, during the preconception period, biomedical, behavioral, and social risks can be identified and modified to protect a woman's health or pregnancy outcomes through adequate prevention and management measures. Preconception care programs include distinct approaches ensuring that adequate nutritional and physiological support are provided to mothers and their developing conceptus to ensure optimal health. Identifying, evaluating, monitoring, and managing the various risks, including toxic exposures, that may predispose to adverse outcomes, is a further important element of preconception care programs.[6,7] Preconception is regarded as an opportunity for mothers to adopt changes in their lifestyle.[3] Interconception care should also be provided to women beginning with childbirth until the birth of a subsequent child to address the continuity of risks from one pregnancy to the next.[8]

The factors that impact the health and development of the conceptus during pregnancy include nutrition, stress and exposure to environmental contaminants.[3,9] The importance of supporting parents and infants in the first 2 years after birth has been stressed for decades, and in each country several public health care interventions have been developed in this area.[9] The large amount of data supporting the importance of establishing efficient health care services during a time crucial for the mother-child binomial have not been efficiently converted into comprehensive and integrated programs enabling adequate support to parents and infants during this period.

Positioning the First 1000 Days as Key to Socioeconomic Development

The insufficient attention paid during recent years to the first 1000 days of life may be justified by the global economic and health emergencies that have afflicted the world for more than a decade. However, underachievement in an area of public health may lead to the development of future social and economic costs that might become unaffordable in the long run. As reported by the World Bank, countries that fail to invest in the well-being of women and children in the first 1000 days lose billions of dollars owing to lower economic productivity and higher health costs.[10] Several of the world's leading economists have called for greater investments in this sensitive period of mothers health and children's development.[10] There are specific areas where

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greater attention is needed to improve the prospects for the next generations, irrespective of whether they live in economically advanced or challenged countries.[3] These areas includes maternal diet and health, breastfeeding, infant and toddler diets, noncommunicable diseases, and adequate health care services and support for families, particularly the vulnerable. Programs focusing on social and economic stability of families are additional factors contributing to a balanced development of the mother-child binomial during the fundamental first 1000 days of life.[11]

Implications for the Public Health Sector on the First 1000 Days of Life

In 1997 a seminal article introduced first the notion of "economics of attention," describing it as a sub-field of the "internet economics," which reflects the time-consuming dimension of overflowing information and its possible and often predictable negative consequences on social and public issues, including public health.[12,13] The increasing activity of bloggers or the intense use of social networks supports the observation that attention, rather than information or knowledge, has become a critical economic resource for decision-making. Several economists have recognized and debated the subject of limited attention, which has developed as one of the most important topics in behavioral economics, leading to important economic consequences.[14] This phenomenon was described as a rational inattention producing significant effects in the area of macroeconomic policies.[15] Central bankers now regard this phenomenon as one of the lessons to be drawn from the world financial crisis of 2008, which caused profound social and public health disorders in many countries.[16] Similar to the Leibniz metaphor of one's loss of awareness of the constant sound of a waterfall, the importance of fundamental needs ensuring optimum health, growth, and development to children across the lifespan could cease to be perceived without specific attention.[17]

However, the socioeconomic issues raised by the scarcity of attention have stimulated innovative research aimed at finding solutions to correct the social distortions caused by inattention. Different methodologies are currently explored to enhance the understanding of the role that attention plays in various contexts of decision-making in economics. The nudging approach pursues the idea that it is possible to countervail behavioral biases in a noninvasive way to enhance both individual and social welfare and achieve significant changes in the development of public policies,[18,19] The nudging approach would enable decision-makers to redirect their investment strategies toward public health solutions, such as the importance of well-being for the mother-child binomial This process might create brighter and more prosperous conditions for future generations, while at the same time containing public health costs through adequate health prevention programs.[20,21]

Conclusions

The implementation of integrated and systemic interventions, including changes to health care law and policy that promote equality of health care delivery, would improve dedicated services and target special needs during the first 1000 days.

Focusing on service provision during the first 1000 days is the most effective and efficient means of preventing poor health and diseases, while promoting well-being, learning and development outcomes later on in life.

Greater investment should be directed toward services that target the most impactful interventions for future parents and new families, such as nutrition or antenatal smoking cessation programs.[22] Targeted services should be provided for parents, families, and children showing greater and complex needs and in general for populations considered at risk. As emphasized by the World Bank, targeted interventions and special services should include not just provision of information and periodical schedule of controls, but where possible, direct programs aimed at helping families to implement best practice at home.[10,23,24] ■

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Advocating for Children Trapped in the Midst of Armed Conflicts

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Natural and human-made disasters, including civil unrest, terrorism, biological and chemical threats, and war, have affected the world on a recurring basis.[1] These events have caused suffering and misery to populations and have revealed a low degree of self-sufficiency and a high degree of unpreparedness on the part of governments to deal with the consequences.[1] Natural and human-made adversity typically generate public health crises and economic instability,[2] with lasting negative effects on the socioeconomic status of populations of all ages. These adverse effects affect children, who are among the most marginalized and vulnerable members of society and rarely consulted when communities make decisions that directly affect them.

War is one of the world's most devastating events, requiring short-term interventions and complex long-term recovery planning, articulated in 4 phases—mitigation, preparedness, response and recovery[3]—that focus on the rights of children who are in vulnerable circumstances and, therefore, at greater risk of harm.

This commentary, authored by members of the board of directors of the European Pediatric Association–Union of National Pediatric Societies and Associations (EPA-UNEPSA), briefly discusses the plight of children exposed to situations of terror and horror during war, including severe loss and disruption in their lives, which can result in the lasting effects of post-traumatic stress disorder. Our goal is to raise awareness among pediatricians and public health authorities of the importance of developing programs directed toward the rehabilitation of children affected by war, including social healing and peace culture education, as a key approach to primary prevention of the recurrence of war.

Children Affected by Armed Conflict Are at Increased Risk of Serious Violations of Their Human Rights

EPA-UNEPSA align with the American Academy of Pediatrics in defining armed conflict as any organized dispute involving the use of weapons, violence, or force, whether within national borders or across them, and involving state actors or non-governmental entities. Included in this definition are international wars, civil wars, and conflicts between other types of groups, such as ethnic conflicts.[4]

Armed conflict has escalated over the past decade in several parts of the world, including Afghanistan, Ethiopia, and Myanmar, pushing millions of children and their communities to the brink.[5] The number of children affected by armed conflict has risen by over 100% in the past decade. Some 450 million children—about a quarter of the world's children—live in countries affected by conflict of varying nature and intensity and affected by disasters[5] (**Figure**; available at www.jpeds.com). In particular, armed conflict is estimated to have killed more than two million children and physically maimed 6 million more. More than 45 million have been forcibly displaced from their homes, increasing their exposure to severe loss and hardship and making them vulnerable to exploitation and violence.[6,7] Conflict deprives children of their parents, caregivers, basic social services, health care and education.[8] Humanitarian organizations, including the World Health Organization and United Nations Children's Fund, estimate that there are currently some 20 million displaced or refugee children in the world as a result of armed conflict.[9,10] However, the recent armed conflict in Eastern Europe, Ukraine, showed that such events might not take place gradually but happen unexpectedly, therefore, generating complex humanitarian emergencies.[11] Children can be caught up in violence while being cut off from essential medical care, clean water and food.

Of the estimated 8 million refugees who fled Ukraine by the end of March 2022, more than 1.8 million children are estimated to have crossed into neighboring countries as refugees and 2.5 million are internally displaced within Ukraine, which is one of the fastest large-scale displacements of children since World War II.[12] Many of them are unaccompanied or have been separated from their parents or family members. Complex humanitarian emergencies affecting children trapped in the midst of armed conflict can result in various types of exploitation that produce profound short- and long-term impacts on children's lives. In this regard, humanitarian organizations have sounded a strong alarm[9,10] about the trafficking risks faced by children living in Ukraine. These include the sale of abducted children, forced labor, illegal adoption, forced organ donation and various forms of sexual exploitation.[12-14] Additional issues include the monitoring of children's vaccination status and the possibility for them to use the public health system of the hosting countries.

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Protecting Displaced Children

When these children are moved across borders, the risks of their human rights being violated multiply. Neighboring and affected countries must ensure the immediate identification and registration of unaccompanied and separated children fleeing conflict, once they have been allowed access to their territory.[10]

Under international human rights and humanitarian law, governments and all parties involved in conflict have an obligation to protect the rights of displaced children. Authorities responsible for protecting displaced children should be made aware of their rights and ensure their protection through strengthening national and local institutional capacities to address internal displacement. Part of the blueprint for an effective protection strategy is the designation of national institutional focal points to address internal displacement.[11] This includes offices dedicated to addressing the plight of internally displaced children and ensuring that all relevant national authorities, including the military and police, receive adequate training that effectively empowers them to deal with such emergencies in the short and long term. States should provide safe spaces for children and families immediately upon crossing borders, and link them to national child protection systems.[11] As the current emergency also calls for rapid expansion of the capacity of emergency assistance agreements with selected caregivers, as well as other services for child protection, including against gender-based violence, and family tracing and reunification mechanisms.

As demonstrated during the recent armed conflict that erupted in Eastern Europe, children also may be exposed to mishandling of their plight. For example, children displaced across borders without their families and temporarily under various forms of foster care by local or external authorities or other community-based care are often offered critical protection. However, adoption should not occur during or immediately following emergencies. Instead, every effort should be made to reunite children with their families, as such reunification is in the best interests of the children.[15,16]

Special attention also should be paid to children living in institutions and boarding schools. Although humanitarian evacuations may, in particular circumstances, be a lifesaving effort to ensure the safety of these children by relocating them to neighboring countries or beyond, it is essential that, in the best interests of the children, extraordinary measures be taken after obtaining the consent of the family or guardian.

Fostering Resilience in Children Affected by Armed Conflict and Displacement

Several studies have emphasized that a child's ability to manage their well-being, develop resilience and adapt to and cope with adverse events is the product of highly complex processes that result from the interplay of risk and protective factors at individual, family, community and sociocultural levels. Children and adolescents who have experienced significant adversity, such as armed conflict, are at risk of failing to cope.[2] Resilience processes have been extensively articulated.[17] They are therefore both historically and culturally determined and the result of long-term planned educational programs. The reshaping of life resulting from adversity brings significant challenges because of the need to adapt to new circumstances. Therefore, understanding the complex pathways and processes by which children adapt to adverse conditions and recover from stress and trauma is critical to developing effective interventions to support the well-being of youth affected by conflict and displacement.[18]

Caring for Children After Armed Conflict Ends

Disasters affect children differently from adults. Specific short- and long-term needs characterize children's lives after armed conflict ends. They include, tracing of family members, reparation and social reintegration, psychosocial rehabilitation programs, participation in disarmament, demobilization and reintegration programs. In this regard, EU countries are pursuing the creation of a forum to follow up on the Paris Commitments,[19] focusing on coordinating and facilitating international support for such programs. In particular, reintegration of children through investments that aim to adopt an inclusive approach, prioritize family reunification, and provide support, including financial support, to enable full reintegration into civilian life.

Conclusions

By protecting children from harm in armed conflict, we keep hope alive and commence the preparation of children to forge a peaceful future for themselves and their countries. By acting together, pediatricians, allied child health care providers, public health professionals, researchers, and policymakers can effectively address the impact of armed conflict on children as a critical and priority issue, and insist with national and international leaders that protecting children during armed conflict is the cornerstone of our shared humanity.[20,21] EPA-UNEPSA is fully committed to advocating for children, protecting them from violence, abuse, and exploitation, and providing the services necessary to help every child, of every age, everywhere, overcome armed conflict with hope for a better future. ■

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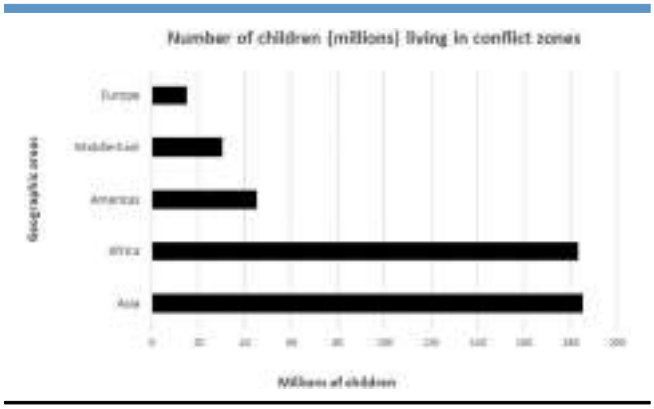

Figure. Geographic distribution of 450 million of conflict-affected children. Data elaborated by the EPA-UNEPSA working group on social pediatrics.

Social Media and Functional Gastrointestinal Disorders in Children

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Although social platforms allow people to stay in touch with each other, they are also a source of stress.[1] Social media posts that focus on the positive may cause stress for users who are not happy to see how everyone else seems to be doing well in life while they are dissatisfied with their lives. Social media also can provide a platform for the spread of dissenting opinions and hostile and unfriendly comments, which can cause distress.[2,3] However, it is unclear how stress triggered by social media can cause physical problems and adverse effects on gut health and related body systems.[4,5] Studies are limited and insufficient to fully elucidate how social media use may affect gut health. Children, vulnerable members of society, are exposed to the negative influence of external factors on their health and well-being. This commentary, written by members of the Working Group on Social Pediatrics of the European Association of Pediatrics, Union of European National Societies and Associations of Pediatrics, discusses the role of social media as a cause of FGIDs in children. The goal is to raise awareness among general pediatricians and families about this phenomenon, which often affects children and adolecsents.[6-8]

The Use of Social Media by Children

Social media is now used by more than two-thirds of all internet users.[9] The first social media site to reach 1 million monthly active users was MySpace, in 2004.[10] Most of the social media platforms that have survived have changed significantly in what they offer to users. One popular social media platform, Twitter, did not initially allow users to upload videos or images. However, in 2011, a policy change by the owning company made this possible, and today more than 50% of the content viewed on Twitter includes unsupervised images and videos, which typically have a strong immediate impact on children.[7]

By 2019, the average age of first internet use had progressively dropped to 8 years in several European countries,[11,12] where the daily time spent on the internet using various devices by young people varied between 2.75 and 6.03 hours (**Figure**; available at www.jpeds.com). A similar increase in children's internet use has been reported for the US, where in 2019, according to the American Community Survey, approximately 95% of 3- to 18-year-old children had internet access from home, showing a significant increase from 2013 (57%), and 10 times greater than in 1997[13] (11%).

Especially for older teens, social media is often a key part of how they connect with friends. However, unawareness of the risks posed by use of digital media can expose them to serious cognitive, social, psychological, and physical consequences. A growing number of reports suggest that excessive and/or unskilled use of the internet can adversely affect the psychological and physical dimensions of users.[14] Several studies have drawn attention to the important role of bidirectional interactions between the brain and the gut in generating stress and emotional responses.[15,16] Thus, stressful conditions due to the use of internet tools such as social media may cause a range of adverse health outcomes, including gastrointestinal (GI) manifestations with an impact on children's health and well-being.[14]

Relationship Between FGIDs and Psychosocial Factors

FGIDs, also known as gut–brain interaction disorders,[17] are due to abnormal functioning of the GI tract and are characterized by a set of recurrent or chronic symptoms that vary with age and are not associated with an underlying organic disease.[18] The most common and widely studied FGID is irritable bowel syndrome, described as abdominal pain associated with altered bowel habits of diarrhea, constipation, or alternation of both.[19] FGIDs also include functional dyspepsia, which is characterized by pain or discomfort in the upper abdominal area, sensation of fullness, bloating, or nausea, functional vomiting, functional abdominal pain, and functional constipation.[18]

The overall prevalence of FGIDs in children and adolescents ranges from 9.9% to 29% and can be as high as 87% in clinical samples.[20] FGIDs include approximately 20 functional GI disorders, affecting any part of the GI tract, including the esophagus, stomach, bile duct, and/or intestines.[21] Individuals with FGIDs are diagnosed according to the Rome criteria, based on clinical symptoms and in

FGID	Functional gastrointestinal disorder
GI	Gastrointestinal

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the absence of inflammatory, metabolic, or anatomic abnormalities.[19]

Functional symptoms later in life may originate from abnormal behavioral responses to internal or external stimuli, such as functional constipation caused by painful defecation or due to forced toilet training.[22] Physiological, psychological, and sociocultural conditions may increase the perception of symptoms as severe and disabling, with a major impact on activities of daily living.[23] Despite recent advances on the pathophysiologic mechanisms of some FGIDs, no gold standard diagnostic test is currently available.[18,19,24]

A biopsychosocial approach has been proposed to explain FGIDs, and internal and external factors, including genetics, influence of family behavior, abuse, and social media pressure, have been recognized as causative elements.[25] Alone or combined, these factors may influence children's physiopsychological condition, cause increased susceptibility to stress, and likely be the trigger of gut dysfunction.[25] Thus, FGIDs can be considered the clinical product of the interaction between psychosocial factors and altered gut physiology, through the brain–gut axis.[14,26] Social media, which is a recognized cause of stresss,[27] can be included among the psychosocial environmental factors influencing the development of FGIDs in children using these digital interaction media.[27]

Negative Effects of Social Media on the Gut–Brain Axis

Some empirical evidence and reports from the literature indicate that social media use can be beneficial to the mental health and well-being of children and adolescents.[28,29] Social media can provide individuals with a platform that transcends the barriers of distance and time, allowing them to connect with others and thereby expand and strengthen their personal networks and interactions.[29] However, multiple studies have shown a strong link between heavy social media use and depression, anxiety, loneliness, self-harm, and suicidal thoughts in children, which also show comorbidity with FGIDs.[30,31] A high prevalence of social media use has been reported in adolescents with FGIDs, which is likely related to the severity of their symptoms.[27,32] Studies have demonstrated a correlation between excessive social media use and psychological problems such as depression and anxiety,[7,8,31] and many individuals with FGIDs, including recurrent abdominal pain,[18,19] often complain of psychological symptoms.[23]

Conclusions

Studies investigating the association between social media use and FGIDs in children are scarce. The European Paediatric Association–Union of National European Paediatric Societies and Associations suggests that social media use may play an important role in causing FGIDs. Pediatricians and families could play a key role in helping children and adolescents with unhealthy social media use through appropriate policy interventions that help them use social media platforms more responsibly[33-35] (**Table**; available at www.jpeds.com). ■

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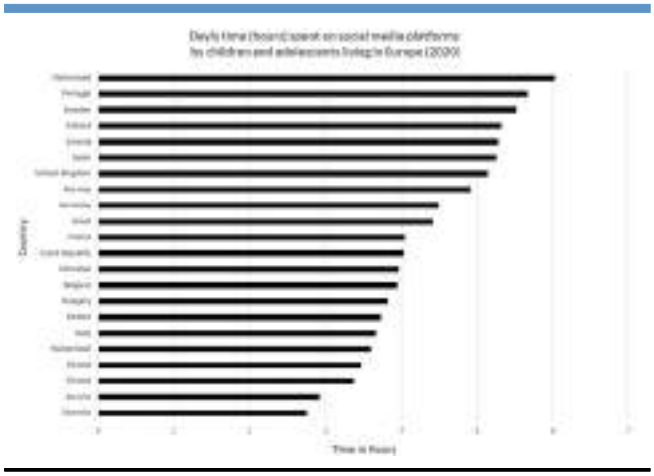

Figure. Use of social media by children and adolescents living in European countries, measured in hours per day.

Table. Recommendations for helping children and adolescents avoid unhealthy social media use

- **Refrain from taking drastic measures.** Avoid simply confiscating phones or other devices, as it may create further problems, which include separating children and adolescents from their friends and canceling the positive aspects of social media.
- **Monitor and limit social media use.** Parental control apps can help limit children's and adolescents' data use or restrict their phone use to certain times of the day. An additional measure is to adjust privacy settings on the different platforms to limit their potential exposure to bullies or predators.
- **Enforce breaks in social media use.** Forbid the use of social media until the users have completed their homework, do not allow phones at the dinner table or in their bedroom, and plan family activities that preclude the use of phones or other devices. To prevent sleep problems, it is advisable to insist that phones are turned off at least 1 hour before bed.
- **Talk to children and adolescents about underlying issues.** Problems with social media use often can mask serious issues. They may include relational problems at school, suffering from shyness or social anxiety, covering stress conditions due to problems at home, or suffering from abusive behaviors.
- **Encourage exercise and offline interests.** Encourage children and adolescents to pursue physical activities and hobbies that involve real-world interaction. Practicing sports and group activities relieve anxiety and stress, boost self-esteem, and improve mood, particularly if these activities are performed as a family. The more engaged children and adolescents are offline, the less their mood and sense of self-worth will be dependent on how many friends, likes, or shares they have on social media.
- **Teach that social media is not an accurate reflection of people's lives.** Families, caregivers, or pediatricians may explain to users that they should not compare themselves or their lives negatively with others on social media, as other people's post are misleading because they only post what they want others to see. Also, explain that images are often manipulated or intentionally selected and published. Teach children and adolescents that having fewer friends on social media does not make them less popular or less worthy.

Recommendations suggested by the European Paediatric Association–Union of National European Paediatric Societies and Associations working group on social pediatrics useful in helping children and adolescents with unhealthy social media use.

Addressing Weight Stigma and Weight-Based Discrimination in Children: Preparing Pediatricians to Meet the Challenge

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Overweight and obesity affect more than 17% of children worldwide.[1] In the European region, 1 in 3 children between the ages of 6 and 9 years currently has overweight or obesity,[2] whereas in the US, childhood obesity rates have tripled over the past 3 decades and currently about 1 in 3 children is has overweight or obesity.[3] The prevalence of obesity in the population aged 2-19 years residing in the US during 2017-2020 was 19.7%, affecting about 14.7 million children and adolescents.[4] Children and adolescents living with overweight and obesity often are stigmatized by peers and viewed negatively because of their distinguishing characteristic, which is considered by many a social disadvantage.[1] Weight stigma has important social implications and can hamper the success of antiobesity treatments. Children and adolescents are particularly vulnerable to the negative consequences of weight stigma in their families and communities. Discrimination against children based on weight is equal to that of other types of stigma, including that based on race, religion, or physical disability.[5] This commentary, prepared by a working group of international experts in the field convened by the European Pediatric Association, Union of National Pediatric Societies and Associations, aims to raise awareness of weight stigma and its negative effects on children and adolescents and to emphasize the importance for pediatricians to be adequately trained to address this challenge in their practice.

Definition of Weight and Obesity Stigma

Stigma defines a negative attitude or discrimination against individuals based on a distinguishing characteristic of various kinds, including sexuality, race, religion, culture, and health condition.[6] Misconceptions and prejudice can exacerbate the suffering and distress of individuals with many health conditions and generate disease stigma, as in the case of obesity. Specifically, weight stigma refers to discriminatory actions directed at individuals because of their weight, size, and look. Prejudices that generate weight stigma are frequently supported by negative ideologies associated with obesity, which may include laziness, lack of willpower, lack of moral character, poor hygiene, low intelligence, and lack of attractiveness.[6]

Weight Stigma and Identity Threat in Children

Weight-related prejudices, stereotypes, and preconceptions induce a threat to social identity in children and adolescents who experience stigma.[7-9] Victimized individuals often are ridiculed or bullied by peers or regarded unfairly by people, frequently due to the common perception that weight stigma is justifiable and motivates children to adopt healthier behaviors. Children living with obesity who experience discrimination related to their weight often show poor psychological and emotional health.[7-9] Existing evidence suggests that weight stigma causes long-term negative effects and severe implications for the physical and mental health of children and adolescents, which may continue into adulthood.[7-9]

Internalized Weight Stigma

Literature on the processes that lead to the internalization of weight stigma by children and adolescents is scarce.[10] Experiencing weight stigma does not necessarily lead to its internalization.[11] However, several studies report the negative effects of internalized weight stigma on mental health in particularly fragile subjects such as children and adolescents.[12] These subjects may undergo a process of self-stigmatization similar to that observed in mental illness and thus suffer a form of self-devaluation resulting from weight stigma.[12] Individuals experiencing internalization processes accept and agree to a different extent with the external description of their weight condition and apply these connotations to themselves. This process, described as internalization of weight bias,[13] can further increase the negative consequences of stigma and, in some circumstances, is considered more important than the experience of stigma or weight status alone.[12] Increased negative health outcomes are often associated with the early onset of mental health problems.[12]

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Weight Stigma in Different Contexts and Its Many Consequences

Weight stigma is prevalent among youth, the media, schools, workplaces, and even families and health care facilities. Victimization, mockery, and bullying characterize the practice of weight stigma by young people.[14] Beginning in kindergarten, children may apply negative stereotypes to their classmates with larger builds. Increasing reports show that educators and parents also exercise weight stigma through weight-based victimization of youth. Teachers and parents hold lower expectations in various areas, including sports, social relationships, and academic abilities, for children and adolescents living with overweight and obesity, who are considered disadvantaged compared with children of normal weight.[14] An additional source of weight stigma is television and other media that young people commonly watch for several hours a day, where entertainment shows and movies often use easy stereotypes such as characters with larger builds who are portrayed negatively and as targets of humor or ridicule to increase viewership. The use of social networks has facilitated the rise of new forms of victimization such as cyberbullying, which can spread through the network with extreme ease and in a severely invasive manner. Cyberbullying often uses weight stigmatization as a strong form of discrimination and offense.

Weight stigmatization also can occur in healthcare settings, wherein healthcare professionals often express various forms of weight stigma toward children with obesity. The use of terms and definitions that are perceived as undesirable, stigmatizing, or blaming by children and adolescents, such as fat, obese, or extremely obese, are often the cause of a lack of motivation. These attitudes can affect patients with obesity who may suffer from stress, showing avoidance of treatment and worse outcomes due to distrust of doctors and low expectations of treatment. Finally, weight stigma causes various psychological, emotional, and social consequences, impacting the physical health of children and adolescents,[15] including negative outcomes that may reinforce unhealthy behaviors, which promote obesity and weight gain[16,17] (**Table I**; available at www.jpeds.com).

Addressing Weight Stigma by Pediatricians and Educators

Pediatricians play an important role in protecting children from the risks of adverse events.[18] They must engage in strategies that address the sensitive issue of weight to promote resilience and help children and their families cope with stigma (**Table II**; available at www.jpeds.com). Countering stigma in general and weight stigma in particular should play a central role in educational programs.[19] Appropriate academic training and continuing education programs committed to countering stigma should be dedicated to all professionals considered central to these strategies, including pediatricians, other health professionals, and educators. Efforts should be made to involve public and private organizations, including professional, scientific and community associations[20] in countering "weight stigma" and learning how to deal with this form of discrimination and its consequences, while developing healthy attitudes and positive relationships in families (**Table III**; available at www.jpeds.com).

Conclusions

Childhood and adolescence are periods of life in which social relationships are forged, and the experience of discrimination by weight stigma can be a damaging experience, particularly painful if experienced at a time when peer rejection is keenly felt.[8,9] Pediatricians and pediatric health care providers can play an important role in addressing any form of discrimination, including child and adolescent stigma, by raising awareness that weight stigma is a form of discrimination and its related stereotypes do not reduce obesity or improve healthy behaviors.[14] ■

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Table I. Psychological, physical, and social effects of weight stigmatization in children and adolescents

- Emotional and psychological consequences

Weight-based stigmatizing experiences may trigger emotional and psychological effects, including low self-esteem, increased vulnerability to mental diseases, depression, anxiety, drug and other substance use, and poor body image. Self-harm and suicidal behaviors are greater in children and adolescents victimized about their weight compared with peers of the same age and weight who have not been target of weight stigmatization

- Social isolation and poor academic outcomes

Weight-based victimization induces social isolation and is the cause of poor academic outcomes. Weight-based discrimination in school influences the relationships between students and generates a progressive decline in school performance compared with previous years. Often children and adolescents disengage from their academic duties and school environment.

- Unhealthy eating behaviors

Weight-based harassment worsens unhealthy eating behaviors.

- Reduced physical activity

Exercise and physical activities are severely impacted by weight-based stigmatization. Socializing physical activities are significantly reduced, further influencing the relationships with peers and minimizing the motivations to follow antiobesity treatments.

- Worsening obesity

Being victims of weight-based stigma may often demotivate the victims, who perceive as useless their efforts to improve their condition. Weight stigma and discrimination increase the risk of developing and continuing to have obesity over time.

Table II. Recommendations for the contrast of weight stigma to be shared with public and private institutions involved in childhood care

- Acknowledge obesity as a chronic disease.
- Provide training for health care professionals on obesity and weight stigma.
- Require all accredited health care facilities to address obesity with trained professionals and adequate equipment, to facilitate access to care and sustainable change toward healthier lifestyles.
- Avoid stigmatizing and/or weight-centered advertising campaigns.
- Spread the antistigma culture in all areas: health, education, politics, and media. Eliminate negative language, words, images when referring to children and adolescents with obesity and their families.
- Carefully evaluate reports, interviews, and articles published regarding the choice of words and images, to promote a culture which does not promote stigma in the media.
- Fund research on the treatment of obesity and stigma proportionally to the prevalence and impact they have on health.

Support "strong" policies to ban stigma on weight as a violation of the right to physical and mental health.

Table III. Tackling weight stigma in children: recommendations for pediatricians and health professionals

- Ask for permission to discuss the child's/adolescent's weight before addressing the topic.
- Respectfully evaluate the weight status of each child/adolescent, with the body mass index z score, and communicate the diagnosis to children and parents in a nonjudgmental way. Help the patient and family to understand the complex nature of obesity and the responsibility of the current obesogenic environment.
- Provide a comprehensive evaluation of each child/adolescent on a physical and psychological level.
- Investigate with adequate language about previous episodes of ridicule, discrimination, internalization of stigma (possible questions: "Do you think that your weight influences the evaluation you have of yourself?"; "How do you see yourself?"; "What do you think of yourself?").
- Contextualize the official recommendations for the care of obesity to the family and the child/adolescent and ask for their participation in making a personalized and sustainable care plan; arrange for integration with other professionals in specific cases. Explain the changes and avoid unjustified simplifications (eg, the presumption that "small, easy daily changes in diet and physical activity are enough").
- Periodically provide a global assessment of the child/adolescent, to empathically support strategies to improve behavior and well-being. Don't assume that if weight hasn't changed, neither have behaviors.
- Help parents become aware of weight stigma and to investigate any incidents of ridicule, discrimination, bullying, and cyberbullying at school or in the family itself, and to address them appropriately.
- Refer children/adolescents with severe or complicated obesity who do not respond to treatment to second-level centers, accompanying them and taking care of their transition to the general practitioner.

Adequate Training and Multidisciplinary Support May Assist Pediatricians in Properly Handling and Managing Gender Incongruence and Dysphoria

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What we call "sexual identity" refers to the complex relationship between biological sex, gender identity and role, and sexual orientation.[1] "Gender identity" means the unified and persistent perception of oneself as belonging to the male or the female gender or ambivalent. For many, gender identity coincides with sexual identity; traditional culture has long provided for the definition of only 2 genders, corresponding to the 2 biological sexes. The person with gender incongruence experiences a disharmony between biological aspects and gender identity, with the constant awareness that he or she belongs to the opposite gender and is imprisoned in a body that does not represent him or her.

General pediatricians and practitioners are frequently the first formal contact for gender-nonconforming children and their families seeking support and guidance on how to address their children's emotions and needs.[2] However, health professionals may not always be adequately prepared. This commentary, prepared by the working group of Social Pediatrics of the European Pediatric Association, Union of National Pediatric Societies and Associations, aims to raise awareness of the increasing number of children and adolescents presenting gender incongruence[3] and to emphasize the importance for pediatricians to be adequately trained to properly address this challenge in conjunction with local multidisciplinary teams of specialists.

Terminology and Gender Identity Development in Children and Adolescents

The terminology used to describe a condition in which the gender identity of a person does not align with the gender associated with their birth sex (which is based on physical sex characteristics) has varied frequently. The *International Classification of Diseases, 11th Revision*, by the World Health Organization[4] and the Psychodynamic Diagnostic Manual[5] reflect an effort to articulate a psychodynamically oriented diagnosis that would bridge the gap between clinical complexity and the need for empirical and methodologic validity.[6] Therefore, gender incongruence was from the psychiatric category and included in sexual disorders.[2,4]

The term gender identity is generally used to classify a child or an adolescent as being male, female, or neither/both. The condition in which the gender identity of an individual is unaligned with the gender ascribed at birth is currently indicated as gender incongruence, which replaced the previously used terms transsexualism and gender identity disorders. Gender dysphoria describes the distress and anxiety experienced by persons who feels adversity to the anatomy and function of their body.[7] The variety of gender identities across the gender spectrum, including the transgender, is described in the **Table** (available at www.jpeds.com).

A controversy rose around the possibility of a rapid-onset of gender dysphoria condition (ROGD) in children, which was suggested to be a subtype of gender dysphoria caused by peer influence and social contagion.[8] However, major medical associations, including the American Psychological Association, the American Psychiatric Association, and the World Professional Association for Transgender Health, do not recognize ROGD, due to a lack of consistent scientific evidence for the concept, and discourage its use. Finally, although recent studies analyzed clinical data of teenagers seen in gender clinics and found no support for ROGD being a distinct phenomenon,[9] the issue is still open.[10,11]

During the last decade, the number of children and adolescents with gender incongruence and gender dysphoria seeking help from health professionals and institutions has increased significantly.[2] Although differences in the selection of study cohorts, subjects' ages, and method of investigation may have influenced available statistics, the prevalence of gender incongruence and gender dysphoria in children and adolescents currently is reported to be in the range of

Keywords
ROGD Rapid-onset of gender dysphoria

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0.6%-1.8%.[2,3,12] A meta-analysis on broad range of prevalence studies on transsexualism in the population from Europe, US, and Australia report an overall prevalence of 0.46/10 000 (0.68 for birth assigned males and 0.26 for birth assigned females).[13]

Mental Health and Gender Nonconformity

Studies investigating the prevalence of mental disorders in people attending transgender health care services report, although not conclusively, high rates of mental health disturbances, including psychiatric and psychopathology conditions.[14] Studies on the mental health of children and adolescents with gender incongruence and gender dysphoria are scarce and not conclusive. Typically, children begin to affirm their gender identity at an early age being linked to the anatomical sex, and in the majority of them their social development evolves concurrently.[1] In the preschool and school period, a limited number of children identify as transgender. However, available data indicate that approximately 80% of those who identified as transgender before the onset of puberty return to identify with their birth gender.[1]

Currently, no evidence-based guideline for psychological support in children and adolescents is available. However, significant attention must be given by health professionals to decreasing distress and anxiety possibly caused by the gender incongruence. In particular, they should put their efforts to preparing and assisting the children and their parents in the management of this condition when the children's endogenous puberty development begins.[2] It is important to provide psychological counseling aimed to guide adolescents and parents during this process and support them in the event medical treatment will be considered, including hormonal treatment, surgery, and fertility preservation.[1] Parents and caregivers are essential to adolescents' health decisions.[2] Therefore, available options must be discussed with both and balanced with expectations. Support groups or self-help organizations have been shown to be a valuable tool during medical transition.[2,15]

Medical Interventions

Adolescents with gender incongruence/gender dysphoria may experience serious psychological functioning and behavior disorders when they develop their biological secondary sex characteristics.[1] To reduce the discordance between body and gender identity, and to extend the temporal window for gender clarification, centers have used pubertal suppression.[16,17] Prevention or arrest of pubertal development was mainly obtained by the administration of long-acting gonadotropin-releasing hormone analogue to suppress gonadotropins. Studies supporting the clinical utility of puberty-suppression treatments in this group are considered insufficient, and puberty suppression as a treatment for gender-incongruent minors is currently still the subject of debate and ethical discussion among specialists.[17] Endocrine Society guidelines indicate that stopping the progression of puberty is acceptable in presence of manifested dysphoria about unwanted secondary sex characteristics and clear signs of puberty, including Tanner stage 2 and greater.[18] Concerns have been raised about possible secondary effects of endocrine intervention, including those on reproductive system and bone mineralization. Fertility recovery is uncertain after the onset of gonadotropin-releasing hormone analogue, and bone mineralization, which normally takes place during puberty, may be reduced inducing a state of osteoporosis that is nonrecoverable.[1]

Conclusions

With the beginning of puberty, an increasing number of people explicit gender incongruence and seek physical and endocrine support[1] and may request a referral to a specialist pediatric endocrine clinic.[1] Pediatricians and general practitioners are usually the first stop for children with gender incongruence/gender dysphoria and adolescents and their families.[19] However, disclosing sexuality with providers may present several complicated obstacles for children and adolescents with gender incongruence/gender dysphoria, who may experience judgment, insensitivity, and stigma depending on the providers' level of knowledge of gender identity health care.[20] Academic training and education in the management of gender incongruence/gender dysphoria is insufficient, and it should be implemented through dedicated courses by medical schools and allied health programs with scientific organizations.

Finally, a key factor for the adequate management of children and adolescents with gender incongruence/gender dysphoria is the availability of specialized centers and local multidisciplinary team support.[21] These teams should include a panel of specialists that provides assistance in several areas, including gynecologic and urologic care, reproductive science,

voice and communication therapy, nutrition, and endocrinology.[22-25] Gender and psychosocial development and family functioning should be evaluated in youngsters with gender incongruence and gender dysphoria, who also may show various associated mental health problems, including depression, anxiety, and suicidal feelings. Therefore, mental health professionals should work within a multidisciplinary team or in close contact with other gender specialists, providing assessment, counseling, and psychotherapy, where needed.[1,14] ■

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50 Years Ago in *The Journal of Pediatrics*

Childhood Malignancies Mimicking Inflammatory Arthritis

Schaller J. Arthritis as a presenting manifestation of malignancy in children. J Pediatr 1972;81:793-7.

In 1972, Schaller published a case series of 13 children who presented for rheumatologic evaluation of inflammatory arthritis-like symptoms but were later found to have malignancy. Her article showcased how malignancies and rheumatologic conditions like juvenile idiopathic arthritis can present similarly and how difficult it can be to differentiate between the two. In the article, 10 of the children had acute lymphoblastic leukemia (ALL), but the cases also included rarer malignancies. Most of the patients presented with oligoarticular pain, swelling, and/or limited range of motion of the large joints, but some had polyarticular involvement. Seven of the patients with ALL presented with abnormal blood counts, 8 had elevated inflammatory markers, and 2 patients had positive rheumatoid factor. A minority of the patients had radiographic findings concerning for leukemia at presentation, but others had nonspecific changes, and 1 case had bony erosions of the sacroiliac joints. Eight of the patients were diagnosed correctly with leukemia shortly after initial evaluation, but others had nondiagnostic initial workups or were treated as having rheumatologic disease for a few months before the correct diagnosis was established. In the 10 patients with ALL, the most helpful distinguishing features were severe joint pain and hematologic abnormalities.

These cases emphasized the importance of maintaining a high suspicion for malignancy in the differential of inflammatory arthritis; this lesson still holds true today. Brix et al recently published a cross-sectional retrospective study comparing clinical manifestations and laboratory results of 26 children with ALL and arthritis vs 485 children with juvenile idiopathic arthritis and similarly concluded that distinction on clinical grounds was difficult; in this study, neutropenia and thrombocytopenia had the greatest ORs for identifying malignancy.[1]

Schaller's article is still relevant because, 50 years later, medicine has yet to develop tests that reliably differentiate between inflammatory arthritis and arthritis as initial presentation of malignancy. Blood counts, inflammatory markers, autoantibodies, and imaging studies, although helpful, are only supportive information, and the decision to pursue further evaluation still relies on the judicious clinical discernment of physicians. Research into biomarkers for the diagnosis of rheumatologic diseases is ongoing; in the meantime, a high index of suspicion is still needed to identify atypical presentations of malignancy and successfully treat these patients.

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Table. Gender-linked terminology across the wide spectrum of gender definitions

- **Birth-assigned gender:** Gender associated with the birth sex. It is assumed based on physical sex characteristics at birth.
- **Gender identity:** is the individual's personal sense of their own gender as male or female, neither, or both. Gender identity is not visible to others.
- **Gender identity disorders:** any medical condition, including mental, attributed to persons who do not align with the gender associated with the birth sex.
- **Gender incongruence:** describes individuals feeling discontent with their assigned gender. A condition in which the identification with a gender associated with their birth sex based on physical sex characteristics is perceived as not satisfactory.
- **Dysphoria:** describes the internal distress experienced due to the discordance between gender identity and birth-assigned gender. The term dysphoria is linked to the unease experience and frequently used as a diagnosis (see DSM-5).
- **Gender role:** behavioral attitudes and conduct that the civil societies associate to people in accordance with the gender assigned at birth. Birth-assigned gender profiling. It varies based on geography, cultural differences, and historical periods.
- **Gender expression:** refers to the external manifestations of gender. It is the way the gender identity is communicated in the social context. Gender identity often is perceived and interpreted by others based on gender expression and the external manifestations of gender. People usually perceive the gender as based on traditional gender roles (dresses, mannersisms, sports practiced)
- **Gender attribution:** How single individuals or a community view a person as masculine or feminine.
- **Transgender:** is an umbrella term that refers to the broad spectrum of individuals who identify with a gender other than that associated with their birth sex. Notably, not all transgender individuals experience a complete cross-gender identity. Transgender individuals do not necessarily demand hormone therapy or surgery.
- **Transman or transboy:** Term used to identify a birth-assigned female whose gender identity is male. Therefore, a person born phenotypically female (natal female), registered (assigned) female at birth, who identifies as male. Often defined as male (FtM).
- **Transwoman or transgirl:** Term used to identify a birth-assigned male whose gender identity is female. Therefore, an individual born phenotypically male (natal male), registered (assigned) male at birth, who identifies as female. Often defined as male to female (MtF).
- **Transitioning:** a status in which individuals begin to live their lives in accordance to their affirmed gender. Although hormonal and/or surgical treatment may or may not be involved.
- **Gender variance and gender diversity:** terms used to describe the wide range of gender identifications outside conventional gender categories, including gender expression and/or identity inconsistent with prevailing societal expectations and norms
- **Nonbinary:** a lack of identification with conventional maleness or femaleness. They may show features of both genders or neither.
- **Cisgender:** People whose birth-assigned gender aligns with their identify. Individuals who have a gender identity congruent with or the same as their birth-assigned gender.

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Child Brides and Forced Marriages: An Aspect of Child Abuse and Neglect

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Child brides and forced marriages, involving the population aged <18 years, occur across continents, cultures, and religions. Globally, 1 in 5 girls marry before the age of 18, and one-third are under 15 years old. Every day worldwide, 39 000 girls marry before reaching the age of majority, and 12 million girls marry before that age each year.[1] Child brides and forced child marriages have devastating effects on emotional and social development.[2] In most cases, girls are deprived of their rights, including education, family life, play, and recreation and are forced to assume adult responsibilities, including forced pregnancy. Childhood denied, along with the severe physical or emotional damage caused by child brides and forced marriages, can have long-term consequences for health, life opportunities, and well-being, endangering their lives, the lives of their children, and the future of their community. Child and forced marriages can be considered a serious form of child abuse and neglect, exposing girls to various forms of physical violence with severe long-term effects.

The Working Group on Social Pediatrics of the European Association of Pediatrics, the Union of European National Pediatric Societies and Associations, and the Board of Directors of the Turkish Pediatric Association are working jointly to develop recommendations to counteract child brides and forced marriages and their physical, psychological, and social impacts. The purpose of this commentary is to raise awareness among pediatricians and health professionals[3] about this issue and its possible lifelong risks. The authors point out that pediatricians can be influential advocates and play an important role in programs established to monitor and prevent the negative personal and social impacts caused by these practices.

Definitions of Child and Forced Marriage

The United Nations Convention on the Rights of the Child, established in 1990 and ratified by 191 of the 193 member states, defines a child as any human being aged <18 years, unless the law in a particular country provides for the child to attain the age of majority earlier.[4] Therefore, the widely accepted definition of child marriage is any formal marriage or informal union between a child aged <18 and an adult or with another child.[5,6] Establishing a minimum age for marriage can legally protect children from abuse, harm, violence and exploitation. Child marriage is considered a form of forced marriage that includes forced brides of any age.[7] Parties who have not personally expressed their full and free consent to the union are vulnerable to domestic violence, sexual abuse, dangerous living conditions, and infectious diseases, including HIV and other sexually transmitted diseases.[7,8]

Legal Aspects of a Global Phenomenon

Child marriage is a complex practice rooted in cultural beliefs and customs, linked to various other structural factors and social determinants that characterize many different countries, including their national legal systems. Since 1948, many international agencies, including the United Nations, have sought to end this culturally archaic practice. As stated in Article 9 of the European Union (EU) Charter of Fundamental Rights, each member state is responsible for legislating the right to marriage and its possible limitations. Article 12 of the European Convention on Human Rights and Article 16 of the Universal Declaration of Human Rights guarantee the right to marry only to those considered "of marriageable age," according to different national laws, while also recommending that the minimum age be set at 18 for both girls and boys, and state that any country that allows any form of child marriage is committing a violation of human rights.

Although laying the groundwork for a viable solution to this cultural problem, simply changing the laws in countries that are not aligned with the widely accepted standard age of 18—established by the United Nations Convention on the Rights of the Child to legally identify a child as such—will not end child marriage. It is important to ensure that legislative changes are widely communicated to the population and effectively implemented. In Indonesia, for example, the local

COVID-19	Coronavirus disease 2019
EU	European Union

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parliament has committed to eliminating the practice by 2030, in line with the Sustainable Development Goals. In 2019, the parliament raised the minimum legal age of marriage for girls by 3 years to 19, followed by education and implementation programs. Previously, Indonesian girls could marry as young as 16 and men as young as 19. Commitments need to be followed by concrete action, as evidenced by the situation in Indonesia, where the rate of child marriage has begun to decline (albeit slowly at first), by 3.5% from the 14.6% recorded in 2008 to 11.2% in 2018.[9]

However, in many countries there are legal exceptions where parents can ask religious courts or local officials to allow the marriage of girls age <16. South Asia has the highest rates of child marriage in the world, with nearly one-half (45%) of all women between age 20 and 24 marrying before age 18. Nearly 1 in 5 girls are married before age 15.[10] Underlying this practice are profound differences in legal systems and sociocultural and structural factors.[10]

Although child marriage is particularly prevalent in South Asia and sub-Saharan Africa, it also occurs throughout Europe as a practice "hidden in plain sight" because national legal systems are insufficient to fully protect children. All European countries are affected by the harmful practices of child marriage and forced marriage, whether forced marriages performed in Europe, forced marriages of European citizens or residents performed elsewhere, or forced marriage of people before arriving in Europe. Several EU member states still allow child marriage. Although some countries, such as The Netherlands, Germany, and Sweden, have declared child marriage illegal, others, such as Austria, Belgium, Italy, Spain, and the United Kingdom, have laws that allow children under age 18 to marry under certain circumstances, with parental consent[11] (**Table I**; available at www.jpeds.com).

Comparable statistics are scarce[12]; however, reports from various EU states show that child marriage is a phenomenon that occurs in all states, albeit at different rates. For example, 813 child marriages were reported in Germany from 2017 to 2020.[13] A high risk of early and forced marriage is reported for Roma girls and women in Italy, 64% of whom marry before age 18 and 30% before age 16, and in immigrant communities, an average of 17.7% marry by age 15 and 50.8% marry by age 18.[12] These human rights violations affect mainly women and girls and in a small percentage, minor boys. Each year hundreds of British girls are "given in marriage" as children because British law does not adequately protect them.[14] The 759 cases reported in the United Kingdom in 2020 represent a 44% decrease from the average number of cases (1359) reported annually between 2011 and 2019.[14,15] The EU Committee on Equality and Non-Discrimination is currently working to equalize the minimum legal age of marriage across all EU states.[1]

In the United States, although the average age at the time of first marriage has increased year by year, underage marriage remains a problem. A 2021 study reported by the University of Cincinnati Law Review showed that approximately 300 000 minors were legally married between 2000 and 2018.[16] As of January 2022, there is no minimum legal age for child marriage in 9 states, if all exemptions are considered, and only 6 US states prohibit child marriage without exception. This means that child marriage is technically legal in 44 states in the Union.[16,17]

Child and Forced Marriage as a Form of Child Abuse

Currently, more than 700 million women are married before they turn 18, and 1 in 3 are married before age 15.[18,19] Predisposing factors include gender inequality, poverty, cultural traditions, insufficient legal norms, and social insecurity. Child and forced marriage violate the child's most intimate sphere, causing severe physical and psychological harm and, like child abuse and neglect in US and EU legislation, can be described as the result of an act or omission that causes severe physical or emotional harm, sexual abuse, or exploitation.[20-22] Girls forced to marry against their will often end up being condemned to a life of servility and abuse. Nontraditional, religious, cultural, economic, and possibly security considerations may justify a practice that can be considered in many ways a form of slavery.

Conclusions

Child brides and forced marriages are complex and persistent phenomena associated with profound global cultural, religious, and economic contexts. Variables, such as the Coronavirus disease 2019 (COVID-19) pandemic, can increase their impact on society. UNICEF reports show that the socioeconomic consequences of COVID-19 are pushing many families into poverty, increasing the risk of children being forced into labor and early marriage.[23,24] Statistics estimate that 10 million more girls are at risk of child marriage due to pandemics like COVID-19.[23]

The European Association of Pediatrics, Union of European National Pediatric Societies and Associations, and Turkish Pediatric Association are currently working to develop joint recommendations to combat child brides and forced marriage.[25] The strategy used by their task force involves using existing guidelines and systematic reviews, and developing their findings.[26] They are working as described in the risk assessment for child marriage shown in **Table II** (available at www.jpeds.com) to develop a plan based on adopting existing recommendations, adapting existing recommendations, developing new recommendations using appropriate existing systematic reviews, and developing new recommendations using input from an expert panel. ■

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Table I. Age at which children can marry with consent of a public authority (judicial or administrative body) and/or parents in the EU 27 countries plus the United Kingdom (last update 2019)

- No possibility to marry below the categorical value of age 18 years: Denmark, Germany, The Netherlands, and Sweden, and Poland, but only with regards to men
- Countries in which the absolute minimum age of 16 is explicitly set for marriage with consent, either parental or by a public authority: Austria, Bulgaria, Cyprus, Czech Republic, Spain, Croatia, Hungary, Italy, Lithuania, Latvia, Malta, Portugal, Romania, Slovakia, and the United Kingdom, and Poland, but only with regards to women
- Country in which a minimum age at 15 years is required for marriage: Estonia.
- Countries in which the categorical value lowest age is not regulated: Belgium, Greece, Finland, France, Ireland, Luxembourg, and Slovenia

In Scotland, the legal age of marriage is 16 years, which is also the age of majority.

Table II. Prevention of child marriage

Basic recommendations to avoid actions against child marriage could cause harmful unintended consequences to the children involved, their families and other members of the community related to the children's family

The safety and best interests of the child need to be prioritized. Therefore, before approaching a circumstance potentially at risk for child marriage:

- Explore the child's family and community context
- Recognize whether there are social and psychological pressures on the child
- Understand the child's situation and her/his willingness
- Assess and plan for safety
- Provide information and support to the child and family
- Connect the child to people and services that can be supportive and useful.

If a child is facing an immediate safety concern, connect them with services (ie, social, legal) that can provide short-term protection and potentially lead to a longer-term protective option.

- Ensure that at least one-half of personnel involved in the protection program are female.
- Ensure that all staff and volunteers involved in the program are trained on child protection and familiar with the concepts, principles and guidelines of gender-based violence and violence against children, so they can safely refer according to agreed standards.
- Ensure that the personnel involved is knowledgeable on prevention of sexual exploitation and abuse and able to provide safe referrals and child safeguarding.
- Ensure that staff and volunteers have access to the updated online contacts of major organizations that provide support to conditions of child marriages, to provide safe referrals.

Epidemiologic Changes Caused by the Preventive Measures for the Coronavirus Disease 2019 Pandemic: An Additional Challenge for Pediatricians

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After the World Health Organization declared pandemic status and implemented restrictive measures to counter the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there was a reduction in major pediatric diseases caused by common seasonal viruses.[1,2] The typical increase in pediatric outpatient visits and workload in emergency departments and hospital wards that characterizes the winter season, usually dominated by respiratory syncytial virus (RSV) and influenza viruses, was not seen. Diseases such as bronchiolitis, asthma, and gastroenteritis, the protagonists of pediatric age, had drastically reduced or disappeared.

This commentary, prepared by the Social Pediatrics Working Group of the European Association of Pediatrics, Union of National Pediatric Societies and Associations, reports and briefly discusses data from the literature and the impact of preventive measures, established in various countries to contain the coronavirus disease 2019 (COVID-19) pandemic, on the seasonal epidemiology of various pediatric infectious diseases. The purpose of the article is to raise awareness of this anthropogenic epidemiologic phenomenon and to emphasize the importance of being adequately trained to properly address this new challenge in their practice.

Changes in the Seasonal Pattern of Pediatric Infectious Diseases Caused by COVID-19 Preventive Measures

Preventive measures taken to contain the COVID-19 pandemic have changed the spread of SARS-CoV-2 infection and also the predictable seasonal pattern of many endemic viral diseases in children.[2] Preventive measures have included the use of universal masks, school closures, travel restrictions, bans on mass gatherings, and other public health and physical removal measures to control COVID-19. Before 2020, outside tropical areas, RSV, and nonpandemic influenza viruses had their peak epidemic in winter in the Northern and Southern Hemispheres. In temperate climates, enteroviruses circulated from summer to fall, according to established cyclical and epidemiologic patterns.[3] The COVID-19 pandemic altered these patterns, and in many regions of the world, the usual circulation of these viruses was absent for more than a year only to reoccur unexpectedly.[2] An unprecedented low incidence of respiratory viral infections[4,5] was recorded in 2020. Notably, there was no typical winter increase in RSV-related pediatric hospitalizations.[4,6]

However, following the reduction in COVID-19 measures, an unseasonal increase in respiratory viral infections has been observed in many temperate areas of the world, such as in Europe and the United States, where climatic factors, including temperature, humidity, and ultraviolet radiation, may play a role in viral spread.[7] In many European countries, there was a complete absence of RSV cases during the Fall/Winter of 202020/21, and a resurgence of interseasonal cases was observed during May-June 2021, with epidemic spikes affecting several age groups, including young children, particularly those from neighborhoods with lower socioeconomic status.[4,8] After the collapse of global influenza circulation in early 2020, unseasonal outbreaks of influenza A occurred in the Spring-Summer of 2022 in the Northern Hemisphere, although strain B remained absent.[9] Enterovirus D68 infection, suspected of causing a polio-like illness called acute flaccid myelitis, did not occur in 2020; however, the virus reappeared in the fall of 2021 in Europe outside the expected 2-year cycles.[9]

Return patterns of these viral outbreaks have been heterogeneous among locations, populations, and among different pathogens, making any prediction difficult.[9] Although many infections, and associated morbidity and mortality, were prevented by measures taken to prevent COVID-19 infection, this resulted in reduced exposure to endemic viruses and created an immune gap in susceptible groups of individuals who avoided infection and subsequent response to protect

COVID-19	Coronavirus disease 2019
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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themselves from future infection.[10] The decline in childhood vaccination that has occurred in some settings may have contributed to this immune gap for vaccine-preventable diseases such as influenza, measles, chickenpox, and, in some countries, polio.[9,10] The cumulative effect of new susceptible birth cohorts decreasing immunity over time with reduced exposure to common endemic viruses and delayed vaccination rates in some settings widen this immunity gap and increase the potential for future outbreaks of endemic viruses.

Public Health Systems and Pediatricians Must Be Ready to Address Seasonal Changes in Immunity and Host Susceptibility to Infectious Diseases

The case of COVID-19 pandemic suggests that in the future, health services are likely to face unexpected nonseasonal epidemic outbreaks due to groups of more susceptible populations of children who are simultaneously exposed to multiple endemic viruses.[9] The size and timing of outbreaks of specific pathogens are difficult to predict because they depend on many dynamic factors, including the seasonality and transmissibility of individual pathogens and the duration of preventive measures for containment, as in the case of COVID-19 infection. The imposition of public health preventive measures could have a great impact on the magnitude of future epidemics of endemic viral diseases in children and generate seasonal changes in immunity and host susceptibility of various infectious diseases.[11] The unprecedented natural experiment that occurred during the COVID-19 pandemic may offer a unique research experience for understanding the dynamics of typical childhood viruses. The observed differences among pathogens could help elucidate the role of behavioral factors, climate, immunity, and, more generally, current lifestyle, in influencing the transmission of endemic infectious diseases among children.[12] Another likely effect of the delay in circulation and the resulting immune gap could be a temporary change in the age distribution of viral infections, as susceptible children may be exposed for the first time to some infectious pathogens at a later age than in the past.[12] In addition, decreased maternal exposure and immunity to common endemic viruses, resulting in a lack of transplacental antibodies transferred to the newborn, could make young children more vulnerable to infection.[9] In this regard, age-related differences in disease presentation are also likely to vary by pathogen. For example, the risk of severe RSV disease is greater in younger children, so delayed exposure might reduce the severity of disease in infants and even adults infected later in life,[12] although young children, unprotected by maternal antibodies, might be more likely to develop more severe disease.[11]

Conclusions

In view of the possibility of a re-emergence of SARS-CoV-2 infection or further unexpected pandemics in the next years, public health authorities should raise awareness among community health workers about the need to ensure access to services and continuity of vaccination programs. Pediatricians should be informed so that they can adapt their diagnostic and reporting algorithms accordingly. This should be an integral part of the overall delivery of health care to their patients during new infectious emergencies. Ensuring continuity of routine immunization and addressing gaps in previous immunization history is an essential element of public health support during new pandemics. Surveillance systems should be strengthened by increasing the awareness of health workers to ensure that vaccine-preventable and other communicable diseases are detected appropriately despite a possible change in their typical epidemiologic patterns.

Many infectious diseases that showed unusual seasonal patterns during the pandemic are likely to return to prepandemic endemic patterns. However, further studies are needed to determine the potential of synergistic and antagonistic interactions of the various pathogens with SARS-CoV-2, and their impact on the severity of clinical presentations or circulation patterns. This will enable to set up appropriate prevention programs by public health systems[9,13] and acquire appropriate skills from pediatricians to be able to adequately address possible future epidemiologic variations of even the most common infectious diseases. ■

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Lost in Transition: The Issue of Vanishing Unaccompanied Alien Children in Europe

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Unaccompanied migrant children are one of the most vulnerable groups at risk for human trafficking and slave labor. An average of 17 unaccompanied alien children[1] go missing every day in the 27 countries of the European Union (EU-27). According to a recent report by the European Commission[2,3] and the organization Lost in Europe,[1] from January 2018 to 2021, a striking 18 292 unaccompanied migrant minors (90% boys) went missing after crossing the borders of the EU and while passing through to various destinations in Europe; 17% were under age 15. However, the magnitude of this phenomenon seems to be much greater, because not all EU-27 countries provided useful data to complete the report. In a 2016 editorial in *The Journal of Pediatrics*, the European Paediatrics Association Union of European National Pediatric Societies and Associations (EPA-UNEPSA) highlighted the risks faced by unaccompanied migrant children traveling through Europe, including the phenomenon of missing children and their poor health.[4] This phenomenon seemed then limited to southern European countries experiencing a migration wave then considered exceptional because of conflicts in neighboring Mediterranean regions. However, just a few years later, the flow of unaccompanied foreign minors has not decreased, despite public order measures and laws adopted by EU-27 countries to limit the phenomenon. This finding suggests that unaccompanied minors going missing is not simply a manifestation of periodic migration flows, but also possibly the result of criminal activity in this form of child abuse.

This commentary, prepared by the Social Pediatrics Working Group of the EPA-UNEPSA, briefly discusses the phenomenon of the disappearance of unaccompanied minors and its possible relationship to child trafficking within the EU. The purpose is to raise awareness among stakeholders, including lawmakers, public health authorities, and even pediatricians about this phenomenon of great social impact.

EPA-UNEPSA	European Paediatrics Association Union of European National Pediatric Societies and Associations
EU	European Union
EU-27	27 countries of the European Union

Definition of Unaccompanied Minor by the EU

The terms "child" and "minor" are considered synonymous and, thus, include any third-country national or stateless person under the age of 18 years.[5] In the EU, an unaccompanied minor is a child who arrives on the territory of 1 of the 27 EU member states, unaccompanied by an adult responsible for him or her, either by law or by the practice of the EU member state concerned, and for as long as he or she is not actually in the care of that responsible adult. An individual who is left unaccompanied after entering the territory of one of the EU member states is also considered an unaccompanied minor. Unaccompanied minor status applies to several conditions shown in the Table, which are important in protecting children from possible trafficking or abuse.

The Phenomenon of the Vanishing Unaccompanied Foreign Minors in the EU-27 and Its Dimension

Data on the disappearance of unaccompanied foreign minors traveling in the EU are scarce. A recent 2022 update published by the European Parliament states that the current reports available in the EU are incomplete and inconsistent, thus unable to provide a true dimension of the phenomenon.[6] The previously mentioned Lost in Europe report collected data on missing unaccompanied minors from all 27 EU countries, but some countries (eg, Spain, Belgium, and Finland) provided data until the end of 2019, whereas others (eg, Denmark, France, and the UK) have not, so the total reported number of 18 292 missing unaccompanied migrant minors may be an underestimate.[1] Despite the report's great importance, in the absence of other institutional data, the EU Parliament believes the figures represent a much higher percentage of total asylum claims than in 2014 through 2017, when more than 30 000 migrant children

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went missing.[6] The EU stresses the importance of identifying vulnerable groups and swiftly appointing guardians for unaccompanied minors, calling on child protection services in the host country to monitor continuously these children for their well-being and whereabouts after their arrival in the EU.[6] The European Parliament also expressed strong concern about the risk of children being victims of human trafficking, especially in relation to the situation of Ukrainian migrant and displaced children.[6]

Despite the disturbing information available, it is not possible to establish adequate measures to address the phenomenon of unaccompanied minors' disappearance unless reliable statistics are made available, reporting data on this group of children from all EU-27 countries. Official data collected by the Italian Ministry of Labor, which EPA-UNEPSA was able to access, show that, after their entry to Italy, an increasing number of unaccompanied minor migrants vanished in the years 2019, 2020, and 2021 (a total of 2676, 3099, and 5272 per year, respectively); indeed, 2416 unaccompanied minors have gone missing in the first 6 months of 2022.[7] These figures, which are comparable with those previously reported by EPA-UNEPSA for the years 2012 through 2015, suggest that the scale of this phenomenon may also be much larger than expected in other EU-27 countries, exposing a large number of children to the risk of various types of exploitation, as pointed out by the European Crime Prevention Network.[4,8]

Risks and Problems of Unaccompanied Minors Migrating to the EU

Unaccompanied foreign minors are normally identified and registered in the information systems of the country of first entry into Europe and sent to residential care centers. However, approximately one-half of them disappear within days or even months of their arrival.[4] In many cases, their dual legal status between legality and illegality, which is characteristic of the unaccompanied migrant situation, plays a decisive role even after their placement in reception channels.[4] The status in illegality has various reasons, including the search for an immediate economic foothold, disorientation owing to intolerably long asylum and family reunification procedures, and, very often, arrangements made by the family of origin that include the need to repay travel debts. Indeed, the journey of unaccompanied alien minors from their countries of origin, across European borders, to their unclear final destination is likely to be managed by a long and well-coordinated chain of transnational, national, and local organized criminal groups.[9] According to the United Nations, more than 500 different child movement and trafficking routes coordinated by organized crime have been identified in recent years.[10] Through deception, coercion, and abuse of children's vulnerability, human traffickers violate their human rights by systematically reducing them into slavery or servitude, forced labor, prostitution, pornography, and begging.[10,11] For many along the way and in some countries even after arrival, exploitative labor situations force at-risk minors and unaccompanied migrant children to work between 10 and 12 hours a day, living in extreme poverty. As for girls, sexual slavery and the risk of rape are sometimes associated with other forms of trafficking, including, especially in some regions, child marriage and sale for forced marriage.[10,12]

Conclusions

In today's diverse immigration landscape, vanishing unaccompanied foreign minors constitute a "new" category of migrants both in Europe and in other parts of the world. Effective reduction of this phenomenon includes not only the natural measures to counter poverty in the migrant children's countries of origin, but also all possible measures to combat organized crime. Among these, a strengthening of European information systems that enable the cross-referencing and integration of information and its reception in all member states in cases of missing children can certainly be of great benefit.[13] In recent years, these systems have been equipped with artificial intelligence-based technologies and other highly advanced functions. However, their enhancement has been used and aimed mainly to monitor and control migration flows, but not to protecting vulnerable cases. In the absence of a reorganization in the use of these technological tools by national and international institutions, the disappearance of unaccompanied foreign minors is bound to remain an emergency.

Recently, some private organizations dedicated to child protection (eg, Hermes 6 Center for Transparency and Human Rights Digital and Lost in Europe) have developed a specific digital whistleblowing platform (https://tip.lostineurope.org/#/), which they use specifically for the defense of missing foreign minors. This digital technology can be used effectively in this sensitive area. The platform allows anyone to share sensitive information or make a sensitive report securely by accessing the platform's website and releasing information completely anonymously and untracked. Key stakeholders, including legislators and public health authorities, need to be aware of the importance of addressing the growing phenomenon of missing unaccompanied alien migrants, and pediatricians need to be properly trained to assist this vulnerable group of children.[14,15] ■

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Online "Sharenting": The Dangers of Posting Sensitive Information About Children on Social Media

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The term "sharenting," which is a portmanteau of "sharing" and "parenting," describes the growing habit of parents to share photos, videos, and other identifying information about their children on personal social media accounts.[1] A recent European study reports that parents share online an average of about 300 photos and sensitive data concerning their children each year.[2] The top 3 destinations for these photos are Facebook (54%), Instagram (16%), and Twitter (12%).[2] The risks and consequences of sharenting are different in nature and often much more complex in their interpretation than imagined, as they also involve legal issues relating to the protection of the child's image, confidentiality of the personal data, and digital security. Even if unintentional, this growing phenomenon can expose children to several serious risks, including sexual exploitation, future emotional distress, and digital kidnapping.[1] Sharing images, videos, and any kind of content starring children means, in fact, building a child's "digital dossier" without his/her consent or even him/her being aware of it.[3]

This commentary, prepared by the European Paediatric Association/Union of National European Paediatric Societies and Associations Social Pediatrics Working Group, briefly discusses the recent phenomenon of sharenting and its risks to children. The purpose is to draw pediatricians' attention to the growing practice of parents and families publicizing sensitive content about their children on internet platforms and the serious risk that potential abusers may intrude on their privacy and exploit data made unwittingly available on the Web. Pediatricians can play a central role in alerting parents and families to the risks of this practice.

The Social Dimension of Sharenting

Social issues generally refer to common problems that affect people within a community. However, as the result of changing cultural, economic, or social circumstances, single issues such as "sharenting" can develop into a larger phenomenon involving many people.[4] Sharenting is often the cause of conflicting opinions about what is perceived as correct or incorrect behavior in personal or interpersonal social life. Recent statistics have revealed its social dimension and potential risks.[5,6] Online posting of children's photos, videos, and stories is increasingly common for parents and usually occurs without the child's explicit consent because of the child's young age. The psychosocial motivations for parental behavior leading to the disclosure of sensitive information concerning children on the internet have been the subject of previous studies, which have analyzed the positive and negative outcomes of this form of ritual. Frequent access to social media, coupled with repeated handling of posted information, often is associated with high levels of stress in new mothers.[7] In general, the motivations behind parents' sharing behaviors are usually positive and not malicious.[7,8] Parents often share pictures and stories of their children with the intention of showing affection and pride in their children's achievements. In return, they receive support and encouragement from family members and friends in their family network, which help mitigate any stressful conditions, foster a sense of security,[9] and help them develop and maintain social ties. Sharenting is also associated with various positive outcomes, including normalizing male parenting through sharing personal experiences of parenthood or helping other parents improve their parenting experience.[7] However, the practice of sharenting is controversial because of the significant potential risks associated with sharing children's photos and other sensitive information online. A recent study found that on average 81% of children living in Western countries have some sort of online presence before age 2 years, 92% in the US and 73% in Europe.[10,11] The digital birth phenomenon occurs in children at approximately 6 months of age, and recent data show that within a few weeks of birth, 33% of children have their photos and information posted online.[11,12] In Australia and New Zealand, 41% of infants have an online presence from birth; in the US, the percentage is 37%.[10-12] More than 30% of mothers regularly post photos of their newborns and, thanks to sharenting, an increasing number of babies are born digitally even before natural birth.[11] The phenomenon of posting pictures of ultrasound scans, recounting personal experiences during pregnancy,

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and even activating email addresses and social network profiles is on the rise, and a quarter of babies are reported to have some type of online presence before birth. In the US, 34% of parents routinely post ultrasounds online, 13% in France, and 14% and 15% in Italy and Germany, respectively.[11,12]

The Dangers of Sharenting and the Right to Privacy

The practice of sharenting through social media is relatively low risk, providing that children are not identifiable. Because of the growing concern about the risks of the internet, parents have begun posting photos of their children in which only the back of the head is visible or only after pixelating the child's face. However, most parents continue to share information and pictures of their children without any precautions, often due to a false sense of security about the privacy settings claimed by social media. Sharing is a dangerous practice that exposes children to multiple risks, including violation of their privacy, sexual exploitation, emotional harm, unlawful access to metadata, online persistence, and digital kidnapping.[13]

As soon as images or videos are posted online, any effective control over them is lost. Even home cameras and simple baby monitors that generate digital data can be illegally accessed and may end up in the wrong hands. Therefore, it is advisable to take precautions and technical guidance if families use smart tech in their homes. In the area of online child sexual exploitation, child abuse investigators have found that hundreds of thousands of innocent photos depicting children in their private sphere, shared on social media over the years, have reappeared on pornographic platforms, associated with explicit or inappropriate comments.[14] Ownership of photos uploaded by parents to social media is lost and it is generally difficult to obtain their removal due to a substantial lack of legislation.[15] Even as children grow up, information about their childhood continues to exist, and this can cause emotional damage due to shame or embarrassment over some online content. Despite parents' initial good intentions, the negative consequences of a digital footprint can follow individuals for years after the fact. Metadata attached to images and videos is also a major problem related to sharenting, as it makes accessible a large amount of personal information about subjects, which later can be misused by cybercriminals or data brokers to build social profiles or digital dossiers about the posts.[14,15]

An Important Legal Implication: Identity Theft

Identity theft is one of the major risks associated with sharenting.[15,16] The notion of identity, although recurrent in our everyday language, remains expansive and ultimately indeterminate. Indeed, although various social sciences have attempted to describe its content, we do not have a truly comprehensive definition of what identity is. The term "personal identity" can be given different meanings. However, we can say that with the concept of "personal identity" we denote all that we are, our physical, psychological, and cultural characteristics, starting with our name and date of birth. Every individual has the "right to personal identity," and it is accepted and legally established throughout the world that everyone has the right to the integrity of his or her intellectual, political, social, religious, and professional heritage that begins to develop from the day of birth. Identity theft is a complicated and somewhat-unknown crime. Complicated in that it is difficult to combat and particularly difficult to prevent,[17] and unknown because it is constantly evolving, driven by technological evolution, which continually transforms the crime and the modus operandi of the perpetrators.[15,16,18] Parents often post confidential information, unaware of the possible consequences.[15,16,18] Parents have already shared nearly 1000 photos of their children when their children turn 5 years old. In 19% of cases, parents who post their children's stories also reveal their names and date of birth, and 45% of Facebook posts include the child's first name.[10-12] The availability of this information coupled with illegally obtained social security data on the dark web,[14] can expose children to serious risks (**Table**), including digital kidnapping.[15]

Table. Main types of fraud resulting from digital identity theft

The availability of data provided by the practice of reporting sensitive content on internet platforms can facilitate the following forms of digital fraud

- Identity cloning: the substitution of a person for the purpose of creating a new identity and using it in illicit activities.
- Financial identity theft: identity theft for the purpose of using a person's identifying information to obtain any kind of financial benefit, including credit or financial loans or to open bank or credit cards accounts in the victim's name.
- Criminal identity theft: using a victim's data to perform various types of illicit public acts in the victim's place.
- Synthetic identity theft: use of personal data of different individuals combined to "technically" construct in the laboratory, in whole or in part, a new identity according to one's needs.
- Medical identity theft: use of others' personal data to obtain health care services, other types of medical advantages, or public and individual's health-related crimes.

Conclusions

The practice of parents publicizing sensitive content concerning their children on internet platforms is well-established and increasing. Pediatricians can play a central role[19] in making parents aware of the dangers associated with sharenting.[20] To protect children's privacy, families can be instructed to use defensive strategies such as photo editing and self-censorship. They can also be helped to balance their natural inclination to share pride in their children's progress and educated about the risks associated with this practice. ■

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The Shortage of Amoxicillin: An Escalating Public Health Crisis in Pediatrics Faced by Several Western Countries

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The antibiotic amoxicillin is usually recommended as a first-line treatment for many common infections affecting children, including otitis, pneumonia, sinusitis, and strep throat.[1] It is an effective, relatively inexpensive drug that is available in generic formulations.[2] For years, pediatricians have feared a major health crisis caused by the growing phenomenon of antibiotic resistance.[3] Among the various causes, including unnecessary use of antibiotics in agriculture, poor sanitation practices, and poor infection control in hospitals and clinics, overuse and misuse of antibiotics in clinical practice have been recognized to be the main factors accelerating antibiotic resistance.[4] However, antibiotic shortages have never been considered as a possible critical issue in public health and health care delivery. In particular, the unavailability of essential first-line antibiotics, such as amoxicillin, was considered a remote posibility.[5] Contrary to these expectations, Authorities and Public Agencies in Europe and the US are now reporting shortages of amoxicillin,[6-9] raising concerns that one of the most widely used antibiotics for the treatment of various pediatric conditions[10,11] will be in short supply for the current winter season and for months to come.

This commentary, jointly authored by members of French, Israel, and Italian Societies of Pediatrics, in collaboration with the Confederation of European Pediatricians and the European Pediatric Association/Union of European National Pediatric Societies and Associations, briefly outlines the current public health crisis caused by the shortage of amoxicillin, which exposes children to life-threatening conditions.[12] The goal is to raise awareness among pediatricians, public health officials, and governments about the risks caused by prolonged drug shortages and particularly the unavailability of amoxicillin in Western countries and other areas of the world.[13]

Low Availability of Amoxicillin Causes Concern in Many Countries

More than 86% of European hospital pharmacists are experiencing difficulties in sourcing different types of medicines, and 66% report this as a daily or weekly problem. These shortages in Europe involve originator drugs in 51.8% of cases, and the percentage rises to approximately 60% if we include generic formulations. These alarming figures are presented in the 2022 report of the European Association of Hospital Pharmacists,[13] which surveyed more than 600 hospital pharmacists from 36 different European countries.

The drugs most involved are cancer drugs (54.5%), emergency drugs (30.4%), cardiovascular drugs (30.4%), and anesthetics (26%).[13,14] However, the greatest shortage is found among antimicrobial drugs, particularly antibiotics (56.7%). Among these, the shortage of amoxicillin raises particular alarm because of its importance in the treatment of bacterial infections across pediatrics. Amoxicillin accounts for approximately 70% of prescriptions for the management of acute otitis media.[15]

Some European countries in particular are suffering from the unavailability of amoxicillin. The situation is especially acute in France, where the Directorate General of the Ministry of Health has sounded the alarm about a severe shortage of amoxicillin, either alone or in combination with clavulanic acid, which are subject to severe supply shortages in this country.[16] The unavailability of amoxicillin in its various formulations is considered particularly hazardous to children's health, with possible life-threatening consequences, by the French advisors to the Directorate, including the Pediatric Infectious Pathology Group of the French Society of Pediatrics, the French Association of Ambulatory Pediatrics, and the French Society of Infectious Pathology. They explain these shortages in amoxicillin by the very significant increase in antibiotic consumption coupled with difficulties on industrial production lines. During the coronavirus disease 2019 pandemic, the demand for amoxicillin had fallen sharply, leading to a reduction or even a stoppage of certain production lines, which have not recovered to their prepandemic production capacity. Moreover, if supply chain limitations are severe and/or prolonged, a domino effect of sorts is inevitable, with a shift in prescriptions to other oral compounds, such as cephalosporins, penicillin V, macrolides, adult forms of amoxicillin, and ceftriaxone. Stocks of these antibiotics are

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also not likely to be sufficient because they are much less prescribed, and they will be quickly depleted, perpetuating and exacerbating the shortage and increasing the risk of widespread antibiotic shortages. As noted in France, difficulties in the supply of pediatric forms of amoxicillin and amoxicillin clavulanate have the potential to create a major and unprecedented public health crisis with short- and long-term consequences. In Italy, the government drug agency has declared amoxicillin in its various formulations to be unavailable domestically, and the importation of equivalent drugs from abroad has been authorized to avoid a public health crisis.[17] In Spain, the president of the local Council of Official Pharmacists Associations reported in November 2022 that pharmacies do not have enough stock to meet 50% of demand. He stressed that this is not due to an increase in consumption but rather from a lack of production because laboratories do not have the raw material needed for manufacturing.[18] The Spanish Agency for Medicines and Health Products has reported in December 2022 shortages of 22 different amoxicillin drugs in tablets, powder, and hard capsules amid a wave of respiratory infections.[19]

In the US, the Food and Drug Administration, which lists drugs on its website when overall market demand is not met by product manufacturers, reported in November 2022 that amoxicillin oral powder for suspension used by children is in short supply.[20] Amoxicillin and clavulanate oral preparations in capsules and tablets also have limited availability in the US.[21] Amoxicillin unavailability is reported in several other countries around the world, including Romania, Malaysia, Australia, and Canada.[22-24]

Main Causes of Shortages of Some Critical Drugs

An insufficient supply of drugs is considered one of the most significant problems in public health and medical care delivery.[25,26] Two main factors can explain the drug shortages that periodically plague Europe: production shortages, which often recognize internal problems within pharmaceutical companies, and poor or temporary unavailability of distribution.[27] In Europe, non-European Union countries usually depend almost exclusively on the importation of drugs from larger producing countries, including Germany, Switzerland, and the US, or from non-European suppliers such as Brazil, India, and China. In the European Union, production-related shortages are mainly related to the importation of products between member states with different levels of product availability. Most of the production shortages are associated with various economic factors, including the cost of raw materials and their supply, low prices charged for final products, and the small size of the expected market for old drugs. Distribution unavailability, in contrast, is often caused by interstate market dynamics, which aim to control export (eg, restriction of products for export, or imported products released only after complex bureaucratic notification to the relevant authorities).[28] Sales between wholesalers operating in different markets with different prices, the parallel trade, can often result in the unavailability of drugs essential to public health, as in the case of amoxicillin.

Conclusions

As has been noted in France, supply difficulties with pediatric forms of amoxicillin and amoxicillin clavulanate have the potential to create a serious and unprecedented public health crisis with short- and long-term consequences. Repeated lockdowns related to the coronavirus disease 2019 pandemic have contributed to supply difficulties for many drugs, including antibiotics. However, the risks associated with amoxicillin supply shortages appear not to have been sufficiently assessed, and the crisis we are facing today is serious and particularly dangerous for children's health. Further complicating the epidemiologic situation is the increasing reports of respiratory infections among children, caused by respiratory syncytial virus, which is quite common but can be dangerous for infants and children. The authors of this commentary, on behalf of their respective pediatric societies, wish to raise awareness among pediatricians and public health authorities nationally and internationally of the risks caused by prolonged unavailability of amoxicillin. Without rigorous measures to prevent shortages related to drug production and distribution, populations could face a postantibiotic era in which common infections and minor injuries can result in serious life-threatening situations.[29] ■

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Food Safety: The European Union's Food Safety Initiative and Its Impact on Risks from Microbial and Chemical Hazards in Infant Food Chains

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Food security is understood in its broadest sense as the ability to ensure consistently and satisfactorily food and water to meet the energy requirements the body needs for survival and life under adequate hygienic conditions. The commonly accepted international definition is the one developed at the World Food Summit in 1996 according to which all people, at all times, must have physical, social, and economic access to sufficient, safe, and nutritious food to meet their dietary needs and food preferences to lead an active and healthy life.[1] From a purely health perspective, food safety is also understood as food and feed hygiene safety from the perspective of integrated environmental supply chain. In the legal understanding, food is defined as any processed, partially processed, or unprocessed substance or product intended to be ingested, or reasonably expected to be ingested, by human beings.[2] In any case, the precise definition of food safety is still not so unambiguous, and in the countries of the European Union (EU), the closest notion is that of "food at risk," which is found to be covered in Article 14 of European Regulation EC 178/2002.[2,3] This regulation is a key reference for the evolution of food law in Europe, as the rule introduces the general principles and requirements of food law, which are monitored by the European Food Safety Authority,[4] also establishing procedures in the field of food safety. The European Food Safety Authority is responsible for the scientific assessment of risks, whereas decisions regarding their management are the responsibility of European Union experts.[4] The regulations issued by the European Union[3,4] play a priority role in food legislation, which must be followed locally by the EU countries, and provide some specific principles including risk analysis. Risk analysis is a systematic methodology for assessing the likelihood of occurrence of undesirable effects on human health, associated with a specific type of food, in order to provide for the adoption of effective and targeted measures with the aim of increasing the safety of food use in adults and children.

The EU pays close attention to the certification of foods and their contents, both in terms of allergenic agents and as contaminants.[2,5] In particular, the EU has recently made an effort in the area of infant food safety, sponsoring a project[6] called Safe Food for Infants (SAFFI), developed by a consortium of 14 partners from 7 EU countries, whose goal is to provide solutions to develop a most efficient multi-stakeholder surveillance system in the infant food sector.[7] The project will serve the object to integrate the tools and methods for detecting and managing infant food chain risks from primary production to the consumer. The European Pediatric Association-Union of National European Pediatric Societies and Associations is part of the consortium. The aim of this commentary, authored by board members of European Pediatric Association-Union of National European Pediatric Societies and Associations, is to raise further awareness of decision and policy-makers, including government and legislators, and end-users, including consumers and health care professionals involved in childcare and nutrition, on the impact of the food chain risks on food safety. A second objective is to inform the scientific community of the EU's efforts in this field by supporting a project that aims to develop an extensive and coordinated food risk identification system.

The Problem of Infant Food Contaminants in the EU

The EU's focus on child food safety is due to numerous studies that have reported health risks to children aged 0-3 years old due to the presence of food contaminants.[8] A recent study, published by the French Food Safety Agency, analyzed during a 6-year period 97% of the products that were part of the diets of a study group of children up to 3 years of age.[9] The French Food Safety Agency researchers selected about 5500 products and performed 457 samplings, totaling more than 200 thousand analytical results and analyzed 670 substances belonging to different families of contaminants: metals and minerals, persistent organic pollutants, additives, substances released from food contact materials, newly formed compounds, mycotoxins, natural steroids, phytoestrogens, and pesticide residues, and

DSS	Decision support system
EU	European Union
SAFFI	Safe Food for Infants

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calculated the risk associated with the food products. The results showed that exposure levels and associated risk are considered acceptable or tolerable for only 90% of the substances considered, and for 9 substances and families of compounds the researchers rate the situation as worrisome. The list includes arsenic, lead, nickel, polychlorinated dibenzodioxins and polychlorinated dibenzofurans, polychlorinated biphenyls, mycotoxins T2 and HT2, acrylamide, deoxynivalenol, and furan. In particular, rice and rice products were found to be the main source of arsenic exposure. As for heavy metals, children are exposed to inorganic-toxic arsenic, mainly through rice, rice cereals, and homogenized fish, and vegetables, that must be closely monitored in order to limit their contamination.

Prevention Food Contamination by an Effective Integrated Monitoring System

In a food context, a hazard implies a potential impact on consumers. Pathogenic micro-organisms, chemical contaminants, or physical agents can all pose a threat to food, but hazard is instead defined as a biological, chemical, or physical agent that makes a food unhealthy and exists when its ingestion causes harm. Despite efforts to minimize the presence of hazards, food safety is not absolute, and hazards are frequent. They can be unintentional or intentional,[10] and risk depends on both the likelihood of an adverse health effect and the severity of that effect resulting from a hazard in a food. The research centers involved in the European project SAFFI have adopted an integrated, multitask approach that can be applied to different areas of clinical relevance to food safety. Their integrated research program aims to develop an extensive and coordinated food hazard identification system based on multiple data sources and a risk classification procedure. The project's multitasks and their objectives are summarized herein.

Hazard Identification and Risk Classification

One project working group focuses on hazard identification and risk classification within the infant food chain. The goal of this group is to develop a prototype decision support system (DSS) for hazard identification and a prototype DSS for risk classification. Specific objectives include creating databases for potential microbiological and chemical hazards and risk estimates, as well as developing selection procedures for hazard identification and risk classification. The final goal is integrating these databases and procedures into developed DSS prototypes for both hazard identification and risk classification.

Hazard Control and Mitigation

Research centers working on this task are engaged in the development of a prototype Hazard Control DSS and to set conservation technologies and mitigation strategies to improve food safety management using 4 child food chain models, chosen as case studies from raw materials to consumer. The objective of his task is to define and validate emerging processing and preservation technologies in order to control key contaminants and pathogens as efficiently as classical technologies and to define efficient monitoring and sampling strategies at the operational and governmental levels to improve the effectiveness of food safety management options.

Identification and Discovery of Chemical Hazards

This task focuses on the development of new methods based on analytical chemistry and bioassays for the detection, monitoring, and discovery of chemical hazards. The goal is to develop new innovative approaches by combining the latest innovations in molecular biology and analytical chemistry for chemical hazard detection, monitoring, and discovery and to establish all the elements of a DSS module for chemical hazard detection. Specific goals include developing high-throughput, cost-effective, and robust targeted approaches for detection and monitoring of known priority contaminants to promote self-monitoring by baby food companies and improve safety surveillance coverage by European regulators. An additional key outcome of the Research Centers involved in this task is the development and integration of nontargeted approaches based on analytical chemistry and bioassays for the discovery of unknown or unsuspected contaminants and hazard characterization. The result of this task will be the integration of databases, procedures, and tools into the DSS module dedicated to the identification of hazards related to baby food.

Identification of Microbial Hazards

The involved centers focus their research on the implementation of new omics methods for microbial hazard detection, including the application of a biotyping method to improve the targeted detection of microbial hazards. The objective of this research activity is to determine the presence, distribution (in time and space), and prevalence of target food pathogens in food chains and to update predictive models by implementing and integrating databases, procedures, and tools for microbiological risk detection at critical control points into the DSS module dedicated to risk detection.

Integration of DSS, Cost–Benefit Analysis

The key element of the project is the full integration of DSS prototypes designed by the project tasks dedicated to the identification, risk classification, control, and mitigation of chemical and biological hazards. The reliability, cost–benefit analysis, and use of the final integrated prototype developed by the EU project will be tested on food chains by European end users in order to make it suitable for use by public food authorities or private organizations.

Conclusions

Good and safe nutrition is the key to ensuring the growth and healthy development of children.[11] The European SAFFI project will contribute to the protection of children from unforeseen contaminants through predictive toxicology and improved risk-based food safety management of biohazards and will provide stakeholders with a DSS to improve safety monitoring throughout the food chain. ■

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Burnout in Primary Care Pediatrics and the Additional Burden from the COVID-19 Pandemic

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The term burnout describes a condition of work-related stress that leads individuals to exhaust their mental and physical resources.[1] Burnout is a manifestation of negative psychological symptoms, including apathy, nervousness, restlessness, and demoralization, which may also be associated with physical problems, including headaches, sleep disturbances, and gastrointestinal disorders.[2] This condition can affect any worker performing any task, in any work environment. However, the most severe consequences of a stressful working condition are generally observed in the helping professions,[3-5] including physicians, nurses, pharmacists, social workers, and staff members of private and public health organizations who are dedicated to others.[4] Concern about the problem of burnout in health care workers goes back many years.[6] However, the COVID-19 pandemic, which introduced new and unexpected stressors in almost all areas of life, has significantly increased the workload of health care workers in a short period of time. The level of physical and emotional stress has increased to the point that, because of the threat posed by this condition to the nation's health, several countries in Europe and the United States have declared the health-worker burnout crisis and the protection of their well-being a national priority.[2,7-9] Several studies have highlighted the role of COVID-19 in causing increased burnout in various categories of health care professionals working in different settings and roles, and in other fields including finance, administration, academics, and the military.[10-12] However, limited attention has been paid to the phenomenon of burnout in primary care pediatrics which was exacerbated by the COVID-19 pandemic, with negative effects on public health. Alarming recent data show that the COVID-19 pandemic has significantly increased the pressure on the workforce of general pediatricians and significantly worsened from 10%-30% to 40%-70% of the burnout levels generally observed prior to the pandemic.[13,14]

This commentary, compiled by the EPA-UNEPSA social pediatrics working group in collaboration with the European Confederation of Primary Care Pediatricians (ECPCP) and the Italian Federation of Primary Care Pediatricians (FIMP), briefly discusses the growing frequency of burnout in primary care and in primary care pediatrics, and debates how to reduce the risk of burnout and mitigate stress caused by this condition.

Definition of Burnout

Burnout was first described in 1974 by psychoanalyst Freudenberger,[6] who analyzed the stressful dedication to work, which can cause workers to experience physical signs and behavioral symptoms considered indicators of extreme pressure.[6] Initially, the debate focused on the positive and negative aspects that dedication and commitment to caring for people can entail for health care workers and the consequences caused by an overload of energy leading to a strong feeling of failure.[6,15,16] However, its meaning and use have gradually expanded to include any type of professional, whose occupation has caused exhaustion, apathy, and inability to cope.

Over the past 4 decades, the concept of burnout has become increasingly popular and the condition described by this term has gradually permeated various fields of civil society. The term burnout has evolved to become an indicator of individual distress with important repercussions in various organizational contexts, often far removed from the health care area, including the manufacturing sector, military personnel, and economic, administrative, and academic institutions.[17,18] That is, academic burnout commonly describes students' feelings of debilitation, pessimism, and low self-efficacy, symptoms experienced by students pressured and stressed by demanding school schedules. Academic burnout can also refer to feelings of fatigue and disengagement experienced by teachers due to the need to complete large programs.[19] In military personnel, burnout is currently a commonly used term to describe the level of stress associated with the duties and challenges of professional life for combatants and their families.[20]

In 2019, the World Health Organization (WHO) noted that job burnout has become an important indicator of mental health.[21] Therefore, it proposed its inclusion in the *11th edition of the International Classification of Diseases*[21,22] (ICD-11). However, there is still no unanimous consensus for the definition of the condition of burnout and currently several definitions are used to refer to the same concept, including "occupational exhaustion syndrome," "psychological exhaustion," "fatigue syndrome," and "burned out syndrome".[3] Several studies have

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Table I. Burnout in health care workers: revealing signes

Warning signs of burnout in health care workers
Physical
Migraine or dizziness
Muscle strain or pain
Cramps, persistent nausea, or vomiting episodes
Colitis
Chest sprain or strain or a tachycardia
Changes in sexual activity
Sense of fatigue
Worsened health conditions
Shortness of breath
Loss of appetite
Eating disorders
Sleeping disorders
Mental and emotional
Attention disorders
impaired decision-making ability
Overwhelming thoughts
Negative thinking and constant worrying
Absent-mindedness
Forgetfulness
Loss of self-confidence
Sense of failure
Feelings of hopeless and helpless
Detachment and loneliness
Low motivation and frustration.
Development of suspiciousness and negative outlook.
Feeling of missing accomplishment
Feeling of work overload and excessive job demand
Feeling of pressure
Inability to manage conflicting situations
Feeling poorly rewarded for the work performed
Feeling isolated and emarginated.
Inability to start new relations at work and in the personal life
Perceiving the work to be unfair or inequitable or meaningless
Behavioral
Avoiding responsibilities.
Social isolation.
Slower performance at work
Introducing drugs or alcohol to cope.
Overeating
Oversleeping
Insomnia
Sense of frustration
Irregular attendance at work
Absenteeism
Hyperactivity disorders, irritability
Increased smoking
Loss of personal goals and commitments
Difficulty in keeping relationships active
Breaking friendships
Making careless mistakes
Obstructive and uncooperative behavior
Careless spending

been conducted over the years exploring the relationships between persistent fatigue among employees, burnout, and chronic fatigue syndrome, 3 fatigue conditions that share several conceptual similarities and characteristics.[18] However, results have been indecisive and currently a consensus definition of occupational burnout is still lacking, despite evidence of its impact on society.[5,23] This may explain the large variability in the prevalence of burnout among physicians (from 0% to 80.5%) reported in a recent review of data from 45 countries.[15,24]

Table II. Burnout stress reducing practices

Stress reducing practices recommended to safeguard the well-being of health care workers with burnout
• Making changes in the personal lifestyle
• Making changes in the work environment
• Reorganizing working hours
• Taking breaks during the working days or taking days off during the weeks or months.
• Knowing the list of signs typical of burnout to perform self-examinations.
• Introducing physical exercising in the daily schedule
• Keeping control of the diet and avoid eating disorders
• Keeping control of the daily schedule
• Keeping control of the sleeping schedule
• Avoiding routine activities perceived as stressing factors.
• Avoiding relaxing behaviors that can cause boredom.
• Considering the practice of meditation and yoga
• Socializing with colleagues
• Connecting with a friend or family members and dedicate time to catch up
• Checking in with a therapists.
• Seeking professional help
• Taking advantage of support or advocacy groups

The Issue of Burnout in Primary Care

Burnout has been extensively studied in various types of health care workers in public and private health care organizations. The Physician Health and Wellness guideline published in November 2022 by the American Academy of Pediatrics reports that from 2011 to 2014, the prevalence of burnout in general pediatricians increased by 10%, from 35.3% to 46.3%.[25] The National Physician Burnout & Depression Report 2022, which surveyed more than 15 000 physicians from 29 specialties working in the United States, shows high rates of burnout in many medical specialties, including pediatrics (49%), after 3 years of COVID-19 pandemic management. The report also revealed that a significant increase in burnout was reported by physicians of all specialties in 2021 (47%) compared with 2020 (42%). Not surprisingly, a marked increase in burnout, from 43% to 60%, was also described in emergency medicine physicians during the same period. However, 54% of survey participants reported that burnout had a strong-to-severe impact on most aspects of their lives.[26] However, data on pediatricians working in primary care settings were not included in these reports. Similar studies conducted in Europe show that especially after the pandemic, sleep disorders, stress, and anxiety have affected a large group of health care workers with an impact on their physical, emotional, and psychological well-being. Over the past decade, a considerable number of health care workers have left or are considering leaving their jobs due to physical and mental factors causing chronic exhaustion and unhappiness at work,[13,27] which are characteristic symptoms of burnout.[28,29] In the United Kingdom, the 2015 Commonwealth Fund survey revealed that 30% of general practitioners intended to leave the profession within 5 years, and later in 2019, a study reported a 3-fold increase in their early retirement compared with the previous decade.[13] This

social phenomenon has caused a significant workforce shortage in primary care, which was further exacerbated by the COVID-19 pandemic. Primary care physicians have faced significant levels of stress since the onset of the pandemic, with more than half of physicians under 55 years of age experiencing emotional distress and burnout.[30] A survey conducted by the Federation of Italian Medical Boards reports that after the pandemic, 24% of community physicians experience sleep disturbances, stress, and fear, while depression and anxiety are reported in 20.5% and 25.8% of cases, respectively.[31] However, in studies devoted to burnout and its manifestations in health care workers, the working condition of primary care pediatricians has received relative attention,[32] and studies assessing their state of work-associated emotional, mental, and physical exhaustion are scarce.

Prevention and Reduction of Stress

Early identification of the many physical, emotional, and behavioral factors that are recognized as warning signs of burnout in health care workers[33,34] (**Table I**) can help develop useful strategies to prevent or mitigate this condition and introduce stress-reducing practices into the lifestyle that can safeguard their well-being[35-37] (**Table II**).

Preventive strategies include identifying, removing or reducing stress-causing factors, developing a supportive social network, taking care of personal health, reorganizing work life and setting clear expectations, increasing understanding of self-identity and acquiring a stable and consistent perception of it through careful reorganization of personal values, thinking, and actions.[33-36]

Conclusions

Numerous studies show that health care workers are particularly exposed to burnout.[6,33] Since the COVID-19 pandemic, higher rates of burnout have been reported in all medical specialties, including pediatrics. Burnout can now be considered a COVID-19 pandemic-related health condition affecting an increasing number of primary care physicians. However, only occasional data on the effects of burnout in primary care pediatricians are reported. EPA-UNEPSA, in collaboration with the FIMP and ECPCP, has established a working group to study the condition of burnout in primary care pediatrics in Europe. The goal is to develop a guide for early identification and mitigation of this condition in pediatricians working in primary care settings.[38] ■

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Endocrine Disruptors and Child Health: Food Contaminant Monitoring in the European Union

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Environmental problems concerning the protection of health are often tackled by giving priority to the more striking aspects such as air pollution, caused by emissions of industrial or residential settlements or an excessive use of vehicles, especially in urban areas. These aspects are easily detectable by citizens; they affect their daily lives and, therefore, are the subject of various forms of protest that compel the authorities to take measures verifiable by all.[1] In contrast, little effort is devoted to substances that might undermine people's daily health in a more subtle way and are, therefore, less commonly detectable. However, these agents might be more harmful and capable of serious and very often irreversible damage to various living organisms.[1,2]

During recent years the European Union Commission (EUC) has placed special interest in endocrine-disrupting chemicals (EDCs) that undermine children's health through the food chain by interfering with the normal activity of the endocrine system.[3] There are many substances capable of disrupting the endocrine system, and the EUC has promoted special research programs for which the goal is to make a major contribution to increasing the scientific knowledge, essential for making socially relevant policy and legislative decisions to counter an increasingly widespread and dangerous situation for children's health.[4,5] The European Pediatric Association, Union of National Pediatric Societies and Associations, in collaboration with the experts of the European member societies, took part in the EUC studies to develop a more effective monitoring system of childhood foods along the European food chain, which aims to decrease the risks that food sources may interfere with the normal function of the endocrine system of children.[5] This commentary, authored by members European Pediatric Association, Union of National Pediatric Societies and Associations working group of social pediatrics, aims to raise further pediatricians' awareness of the relationship between food contaminants and endocrine disruptors and inform all about the EUC's efforts to develop appropriate child health monitoring and control systems.

Endocrine Disruptors Definition and Characteristics

Endocrine disruptors are substances of various kinds, either naturally occurring or released into the environment as a result of human activities, that can interact with the endocrine system in different ways. Particularly through the food chain, these compounds have the potential to bioaccumulate and damage the body throughout the life course, from birth through childhood and adolescence and into adulthood.[6] Because of these important characteristics, during recent years EDCs have become a major public health concern and research focus. Assessments by several international agencies indicate that EDCs are a large, heterogeneous, and still incompletely known group of substances that includes compounds used in industrial and consumer products, including dioxins, arsenic, bisphenols, phthalates, perfluorinated compounds, and pesticides.[3,6,7] The assessment of possible risks associated with exposure to EDCs covers several areas and food in particular.

EDCs often mimic the action of hormones and interact with their receptors. They can be classified into 3 main categories, depending on their action. Some mimic hormones, resulting in overstimulation. For example, some can mimic the effects of estrogen, androgens, and thyroid hormones. Others bind to receptors within a cell, preventing binding to endogenous hormone, such as antiestrogens and antiandrogens. Finally, others interfere with the production or control of the use of certain hormones, for example, by altering liver metabolism.[8]

The US Environmental Protection Agency[9] defines EDCs as exogenous agents that interfere with the synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones present in the body and responsible for homeostasis, reproduction, and developmental processes. The EU has adopted a similar, although less detailed, definition referring to EDCs as exogenous substances that alter endocrine system function, causing adverse health effects in an organism, its progeny, or a subpopulation.[10]

Owing to their adverse effects, EDCs have been the subject of research for several years. For example, because of their heterogeneity, toxic substances can alter a variety of

EDCs	Endocrine-disrupting chemicals
EUC	European Union Commission

From the [1]European Pediatric Association/Union of National European Paediatric Societies and Associations (EPA/UNEPSA), Berlin, Germany; [2]Association pour l'Activité et la Recherche Scientifiques, Neouchatel, Switzerland; [3]Albanian Society of Pediatrics, Tirana, Albania; [4]Turkish Pediatric Association, Istanbul, Turkey; [5]Romanian Society of Social Pediatrics, Cluj-Napoca, Romania; [6]Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, Cluj, Romania; [7]European Confederation of Primary Care Pediatricians, Lyon, France; [8]Scientific Institute "Casa Sollievo della Sofferenza", University of Foggia, Foggia, Italy; and [9]Italian Academy of Pediatrics, Milan, Italy

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mechanisms of the complex endocrine system and the multiplicity of possible routes of exposure. In addition, the ability of EDCs to affect numerous organs and systems, including the reproductive, nervous, immune, and thyroid systems, especially in the prenatal and postnatal developmental stages, generate a spectrum of negative clinical effects, the understanding of which is still incomplete.[11] Finally, experimental data also indicate the risk of additive or synergistic effects of EDCs and the possibility that they may have harmful effects at very low doses at vulnerable stages of the life cycle, particularly for compounds that interact with nuclear receptors.[12]

Endocrine Disruptors, Food, and Water

In EU countries, food, water, or materials intended for contact with them are protected by strict regulations and subject to strong controls by authorities. The levels of endocrine disruptors contained are safe in general.[13] However, in many cases, regulations prove insufficient for various reasons that include the identification of new contaminants, or variants of substances already recognized as toxic, attempts to circumvent regulations, or even the introduction of foods produced by other international markets with less stringent rules into the European market.[13] The main sources of endocrine disruptors in foods are meats (especially from carnivorous and omnivorous animals, fish, dairy products, vegetables, and eggs).[7,8]

The prevalence of EDCs in animals and their products is mainly due to their long persistence in the environment, where they can be absorbed by plants and ingested by animals. Moving up the food web, animals may eat greater amounts of food that contains EDCs, so that there will be an accumulation of these substances. Endocrine disruptors are also found in vegetables, either because they are derived from pesticides or because plants naturally produce phytoestrogens that are known to interfere with endocrine activity. So, legumes, fruits and vegetables may contain EDCs.[5-7,14] In particular, soy and other legumes, nuts, whole grains, and sprouts are rich in phytoestrogens.[14]

It is important to remember that food packaging also poses important risks. In fact, some materials that come in contact with food contain EDCs, such as baby food packaging, tubs, greaseproof paper, transparent film, plastic bags, and cans.[15] Pans and particularly nonstick pans also often contain EDCs, such that cookware origin should be checked, and it should be verified whether risk analysis was assessed by the authorities. Water can be contaminated by itself or by the plastic bottles in which it is contained. Thus, it is clear how crucial the need is for continuous updating and improvement of food monitoring systems along the food production chain, from cultivation to packaging.[15] In the US, rigorous policies and regulations ensure a solid protection against the risks of EDCs on public health. In 1996, the Food Quality Protection Act provided an important stimulus for the establishment of the current Endocrine Disruptor Screen Program.[16] In Europe, the EUC Regulation 178/2002 defines the possible risks as a function of the probability and severity of an adverse health effect resulting from the presence of a hazard in food.[17] This regulation provided the ground for the activities of the EU agencies, including the Joint Research Centre, European Food Safety Authority, and the European Chemicals Agency, which are dedicated to monitor the safety of food and the hazards resulting from the presence of toxic substances, including endocrine disruptors.[3] Finally, the EUC allocated €50 million under the research program Horizon 2020, allowing the funding of 8 projects on new testing methods for endocrine disruptors.[3]

Conclusions

The hazards to children's health caused by endocrine disruptors are serious and the risks of children's exposure through numerous pathways are high. Indeed, these are ubiquitous substances with which everyone comes into contact every day, albeit with significant variations in relation to environment, consumption, and lifestyles.[18,19] Food is an important vehicle through which EDCs are a hazard to children.

In Europe, although in the absence of a specific regulation regarding EDCs, the EUC after repeated reminders from the General Court, the EU Parliament, and the scientific community, has begun to introduce some amendments to EC regulation 1107/2009 for plant protection products and to EU regulation 528/2012 on biocidal products. In particular, such amendments have introduced scientific requirements regarding the identification of endocrine disruptors in these products.[3] An additional EUC effort regards the financial support to studies aimed at developing an integrated approach to enhance the identification, assessment, detection, and mitigation of safety risks raised by microbial and chemical hazards all along the infant food chains.[15,20]

In conclusion, there is evidence in the literature suggesting a central role of exposure to EDCs in modulating several endocrine conditions, prenatal and perinatal growth, and pubertal timing in humans.[1,2] However, further studies are needed to clarify how many EDCs may primarily act on epigenetic processes and what our role as clinicians is in being able to limit exposure to these substances, with the goal of improving health in children today and in future generations.[21] ■

Declaration of Competing Interest

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Bullying and Cyberbullying Increasing in Preadolescent Children

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Bullying and cyberbullying are characterized by violent and intentional manifestations of verbal, physical, and social abuse repeated over time by an individual or by several people. Bullying always has been present in our daily lives. However, with the advent of new technologies, bullying has taken new forms, including cyberbullying. There is an imbalance of power between those who attack, to hurt and humiliate, and those who suffer and fail to defend themselves. These are phenomena that express a lack of tolerance and nonacceptance toward those who are considered different due to ethnicity, race, religion, psychophysical characteristics, sex, gender, gender expression, sexual orientation, and particular family realities.

The number of parents whose children and in particular preadolescent children have experienced some form of bullying or cyberbullying is increasing worldwide (**Figure**). In Europe significant rates (18%-23%) of cyberbullying were reported in primary schools.[1,2] In the US, incidents of bullying have been reported in 47% of parents with children aged 6-10 years and by 56.4% and 59.9% of parents with children aged 11-13 years and 14-18, respectively.[2] This commentary, prepared by the Social Pediatrics Working Group of the European Association of Pediatrics/Union of European National Pediatric Societies and Associations, briefly discusses bullying and cyberbullying and their risks to children. The purpose is to draw the attention of pediatricians, social workers, and teachers to these phenomena, which are increasing in preadolescents, emphasizing that these adults can be instrumental in alerting parents and families on the risks of this practice by children and play a central role in programs dedicated to monitoring, controlling, and contrasting these serious acts of violence.

Recognizing Bulling and Cyberbullying

Bullying is an intentional action that lasts for long periods of time. Typically, a student is bullied, prevaricated, or victimized when he or she is exposed, repeatedly over time, to the offensive actions enacted by one or more peers. **Table I** shows the essential conditions that characterize bullying. Cyberbullying is a relatively recent phenomenon, and it is well-recognized as a severe public health issue affecting both adolescents and children. Cyberbullying often looks to be an act of lesser severity than typical acts of physical bullying because such is not carried out directly through physical contact. However, cyberbullying is a violent phenomenon of equal seriousness, which has progressively amplified during the past 2 decades as a result of the widespread use of online media by preadolescents and adolescents. The ease of access to personal computers, smartphones, and tablets allows the cyberbully to commit acts of psychological violence, even anonymously, through social media, and to offend the victim through the dissemination of disparaging material (texts, photos, and images) or even the creation of bullying groups (**Table II**). This is an inappropriate use of the network, carried out outside the control of adults, by which children exchange violent, derogatory, and discriminatory content aimed at peers considered different in physical appearance, clothing, sexual orientation, social class, or national origin.[3] A recent report shows that in the US, the majority of adolescents (59%) have experienced some form of cyberbullying, and 22.6% of adolescents aged 12-17 years have been the subject of a cyberbullying incident in the past 30 days.[2]

The phenomenon of bullying is certainly not new, and it is usually associated to domestic abuse.[1,2] Children who witnessed their parents or caregivers behaving violently toward each other are more likely to bully other kids. Bullying, however, is not to be considered a new form of prevarication, having existed for a long time, perhaps since forever,[4-6] especially among adolescents and children. Before the era of digital media, bullying was typically consumed in places of socialization, such as in schools or generally in locations in which people gathered for recreational activities. However, its severity and impact on the younger generation recently has been amplified by the wide availability of digital tools to not only adolescents but also school and even preschool children.

EU	European Union
HBSC	Health Behavior in School-aged Children Surveillance

From the [1]European Paediatric Association/Union of National European Paediatric Societies and Associations, Berlin, Germany; [2]Association pour l'Activité et la Recherche Scientifiques, Bevaix, Neouchatel, Switzerland; [3]Albania Society of Pediatrics, Tirana, Albania; [4]Residency program in Pediatrics, University of Foggia, Scientific Institute "Casa Sollievo della Sofferenza", Foggia; [5]Italian Academy of Pediatrics, Milan, Italy; [6]Turkish Pediatric Association, Istanbul, Turkey; [7]Juvenile Court, Office of General Prosecutor, Rome, Italy; [8]Second Pediatric Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca; and [9]Romanian Society of Social Pediatrics, Cluj, Romania

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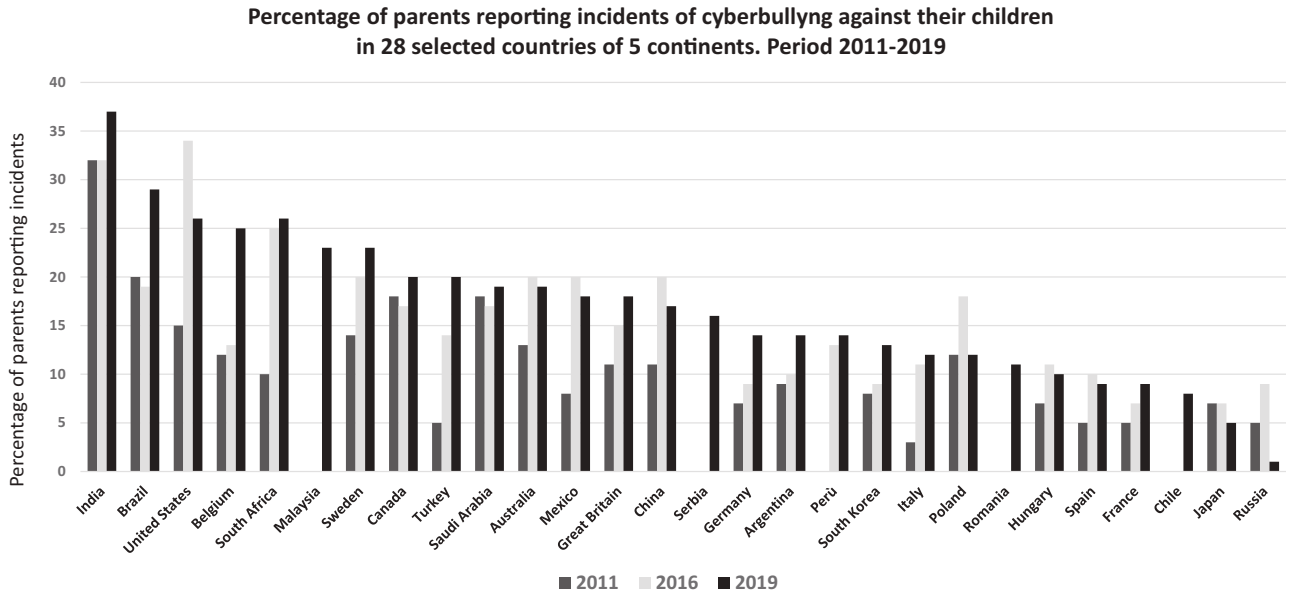

Figure. Incidents of cyberbullying reported by parents against their children in the period 2011-2019. Data from Ipsos International and the European Association of Pediatrics, Union of National European Pediatric Societies and Associations working group on Social Pediatrics modified.

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Data on the Prevalence of Bullying and Cyberbullying in Children and Adolescents

According to data from the World Health Organization's Health Behavior in School-aged Children Surveillance (HBSC),[7] bullying does not primarily affect high school boys or girls. The HBSC report shows that this phenomenon is highly experienced and on the rise in both girls and boys aged 11 and 13 years while decreasing as age increases. This pattern may relate to the growth of empowerment of the subjects and the educational initiatives and awareness programs, which have recently increased the level of awareness in the population regarding this important and negative social phenomenon.[7] Among 11-year-old children, 18.9% of boys and 19.8% of girls are bullied. In the 13-year-old age group, 14.6% of boys and 17.3% of girls experience bullying, whereas in teenagers (>15 years old) are 9.9% of boys and 9.2% of girls.

The HBSC also investigated some aspects of bullying and cyberbullying[7] in family and school life context, such as the relationship of children with their parents, classmates, teachers, and peers. Data show that within families, as age increases, the ease with which boys open up to both parents decreases. Moreover, 13- and 15-year-old girls, compared with boys of the same age, have greater difficulty talking about these phenomena to their father figure. Overall, 68% of boys and 60% of girls report high levels of family support. In 15-year-olds this percentage drops to 52% in girls and 61% in boys. The role of friends is also important, as 87% of 11-year-olds, 79% of 13-year-olds, and 80% of 15-year-olds report having friends with whom they share joys and sorrows, and 76% of 11-year-olds, 69% of 13-year-olds, and 70% of 15-year-olds report being able to talk about their problems with friends.[7]

Table I. Conditions that characterize bullying

Bullying is characterized by the following conditions:

- the protagonists are always children or young people, usually of school age, who share the same context, most commonly school;
- the acts of bullying, harassment, or aggression are intentional, that is, they are enacted by the bully(s) to cause harm to the victim or for fun;
- there is persistence over time: the bully(s)' actions last over time, for weeks, months, or years and are repeated;
- there is asymmetry in the relationship, ie, an imbalance of power between the perpetrator and the victim, eg, because of age, strength, gender, and the popularity the bully has in his or her peer group; and
- the victim is unable to defend themselves, is isolated, and is afraid to report bullying incidents because they fear revenge.

Victims, Victimizers, and the Social Context in Which They Live

Due to the complexity that characterizes bullying and cyberbullying and their impact on the daily lives of boys and their health, great attention must be paid to both the victims and the perpetrators. The bully generally is arrogant, impertinent, boastful, and deceptive. However, it is important to consider that these negative qualities are often the result of the bully's own discontent, which often can be sought in his or her family environment. Pediatricians must be particularly attentive to recognize the signs of distress in children who are under his

Table II. Main types of cyberbullying

Main types of cyberbullying
• **Flaming**. Consists of vulgar, violent, offensive, and provocative online messages containing insults aimed at stirring up verbal battles on social networks or forums.
• **Harassment**. Repeated sending of messages with offensive content aimed at hurting a specific person to whom obvious emotional and psychological distress can be caused.
• **Denigration**. Insulting or defaming someone online with gossip, lies, hearsay, and cruel, hurtful, and disparaging comments about victims through e-mail, text messaging, or instant messaging, to damage the person's reputation or friendships gratuitously and maliciously.
• **Impersonation**. Person substitution or identity theft: the attacker replaces the real person by creating a profile on the Internet with a fictitious identity using personal information, photos, and login information such as passwords and username related to someone's account, to send messages or post deplorable content in order to damage the victim's image and reputation.
• **Exclusion**. Consists of intentionally excluding a user from a group formed on a social network (eg, group of friends, chat rooms, interactive games, telematic forums) with the aim of causing him or her to feel marginalized.
• **Cyberstalking**. Online stalking consists of means repeated and threatening threats, harassment, violence, and denigration with the aim of instilling in the victim terror and fear for his or her physical safety.
• **Trickering (Deception)**. Gaining someone's trust by deception in order to disseminate, publish, and share embarrassing private information or personal images online, revealing secrets of the person and, thus, violating the confidentiality of confidences.
• **Sexting**. Sending sexually oriented messages, texts, photos, and videos that are disseminated through electronic means such as smartphones and the Internet.
• **Doxing**. Public dissemination of the victim's personal and private information or other sensitive data via the Internet, enacting an act detrimental to privacy.
• **Cyberflashing**. Sending explicit images in which targeted individual didn't ask.
• **Revenge porn**. Sharing or disseminating sexually explicit images or videos of individuals without their consent. The material disseminated may have been made by a partner in an intimate relationship with the knowledge and consent of the subject at the time, or it may have been made without their knowledge.

or her care and should be able not only to stop bullying and protect those who suffer it but also to extend their attention to their abusers. Pediatricians are, in fact, in a position to intercept situations of family discomfort that are often hidden behind bullying manifestations by those who carry out this form of criminal behavior. Schools play an important positive role in preventing and monitoring the emergence of the bullying and cyberbullying phenomena. To this regard, further data from the HBSC report show how 85.7% of 11-year-olds, 75% of 13-year-olds, and 61.8% of 15-year-olds say they have a positive and trusting relationship with teachers.[7]

Recognizing episodes of bullying and having the ability to intervene on the perpetrator of bullying takes on important social value and emphasizes the importance of close collaboration between the pediatrician and professionals working in social services, who are professionally trained to handle serious situations of family distress.

Family friends, parents, teachers, schoolmates, and pediatricians are all figures with a potentially decisive role in intercepting, interrupting, and preventing a physically and psychologically painful action. It is therefore greatly important to implement synergistic actions of prevention and early intervention particularly in school. Well-established evidence shows that the most effective treatments for antisocial conducts involve the development of emotional and relational skills through school activities that begin early, that is, in childhood and preadolescence, and promote the so-called "positive mental health" of students, including control of aggression, resilience, self-esteem, and self-efficacy.[8,9] This can be achieved through the strengthening of skills such as the ability to self-regulate emotions, personal goal setting, problem solving, and relational skills.[9] This makes it possible to prevent phenomena of discrimination, social marginalization, and persecution in the school environment, that can give rise to forms of aggression and irreparably affect the personality and mental health of victims.[8,9]

The Contrast of Cyberbullying in the European Union

Within the Member State of the European Union (EU), cyberbullying is scarcely regulated by common laws. In particular, there is no official EU law aimed at regulating this issue in a comprehensive matter. In 2017, Italy was the first European country to issue a national law (law no. 71/2017) that established, for the first time in EU history, that any form of pressure, aggression, harassment, blackmail, insult, denigration, defamation, identity theft, alteration, unlawful acquisition, manipulation, or unlawful processing of personal data to the detriment of minors carried out by electronic means must be punished. Furthermore, this law punishes the dissemination of online content also targeting 1 or more members of the minor's family whose intentional and predominant purpose is to isolate a minor or a group of minors by carrying out serious abuse, harmful attack, or their ridicule.[10,11] Most importantly, it establishes that a minor older the age of 14 years, victim of cyberbullying, or a family member, may ask the responsible website or data owner to obscure, remove, or block the harmful content published on the network.[12] In the event that such a holder does not comply within 48 hours, the person concerned may apply to the national Data Protection Authority, who will have to intervene within the next 48 hours. This law is currently being considered for adoption by the EU to control this phenomenon in all member countries.

Conclusions

The available data suggest that programs that include a close and coordinated collaboration between schools, social services, and pediatricians is one of the strengths on which to build effective programs to prevent and eliminate bullying and cyberbullying both nationally and within local communities. ■

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Drug Shortages in Pediatrics in Europe: The Position of the European Pediatric Societies

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Prescription and nonprescription drug shortages are not a new phenomenon.[1] The recent health crisis caused by the COVID-19 pandemic has further highlighted a chronic shortage of drugs and medical equipment in many western countries. This is a growing problem for Europe's national health systems. In recent years, shortages of all types of drugs have become increasingly common in hospital pediatrics and primary care and pose a threat to the health of adults and children in Europe and the US.[1-3] As early as April 2020, the Alliance of European University Hospitals warned that the increasing demand from intensive care units for anesthetics, antibiotics, muscle relaxants, and "off-label" drugs for the treatment of COVID-19 could lead to stock-outs.[3] However, after 2020, with declining production, logistical problems, and export and storage bans due to the current pandemic-related health crisis, the risk of shortage has increased.[4]

In September 2020, the European Union (EU) Parliament voted on a resolution calling for the EU to become more self-sufficient in health care.[5] In the text, the members of the European Parliament called for securing stocks, restoring local production of medicines, and ensuring better European coordination of national health strategies. Unfortunately, 2 years later, the problem has not been solved, but to the contrary has worsened. Currently, public health systems are facing a drug shortage crisis of unforeseen magnitude, one, ie, seriously undermining the public health of European nations.[3] In particular, primary care pediatrics is in great distress[6] due to the shortage of essential drugs to ensure the health of the pediatric population.

Between 2000 and 2018, drug shortages in the EU grew up to 20 times.[7] However, according to a note from the European Commission, the availability of widely used essential products continued to decline significantly after that date.[7] As discussed by the EU report, the causes are complex and include production problems, industry quotas, and legal parallel trade, ie, the import of medicines from other member states where the price is lower.[7] Other causes are epidemics and natural disasters, which cause unforeseen increases in demand, and the cost of medicines, which is set at the national level.[7] The EU is increasingly dependent on third countries, particularly India and China, for the production of active pharmaceutical ingredients, chemical raw materials, and drugs.[7,8] Unfortunately, the solutions adopted by the EU do not seem to have succeeded in mitigating the problem of drug shortages, despite the fact that the European Parliament had called for strengthening the production of medicines in Europe and setting minimum quality standards for health care, adopting best practices for stockpile management, increasing joint purchasing of medicines, and simplifying the transfer of medicines between member states.

In its 2017 resolution, the European Parliament called for better tracking of research and development costs, public funding, and market expenditures to make medicines more affordable.[9] In April 2020, the European Commission issued guidelines to counter drug shortages due to the coronavirus pandemic,[10] calling on member states to suspend export bans, avoid national stockpiles, and increase and reorganize production.[11] However, the problem of drug shortages still seems to be unresolved and a threat to the health of children.

This commentary, jointly authored by the European Confederation of Primary Care Pediatricians and the European Paediatric Association/Union of National European Paediatric Societies and Associations, highlights a joint statement issued by the 2 leading European pediatric societies addressing the serious problem of drug shortages in primary care pediatrics in Europe (**Table**).

Children are a particularly vulnerable patient group[12] with very limited pharmaceutical treatment options.[12] This limitation exposed them to adverse outcomes caused by shortages of essential medications. The European Confederation of Primary Care Pediatricians and European Paediatric Association/Union of European National Paediatric Societies and Associations emphasize the importance of ensuring optimal use of pediatric drugs in hospitals and ambulatory settings, through stock redistribution, consideration of alternative drugs, and optimization of pharmacy sales. Finally, the 2 societies jointly emphasize the dual need, on the one hand, to strengthen the EU production and supply resilience and, on the other hand, to increase price transparency and public funding for research and development.[7,9] ■

EU	European Union
APIs	Active pharmaceutical ingredients
ECPCP	European Confederation of Primary Care Pediatricians
EPA-UNEPSA	European Paediatric Association/Union of National European Paediatric Societies and Associations.

From the [1]European Confederation of Primary Care Pediatricians, Lyon, France; and [2]European Pediatric Association, Union of National European Pediatric Societies and Associations, Berlin, Germany

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Table. Addressing drug shortages in primary care pediatrics in Europe

Joint statement by

- ECPCP
- EPA-UNEPSA

Drug shortages challenge health care systems around the world. Authorities and public agencies in Europe and the US are now reporting shortages of commonly prescribed medications in pediatric settings. This situation raises fears that most of the drugs used to treat various pediatric conditions will be in short supply for the current winter season and for months to come.

ECPCP and EPA-UNEPSA emphasize that drug shortages can pose health risks to patients through undertreatment, medication errors, increased length of hospital stay, and adverse reactions due to attempts to replace unavailable drugs. Populations around the globe are in the transition phase from pandemic COVID to endemic COVID. The unseasonably early increase in respiratory infections in Europe during the winter 2022-23 is caused by unusual immunologic gaps. The early winter flu wave in children places an unexpected burden on pediatric primary care and increased demand for specialty anti-infective drugs. Children are a particularly vulnerable patient group with very limited pharmaceutical treatment options. This exposed them to adverse outcomes caused by shortages of essential medications. Problems with production and supply of existing drugs reduce the availability of critical products and preparations.

ECPCP and EPA-UNEPSA stress that a joint effort to understand the source of the problem can help resolve the current emergency and strengthen the preparedness of public health systems to deal with the next inevitable crisis.

Finally, the 2 leading European pediatric societies raise awareness among stakeholders, including health care professionals, legislators, and public health administrators, of the problem of drug shortages in primary care pediatrics and emphasize the importance of their close and effective interaction and collaboration to adequately address the recurring problem of drug shortages in this key public health area.

The appendix to this statement briefly discusses the general issue of drug shortages, its implications for primary care pediatrics, and possible useful measures to address this problem at the international, national, and local levels.

APPENDIX

- **Global geopolitical dimension of medicine shortage**

Drug shortages have taken on a global geopolitical dimension. The COVID-19 crisis has made the geopolitical dimension of drug shortages evident, highlighting the dependence of the European Union and the US on countries outside their borders for the production of active pharmaceutical ingredients (APIs) and drugs. According to information from the generic drug industry, China is a major producer of pharmaceutical inputs, particularly raw materials, intermediates, and APIs. The country is also considered by far the largest supplier of APIs or key intermediates for some essential drugs, such as analgesics (painkillers) or anti-infectives.

- **Challenges by new seasonal epidemiological features**

An unusually rapid onset of the annual flu season, caused by respiratory syncytial virus, influenza A and B, and many other viruses, has created a surge in demand for prescribed amoxicillin and pain relievers that parents can purchase without a prescription. Because these epidemiological features were unexpected, they could not be predicted and the increase in demand could not be anticipated.

- **Medicines fall short in pediatric primary care**.

More than 86% of European hospital pharmacists are experiencing difficulties in sourcing different types of medicines, and 66% report this as a daily or weekly problem. These shortages in Europe involve originator drugs in 51.8% of cases, and while the percentage rises to about 60% if we include generic formulations.[1] In particular, the prescription antibiotic amoxicillin is in short supply due to increased demand. Certain liquid formulations and suppositories of paracetamol (US: acetaminophen) and ibuprofen which are frequently recommended as fever-medicine and painkillers fall short in 26 European countries (as reported by the European Medicines Agency) and in the US.

- **Missing priority for pediatric medicine**.

Child-friendly medicines are neglected when measuring accessibility to medicines. There is no comprehensive overview of available data on children's medications. Children do not have a voice and cannot advocate for themselves by demanding more attention and investment in the production of children's medicines, which is currently limited probably because of limited earnings. Children need advocates on their behalf to obtain adequate data and improve access to child-friendly medicines.

Tackling children's medicine shortage in primary care pediatrics:

There is no magic solution to avoid the shortage of children's medicines in primary care. However, actions are needed to respond to the shortage at different international, national, and local levels with different stakeholders.

- **Actions expected by international organizations and agencies (European Commission, European Union, European Medicines Agency, World Health Organization)**.

Ensure the production and supply of essential medicines for children in all countries. Proposed changes to European Union pharmaceutical law should include more stringent obligations for the supply of medicines and more timely notifications of shortages. Improve communications among different countries regarding medications supply and stock files to better balance between demand and supply

- **Actions expected by the national governments and public health authorities**.

Protection of children's health through improved monitoring of causes of drug shortages and consideration of new regulations and legislation to ensure sufficient production and supply of essential medicines for children in hospitals and primary pediatric care. Promotion of healthy lifestyle for children and adolescents. Assure the prevention of infections with public promotion of vaccines and nonpharmaceutical personal protection to interrupt transmissions.

- **Actions expected from the pharmaceutical industry**.

Avoid production shortages, which often recognize internal problems within pharmaceutical companies, and poor or temporary unavailability of distribution. Promote independent national production and storage of primary substances for essential drugs.

- **Actions expected by pharmacies**.

Improve frequent communication with prescribers and providers about available medications. Advise parents on over-the-counter medications and alternatives. Check in-store alternatives first if some products are not available. Improve promotion of the use of generic versions of brand-name products, which are perfectly safe and often a much more convenient option.

- **Actions expected of pediatricians**.

Ambulatory pediatric care providers must be advocates for the safety of patients and protect children from drug shortages. They must be aware of current shortages and implement mitigation strategies. Implementing resilience strategies. Avoid unnecessary treatment of fever and viral infections. In cases of nonsevere otitis media, upper respiratory tract infections, and sinusitis, waiting is an option. Patients will be satisfied if the reasons for forgoing antibiotic treatment are explained. If amoxicillin is indicated and liquid formulations are not available, prescribe drugs that have not been affected by the shortage, including amoxicillin in tablets, chewable tablets, or dispersible formulations that are able to take. When amoxicillin cannot be used, consider the following alternatives: amoxicillin/clavulanate. Avoid cephalosporins, as resistance problems are becoming more important. If antipyretics/analgesics are indicated, including acetaminophen, paracetamol, or ibuprofen, and liquid formulations are not available, prescribe tablets, chewable tablets, or dispersible formulations for children who are able to take these formulations. The latter have been affected by the shortage to a lesser extent. Consider prescribing alternative drugs. Advise parents and caregivers that most tablets can be split/shredded and capsules can be opened. Both can be mixed with any tasty liquid. Chewable tablets can also be divided. Consider using complementary and alternative medicine, when possible. Follow guidelines regarding judicious usage of antibiotics, antipyretics, and other medications

- **Actions expected from parents.**

Avoid wasting medicines (disposing medicines before their expiration date). Avoid pressuring doctors to prescribe antibiotics for minor illnesses. Strengthen the ability to cope with infectious symptoms. Use natural methods and medicine whenever it is safe, applicable, and advisable.

ECPCP, European Confederation of Primary Care Pediatricians; *EPA-UNEPSA*, European Paediatric Association-Union of National European Paediatric Societies and Association.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Ten Years of Partnership Between the European Pediatric Association, Union of National European Pediatric Societies, and Associations and *The Journal of Pediatrics*

Massimo Pettoello-Mantovani, MD, PhD, and Mehmet Vural, MD

The European Pediatric Association, Union of National European Pediatric Societies and Associations (EPA-UNEPSA) celebrates 10 years of collaboration with *The Journal of Pediatrics*. The society is proud to have established and successfully maintained a long and productive collaboration with this important journal, published monthly by Elsevier. For the past decade, EPA-UNEPSA has adhered to *The Journal*'s mission to promote "pediatric research of the highest value for a diverse audience of pediatric healthcare professionals, and advance further scientific discovery to improve the quality of care and the health of infants, children, and adolescents."[1] The EPA-UNEPSA section, published periodically in *The Journal*, hosts invited commentary and insightful editorials from experts, discussing advancements in clinical and academic pediatric medicine related to every aspect of children's health, with the goal of promoting the latest developments in pediatric medicine, children's health, policy, and advocacy.

Over the years, the editorial board of EPA-UNEPSA, initially under the responsibility of the Chief Editor Jochen Erich of the University of Hanover, Germany, and since 2019 under Massimo Pettoello-Mantovani of the University of Foggia, Italy, has worked closely with *The Journal*'s Editors-in-Chief William Balistreri and Paul Graham Fisher to fulfill the common goal of advancing pediatric research and serving as a practical guide for pediatricians who manage health and diagnose and treat the disorders of infants, children, and adolescents. The purpose of this editorial is to celebrate the long and successful collaboration between EPA-UNEPSA and *The Journal of Pediatrics*.

A Decade-long and Fruitful Collaboration between EPA-UNEPSA and *The Journal of Pediatrics*

From 2012 to 2021, the EPA-UNEPSA has published 78 commentaries and editorials that received 1490 citations, as well as a special issue dedicated to the topic of "Diversity of Child Health Care in Europe,"[2] considered a seminal study in European public health, which received 285 citations. Another 18 articles that commented on major pediatric public health issues were published by EPA-UNEPSA experts in the period from 2022 to the present. The 2020 EPA-UNEPSA section article on "Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic"[3] is the most cited of all articles published in *The Journal* between 2020 and 2023.

The collaboration between EPA-UNEPSA and *The Journal* has contributed greatly to the mission of EPA-UNEPSA over the past 10 years. EPA-UNEPSA was founded in 1975 in Rotterdam by visionary colleagues from several Western European countries, with the goal of building scientific bridges between different countries and health systems across the Iron Curtain, during the difficult times of the Cold War.[4] The founders followed the principle and vision that children are not responsible for the political decisions of adults and all deserve the utmost attention and access to the latest therapies, and that all families should receive adequate support, regardless of their country or origin. This vision still seems to be tragically relevant today as Europe is shaken by new winds of war.[5] Since then, EPA-UNEPSA has grown to currently represent >50 national pediatric societies throughout Europe and is perceived internationally as the leading pediatric association in Europe and neighboring areas, representing the main operating standards to unite European pediatricians and facilitate their joint efforts to work, learn, and grow together.

EPA-UNEPSA is particularly proud of its partnership with *The Journal*, which represents a concrete and solid example of successful scientific collaboration between European pediatrics and one of the most influential and prestigious scientific journals published in the United States in the area of pediatrics. The EPA-UNEPSA section of *The Journal* focuses on topics of common interest in pediatrics and promotes knowledge transfer among health professionals and, in particular, from specialist pediatrics to general pediatricians, discussing how best to use new research data at the clinical level, a widely recognized challenge. This collaboration has produced a profound educational effect on EPA-UNEPSA members, greatly improving its members' access to new, original clinical research articles.

The shared characteristic of *The Journal* and EPA-UNEPSA is to focus on the quality of articles and their value

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

From the European Pediatric Association, Union of National European Pediatric Societies and Associations, Berlin, Germany.

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for the end user. During the years of their collaboration, *The Journal* has provided EPA-UNEPSA members with faster access to first-rate pediatric research. New technologies make it possible to publish research more quickly and effectively translate new findings into new best practices that can make a difference for patients. Facilitating access to new high-quality data and making primary clinical research available to EPA-UNEPSA members has helped to improve their ability to make clinical decisions.

The Important Collaboration Between Medical Societies and Pediatric Scientific Journals to Promote Children's Health by Sharing Expertise

In the dynamic field of pediatrics, collaboration between medical societies and scientific journals is of immense importance in promoting the well-being and optimal care of children. The multifaceted nature of pediatric health care requires a collective effort in which professionals and specialists from various disciplines join scientific journals to address the diverse and evolving needs of young patients.[6] Pediatrics encompasses a broad spectrum of medical specialties. Each subspecialty contributes its knowledge and expertise to the field, making collaboration vital to the comprehensive understanding and treatment of pediatric diseases.

Collaboration of top scientific journals, like *The Journal of Pediatrics*, with pediatric medical societies enables the sharing of knowledge, research findings, and best practices. By bridging gaps between pediatric disciplines, professionals can access a wealth of information, gain new perspectives, and integrate different approaches to improve patient care. The exchange of expertise encourages continuous learning, stimulates innovation, and helps to translate scientific advances into practical solutions that directly benefit children.[7] Through collaborations, medical societies and scientific journals can pool resources, combine research efforts, and make available to readers large-scale studies that help to improve pediatric care through robust and reliable results. Publishing collaborative research and consistent datasets facilitates in-depth analyses and increases statistical power. This collective approach improves the generalizability of research findings and accelerates the translation of scientific results into clinical practice, leading to improved health outcomes for children.[8] The purpose of the EPA-UNEPSA section of *The Journal* is to contribute to this important process through commentaries and editorials published by its experts.

Conclusions

In the EPA-UNEPSA section of *The Journal*, pediatricians around the world read about new EPA-UNEPSA initiatives and the progress of its ongoing and long-term projects. They will be able to follow the society's current thinking on how European pediatrics can be improved further. Overall, these pages will continue to share important information about the society and its relentless efforts to advance pediatric knowledge internationally. Readers will also be able to explore the activities planned by EPA-UNEPSA in Europe, many of which will be open to collaboration beyond European borders. EPA-UNEPSA believes in providing general pediatricians with the best available research in the field, so that they can make informed decisions for individual patients, a mission shared by *The Journal*.[1] We hope that the information published in this section will continue to provide pediatricians with stimulating reading, including news from the research front and information about EPA-UNEPSA's educational programs.

In conclusion, EPA-UNEPSA will continue its scientific activities in an energetic and collaborative environment, supported by its more than fifty European member societies and working closely with *The Journal of Pediatrics* in a joint and collaborative effort to successfully achieve common goals and overcome the challenges presented by a dynamic and ever-changing world. ■

Declaration of Competing Interest

The authors declare no conflicts of interests.

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REVIEW

Open Access

Use of complementary and alternative medicine in children affected by oncologic, neurologic and liver diseases: a narrative review

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Abstract

Complementary and alternative medicine (CAM) consist of a broad group of restorative resources often linked to existing local cultures and established health care systems and are also increasingly used in children with some serious illnesses. In this narrative review, we examine the epidemiology of the use, efficacy, and safety of complementary and alternative medicine in pediatric oncology, neurology, and hepatology. We searched for relevant articles published in Pubmed evaluating CAM use and its efficacy in safety in children affected by oncologic, neurologic and liver diseases**.** CAM is used to improve the success of conventional therapies, but also to alleviate the pain, discomfort, and suffering resulting from the diseases and their treatment, which are often associated with a significant burden of adverse effects. CAM use must be evaluated in children with neurological, oncological and liver diseases.

Keywords Alternative and complementary medicine, Children, Medications, Oncology, Neurology, Liver diseases

Introduction

The term complementary therapy is used in conjunction with alternative therapy to describe medical procedures, based on the connection between body and mind, which can help patients affected by severe health conditions feel better and improve their quality of life. The use of complementary and alternative medicine in pediatric oncology has increased significantly in recent years. In the 1970s, when these disciplines first appeared on the health care scene, they were provided primarily as an alternative to conventional health care and thus came to be known collectively as "alternative medicine." The name "complementary medicine" developed when the two systems began to be used alongside each other (to "complement"). Over the years, the term "complementary" has moved from describing this relationship between unconventional health disciplines and conventional care to defining the group of disciplines themselves. This change and

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overlapping terminology may explain some of the confusion surrounding the topic [1].

Currently, the terms are often used in one combined definition, complementary and alternative medicine (CAM), although substantial differences exist between the two. Complementary medicine is increasingly being adopted as supplementary therapeutic modalities supporting standard therapies to relieve symptoms, while alternative medicine is used instead of conventional treatments [1]. However, replacing standard care with alternative treatments can expose patients to life-threatening consequences. In contrast, complementary therapies taken together with standard medical care can help patients better manage symptoms caused by cancer or mitigate side effects associated with therapy [2].

CAM includes a variety of health care practices summarized in Table 1. According to Cochrane, CAM consists of a broad group of restorative resources, which may involve therapeutic methods and practices and related theories and beliefs, often linked to existing local cultures and established health care systems [3].

In summary, the purpose of using complementary therapies in clinical practice is to improve the quality of the therapeutic environment and therapeutic relationships, with the goal of optimizing the patient's ability to heal, in conjunction with traditional therapies [4]. However, there are still many gaps in scientific research on complementary therapies, and the impact caused by the side effects of various CAM therapies may be underestimated due to the lack of comprehensive data. This paucity of data may be due to a lack of funding or commercial interest of pharmaceutical companies and the scarcity of adequately trained professionals on the use of CAM and the performance and interpretation of systematic reviews and methodological issues [4–7].

This informational article briefly discusses the use of CAM in pediatric patients affected by some serious, chronic and disabling diseases, specifically focusing on oncological, neurological, and liver diseases. In fact, many complementary and alternative medicines claim to relieve symptoms in cancer patients or during cancer treatments, reduce the burden of neurological conditions, relieve symptoms of liver disease, or reduce the risk of developing liver diseases. This article aims to further raise awareness among general pediatricians about the importance and risks of complementary therapies in clinical practice.

Table 1 The most commonly used complementary and alternative medicines in patients with severe health conditions

Major complementary/alternative therapies (CAM) frequently used in patients with severe health conditions	
• Acupressure	• Lifestyle changes
• Acupuncture	• Massage
• Applied kinesiology	• Meditation techniques
• Aromatherapy	• Nutritional therapy
• Ayurveda	• Osteopathy
• Biofeedback	• Physical activity
• Chiropractic	• Reflexology
• Dietary changes	• Self-help groups
• Herbal medicine	• Stress management techniques
• Homoeopathy	• Shiatsu
• Hypnosis	• Yoga

Materials and methods

This is a brief narrative review that focuses on the use of CAM in pediatric patients with oncological, neurological, and liver conditions. Article selection was performed using established methods as described elsewhere [8]. In this article the authors summarize key information on the use of CAM in pediatrics obtained from scientific articles published during the past 20 years, including original studies, systematic review and meta-analysis. Articles search was performed using top academic search engines [8], including the classic academic databases Web of Science, Science.gov, Core, Scopus and PubMed, the search engine of the United States National Library of Medicine. Inclusion criteria involved all peer-reviewed articles published in English language, limited to child studies and published since 2003 (20 years). There was no geographical limitation for the articles considered for the review.

Overview on complementary and alternative medicine

Therapeutic use of CAM

Many CAM practices have already been used for years, and their beneficial effects on the mind and body have been known since ancient times. In recent years, evidence has increased that these practices can play an important role in the treatment of some specific diseases, including cancer, neurological and liver diseases [1, 9].

One element shared by most complementary therapies is the multifactorial, multilevel view of human disease. According to complementary disciplines, the disease is no longer seen as a single pathological process but as a collection of physical, mental, social, and spiritual disorders. They also emphasize the human body's ability to recover faster in comfortable situations and under appropriate conditions.

Based on this holistic approach, complementary therapies aim to heal individuals by restoring their physical and inner balance. The goal is to stimulate and facilitate the body's positive responses in association with, not as an alternative to, "conventional" therapies, rather than targeting individual disease processes and troublesome symptoms [6].

Efficacy of CAM

Numerous controlled clinical trials have demonstrated the usefulness of complementary therapies in treating various diseases with significant public health impact. The importance of CAM is further emphasized by the U.S. National Institutes of Health (NIH), which established the Office of Alternative Medicine, later named the National Center for Complementary and Integrative Health (NCCIH), to study the efficacy and safety of alternative therapies [7].

A wealth of information on the effectiveness of complementary and alternative medicine is available in the literature, including peer-reviewed publications, evidence-based reviews, expert group papers, and authoritative textbooks. However, no consensus has been reached on its effectiveness. Many CAM procedures have been studied and found to be effective in combination with conventional treatments, while other studies have found CAM to be ineffective or have reported contradictory and inconsistent results [9].

Standardization of data in CAM studies is difficult, which may explain the difficulty in reaching a consensus on their use in combination with the treatment of many conditions. In fact, complementary therapies cannot be standardized for individual conditions because, in most cases, their use is based on the patient's characteristics or experiences rather than on a clinically diagnosed disease in the traditional way. Outcomes are also difficult to standardize because they are often specific to individuals rather than based on objective, uniform measures such as blood pressure, blood glucose and inflammation indices. In addition, many studies lack a placebo control, which precludes any reliable conclusions. However, despite the lack of consensus on the efficacy of CAM, many studies have provided substantial data in favor of their use as integrated treatments in various serious disease conditions [9, 10].

Safety of CAM

Unlike conventional medical treatments, which are thoroughly tested and regulated, most complementary therapies have not yet been sufficiently tested for their safety. Some studies have examined suspected CAM-related adverse reactions in the pediatric population and have warned of the risks and dangers of CAM in children, especially in "fragile" patients, such as those with cancer or neurology and liver diseases [11]. Studies have also provided insights into factors that might increase the risk of serious adverse reactions associated with the use of CAM in children. Indeed, their common description as natural remedies may suggest the assumption of safety, whereas the potential effects of CAM may instead represent an increased iatrogenic risk. In particular, the use of products containing more than two components and administered concurrently with conventional medications may pose a potential risk in younger patients [11], because responses to standard treatments in this population are often unpredictable and individual-based, and complementary treatments are usually not standardized [5, 7]. Adverse effects have also been reported in the use of herbal dietary supplements (HDS), as they can affect different physiological systems [12]. Studies on the adverse effects of CAM are significantly advancing knowledge in this area. However, health care providers should familiarize themselves with CAM practices and carefully balance the associated benefits and risks to best care for their patients.

Use of complementary therapies in oncological diseases

Complementary therapies are used effectively in children with slow-moving forms of cancer to help cure or alleviate symptoms. Preferably, integrative pediatric oncology should be provided in pediatric hospitals or medical centers that participate in clinical trials or belong to pediatric oncology networks [13]. Complementary therapies, which in general are usually used in cancer patients, are summarized in Table 2.

The inclusion under the term CAM of several and various types of complementary practicesused for pediatric cancer patients may explain the wide range of prevalence, depending on the country (6%-91%), reported in a recent systematic review [13]. In particular, large differences have been reported between North America and Europe, which may also have been influenced by the time period over the past 30 years when CAM alone or CAM has

Table 2 Complementary therapies frequently used in cancer patients

Complementary therapies frequently used in cancer patients
• Touch therapies: acupuncture, aromatherapy, reflexology, and massage
• Mind–body therapies: relaxation, guided imagery and hypnosis, yoga, meditation, tai chi
• Energy therapies: Reiki, therapeutic touch, and healing touch
• Talking therapies: trained counsellors (one-to-one) or group sharing experiences
• Changes in Daily lifestyle: physical activity, healthy diet, vitamins, probiotics, herbalism

been introduced in different countries, either in support of or as an alternative to cancer therapy [14, 15].

The increased use of CAM to relieve symptoms in oncology patients

Parents of pediatric oncology patients are inclined to introduce unconventional treatments to reduce harming symptoms and alleviate complications of therapy[14]. The most common symptoms during cancer therapy are nausea and vomiting, whose multifactorial origin is typically related to chemotherapy [14, 16]. According to a 2022 review, CAM practices have helped to alleviate nausea, vomiting, mucositis, weight loss, anxiety, pain, and, most importantly, to improve children's quality of life [13].

The routine use of CAM, in addition to standard cancer therapies, has significantly increased during the past recent years by families and caregivers of cancer patients. Currently, these therapies are often an integral part of supportive care, especially used to control the side effects of cancer therapies. However, the use of CAM in cancer therapy is still debated, and there is no final consensus regarding its effectiveness and safety [17].

Different types of complementary therapies are used during cancer treatment. The National Center for Complementary and Alternative Medicine (NCCAM), popular categories of CAM are natural products, including plants/herbs, a practice also known as "herbalism," vitamins and other dietary supplements, mind–body practices (prayer, meditation, yoga, acupuncture, guided imagery, hypnotherapy, tai chi) manipulative practices (e.g., massage, chiropractic), new "biological field therapies" (e.g., Reiki, healing touch, qi gong), traditional healers, and other medical practices such as Ayurvedic medicine or traditional Chinese medicine, when used as a support to conventional medicine [18]. Homeopathy, dietary treatments and nutritional supplements seem very popular in Germany [7], while herbal extracts are mostly used in Mexico and water therapy and Spirulina in Malaysia[17]. Although often used during cancer treatments, chiropractic care needs further studies to demonstrate its effectiveness in pediatric oncology[19]. A recent review reports that several studies first observed the effects of CAM modalities on symptoms related to cancer therapy, and that hypnosis, imagery/visualization and music therapy were found to be most useful in relieving procedure-related pain [19].

This section briefly discusses some of the most commonly used CAM procedures in pediatric oncology.

Massage

One of the most used CAM interventions for children with cancer is massage. An extensive review of massage practice in pediatric patients, which reports 24 randomized controlled trials between 1992 and 2006, found that massage was strongly effective on anxiety in children, especially after multiple sessions of this intervention [20]. In addition, evidence has been reported of other side symptoms relieved by massage, including nausea, pain, depression, stress, anger, and fatigue [21–23]. A study on a limited cohort of pediatric oncology patients of different ages and mixed diagnosesreported positive results in reducing heart rate and anxiety and very positive evaluations of the massage experience by the participants [24].

Studies on massage in children undergoing bone marrow transplantation (BMT) are scarce. In one study, fifty young cancer patients undergoing BMT received professional massage, parental massage, or constituted the control group. There was a significant difference in incision days after BMT in the combined group that received massage (parental and professional). A significant reduction in anxiety and immediate discomfort was seen in the group that received professional massage [21]. Another follow-up study conducted by the same team found no differences in depression, quality of life, or posttraumatic stress between a child intervention group (humor and massage), a parent intervention group (massage and relaxation), and a control group receiving only standard care, although an improvement and adjustment of symptoms were observed in all groups [25]. In a smaller pilot study, the combination of tri-weekly massage and acupressure versus standard care demonstrated benefits in terms of nausea, fatigue, pain, and reduction of mucositis and benefits were reported by caregivers using this practice [24].

Yoga

There is evidence that yoga improves physical strength and flexibility as well as mental health through toning, stretching, and relaxation exercises. It has also been shown to beneficially influence the autonomic nervous system [26] by decreasing salivary cortisol levels, plasma renin levels, and urinary norepinephrine and epinephrine levels, as well as reducing blood pressure and heart rate [27]. In two studies yoga has been shown to be safe and feasible in pediatric cancer patients undergoing chemotherapy [28, 29]. However, further research is needed to demonstrate its efficacy in effectively controlling the symptom.

A recent study reports that a significant improvement in pain was achieved in patients using yoga regardless of their age. In addition, this study also reports the benefits of yoga in parents caring for their children. It was shown that one yoga experience was important enough for parents to control emotions and contain anxiety. In

summary, this study emphasized that it was feasible for children and adolescents with hematologic or oncologic disease and their parents to participate in the yoga intervention [30]. Similarly, a different study suggested that patients' guardians experienced a significant decrease in anxiety after using relaxation practices [31]. Finally, yoga has been shown to be significantly effective in reducing fatigue symptoms in pediatric brain tumor patients and in improving their sleep.

Acupuncture and acupressure

Acupuncture includes a group of techniques in which small needles, heat or electrical stimulation are placed at specific anatomical points. Acupuncture points are located on meridians along which qi (a "life energy") flows, while acupressure uses pressure applied with hands or other devices on the same acupuncture points [32]. Children have been shown to tolerate acupuncture well [33] and to have no bleeding problems. In addition, acupuncture has been reported to be effective in reducing chemotherapy-induced nausea and vomiting during or at the end of chemotherapy treatment [34]. In a meta-analysis that evaluated the effects of acupuncture on postoperative nausea and vomiting, acupuncture was shown to reduce vomiting and nausea [34].

Acupressure is similar to acupuncture but uses pressure instead of needles. This practice can be helpful for children who suffer from agophobia or when an acupuncture expert is not accessible. The most popular type of acupressure is the use of wrist bands that apply pressure to the ventral surface of the wrist. A cross-over pilot study of pediatric cancer patients showed that acupressure is risk-free, feasible and well-accepted [32].

Mind–body therapies

Many mind–body therapies, such as cognitive distraction, meditation, imagination, creative arts therapy, and hypnosis, are reported to be useful for treating procedure-related anxiety, pain, and distress in pediatric cancer patients. In a small retrospective study, meditation was found to significantly reduce the use of analgesic therapies in children with neuroblastoma on monoclonal antibody therapy [35]. In particular, non-pharmacologic interventions for procedure-associated pain, such as hypnosis, seem beneficial in cancer therapy [36]. A study showed this practice to be particularly useful for pediatric patients (age range 7–14 years) who seem to be more sensitive to hypnosis when used in conjunction with pharmacological therapies [37]. Hypnotherapy refers to many different practices, including relaxation, imagination, and aromatherapy, which are the most used in pediatric cancer patients. Hypnotherapy is the most used mind–body therapy to control nausea and vomiting, the main symptoms associated with sympathetic stimulation, in children with cancer. Through a state of deep relaxation, hypnotherapy helps people easily overcome automatic thoughts such as anticipated nausea and vomiting derived from cancer treatment [37]. A review of all CAM studies for procedure-related distress in pediatric oncology showed that hypnosis is also effective in painful procedures (e.g., lumbar puncture, bone marrow) and for reducing anticipatory anxiety [35].

Energy therapies

Reiki, therapeutic touch, and healing touch are part of energy therapies. They have not been extensively studied in adults with cancer. Energy healing therapists, also known as biofield therapy practitioners, channel healing energy through the hands into the patient's body to rehabilitate normal energy balance and health. In a review of biofield therapies, it was reported that adults with cancer showed commonly positive effects on reducing pain and psychological distress characterized by anxiety, depression and stress, and improved quality of life [19]. Data on pediatric cancer patients are limited. A small study of healing touch versus a "read/play" control showed a reduction in pain, stress, and fatigue for patients, parents, and caregivers [36]. Energy therapies are well accepted by children and adult cancer patients, as they show no adverse effects. However, conclusive data in favor of their use are lacking [19].

Selected herbs and biological therapies

Many cancer patients use many herbs and biological therapies [38]. Traditional Chinese Medicine (TCM) is a health management that includes herbal medicines and various mind and body practices to prevent and treat diseases. Usually, TCM practitioners integrate many herbal medicines, and each herbal therapy is planned for each patient. The use of Chinese herbs in the adult and pediatric oncology population is controversial because several reports indicate contamination of the herbs used in therapy with drugs, toxins, or heavy metals. Therefore, their use is currently under monitoring and their content is under evaluation to acquire conclusive data about their safety [37].

Probiotics are biological CAM frequently used in children and adolescents [39]. Probiotics could have a positive effect on allogeneic stem cell transplantation (SCT). Experimentally, significant survival and reduction of acute graft-versus-host disease (aGVHD) before and after transplantation was reported using L. rhamnosus GG in a mouse model of aGVHD [38]. In a small study of chemotherapy-treated children, the use of Bifidobacterium breve strain Yakult reduced fever episodes and improved the presence of anaerobes in the gut microbiota [39].

Glutamine is an essential amino acid that has been used for the prevention of peripheral neuropathy and mucositis. Although the ideal dose and route of administration have not yet been defined, it represents a future option in CAM therapy for adult and pediatric cancer patients. In children undergoing stem cell transplantation, glutamine has helped reduce the duration of fever, and the use of total parental nutrition (TPN) and narcotics has been related to the standard of care protocol [40].

Use of CAM to relieve pain and anxiety

Pain is a common symptom frequently related to cancer diagnosis procedures and treatment, and it can also result from disease progression, due to obstruction of nerves, tissues, or organs by tumors at any stage of the cancer process [41]. Many studies emphasize the importance of complementary modalities in helping children undergoing cancer treatment in general and especially in painful procedures, including lumbar puncture, bone marrow aspiration, access to implanted ports, and venipuncture [42, 43].

In several studies investigating various painful procedures, mind–body techniques and hypnosis have shown positive results in reducing pain and anxiety. These two noninvasive techniques are reported to help mitigate or control the effects of painful procedures in children during cancer treatment [43, 44].

The importance of communication in the use of CAM

The most important motivations for the use of CAM have been the goal to improve the patient's overall condition, strengthen the immune system, and reduce the adverse effects of conventional therapy. Parents often do not choose CAM because they lack information about it, are convinced that it is ineffective, and want their children to be stress-free [14].

A recent study emphasizes a lack of communication between pediatric oncologists and their patients [9]. According to this report, 7% of pediatric oncologists never ask their patients an open question about CAM use, while 43% sometimes ask their patients a general question about their use. Pediatric oncologists' questions to their patients about specific CAM therapies depend greatly on the type of therapy. For example, more than one-third of pediatric oncologists routinely ask their patients about the use of dietary supplements, phytotherapy, special diets and vitamins. However, the use of aromatherapy, enzymes, acupuncture, homeopathy, magnets, prayer, chiropractic, guided imagery, martial arts, meditation and yoga is never asked to pediatric patients by their oncology team. The use of vitamins, special diets, nutritional supplements, herbal medicine, and antioxidants is often requested by cancer patients from their physicians. However, they are often discouraged. The reasons why pediatric oncologists do not ask their patients about CAM therapies are lack of time in 49% of cases and lack of knowledge in 47% of cases [9].

In conclusion, the main reasons for cancer patients to use CAM are improvements in physical and psychosocial well-being and increasing hope[45], but also despair, disappointment with some features of standard healthcare, lack of physician–patient relationship, availability, and perceived efficiency [46].

Complementary therapies in neurological diseases

Use of CAM in neurological diseases has increased in recent years, mainly because they are usually chronic conditions and often associated with various comorbidities. A survey reported that children affected by neurological diseases used CAM more frequently than healthy children (24% vs. 12.6%, respectively) [47].

In Canada, 44% to 76% of children with common neurological conditions reported the use of integrative medicines [48, 49].

CAM therapies mainly used in neurological diseases range from nutritional supplements such as herbs and vitamins to massage and osteopathic manipulation, acupuncture, mind–body therapies and relaxation techniques (Table 3) [47].

Here in, we analyzed the most common neurological diseases where CAM is used (Fig. 1).

Cerebral palsy

Cerebral palsy (CP) is a group of disorders characterized by a spectrum of motor and posture impairment caused by non-progressive damage that may happen during prenatal, perinatal, or postnatal stages of the development of the nervous system [50].

The prevalence of CP is estimated to range between 2 and 3 per 1000 live births, representing the leading cause of pediatric disability [51].

Children affected by CP present various neuromotor limitations in their physical activities, leading to a psychological, social and functional impairment [50].

Although neurological injury may happen during each stage of neurological development, perinatal injury accounts for about 90% of all cases and it must be kept in mind in order to prevent and early recognize CP. The principal manifestations of CP are posture, reflexes and muscular impairment, usually associated with sensory problems, coordination imbalance and learning, speech, and cognitive disabilities [52]. Moreover, CP is frequently associated with other neurodevelopmental disorders, particularly attention-deficit hyperactivity disorder (ADHD) represents the most frequently associated comorbidity [53].

Table 3 CAM therapies mainly used in neurological diseases

	Cerebral palsy	Epilepsy	Headache	ASD	Tourette syndrome	ADHD
Acupuncture	+		+	+	+	+
Massages and manipulation	+		+	+		+
Nutritional supplements		+	+	+	+	+
Music therapy	+					+
Hippotherapy	+			+		
Behavioral treatments		+	+		+	+
Homeopathy			+			+
Other specific therapies	Hyperbaric therapy	Yoga	Aromatherapy			

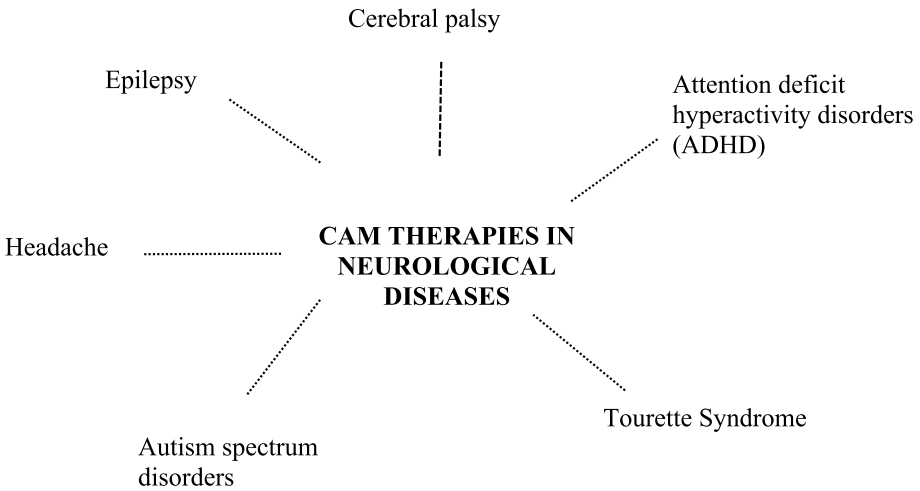

Fig. 1 Summary of neurological diseases where CAM therapies are more commonly used

Signs and symptoms of CP may be various and range from mild to severe clinical presentations and they may be evaluated according to Gross Motor Function Classification System (GMFCS) [54].

Until now, there is no curative therapy for CP, and the available treatments depend on the specificity of the symptoms. Usually, a multidisciplinary approach is fundamental to reduce the symptoms and improve the quality of life [55].

Many types of therapies are used. The most used conventional treatments include occupational therapies to improve movement and balance impairment, selective dorsal rhizotomy, systemic muscle relaxants, intramuscular on botulinum toxin A to reduce spasticity, and pharmacological therapies to improve neuropsychiatric comorbidities [56]. Among conventional treatments are also included "Vojta therapy" and "Bobath therapy", which mainly aim to reduce postural and motor imbalance through the reflex mechanism of neurostimulation [57].

On the other hand, as in other chronic neurological conditions, CAM started to be used, especially in the last years. The use of CAM in children affected by CP varies from 27 to 56%, with differences depending on the availability and knowledge of CAM in the different areas [58].

The principal factors associated with CAM use seem to be the type of CP (particularly spastic quadriplegia), the presence of severe motor disabilities and parental use of CAM [59].

Massages are one of the most used CAM practice, particularly in children with severe motor limitations with a prevalence of 15–50% depending on the studies [57, 58]. Hyperbaric oxygen therapy (HBOT) is also a popular therapeutical option; its rationale consists of the reactivation with pressured oxygen of the damaged neuronal cells and the reconstruction of the synapses [60].

A recent systematic review demonstrates high-level evidence that HBOT is ineffective in improving motor and functional performance in children with CP and is associated with some adverse effects such as middle ear

barotrauma [61]. Therefore, HBOT is not recommended in CP. Manipulative treatment (OMT), particularly craniosacral treatment and myofascial releases, seems to be useful to improve motor abilities, especially in children with moderate to severe spastic features [62].

Acupuncture use is diffused in children with CP; its benefits are improving the use of legs and arms, warming the extremities, decreasing in the spasm and permitting a better bowel function and sleep [63]. Laser acupuncture is a new type of acupuncture that uses a laser light with low intensity to induce biostimulation of cells and tissue, with similar effects to classic acupuncture but without mechanical effect [64]. Some studies have confirmed the efficacy of laser acupuncture in improving spasticity through biochemical changes in cells and the positive impact on the autonomic system and the neuroprotection role, mediated by increasing the production of neurotropic factors and antioxidant enzymes [65, 66]. Tang et al. have conducted a recent systematic review and meta-analysis to evaluate the clinical efficacy of acupuncture with evidence that it has great effect in improving musculoskeletal dysfunction [67].

Music therapy has also been successfully used in CP. Actually, music therapy seems to increase the synchronization between motor and sensorial aspects, facilitating neuroplasticity, and it improves communication and social abilities [68].

Aquatic therapy is a quite recent practice introduced in children with CP. It exercises mechanical (including hydrostatic and hydrodynamic) effects and thermal effects. In fact, aquatic therapy removes gravity, permitting it to perform much more activities than on the land. Lai et al. have conducted a single-bind prospective study analyzing the efficacy of aquatic therapy on sensorial and motor abilities, on all activities of daily living and on the quality of life with the evidence of great benefit on gross motor function and on enjoyment than the in control group [69]. Moreover, equine therapy started to gain visibility due to its mental and physical efficacy in CP. Equine therapy is a holistic practice that provides motor and sensitive stimulation through the horse's movement and improves social and relational abilities [70]. Although in many countries, equine therapy has many successes in improving CP-associated symptoms, it frequently remains a poorly used practice due to the high costs and parents' doubts regarding its effectiveness and the benefit-risk ratio [71].

Recent studies have analyzed the efficacy of equine therapy with the evidence that it has many positive effects, not only on spasticity, motor and balance control, but also on relational abilities and attention, resulting in an alternative therapy that can be used especially in children with both CP and ADHD [71, 72].

Headache

Headache is one of the most common disorders, affecting almost 60–75% of children by the age of 15 [73].

Since headache in childhood represents an important physical and psychological disorder with a great impact on the quality of life, multidisciplinary and integrative treatments, based on pharmacological and non-pharmacological approaches, are the best choice to prevent chronicity of symptoms and reduce medication abuse [73].

The use of CAM treatments in childhood headache is increasing, especially in the last years, reaching 76% in some cases [74]. It was observed that parents usually recur to the use of CAM in headache treatment to avoid adverse pharmacological effects and to explore all possible therapeutical options. According to Gaul et al., the use of CAM treatments generally depends on the duration of headache, types of headaches, number of headache episodes and use of CAM for other symptoms [74].

Nutraceuticals are dietary supplements in the form of minerals and vitamins. Riboflavin, coenzyme Q10 and magnesium are the most frequent supplements used in migraine. Riboflavin is involved in cellular function, reduction of oxidative stress and membrane stability [75]. Coenzyme Q10 (CoQ10) acts as an antioxidant agent and maintains an adequate mitochondrial function [76]. Magnesium plays a role in brain cellular homeostasis through interaction with calcium channels, N-methyl-D-aspartate (NMDA) receptors and reducing inflammation. According to the American Academy of Neurology and American Headache Society (AHS/AAN) guidelines, magnesium and riboflavin are considered as Level B of evidence (probably effective for migraine prevention), instead, CoQ10 is considered Level C (possibly effective for migraine prevention) [75].

Interestingly, also vitamin D and melatonin have been used with success to reduce disability and the frequency of headache [77]. Instead, the use of butterbur is no more recommended due to the risk of hepatotoxicity. Danno et al. have demonstrated that also homeopathic medicines, especially *Belladonna*, *Iris versicolor*, *Ignatia amara*, *Gelsemium* and *Kalium phosphoricum* may be useful to reduce severity and frequency of migraines attacks [78].

Massage therapy may be useful during the attacks. A wide range of massage techniques are available and should be tailored to the type of headache and the patient. The most frequently used massages include deep tissue massage, which acts especially on a chronic tension-type headache; trigger point therapy, based on cycles of pressure and release on a specific point; and Swedish massage, which provides a light-medium pressure [79]. Also, acupuncture practice is widely diffused as CAM in headache. It has been demonstrated its efficacy

especially in tension headache and episodic migraine, explaining anti-inflammatory, analgesic, and neurobiological actions. Acupuncture may activate the endorphin-enkephalin system inhibiting pain pathways in the spinal cord and midbrain [80, 81]. Interestingly, Li et al. evaluated the effects of standard acupuncture on right-fronto-parietal networks (RFPN), which are involved in the perception of pain with evidence of reduced activity after 4 weeks of treatment [82]. A Cochrane review demonstrated that acupuncture may be more effective in reducing migraine frequency than prophylactic drug treatment and not receiving acupuncture [83].

Aromatherapy, the medical use of oils derived from plants, is often used in addition to acupuncture due to its anxiolytic properties. It has been observed in a trial that inhaling lavender essential oil for 15 min may significantly reduce the severity of migraine respected the placebo control group [84]. Moreover, the United States Headache Consortium Guidelines recommended with a grade A evidence cognitive behavioral therapy, relaxation techniques and biofeedback in migraine prevention [85]. Cognitive behavioral therapy (CBT) represents one of the leading CAM interventions in children with migraine. The aim of CBT is teaching relaxation, behavioral and cognitive skills to manage attacks and reduce comorbidities and disabilities associated with headache. A recent Cochrane review of psychological therapies for the management of chronic pain evidenced that CBT reduce the number and the severity of attacks [86]. Interestingly, Nahman-Averbuch et al. found that patients with migraine after only 8 sessions of CBT had modifications in connections between prefrontal cortical activity and the amygdala, suggesting a possible organic role in changing the brain area, which regulates emotions and pain regulation [87]. Similarly, relaxation techniques, including muscle relaxation, meditation and diaphragmatic breathing, are mostly used to increase pain control and decrease stress and sympathetic overstimulation [88]. Biofeedback is a self-regulation strategy that aims to regulate autonomic features related to pain and stress, such as breathing, temperature and heartbeat. A metanalysis evaluated the effectiveness of biofeedback on pediatric migraine with the evidence of reduced frequency and duration of migraine attacks and better pain control during the attacks [89].

Epilepsy

Epilepsy is a chronic condition characterized by a brain predisposition to generate epileptic seizures and it can result from different causes, such as genetic variation or structural brain lesions [90]. In Europe, the estimated number of children and adolescents suffering from epilepsy is 900.000 and worldwide about 10.5 million [91]. The conventional treatment of epilepsy is based on antiepileptic drugs (AEDs), surgery, ketogenic diet and vagus nerve stimulator. AEDs are usually the first-line treatment, but only about two-thirds of patients who use AEDs have optimal control of seizures and AEDs are often associated with adverse effects [92]. Therefore, CAM use in epilepsy has become popular, especially in the last years; however, only a few data are available on the worldwide prevalence of CAM use [93]. A recently published scoping review has shown that CAM usage among children with epilepsy is ranging from 13 to 44% [94].

The main predictor factors of CAM use seem to be the duration and severity of epilepsy, parental use of CAM and incidence of the adverse effect of AEDs [95, 96].

Multivitamins and herbal products are among the most frequently used CAMs and they are generally safe. However, it was reported that some products, such as ginseng and gingko biloba, could trigger seizures due to a pharmacokinetic interaction with AEDs reducing their effectiveness and leading to an exacerbation of seizures [97]. Recent studies evaluated the effectiveness of omega-3 supplementation in patients with epilepsy with the evidence that children supplemented with omega-3 have a significant decrease in the number and severity of seizures. The rationale of omega-3 use seems to be linked to the decrease omega-3 levels observed in patients with epilepsy; actually, omega-3 is involved in the endoplasmic reticulum and myelin function of brain cells, so, a reduction in omega-3 levels may develop seizures [98]. Interestingly, the use of cannabis-related remedies, such as medical marijuana or cannabidiol oil (CBD oil) has increased, especially in refractory epilepsy. The exact antiseizure mechanism is not still known in humans, however, the neuroprotective and anti-inflammatory properties of cannabidiol may influence the protective action of cannabis-related products in epilepsy [99]. A telephone survey conducted among 200 parents/caregivers of children with epilepsy in Pennsylvania reported that 13% of respondents used CAM, particularly, cannabis-related products, with benefits on the frequency of seizures [99].

Also, yoga has been reported in childhood epilepsy [100]. Kanhere et al. have conducted a RCT analyzing the effectiveness of yoga practice as additional therapy to AEDs on epilepsy, and they found that it was associated with seizure freedom respect the control group and, interestingly, with an improvement of EEG with normalization after 6 months of therapy. The probable mechanism of action is a brain desynchronization, increase of gamma-aminobutyric acid (GABA) levels with a shift to a parasympathetic cerebral dominance [101].

Then, it has been reported the use of neurofeedback. Neurofeedback, also known as EEG biofeedback, is a form of conditioning training that aims to regulate brainwaves based on real-time feedback to people about their brainwaves through EEG [102]. Nigro et al. have conducted research regarding the effectiveness of neurofeedback on pediatric epilepsy and they found that still now there is a lack of evidence in the literature to suggest neurofeedback [103]. However, it may be considered as possibly efficacious (level 2) according to association for applied psychophysiology and biofeedback (AAPB) criteria [104].

Autism spectrum disorders

Autism spectrum disorders (ASD) is a disorder, which usually begins from childhood, characterized by communication and social deficits, associated to restricted interests and anomalous behaviors [105]. The prevalence of ASD is estimated to be under 1%, but it is increasing especially in high-income countries, probably due to increased surveillance [106]. Etiopathogenesis is poorly understood and is thought to be a complex of genetics and environmental factors [107]. The core deficits may range from mild to severe [107]. As well as other neurological chronic conditions, ASD requires long-term and multidisciplinary management [108]. Until now, no specific treatment is known for ASD; nevertheless, many medical and behavioral actions may be useful to improve the relational deficits and the associated comorbidities, such as insomnia, anxiety, hyperactivity and aggression[109]. Based on current healthcare literature, limited conventional treatments are available such as speech and behavioral therapy for communication deficits and occupational therapy to improve motor and sensorial skills. Also, medications such as stimulants, antipsychotics, alpha agonists, antidepressants are often used to improve behavioral defects like aggression, anxiety and agitation without effects on the stereotypy features and social skills. Due to the limited therapeutical options, many parents of children with ASD are interested in CAM. CAM use seems to be particularly associated with ASD severity, parental educational level and length of illness [110].

Nutritional aspects and integration have been extensively studied in the recent years. Particularly, it was found that children with ASD have high levels of harmful amino acids such as tryptophane and phenylalanine and low levels of vitamin B6, vitamin B12, choline and folate which are associated with scarce behavioral and language skills and poor clinical profiles [111]. According to the last evidence, these findings support that vitamin B12 and folate supplementation may be a feasible therapeutical strategy for autistic children [112].

Moreover, some evidence supports a correlation between gut microbiota and ASD. The gut microbiota plays a fundamental role in neuromodulation and inflammation due to its interaction with the enteric nervous system [113]. Autistic children have an altered gut metabolism, with a more absorption of mono-disaccharides in the large intestine, leading to an increase of gastrointestinal fermenting bacteria and a change in a gut microbiota causing osmotic diarrhea. Probiotic administration may modulate gut microbiota and reduce the overproduction of noxious metabolites, promoting the balance between "gut-brain axis" [114]. Do et al. demonstrated that probiotic mixture supplementation *(B. longum and B. bifidum L. acidophilus, L. casei, L. delbrueckii)* improves both gastrointestinal symptoms and communication, social affect score and physical behavior [115]. Similarly, Grossi et al. reported a case of a 12-year-old child with an important cognitive disability that increases social abilities after 4 weeks of probiotic supplementation *(L. paracasei, L. bulgaricus, delbrueckii subsp., S. thermophilus, S. salivarius subsp. B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum)* [116].

Moreover, it was reported a correlation between behavior disorders of ASD and an excess of opioid receptor agonists; particularly, it was supposed that gluten and casein products may increase opioid-like metabolites which reach the blood–brain barrier, leading to an inflammatory response that can negatively influence the neurological development and ASD-correlated symptoms [117, 118]. Knivsberg et al. have studied the efficacy of gluten and casein-free diet, and they suggested avoiding any exclusion diet as a standard treatment [119]. A recent review confirms that there is still insufficient evidence to support a gluten and casein-exclusion diet in all autistic patients [120]. Similarly, omega-3 fatty acids (FAs) supplementation is not effective on ASD-related symptoms and is not recommended [121].

Animal-assisted therapy has also become popular for improving the core deficits of children affected by ASD [122]. Animal-assisted therapy, especially therapeutical horseback riding, may improve communication and social abilities and increase the self-esteem and happiness of children with ASD [122]. Chen et al. have recently conducted a systematic review and metanalysis to evaluate the effectiveness of horseback riding on communicative and social abilities confirming that it can decrease maladaptive symptoms, such as speech impairment. However, they did not find evidence regarding an improvement in stereotypy and hyper sensibilization [123].

Massage therapy has often been performed in children with ASD. Swedish massage, traditional Chinese massage (Tui na) and traditional Indian massage are the most frequently used massages [124]. Some studies reported

that massage therapy may increase oxytocin levels and reduce betaendorphin, nitric-oxide and adrenocorticotropin with improvement in the neural circuit, which regards social and communication abilities [125, 126]. On the other hand, Ruan et al. have systematically reviewed the literature-based evidence regarding the effectiveness of massage therapy in children with ASD and reported a lack of data to support massage therapy in children with ASD [127].

Regarding the use of acupuncture, scarce data on its effectiveness in ASD are available. Acupuncture is poorly used in the United States; on the contrary, in China is a widely used treatment, becoming one of the most important CAM used in children with ASD [128]. The main types of acupuncture are scalp acupuncture, electroacupuncture and total body acupuncture [129]. Many studies reported that acupuncture may improve sleep disorders, functional development and control of emotions in children with ASD. Wang et al. conducted a systematic review and metanalysis to evaluate the effectiveness of acupuncture on the core symptoms of ASD. Interestingly, they found that acupuncture may be considered a safe practice and improves attention deficit and affective skills. Nevertheless, they highlight the need for rigorous acupuncture method and prescription, which are still heterogeneous [129].

Attention deficit hyperactivity disorder

ADHD are common behavioral disorders, with an estimated worldwide prevalence in children of about 5–10% [130].

ADHD is a pervasive disorder that affects sociality and intellectual performance, with a great impact on the quality of life. Clinical manifestations include motor activity, inattention, and impulsivity [130]. Treatment of ADHD is based on a complex of medical, educational, and environmental interventions. The most used and effective medical treatments have been psychostimulants such as primarily methylphenidate [131]. However, although their positive effects, psychostimulants have side effects such as reduction of appetite and sleep disturbance [131]. Therefore, many parents of children with ADHD often recur to the use of CAM treatments. As well as other conditions, high parental education seems to be the most important predictor factor for CAM use [132]. Biochemical treatments, such as herbal treatments, vitamins and nutritional supplements, are considered the most common CAMs administered in ADHD [133]. Herbal remedies, such as kava kava, valerian, chamomile and ginkgo biloba are considered to be useful for their anxiolytic properties to reduce attention deficit and sleep disturbance related to ADHD. They are usually safe, nevertheless, kava kava may interact with alcohol and benzodiazepines increasing their depressant action on the central nervous system [134]. Vitamin and nutritional deficiencies, such as iron deficiency, have been supposed to contribute to hyperactivity and cognitive impairment. Even if they are generally considered safe substances, it must be kept in mind the possible toxic effects of overdoses and the possible contamination with dangerous substances, such as heavy metals [134]. Moreover, until now, in literature strong evidence lacks that integration with vitamins or minerals is effective in ADHD [135].

Mechanical therapies, such as massages and body manipulation, are also frequently used in patients with ADHD. The rationale of massages is to reduce stress, promote relaxation and increase affective and behavioral skills. Ni XQ et al. have conducted a narrative review demonstrating the effectiveness of massages alone or in combination with pharmacotherapies in improving ADHD symptoms [136]. A recent systematic review confirms that massage therapy is efficacious in reducing anxiety and asocial behaviour.

Bioenergetic interventions, such as acupuncture and homeopathy, have also been described in children with ADHD. Ni et al., in a 2015 metanalysis, found that acupuncture was a safe and effective practice, used alone or in combination with medications [137]. Xing et al. have more recently confirmed that acupuncture may be a valid treatment option for ADHD, contributing to relax viscera and promote mind serenity [138].

Homeopathy is a practice based on the "disruption of vital energies" as the origin of illness. Homeopathic treatments are made by the principle that *"like cures like"*; the homeopathic remedies are extreme dilution of plant-derived or animal biomolecules which are target to each specific illness. Only a few data are available in literature; however, according to the recent first systematic review and metanalysis conducted by Gaertner et al., individualized homeopathic remedies may be useful to treat ADHD symptoms [139]. Relaxation techniques, mind–body therapy, biofeedback, hypnosis and meditation have been used to reduce hyperarousal to stress and reduce stress. Particularly, neurofeedback has been reported with good results in controlling impulsivity and aggression. Actually, children with ADHD have an aberrant prevalence of theta waves and low levels of beta waves which conduct to a poor motor, sensorial and impulse control [140].

Moreover, as well as other neurodevelopmental disorders, also in ADHD, the effectiveness of musicotherapy has been evaluated, particularly relating to its effects on cognitive performance which are usually compromised in children with ADHD [141]. Chen et al. analyzed the effect of white noise on cognitive abilities and found that it positively impacts working memory and levels of arousal [142]. Zhu et al. conducted a randomized

control trial (RCT) on the effect of musicotherapy associated with cognitive behavioral intervention evaluated by cross-attention tests and found that after 16 weeks of musicotherapy and cognitive behavioral intervention, a dramatic increase in behavior and attention score [143].

Tourette syndrome

Tourette syndrome (TS) is a neuropsychiatric disorder usually developed in childhood or adolescence and characterized by phonic and motor tics, lasting almost one year. Genetic factors and the increased dopamine circuitry are the most important factors in etiopathogenesis in TS. Since TS is a chronic condition and is frequently associated with many comorbidities, such as ADHD, a multidisciplinary approach is fundamental [144].

Pharmacological intervention plays an important role in the treatment of TS and, although a wide range of therapies are available, only 3 are Food And Drugs (FDA)-approved: aripiprazole (from 6 to 18 years old), pimozide (over 12 years old) and haloperidol (over 3 years old) [145].

Nevertheless, pharmacotherapy has many side effects which may add up over time, and therefore, usually, parents tend to prefer a non-pharmacological approach [146].

Behavioral interventions, including relaxation training, biofeedback, psychoeducation and behavioral rewards, are considered the first-line treatments. Actually, behavioral interventions are useful to reduce the frequency of tics and their severity, although they have a limited effect in case of a severe form of TS [147].

A recent metanalysis of 22 RCTs reported that acupuncture in TS is more effective than medical treatment, considering the reduction of recurrence and severity of the tics the low rate of adverse effects [148]. Interestingly, two metanalysis reported that two Chinese medications (choudongning and ningdong granule) may reduce tics, modulating the dopaminergic pathways [149, 150].

Moreover, it was reported that also other types of supplementations, such as taurine added to tiapride and vitamin D, may improve tics compared to placebo, although more studies are needed to evaluate their effectiveness [151].

Complementary and alternative medicine (CAM) in liver diseases

Acute and chronic liver diseases have an increasing impact on patient's quality of life. Conventional medical therapies are sometimes of limited efficacy, and patients seek other approaches considered safer and better, due to the possible side effects of the classic drugs. Recent decades have seen an increase in the use of CAM in treating liver disease. Studies in different countries have revealed that 33 to 75% of patients with liver disease use CAM, most frequently in countries where traditional medicine is still widely used. The use of CAM occurs without the advice or knowledge of their physicians, in fact, up to 40% of patients have not disclosed it to their physicians [152, 153]. On the other hand, physicians know little about CAM and mostly discourage its use due the hepatotoxicity [153]. In addition, the risk of toxicity and adverse effects is higher in these patients because of underlying liver disease [154]. Patients with chronic liver disease choose to use CAM in search of benefits in regulating immunity, postponing disease progression, improving quality of life, alleviating adverse effects of conventional therapies or poorly controlled extrahepatic symptoms, and improving survival [153–155]. Phytotherapy has been recommended since 2100 before Christ (BC) [152]. Today it is used in up to 50% of patients with liver disease [153]. Studies have shown that multivitamins and herbal products are mostly used by patients with chronic hepatitis C virus (HCV) infection [156, 157]. Other CAM options would be less used, such as homeopathy by only 4% and acupuncture by 9% of HCV patients in the United States [153]. In addition, liver cancer patients use acupuncture to relieve postoperative pain [158]. CAM most commonly used in liver diseases are reported in Table 4.

Table 4 CAM used in liver diseases

Complementary and alternative medicine in liver diseases	Herbs	Silymarin, Glycyrrhizin, *Phyllantus ammarus* Blended herbal products: Chinese Traditional Medicine (HM861, CH100) Japanese (TJ-9) Ayurvedic medicine (LIV52)
	Antioxidants	Vitamin E, polyphenols derived from green tea, N-acetyl cysteine, pro-cysteine
	Immune modulators	Polyamines, S-adenosyl-methionine
	Homeopathic drugs	
	Acupuncture	

Herbal products

Of all the options offered by CAM, the most widely used in liver disease are herbal products. Numerous herbs used by patients with liver disease are considered beneficial, and some have been shown to have effects in experimental studies and animal models. However, the efficacy of these herbal products has been tested in many RCT studies, with some design problems. Most data come from case reports, case series, and uncontrolled studies, many without objective endpoints (histology, viral load, survival) [152, 159].

Silymarin

Silymarin (Milk thistle) is extracted from Sylibum marianum, a flowering herb related to the daisy and ragweed family, native to Mediterranean countries. It is a complex mixture of polyphenolic molecules. The most important component is silybin (80–90% of the herb's components). Silymarin has been used in Europe since the sixteenth century for liver disease and jaundice and is one of the most extensively tested herbal products in animal models and human studies. The composition and efficacy of silymarin are well documented [159].

Experimental data, in vitro and animal models, have shown that it has many effects that could be considered helpful in liver disease. Silymarin is an important antioxidant and free radical scavenger, prevents glutathione depletion, induces glutathione S-transferase catalase, and prevents free radical formation [160–162].

It has an anti-inflammatory effect by inhibiting nuclear transcription factor (NFκB) and reducing inflammatory cytokines [163]. It also has an antifibrotic role by blocking stellate cell proliferation, regulating TGF beta [164] and reducing collagen accumulation [164]. Silymarin is considered hepatoprotective because it stabilizes the cell membrane of hepatocytes, preventing toxic effects. It prevents liver injury produced by Amanita phalloides, carbon tetrachloride (CCl4) and paracetamol. The maximum effect was demonstrated in the case of pretreatment, but also after exposure of the Balb/c mouse animal model to the toxic substances to induce experimental liver injury [153].

Regarding human studies, the first RCT study, although having several design elements, showed important effects in terms of improved survival in patients with mild cirrhosis (Child A) and alcohol-induced liver injury. No side effects were reported [165]. Other studies on alcohol-related liver disease have not made a clear conclusion on the usefulness of silymarin [165, 166].

In studies that included patients with chronic viral hepatitis, some decrease in alanine-aminotransferase (ALT) level was reported, but no change in HCV viral load [166, 167]. Other studies have shown no change [168].

Regarding acute hepatitis, studies have shown a shorter duration of hospitalization and an improvement in liver enzyme levels [152] but there have been studies with contradictory results [169]. There have been no significant improvements in patients with primary biliary cirrhosis [170]. A major problem with studies using silymarin is the lack of a reliable formulation for studies and a large variability in peak drug levels. On the other hand, silymarin in an intravenous form is recommended to treat mushroom poisoning [152, 171] as it demonstrates a protective role against various drugs and toxins.

A recent systematic review including 17 studies and a meta-analysis including 6 studies on the role of silymarin in patients with nonalcoholic fatty liver disease (NAFLD) showed that there was an association with reduced liver enzyme levels, but without clinical significance, and it was well tolerated and without adverse effects [172].

Glycyrrhizin

Glycyrrhizin (licorice root extract) is an aqueous extract of licorice root, Glycyrrhiza glabra, native to the Mediterranean region and the Middle East [152, 153]. It is recommended to treat cough, bronchitis, gastritis and liver diseases [173]. The main constituents are glycyrrhetinic acid, flavonoids, isoflavonides, hydroxycoumarins, triterpenoids, and polysterols [152]. Glycyrrhizin is a component of many herbal medicines [152].

Experimental studies, in vitro and animal models, have shown that glycyrrhizin inhibits the activity of 11-beta-hydroxysteroid dehydrogenase, inhibits the production of prostaglandins (PG) E2 by macrophages, and modifies the metabolism of arachidonic acid [174]. It has antioxidant activity by inducing the activity of glutathione-S-transferase and catalase and decreasing the formation of oxidative products of polymorphonuclear cells. It has proven antifibrotic activity, blocking the activation and action of NFkB [175] and inhibiting tumor necrosis factor (TNF) [176].

In clinical studies, a possible benefit in HCV infection was considered, with an improvement in liver enzymes, but without a demonstrated change in viral load. The same results were obtained in studies that included patients with hepatis B virus (HBV) infection [152].

Glycyrrhizin includes a beta-sitosteroid, which may have glucocorticoid and mineralocorticoid activity. Side effects due to mineralocorticoid activity have been reported in clinical trials: increased severity of cirrhosis, fluid retention, and hyperkalemia. Because of these effects, glycyrrhizin should be avoided in patients with cirrhosis [153].

Cucurmin

Curcumin is the principal curcuminoid of turmeric (Curcuma longa), a member of the ginger family, Zingiberaceae. It is a natural polyphenolic compound used in liver diseases for its antioxidant and anti-inflammatory effects, and it was recommended as early as 250 B.C. in Ayurvedic medicine to counteract food poisoning [177]. Numerous reports and clinical studies support its beneficial role in NAFLD, autoimmune hepatitis, HCV, and hepatocarcinoma (HCC) [178, 179]. In vitro studies have demonstrated its action as a free radical scavenger, reducing lipid peroxidation, increasing the expression of glutathione-S-transferase, glutathione reductase and peroxidase, superoxide dismutase and catalase, reducing ossid nitric (NO) production and inhibiting Reacting Oxygen Species (ROS) formation [180, 181]. It also suppresses NFκB and intervenes in other steps of fibrogenesis [179]. In a systematic review and meta-analysis on the role of curcumin supplementation in patients with NAFLD, including 9 RCTs, the favorable effect on metabolic markers and anthropometric parameters was supported [182].

In addition to unique herbal products, blended herbal formulations or extracts are used in different cultures. Traditional Chinese, Japanese, Ayurvedic, and other medicines use herbs in blended products, and practitioners find it challenging to analyze each component separately, as efficacy may be lost [183].

Traditional Chinese medicine includes several practices, such as acupuncture, herbal therapies, moxibustion (dermal therapy against irritation), massage, and exercise therapy (Qi Gong) [153]. Of the more than 100,000 known herbal therapies in traditional Chinese medicine, about 76 mixtures are used in liver diseases [153].

Plantago asiatica seeds have a hepatoprotective role and lower toxicity due to its active compound, aucubin. In vitro and animal model studies have shown that aucubin inhibits HBV replication, but human studies have shown that this is only a temporary effect [184]. It is known to modulate cytokine release through the NFkB pathway [185] with an antifibrotic and anti-inflammatory effect.

Herbal Medicine 861 (HM861) is composed of 10 herbs, including Salvia miltiorrhiza, Astragalus membranaceus, and Spatholobus suberectus [186]. In vitro studies have shown that HM861 inhibits proliferation and induces apoptosis of hepatic stellate cells (HSCs) [187] and corrects the imbalance between extracellular matrix synthesis and degradation. Human studies have reported antifibrotic activity in patients with HBV infection (improvement in transaminase level, spleen size, portal pressure, and serum level of procollagen peptide and laminin, with a demonstrated histologic reduction in fibrosis and inflammatory infiltrates) [153].

CH-100 is composed of 19 herbs. In animal studies, it protects against ConA-mediated hepatitis or CCl4 liver injury in rats [188]. Human studies showed a decrease in transaminase levels, but there was no change in viral load in HCV patients [189].

Traditional Japanese medicine with Kampo extracts also originates from traditional Chinese medicine. TJ-9 (Sho-saiko-to) is a dried decoction of 7 herbs (scutellaria root, glycyrrhizin, bupleurum, ginseng, pinella tuber, jujube fruit, ginger rhizome) [152]. Studies in vitro and animal models have shown that TJ-9 reduces fibrosis through inhibition of HSC activation, decreases hepatic collagen levels, alpha-smooth muscle actin and collagen type 1 expression [153, 190] and also inhibits lipid peroxidation (due to scutellaria, baicalin, and biacal alkaloids) [152]. In human studies, along with conventional treatment in HBV patients, TJ-9 improves liver function, with decreased development of HCC, increased survival, and increased TNF-alpha and granulocyte colony-stimulating factor. No adverse effects have been found, but it may produce interstitial pneumonia when used together with interferon or even hepatotoxicity (without knowing the component that induces it) [152].

Ayurvedic medicine, traditional Indian medicine with a history of more than 5,000 years, considers the liver as part of the harmony of the whole body and includes diet and meditation in addition to herbs [153]. LIV 52 is an herbal formulation that includes Capparis spinosa (capers), Cichorium intybus (wild chicory), Terminalia arjuna (ajuna), Solanum nigrum (black nightshade), Cassia occidentalis (Kasamarda), Achillea millefolium (yarrow), Mandur bhasma, Tamarx gallica (tatarisk). In animal models, LIV 52 protects against liver injury produced by CCl4 or alcohol. It improves liver function in acute hepatitis, but studies in alcoholic hepatitis have shown worse survival in patients with severe cirrhosis (Child C) [191].

Phyllanthus amarus, also known as bahupatra, contains philanthines, hypophyllanthines, and polyphenols. There are conflicting reports on its possible role in chronic HBV infection. In vitro studies have shown that it has a role in HBV down-regulation [192]. One article, reporting a group of RCT studies, showed a beneficial effect in HBsAg elimination [193], but other studies have failed to demonstrate this [194].

Drugs targeting immune dysregulation as a component of liver disease pathogenesis could effectively treat these patients. Antioxidants (vitamin E) or glutathione prodrugs (N-acetylcysteine, procysteine) have been shown to inhibit TNF, IL8, or IL6 produced by PMNs, monocytes,

Table 5 Herbal products with well-documented hepatotoxicity [152, 199]

Type of liver disease or injury and the causative herbal product
Veno-occlusive disease: pyrrolizidine alkaloids (Senecio longilobus, Heliotropium europaenum, Crotalaria species, Symphytum officinale, Grodolobo herbal tea)
Zone 3 necrosis, cirrhosis: chapparal leaf (Larrea tridenta), germander (Teucrium chamaedrys), pennyroyal (squawmit oil, Mentha pulgeium)
Acute liver injury: Jin Bu Huan, tradititional Chinese herbs, Kava, Kombucha mushroom (tea)
Microvesicular steatosis: margosa oil
Microvesicular steatosis: margosa oil

and Kupfer cells and could be effective in alcohol-induced liver disease [152]. Polyphenols derived from green tea (Camellia sinensis) have antioxidant and anti-cytokine roles and may be helpful in autoimmune liver disease [153, 195]. The use of polyamines and S-adenosyl-methionine (known as immunonutrition) protects against TNF hepatotoxicity, in vitro and animal models. Their use has also been evaluated in human studies of alcohol-induced liver disease [196, 197]. Still, a Cochrane systematic review failed to demonstrate a benefit Zinc, selenium, and vitamin C may regulate liver tissue repair by acting on DNA metabolism [198] and, together with vitamin E, may play a role in improving fibrosis in nonalcoholic steatohepatitis [195].

Herbal toxicity

It is important for physicians and their patients to know the risk of hepatotoxicity from various herbal products. There are many reports on the possible toxic reactions of CAM. Because patients keep CAM use to themselves, diagnosis is difficult, and physicians should openly discuss all products used with their patients [153]. Although it is challenging to evaluate reports of hepatotoxicity because of the lack of manufacturing standards, or possible experimental studies without feedback in clinical life, here we present some agents with well-documented evidence of hepatotoxicity (Table 5). In addition to direct hepatotoxicity, possible interactions between conventional drugs and herbal products are to be considered [153]. Herbs may be safe when used alone, while adverse reactions increase when used together with conventional drugs [197].

In summary, there is an increase in the use of CAM in patients with liver disease, and generally without physicians' knowledge. Therefore, physicians should openly and routinely discuss the use of CAM as part of their patients' medication use history. In addition, they should be aware of the efficacy and safety of different alternative methods. By far, the most widely used CAM in liver disease patients are herbal products, which have shown protective actions in vitro or animal model studies, but whose efficacy has not been demonstrated in adequately conducted RCT studies. A reliable and standardized preparation of these products is needed to conduct well-designed studies demonstrating their efficacy and safety, as hepatotoxicity can be a severe effect of using herbal products.

Conclusion

The use of CAM is increasingly becoming part of the treatment of some serious diseases in pediatric patients. CAM is used to improve the success of conventional therapies, but also to alleviate the pain, discomfort, and suffering resulting from the diseases and their treatment, which are often associated with a significant burden of adverse effects. The use of CAM in children also has a major impact on parents' ability to cope with their children's serious illnesses, as it can provide relief from symptoms that most affect their quality of life.

This review has some limitations. Firstly, its narrative nature, that is mainly descriptive, has no systematic and formal approach; therefore, it can include an element of selection bias. The literature on the use of CAM in oncological, neurological and liver diseases in children is abundant and growing; however, knowledge of their efficacy and safety is still incomplete, especially for some products. As a second limitation, in this review we focused only on these conditions; however, use of CAM is increasingly becoming common in other conditions and diseases, too. Therefore, more high-quality studies are still needed to provide advice on product types and indications for use. Finally, a better understanding by physicians of the opportunities offered by the use of CAM is advisable.

Abbreviations

CAM	Complementary and alternative medicine
NIH	National Institutes of Health
NCCIH	National Center for Complementary and Integrative
HDS	Health herbal dietary supplements
NCCAM	National Center for Complementary and Alternative
BNT	Bone narrow transplantation
TCM	Traditional Chinese Medicine
aGVHD	Acute graft-versus-host disease
CP	Cerebral palsy
ADHD	Attention-deficit hyperactivity disorder

GMFCS	Gross Motor Function Classification System
HBOT	Hyperbaric oxygen Therapy
OMT	Manipulative Treatment
CoQ10	Coenzyme Q10
NMDA	N-methyl-D-aspartate
AHS/AAN	American Academy of Neurology and American Headache Society
RFPN	Right-fronto-parietal networks
CBT	Cognitive Behavioral therapy
AEDs	Anti-epileptic drugs
CBD oil	Cannabidiol Oil
GABA	Gamma-Aminobutyric Acid
AAPB	Association for applied psychophysiology and biofeedback
ASD	Autism Spectrum Disorder
FAs	Omega 3 Fatty Acids
RCT	Randomized Control Trial
TS	Tourette Syndrome
FDA	Food And Drug Administration
BC	Before Christ
HCV	Hepatis C Virus
NFκB	Inhibiting Nuclear Transcription Factor
CCl4	Carbon Tetrachloride
ALT	Alanine-Aminotransferase
NAFLD	Nonalcoholic Fatty Liver Disease
PG	Prostaglandins
TNF	Tumor Necrosis Factor
HBV	Hepatitis B Virus
HCC	Hepatocarcinoma
HSCs	Hepatic Stellate Cells
NO	Ossid Nitric
ROS	Reacting oxygen species

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Publisher's Note

Alarming Increase of Eating Disorders in Children and Adolescents

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Eating disorders are potentially life-threatening conditions that affect the quality of life of children and adolescents as well as their families.[1] These disorders can be complex and often severe, relating to atypical eating behaviors that have the potential to impair the overall well-being and function of those affected. Most eating disorders involve extreme body dissatisfaction and an obsessive focus on body weight and food, resulting in dangerous dietary routines that negatively affect nutritional intake, causing adverse effects on the growth and development of children and adolescents. Alternative forms of eating disorders may not be exclusively focused on concern for body image; they may also include behaviors that hinder weight gain or involve an uncontrolled drive to pursue health and fitness.[1] Recent alarming data from several European countries[2] show a remarkable increase in eating disorders of ≤40% in the 6- to 18-year-old population since the beginning of the recent coronavirus disease 2019 (COVID-19) pandemic. Similarly, a significant increase in eating disorders in children and adolescents has been observed recently in the US.[3] These data have prompted increased attention to these disorders and their effects among children and adolescents. The purpose of this commentary, prepared by the Working Group on Social Pediatrics of the European Association of Pediatrics, Union of European National Pediatric Societies and Associations, is to raise further awareness among pediatricians about the danger of eating disorders and the causes of their increase. The economic and social disruption caused by the recent COVID-19 pandemic, which has been associated by several studies with a significant increase of eating disorders, highlights that special attention should be paid to prevent the onset and effects of this serious condition during and after periods of severe social distress.

Definition of Eating Disorders

Eating disorders in children and adolescents encompass a range of behavioral conditions marked by profound and persistent disruptions in eating habits, along with distressing thoughts and emotions.[4-6] These disorders have far-reaching implications, affecting physical, psychological, and social well-being. Varieties of eating disorders include anorexia nervosa, bulimia nervosa, binge eating disorder, avoidant restrictive food intake disorder, other specified feeding and eating disorders, pica, and rumination disorder. Although these conditions can affect individuals of any age or gender, they are most commonly observed during adolescence and young adulthood. Eating disorders frequently accompany various psychiatric conditions, notably mood and anxiety disorders, obsessive-compulsive disorder, and alcohol or substance use disorders. Research indicates a genetic and hereditary influence on the heightened susceptibility to eating disorders in certain individuals.[1,4-6] Nevertheless, these conditions can affect individuals without a familial precedent. Effective treatment requires a comprehensive approach, including psychological, behavioral, nutritional, and medical aspects. The latter may include complications stemming from malnutrition or purging behaviors, such as cardiac and gastrointestinal complications, as well as other potentially life-threatening conditions. The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, provides the latest effort to characterize and classify eating disorders. This revision places greater emphasis on behavioral aspects of this condition.[4-6] Eating disorders frequently observed in children and adolescents, are reported in **Table I** and their main diagnostic indicators in **Table II**.

Eating Disorders Increased in Children and Adolescents Over the Past 20 Years

Eating disorders are on the rise worldwide. Between 2000 and 2018, their prevalence in the general population has more than doubled worldwide (from 3.4% to 7.8%),[7] and a recent systematic review reports that during the period 1999-2022 the global overall proportion of children and adolescents with disordered eating was 22.36%.[8] In the US, from 2018 to 2022, health visits related to eating disorders more than doubled among people under the age of 17, and visits for all eating disorders among this age group increased by 107.4%, from approximately 50 000 visits in early 2018 to >100 000 in 2022.[9] In Europe, a similar increase of eating disorders in children and adolescents was

COVID-19	Coronavirus disease 2019

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Table I. List of main eating disorders in children and adolescents

Disorders	Definition
Anorexia nervosa	An unrelenting determination to shed pounds by limiting food intake and/or engaging in excessive physical activity, even when the individual is already underweight. This behavior stems from a skewed perception of one's body, where young individuals perceive themselves as overweight or obese despite evidence to the contrary. Consequently, a profound apprehension about gaining weight ensues. The convictions associated with anorexia nervosa are so potent that they create substantial obstacles for the individual to consume an appropriate and nourishing quantity of food, resulting in persistent malnutrition. This state of malnutrition can lead to severe medical repercussions.
Atypical anorexia nervosa (AAN)	A youth experiencing atypical anorexia nervosa has undergone substantial weight loss and exhibits all the characteristics typical of anorexia nervosa. Nevertheless, their body weight falls within the normal range or surpasses it. The medical and psychological repercussions associated with atypical anorexia nervosa are equally severe in comparison to those of classic anorexia nervosa.
Bulimia nervosa	A repetitive occurrences of binge eating (rapidly consuming an excessively large quantity of food) accompanied by a sensation of lacking command over this eating behavior. Subsequently, actions are taken to prevent weight gain, including actions like vomiting (purging), misusing laxatives, or engaging in excessive exercise. Individuals affected by bulimia nervosa also tend to harbor harsh self-judgment concerning their bodily form, dimensions, and weight.
Binge-eating disorder	Recurrent instances of indulging in excessive eating. Such episodes are defined by both of the subsequent criteria: within a specific timeframe (eg, 2 hours), consuming a quantity of food significantly surpassing what the majority of individuals would ingest in a similar timeframe and comparable situation, combined with a sensation of inability to manage or restrain the excessive eating during that period. These binge-eating episodes involve ≥3 of the subsequent actions: consuming food considerably faster than usual, eating until reaching an uncomfortably full state, ingesting substantial quantities of food when not experiencing hunger, eating in solitude due to embarrassment about the excessive consumption, and experiencing emotions of guilt, disgust, or sadness afterward. On average, these episodes of binge eating take place at least once a week for a duration of 3 months. The instances of binge eating are not linked with the utilization of inappropriate compensatory practices as observed in bulimia nervosa, and they do not solely occur within the context of either bulimia nervosa or anorexia nervosa.
Avoidant restrictive food intake disorder	An irregular eating pattern (ie, apparent disinterest in eating or food, avoidance based on sensory aspects of food, or anxiety about adverse effects of eating). It is characterized by continuous failure to fulfill appropriate nutritional and/or energy requirements, as manifested by any of the following: substantial weight reduction or, in the case of children, failure to achieve anticipated growth and/or weight gain; notable nutritional deficiency; reliance on enteral feeding or oral nutritional supplements; significant disruption to psychosocial well-being. This disturbance cannot be more suitably explained by the absence of accessible food or by a culturally accepted practice. The eating disruption cannot be attributed to a concurrent medical condition, nor can it be more reasonably accounted for by another mental disorder. If the eating disturbance arises within the context of another condition or disorder, the intensity of the eating disturbance surpasses what is typically linked with the said condition or disorder. This avoidance may lead to a failure to gain weight, nutritional deficiencies, or significant impairment in the young person's life. For example, they may be unable to socialize with others if food is involved.

Modified from the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, American Psychiatric Association, 2013.

observed across all countries.[2] In the UK, the London Center for Eating Disorders and Body Image reports that hospital admissions for eating disorders in UK boys and young men increased 128% from 2015-2016 to 2020-2021, and the number of children and adolescents admitted to hospital with eating disorders has increased by 35% in 2022.[10] An analysis of the UK National Health Service data has revealed the number of children and young people beginning treatment for eating disorders has risen from 5240 in 2016-17 to approximately 11 800 in 2022-2023.[11] In France, the incidence of eating disorders among students doubled between 2009 and 2021, and a worrisome increase in this condition was observed among young students, from 24.0% observed in 2009 to 46.6% in 2021, at the time of the COVID-19 pandemic.[12] In Italy, emergency room admissions and hospitalizations have doubled in the period 2021-2022, and in 2023 the Minister of Health reported a 40% increase in new cases.[13,14]

The Role of the COVID-19 Pandemic in the Increase in Eating Disorders

The repercussions of COVID-19 pandemic have contributed to a global crisis in children's mental well-being,[15] including an increase in symptoms related to eating disorders.[16] There has been a significant increase in both the diagnosis of eating disorders and the display of related behaviors in young individuals who were previously diagnosed, a trend observed since the pandemic's outset. This increase has been attributed to maladaptive methods of asserting control in the face of uncertainty, coupled with sensations of isolation and disruptions to established routines.[16,17] These factors have engendered stress and anxiety, which are believed to be among the major causes for this surge in eating disorder cases. Additional factors contributing to the increase in eating disorders in children and adolescents are multifaceted. The adoption of altered coping mechanisms owing to physical distancing and the consequent inability to interact with friends and support networks has played a significant role.[16,17] The diminished oversight of children by school staff, coupled with parents navigating work commitments, has created a void in close monitoring, potentially exacerbating the situation. Moreover, the considerable escalation in screen time and the consumption of media from various platforms has exposed young minds to detrimental messaging and visuals concerning body image and health assertions, contributing to the escalation of this issue.[16,17]

Table II. Indicators of eating disorders in children and adolescents

Main physical and behavioral indicators of eating disorders in children and adolescents
Physical indicators
Significant loss of weight or rapid instabilities in weight
Experiencing lethargy and persistent tiredness
In females, disruption or absence of menstrual cycles
Diminished ability to concentrate effectively
Increased sensitivity to cold temperatures (frequently feeling cold even in warm surroundings)
Occasional bouts of dizziness leading to fainting
Behavioral indicators
Consistently reducing fat intake, meticulously tracking calorie consumption, skipping meals, fasting and avoiding specific food categories (eg, dairy, meat, or carbohydrates)
Engaging in excessive and/or compulsive exercising. Offering justifications to evade meal consumption
Intense fear surrounding weight gain
Regular self-weighing
Greater fixation on body shape, weight, and appearance compared to the average person
Experiencing distress and/or anger during meal times
Exhibiting unusual eating behaviors (eg, cutting food into minuscule pieces)
Avoiding social gatherings involving food
Frequent trips to the bathroom and/or showers after eating (often followed by self-induced vomiting)
Distorted perception of body image (eg, expressing dissatisfaction with one's appearance when they are actually a healthy weight or underweight)

Eating Disorders Prevention Starts in the First Year of Life: The Key Role of Families

The foundation for the emergence of an eating disorder can take root even within the first year of life, and the guidance provided by parents and family can significantly influence the onset or absence of such disorders. Feeding a child represents an important form of communication between the parents and the child, a process essential to the child's growth. The surrounding milieu must respond readily to the child's needs, aiding in organizing the influx of diverse stimuli, thus enabling the child to comprehend and decipher them. Until this mastery is attained, the child struggles with an amalgamation of impulses and needs, and, without proper guidance, confusion arises, blurring the line between biological and emotional experiences.[18-20]

When parents sense the infant's need for nutrition, often conveyed through cries, and offer him or her food, the child learns to distinguish the feeling of hunger from other tensions and needs. However, if the adult's response is suboptimal, leading to persistent misinterpretation, such as assuming the child is hungry, cold, or fatigued when not, the result will be a situation of confusion and bewilderment. Consequently, the child fails to grasp the management of nourishment-related needs, distinguish hunger from other emotional tensions, recognize the demarcation between hunger and satisfaction, or discern nutritional requirements from other forms of discomfort or tension. Early negative and confusing experiences undermine the ability to recognize hunger and satiety signals, preventing the child from distinguishing the desire for food from other unpleasant signals that are related to other conflicts and problems.

Food should be offered when infants are genuinely and physically hungry and should never be used as a reward or wielded as a punitive tool. Infants should not be forced to eat when they refuse, nor should parents place undue emphasis on eating, especially when the child tends to show opposition. Parents, family, or caretakers thus play a decisive role in helping the child develop an appropriate sensitivity to the hunger impulse, so that he or she recognizes it as an accurate sensation.

Conclusions

Eating disorders, which can be the manifestations of symptoms and conditions that accompany and express deep pain, and often anxiety, fear, and insecurity,[21] are not a new phenomenon. In recent years, many causes have contributed to a significant increase of this condition in the population under the age of 18. However, their incidence in this age group has increased yet further, alarmingly coincidentally with the COVID-19 pandemic. Several studies have linked the harmful socioeconomic effects of the pandemic to a significant increase of eating disorders.[16,17] These findings suggest that special attention should be paid to prevent the onset and effects of eating disorders during and after periods of severe social distress, which in addition to other negative effects may trigger the development of this serious condition. ■

Declaration of Competing Interest

The authors declare no conflicts of interests.

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Challenges Confronted by Orphans of Gender-Based Violence Victims

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Femicide remains a pervasive global issue. In 2022 the United Nations global estimate for femicide revealed that nearly 89 000 women and girls were killed intentionally that year. 48 800 women fell victim to intimate partners or other family members, with approximately 7900 cases occurring annually in the Americas and 2300 in Europe[1] (**Figure**). However, the actual number of victims is likely higher due to the lack of reliably reported statistics.[2] Troubling aspects of this escalating phenomenon include the lack of a comprehensive institutional response to femicide. Orphaned children, grieving parents, and siblings of murdered women are direct victims rarely acknowledged by the public administrations responsible for addressing their needs and by the judicial systems tasked with safeguarding their rights.[2] In particular, legal gaps in addressing femicide obstruct access to justice, leaving these unique victims and the family members of the deceased women feeling overlooked.[2] Such not only hinders effective prevention and prosecution but also denies necessary support to the family members, especially the children, exposing them to repeated victimization during legal proceedings. Some children lose both parents in an instant, along with their home, which may be seized. They lose their toys and routines. They no longer have a mother, who has been killed by a violent partner or spouse, and they no longer have a father, the perpetrator of the violence, often ending up in prison or succumbing to suicide. This commentary, prepared by the European Pediatric Association, the Union of National European Pediatric Societies and Associations Social Pediatrics Working Group, addresses briefly the challenges faced by orphans of gender-based violence victims. Its purpose is to draw attention to the protection of the rights of domestic crime orphans and the importance of training professionals involved in managing children who have survived femicide. These include magistrates, lawyers, psychologists, social workers, and pediatricians. Indeed, pediatricians can play a central role in assisting children to manage the various challenges faced by orphans of gender-based violence victims and to develop the resilience necessary for their health,[3] well-being, and a smooth transition to adulthood.

Femicides and the Issue of Gender-Based Violence Orphans

The escalating global crisis of gender-based violence highlights the serious issue of orphans left behind by victims of femicide, the most severe outcome of such violence.[4] Femicide is deeply entrenched in and a manifestation of power imbalances in society, perpetuating an unequal status for men and women.[5] Femicide can manifest in various forms, including the murder of women due to intimate partner violence, the torture and misogynistic killing of women, and the slaying of women and girls in the name of "honor." Additionally, cultural practices, such as dowry-related murders in the Indian subcontinent,[6] and non-intimate femicide, committed by individuals without a close relationship to the victim, contribute to this alarming trend, as seen in the 2008 large-scale murder of women in Ciudad Juárez, on the Mexico–USA border.[7]

Over the past 2 decades, there has been extensive debate about the accurate definition and terminology for this extreme form of gender-based violence. While the term "feminicide" is often used in Latin American countries[8] as an alternative to "femicide," some scholars employ "femicide" in a broader sense to encompass all killings of women, regardless of motive or perpetrator status, due to the challenge of determining a motive in every case.[9] Nevertheless, according to the current World Health Organization definition, femicide is generally understood to involve the intentional murder of women simply because they are women, encompassing all killings of women or girls in a broader context.[10]

Children orphaned by domestic crimes represent the hidden face of gender-based violence. It is easy to overlook them when addressing the issue of violence against women and femicide as its ultimate consequence. Gender-based violence frequently extends to the most vulnerable, dragging children into the realm of violence for years.[10] This condition affects their imagination, certainties, and their emotional and psychological world.[4] Ultimately, this setting impacts their present and future. Often, a violent domestic situation culminates in 1 parent murdering the other, creating a complex and traumatic experience for the child. In this scenario,

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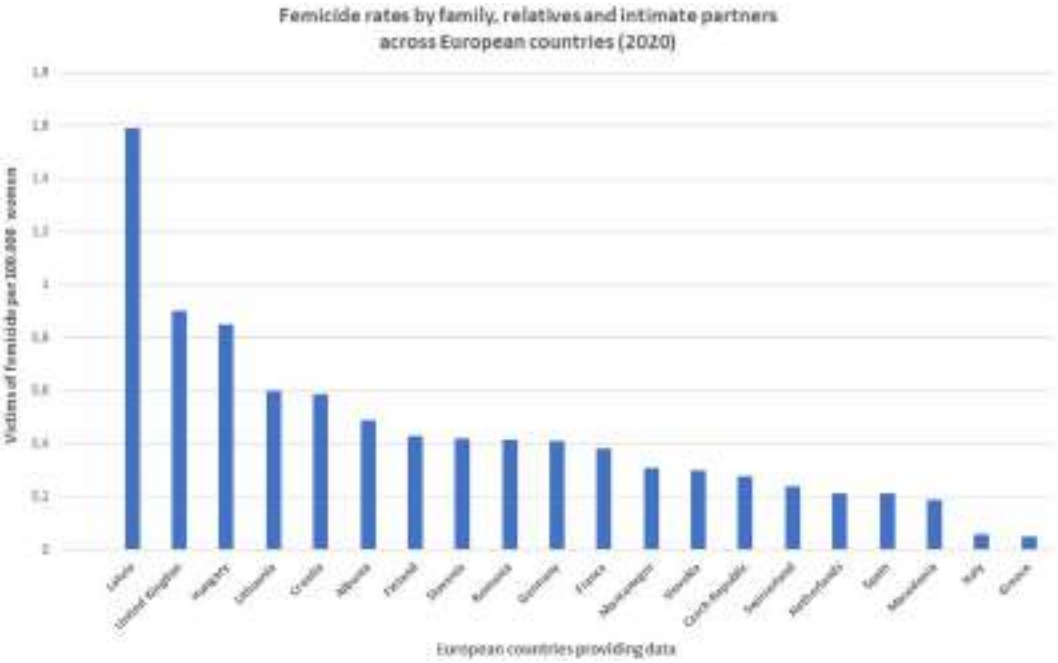

Figure. Femicides rates in Europe. Criminal offense committed by family and relatives and intimate partners. Aggregate data per 100.000 women across selected European countries. Modified from the European Data Journalism Network and the European Pediatric Association, the Union of National European Pediatric Societies and Associations working group on social pediatrics.

the pain of loss is compounded by various challenges of different natures: material, emotional, social, and legal. Orphans of femicide are boys and girls who, at times for years, have witnessed the violence of 1 parent toward the other, experiencing its consequences on their emotional, relational, and cognitive development.[2,4] Caregivers frequently exert pressure on the child to forget the incident by avoiding discussions, discrediting the child's account, and responding with silence and evasion to their questions, hindering effective mourning. This suppression is especially prevalent if the caregivers are relatives. While attention is directed toward the victim and perpetrator of the crime, the children become the overlooked victims. Often, children are orphaned twice; they lose both mother and father in a single moment, especially because those who are imprisoned rarely get to see their own children.

The Unknown Dimension of a Significant Phenomenon

Studies on orphans from femicide are severely lacking, and very few statistics are available to understand fully the extent of the phenomenon and implement effective prevention and support programs for children affected by gender-based violence. A recent study estimates that in Europe, femicide orphans total around 80 000, with an annual average of 2600 over the last 15 years.[11] Meanwhile, in the US, approximately 3300 children are estimated to be affected each year.[4,12] Globally, limited data are accessible, with Italy reporting an estimate of 2000 cases,[2] and Argentina estimating 3000 children orphaned by femicide in the past decade.[13] No further data from extensive studies are currently available.

Legal Protection for the Orphans of Femicide

Considering the particular fragility and vulnerability of this category of children, it would be of great importance for states to introduce legislation that addresses comprehensively all aspects of their needs. For instance, ensuring their support through civil proceedings, providing free therapy, and facilitating access to education and employment opportunities. Simultaneously, the law should guarantee that these orphans receive their inheritance and prevent the perpetrator, especially if such is a spouse, from receiving a survivor's pension. Raising orphans of femicide also presents financial difficulties. The cost of school and extracurricular activities adds up, and frequently families pay for special care needs and private therapists. Moreover, legal protection should allow children to change their surname, a matter some adult orphans emphasize as more crucial than economic assistance. To the best of our knowledge, the countries with currently existing laws that care comprehensively for those orphaned by femicide are Italy in Europe and Argentina, Peru, and Uruguay in Latin America.[14-16]

Physical and Psychological Consequences Encountered by Orphans of Femicide

Based on existing research concerning children who are victims of direct or witnessed domestic violence, as well as studies on the mental health and well-being of children following parental intimate partner homicide, a broad spectrum of outcomes is evident. These outcomes encompass both physical and psychological disorders, such as enuresis, encopresis, sleep disturbances, temper tantrums, flashbacks, dissociation, anxiety, and psychosomatic disorders.[2,4,12,17] Additionally, passive and aggressive behaviors are frequently observed.[2,4,12,17]

Attachment difficulties, fluctuations in weight and appetite, and academic consequences, including declines in school grades, have also been documented in this context.[2,4,12] Notably, a significant majority of children who witness the killing of a parent exhibit symptoms consistent with post-traumatic stress disorder, a contrast observed in those who were absent from home during the tragic event.[18] It is essential to emphasize that without prompt and comprehensive intervention, the adaptive capacities of these children may be severely compromised, leading to both temporary and prolonged challenges in achieving satisfactory and optimal functioning. Consequently, therapeutic help should be available immediately for these children and their families as an indispensable measure to mitigate the potential long-term effects,[19] especially for those who witnessed the killing. It is advisable to place the children with familiar individuals, and primary health care services must be promptly informed about the situation, with early consultations sought from child mental health services. Seeking expert advice is also essential, particularly regarding the feasibility of the children attending their mother's funeral and visiting their father.[20] Looking ahead, long-term planning for permanent placement should start expeditiously, ensuring that emergency placements do not inadvertently become permanent solutions by default.

Conclusions

Often, orphans are at risk of being merely a collateral effect of femicides, as attention is understandably focused on the criminal event, investigations, and the grief of a family losing a daughter, inadvertently overlooking the role of children who require specific attention during those challenging days. For this reason, it is crucial to promote harmonization, coconstruction, and the sharing of best practices to counter the risk of fragmentation in interventions aimed at effectively managing orphans of femicide. To achieve this goal, initiating a close and continuous collaboration among various institutions involved is of particular importance, spanning from the justice system to the protective health care network. This collaboration can be facilitated through the establishment of working groups, multiagency coordination, and multidisciplinary task forces capable of operational intervention, especially in emergency situations. General pediatricians working in the community can play a significant role, given their direct contact with the family environment[21] and often their personal knowledge of children who have experienced the loss of their mother. ■

CRediT Authorship Contribution Statement

Pietro Ferrara: Conceptualization, Data curation, Writing – review & editing. **Ignazio Cammisa:** Data curation, Writing – review & editing. **Donjeta Bali:** Data curation, Writing – review & editing. **Ida Giardino:** Data curation, Supervision, Writing – review & editing. **Mehmet Vural:** Data curation, Supervision, Writing – review & editing. **Maria Pastore:** Data curation, Supervision, Writing – review & editing. **Clara Pettoello-Mantovani:** Conceptualization, Data curation, Writing – review & editing. **Margherita Zona:** Data curation, Writing – review & editing. **Massimo Pettoello-Mantovani:** Conceptualization, Data curation, Investigation, Writing – original draft.

Declaration of Competing Interest

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