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INFECTIVOLOGY

Narrative review

Infectious diseases and pediatrics: a parallel scientific and health care pathway in the last two centuries

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Abstract

Pediatrics and Infectious Diseases reached an autonomous healthcare assistance and scientific pathway in a different mode when comparing the English-American medical world, and the South-European countries, including Italy. Like the late recognition of childhood as human beings deserving a specific assistance by specialist physicians (pediatricians) in the English-American health care system, also Infectious Diseases developed as a subspecialty of General Internal Medicine in the English-American countries, while played their autonomous role especially in some European countries including Italy, where some prominent academic and assistance centres of Infectious Diseases had their roots just in some Pediatric references centres located throughout the country. Aim of our work is also to explore the unmet needs of pediatric infectious diseases assistance still relevant in the third millennium, both in the industrialized worlds, and in developing countries.

Keywords

Infectious Diseases; Pediatrics; Healthcare pathways

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Are children only "small adults"? The european perspective of infectious diseases and pediatrics

Probably it seems somewhat surprising for young physicians of the third millennium to discover the proportionally recent consideration of pediatrics as an autonomous clinical and research disciplinary area, but inpatient and outpatients settings, health care assistance delivery, and research scenarios have been progressively implemented in the area of pediatrics just in the past two centuries (i.e. from early 1800s). Furthermore, since the majority of infectious diseases had and still have a pediatric target, and on the reverse many pediatric disorders have an infectious diseases origin or trigger, therefore the two medical specialities are actually strongly connected [1].

As a consequence of the old Pediatric-Infectious Diseases cultural and assistance connection, both in Mediterranean Europe and in Italy too, many academic schools and tertiary healthcare centres were specifically or mainly dedicated to pediatric infectious diseases, as witnessed by the history of the Medical School of the University of Bologna. In fact, the University of Bologna Medical School has been claimed to belong to the oldest University in the Western word ("Alma Mater Studiorum", founded in the year 1088), and the study of medicine seems to date since 1288 [2]. Also at the University of Bologna the development of a separate Infectious Diseases academic, research, and assistance centre, finds its roots in the general Pediatric department, and was developed an autonomous service and academic institution only since mid-1950s [3]. The Chairman of Pediatrics at that time, Prof. Gaetano Salvioli (Figure 1), put enormous interests and efforts in infectious diseases epidemiology, treatment, and prophylaxis, and acted as a pioneer of researches regarding poliomyelitis and tuberculosis (the Salvioli's inactivated tuberculosis vaccine called "VDS" has been developed under his preliminary intuitions and intense experimental activities which were carried out for a couple of decades) [4,5].

Figure 1. Prof. Gaetano Salvioli (1984-1982), chair of Pediatrics at the University of Bologna. From his Department an independent centre and chair of Infectious Diseases had its early origin in mid-1950s

Figure 2. Prof. Demos Gotti (1915-2007), the first chair of Infectious Disease at the University of Bologna

Later, Prof. Demos Gotti (Figure 2) covered the first chair of Infectious Diseases at the University of Bologna, and continued the Salvioli's indefatigable work on poliomyelitis (also including rehabilitation medicine in his assistance protocols, and a special focus on social and families' problems) [5,6], and kept an elevated attention for all endemic and emerging pediatric infectious diseases (among others, viral hepatitis) [7].

The same situation was replicated in Italy by some infectious diseases centres taking origin

from a prominently pediatric academic school: among others, we can remind those of Genoa, Milan, Turin, Padua, and Palermo, and especially the Istituto degli Innocenti, probably the oldest institution in the world devoted to child care (operating in Florence since 1420).
On the other hand, in the English-American world, the development of infectious diseases centres followed in the majority of cases that of general internal medicine ones, so that in many countries infectious diseases still represent a subspecialty of internal medicine, while pediatrics followed a dedicated pathway only since early 1800s. The Great Ormond Street Hospital of London was active since 1852, while in other European countries the Hopital des Enfants Malades started its activity in Paris since 1802, and the St. Anna Spital operated in Wien since 1837.
Moreover, the need, impact, usefulness, and cost-effectiveness of infectious diseases dedicated wards and outpatient services are still under discussion in the majority of these countries, since in the English-American world the infectious diseases specialists are usually devoted to consultancy only, and more recently to antimicrobial stewardship throughout the entire Hospital (including Pediatric and Neonatal wards), but they lack of an own centre or division, including dedicated inpatient beds in the great majority of Hospitals.

The pediatric-driven medicine in the United States: from 1800 to the third millennium

In a recent comprehensive contribution by Margaret Kendrick Hostetter hosted as an outstanding review of "The New England Journal of Medicine" among the 200th Anniversary initatives [9], the introduction of the term "pediatric" in the medical literature has been attributed even to Sir William Osler in the year 1880 [10]. In the United States, even though the term "diseases peculiar to children" has been retrieved in some lectures by Benjamin Rush of the University of Pennsylvania since the year 1789, however the majority of physicians living and working during the early 19th century failed to formally recognize infants and children as a distinct population, with specific medical needs.
In fact, when examining many medical Journals of that period, the words "infant," and "child," figured only in case reports of obstetrical complications or in records of epidemic-related mortality.
Actually, William Osler adopted the term "pediatrician" not only in order to differentiate these physicians which were "specially connected with pediatrics" from other physicians [9], but he especially underlined that the creation of a novel, dedicated discipline was strongly needed. After Osler's introduction of the term, scientific papers under the name "Progress in Pediatrics" appeared sporadically in "The New England Journal of Medicine" since the year 1904, and the specialty of pediatrics was accorded its own section in the same Journal in the year 1954 [9]. A computational algorithm (elaborated by T.C. Schwartz, at www.timschwartz.org), allowed to search all the archives of "The New England Journal of Medicine" for the term "pediatrics", also gaining a powerful insight into the increasing emphasis on childhood health over the past two centuries. According to the author of the review, this empirical approach demarcated four periods, albeit somewhat arbitrarily defined, which well reflect the emergence and discoveries of pediatrics through the pages of "The New England Journal of Medicine" and paralleling the history of pediatric in the United States in the last two centuries, i.e. the recognition of children as a particular population benefiting from medical practice (years 1812 to1880), followed by the introduction of public health plans aimed to reduce childhood mortality (years 1881 to 1930), the so-called vaccine era (year 1931 to 1980), and finally the global dissemination of pediatric practice (year 1981 through present years). It is not a case, that each of these periods also coincides with particular advances against infectious diseases, which were and still represent the single leading cause of childhood disease and death, in the past as well as today [9,11]. In fact, R.E. Black and coworkers reported their estimates on the causes of childhood deaths worldwide in the year 2008, take into ac-

count of a patient's age ranging from 1 to 59 months [11]. On the whole, neonatal deaths still accounted for 41% of episodes, and multiple infectious diseases-driven life-threatening infections were included in the 2008 report from Black [11]. For instance, lower tract respiratory infectious accounted for 18% of cases, followed by diarrhea (15%), malaria (8%), sepsis (6%), meningitis, AIDS, and pertussis (2% each), tetanus, measles (1% each), and other infectious diseases (accounting for further 9% of overall childhood deaths), as estimated around five years ago [11].

Back to the ancient times, for many centuries, the popular experience prompted the conclusion that childhood deaths were somewhat unavoidable, and nothing could be done — medically, politically, socially, or economically, save to let nature take its course [12,13]. Indeed, In Europe the population mind progressively changed towards a "religious" behavior since the 2nd century, when the Roman emperor Marcus Aurelius in his "Meditations" wrote: «One man prays, `How I may not lose my little child', but you must pray, `How I may not be afraid to lose him'». The same attitude was maintained during low and high medieval ages, and prosecuted under different social, cultural, and economic context in the old continent until the Enlightenment era.

Later, when large epidemics occurred for instance during military and colonial campaigns, the death toll from infection among children was often obscured, when gastroenteritis, cholera, smallpox, diphtheria, malaria, measles, and many other infectious diseases literally killed without respect to age [12,13]. Despite these peaks of morbidity and mortality, there was insufficient awareness of the special susceptibility of children (particularly under the age of five years), for multiple potentially life-threatening infectious diseases, until the diphtheria epidemic in New England (year 1735-1740), recognized 80% of its 5,000 victims among children [9].

By the middle of the 19th century, a child's death, far from being considered an intolerable event, was still frequently viewed as blessed, a release from the torment of hectic infection (as shown by a participated description of a death occurring from croup, by a contemporary physician) [14]. A predominant mood of resignation is presented in the literature, too, like the death of the character of Beth in L.M. Alcott's masterpiece "Little Women".

Anyway, the attitude of helplessness progressively moved, towards inquiry and then responsibility, up to study of prescription for change, including technical and social variables [9], so that children were assessed as a group deserving attention and protection, and dedicated Hospitals, first opened in Philadelphia (1855), and then in Boston (1869) and Cincinnati (1887) in the United States, although these institution were still based on charitable actions, providing food, clothing, and also a sort of nursing care. In parallel, the prohibition of child work and the guarantee of education greatly contributed to systematize the pediatric assistance. Anyway, the most important movement seemed from the emphasis on public health, as exemplified by the fight against cholera or summer gastroenteritis, which accounted for 15-22% of childhood deaths across the US states of New England and New York around the year 1870 [15]. Around 1850s, breast-feeding rates had declined considerably, especially among the urban working poor, who were forced to resort to cow's milk powder needing mixing with milk or water, carrying a frequent risk to contaminate childrens' milk. The universal pasteurization of milk was advocated by the pediatrician A. Jacobi from New York [9]. Nevertheless, at the end of the 20th century, infant deaths due to gastroenteritis failed to decline, despite mandatory pasteurization and all other organizative efforts (including the so-called milk stations).

But other remarkable concepts were successfully applied, especially the hygiene-related ones. The profound effect of maternal education on breast-feeding, home hygiene, and infant care, led to a decrease of infant mortality rate in New York from 144.4 to 88.8 deaths per 1,000 children, in the period 1907-1917 [9]. Concurrently, the implementation of practical principles of household hygiene and child protection (what pediatricians now call anticipatory guidances), led to a dramatic decrease in childhood deaths from diphtheria, even a decade before the diffuse employment of specific vaccination [16].

The nineteenth century represented the prevention-focused time. In fact, the progress attained in public health allowed to overcome or control many problems that had been present for decades. Moving to the next stage required therefore a change in paradigm of global health care became possible: problems could be stopped or at least contained, well before they occurred. The progressive development in the knowledge of immune system response and the development of vaccine technology, preservation and distribution, rapidly expanded the list of diseases we successfully contained, and in some cases succeeded to eradicate worldwide. In an merely chronological report, starting with diphtheria vaccine developed by Von Behring in 1913 [17], continuing with studies on pertussis vaccine conducted by P. Kendrick and G. Eldering from 1934 to1937 [18], with the vaccine trials with combined diphtheria–pertussis–tetanus antigens-toxoids in the 1940s [19], and the intramuscular (type Salk) and especially the oral (type Sabin) poliomyelitis vaccine trials, carried out successfully in the 1950s and 1960s [20,21]. While the poliomyelitis became under control, in mid-1950s, twice as many children died from measles as from poliomyelitis, so that the attention moved to this last common pediatric viral threat, with the development of effective and safe inactivated and then live attenuated measles virus vaccines, which received maximum attention in early and mid 1960s [22]. Later, the combined measles-mumps-rubella attenuated, associated vaccines, developed by M. Hilleman in the year 1971, was an extremely reliable and manageable tool of generations for pediatrics, obstetrics, and infectious diseases specialists [23], and also had the honors of contemporary generalist press and media, for their efficacy, safety, easy of administration, and possibility to expand immunity and coverage against these common infectious disorders.

But the outstanding cornerstone of the vaccine development and success in the entire 20th century was the worldwide eradication of smallpox, by means of generalized vaccination campaigns [24].

Mandatory vaccination, however, solicited a fierce public debate in both the United Kingdom and the United States, until the publication of famous novel by Charles Dickens "Bleak House", which featured the death of the orphaned street sweeper Jo, whose illness (easily recognizable as smallpox), originated from the miasma of impoverished London. Within the year, the British Parliament mandated that every child born after 1853, should be vaccinated for smallpox within 3 months after birth [25]. In the year 1967, when the World Health Organization (WHO) established its smallpox eradication unit, 131,000 cases were still notified worldwide, but 10-15 million cases were believed to have occurred, with a 15 to 20% fatality rate [24].

Over two decades later, the principles underlying the development of successful protein-based vaccines, opened the door to large-scale trials of polysaccharide and conjugate vaccines for other very relevant pathogens in the childhood, like *Haemophilus influenzae* type B by H. Peltola and coworkers [26], and subsequently meningococci and *Streptococcus pneumoniae* [9].

All these extremely positive accomplishments transformed childhood life expectancy especially in industrialized countries. Concurrently, the ease of intercontinental travel and the rise of global economies brought the conditions of developing countries into major focus of worldwide attention.

Among emerging infectious diseases of the 1980s, certainly HIV infection played a major role in infants too, through vertical transmission, and all social-economical problems linked to frequent orphanage due to the disease killing one or both parents [1]. Thirteen years after the first report of HIV infection (in 1981), a relevant ACTG protocol leaded by E.M. Connor established that the use of the antiretroviral zidovudine before, during and after delivery, and post-partum in the newborns, could reduce the mother-to-child transmission rate of HIV by 67.5%. [27]. The association of a caesarean section delivery significantly increased the protection against mother-to-child HIV transmission [28]. The possibility to prevent vertical HIV transmission determined a strong law, ethical, and organizational debate, which later recommended strongly the testing of all pregnant women, their infants, or both: as a consequence, and thanks to the concurrent improvement of highly active antiretroviral therapy, the number of novel cases of congenital HIV infection dropped to virtually zero in developed countries,

and HIV-infected children received an adequate antiretroviral treatment. More difficult challenges are now represented in adapting these approaches for a global worldwide use, in order to meet the needs of economically disadvantaged countries, where pediatric HIV infection is still a relevant health problem, together with other potentially life-threatening diseases which are typically endemic in many developing countries, i.e. especially malaria, tuberculosis, measles, cholera and other gastrointestinal infections, and lower respiratory tract infections. The leading causes of death in children under the age of five years worldwide are not represented by HIV infections, but pneumonia and gastrointestinal infections, each of which killed more than one million children still in the year 2008 [11].

Dr. Hostetter in her recent review [9] sadly observes that the 15% overall mortality rate from diarrhoea today does not differs significantly from that recorded in the US state of Massachusetts in the old year 1873 [15]. Well planned and adequately funded efforts from conjunct public and private institutions may lead further advances in containing the burden of infectious diseases which still afflict the poorer areas of the world, involving especially children. As a first, promising step, the dissemination of vaccines from industrialized countries to developing countries, associated with a stringent analysis of their efficacy, safety, means and costs of distribution and coverage of the entire population, are currently under analysis and discussion; the experience by V. Richardson and Collaborators is of remarkable value [29].

Distinctive characteristics of infectious diseases in children

Although we are perfectly aware that it is virtually impossible to summarize so many items and update all aspects of the evolution of infectious diseases burden in the pediatric population, however we try to give some emerging indication, to be eventually explored by readers with the aid of dedicated textbooks and comprehensive reviews.

The epidemiological and clinical features of pediatric infectious diseases followed those of adults, with special reference to emerging and re-emerging infections in the past 30 years [1,30-34].

The most frequent and impacting pathogens, and their related diseases were represented by:

- re-emerging old pathogens (including Gram-positive bacteria for severe skin-skin structure infection, necrotizing fasciitis, and community-acquired antibiotic-resistant Staphylococcal infections);
- increased resistance and multi-drug resistance of numerous Gram-negative bacilli, with recent individuation of multi-drug-resistant (MDR) species of *Pseudomonas aeruginosa* and *Pseudomonas* spp., *Acinetobacter baumanii*, *Klebsiella pnemoniae*, *Proteus* spp., and so on, for which the availability of novel, effective antimicrobial agents is still limited;
- *Mycobacterium tuberculosis* for pulmonary and extrapulmonary tuberculosis, and atypical mycobacteria in the event of the immunocompromised host. Notably, the increase of MDR and extremely-drug-resistant (XDR) species of *M. tuberculosis* is burdened by heavy clinical and heath care needs, and elevated mortality rates;
- *Plasmodium falciparum* and other Plasmodia of animal origin (i.e. *Plasmodium knowlesi*) [12,35], related to imported cases of severe disease;
- polioviruses, responsible for some outbreaks, occurring also in underdeveloped countries close to Western-Central Europe;
- other bacteria, like *Corynebacterium diphtheriae*, with reference to the re-emergence of diphtheria in several countries; *Vibrio cholerae*, agent of a still worldwide endemic disease; *Yersinia pestis*, still causing lymph node and respiratory plague in some developing countries; and *Bacillus anthracis*, affecting animals, but also used as a tentative bioterrorism agent) [36];
- novel infectious diseases determined by previously not characterized microbial agents: HIV (the causative agent of AIDS), Legionella spp. (responsible for legionellosis), prions (related to the hu-

man variant of spongiform encephalopathy), Coronavirus-SARS (the agents of the life-threatening acute respiratory diseases) [31], and all the novel forms of pandemic influenza viruses [33] (which were targeted by worldwide diagnostic, therapeutic, and preventive measures by public health services all around the world);

- novel pathogens responsible for old diseases, including HCV infection (which is the agent of the often cronicizing hepatitis C), Parvovirus B19 (as the agent of an exanthematic-systemic diseases with multiple organ targets, depending on the pathophysiological status of the host); Herpes virus type 6, 7, and 8 (which are not only agents of benign esanthematic diseases in the childhood, but may act as opportunistic pathogens in the immunocompromised host); Epstein-Barr virus (the agent of infectious mononucleosis which has its peak of clinical incidence in the adolescence, but retains a relevant oncogenic potential); *Borrelia burgdorferi* (responsible for Lyme disease or borreliosis, a systemic disease with skin, joint, nervous, and cardiovascular involvement), and *Helycobacter pylori* (with its recognized role in duodenal ulcer, gastric cancer, and probably other gastrointestinal tract disorders); among others [1].
- old pathogens responsible for novel diseases: i.e. *Chlamydia* spp. (as a possible agent in the development of the atherosclerotic plaque and autoimmune diseases too); Group A streptococcocci, toxin-producing Staphylococci and Streptococci (as the agents of severe skin-soft tissue infections and necrotizing fasciitis) [37].

Furthermore, the increasing easy of travelling and the immigration waves, also affected children, which followed their families looking for a job, or an alternative place of life, escaping poverty, civil or military wars, and other unfavourable situations in their country of origin [38,39].

These immigration waves also interested Italy with a growing impact in the last 20 years, and were responsible of a re-thinking and planning of all maternal-neonatal and pediatric health care centres, aimed to the screening of the most common diseases of immigrants (included those acquired in our country, after the immigration), and in revising vaccination schedules when information were missing or incomplete [40].

The pathogenetic process of each infectious disease is unique, and is usually associated with its origin, site and mode of penetration, microorganisms load, virulence and tendency to reach target body sites and tissues, the role of local and systemic defences of the host, that of concurrent diseases, and many other factors. The extremely complex interplay between infectious agents and the host is even more particular in the childhood, when the immune system competence is still under development, the cytokine network is still becoming competent, and the active immunization calendar is still under completion [1].

Similarly, the incubation time, the disease presentation and course, the prominent signs and symptoms, the outcome (spontaneous or after a pharmacological treatment), and the risk of sequelae, are all hardly influenced by a series of factors in children *versus* adults, based on the different mode and time of response to exogenous antigens. For instance, a typical sign/symptom like fever increases energy consumption and accelerates enzyme reactions; its benefits for the host are more evident at moderate body temperature increases (until 39-40 °C, while could be detrimental in presence of more marked increases (above 40 °C), especially when a risk for febrile seizures is present in young children [41]. In the classical pathway of fever pathogenesis, usually exogenous pyrogens (microbes, toxins, and other cytokine inducers), lead to the synthesis and secretion of the so-called endogenous pyrogens (interleukin-1, tumor-necrosis factor or TNF, and interleukin-6, among others). Via the circulation, these cyrokines stimulate the anterior hypothalamous to change its body temperature set point (via prostaglandin E2). At this stage, an alteration of autonomic mechanisms of heat loss and retention induces the pathophysiological mechanisms of fever [42]. Most data acquired since 1970s show that fever plays a protective mechanisms, although the question of optimal body temperature for patients suffering from an infectious process (especially when a specific treatment is already ongoing), have never been

satisfactory answered by rigorous clinical trials [41]. Another clinical item which is more common in childhood is lethargy, by which a reduction of energy need is obtained; the rest benefits the course of some infections (especially viral in origin), and allows metabolic support to increase host responses. Also myalgia, which is another unpleasant result of skeletal muscle activity and muscle catabolism, is implicated in generating heat in order to elevate body temperature, and provides a source of aminoacids for increased synthesis of proteins involved in host defence molecules and cells [37,43].

From a clinical presentation perspective, the case of Epstein-Barr infection is well known and somewhat emblematic [1]. Usually acquired as an asymptomatic-paucisymptomatic infection in early childhood, is the responsible of the classic infectious mononucleosis in adolescents and your adults. Moreover, the typical, albeit transient cell-mediated immunodefiency prompted by primary Epstein-Barr infection may support concomitant, sometimes life-threatening infections [44]. Among adolescents and young adults a similar clinical picture may be shared by the two herpesviruses Esptein-Barr virus and Cytomegalovirus, which is a well known agent of fetal damage under pregnancy, but may be also responsible for cases of fever of apparently unknown origin in the immunocompetent host [1,45] . Finally, the well known oncogenic potential of Epstein-Barr virus is well known from Burkitt's lymphoma involving children in Africa, and by its involvement in malignant lymphomas in patients living with HIV infection; in these last patient, also equivocal presentations of extranodal lymphoproliferative disorders require an elevated attention and suspect, and adequate morphologic and histopathological studies [46].

Moving our attention of prevention perspectives, the World Health Organization (WHO) since 1999 underlined a series of simple low-cost interventions, to prevent the global burden of infectious diseases regardless of immune-mediated active or passive interventions [47]. Looking to the items which are most relevant among children, we retrieve:

- an integrated management of childhood illnesses (i.e. a combined therapy for common infectious diseases including oral rehydration and low-cost antibiotics, which are expected to prevent up to 3 million deaths per year from pneumonia and diarrheal diseases);
- childhood vaccination (a more widespread use of low-cost vaccines could avoid an additional 1,6 million deaths per years);
- impregnated bed nets (approximately 25% of deaths from malaria could be prevented if children at risk sleep under bed nets at night);
- availability of essential drugs (unfortunately, still in the third millennium more than one third of the world population lack regular access to life-saving drugs, and the problem is even greater for children, who have a reduced number of drugs registered and/or formulated specifically for the early ages of life);
- nutrition, vitamin and mineral supplements (it is estimated that around 25% of child death from infectious diseases could be prevented by vitamin A supplements, and fatal malaria in childhood can be reduced by the use of iron and vitamin supplements for anemia);
- education programs (it is clear since many decades that women's education acts favourably on infant mortality. For instance, health education principles promote good nutrition and hygiene, immunization, safe sex, and parents knowing how to do when their child is sick) [47].

Actually, the mainstay of prevention is based on vaccines and immunization. The use of vaccines give a significant benefit to the subjects who receive the vaccine directly, by preventing them from both acquiring and spreading the disease, and indirectly they protect those who are not vaccinated or unprotected for any reason (i.e. age, or immune deficiency) [1]. Vaccines include biological agents which must be immunogenic, and capable of inducing a strong, measurable, and sustained response in the recipients. The general purpose is to provide artificial immunity by priming the subject's immune system to recognize and attack the disease-causing organisms at the next contact. Immunobiologics are part of a larger grouping that includes antigenic substances (i.e. vaccines and toxoids), and antibody-

containing products (immunoglobulins and antitoxins). The focus of reducing the vaccine-preventable diseases of children has been a major planetary success, as vaccines have become one of the foundations of routine pediatric care. However, despite the availability of safe and effective vaccines, approximately 50,000-70,000 adults die each year in the United States from complication of infections with *Streptococcus pneumoniae*, *Neisseria meningitis*, Influenza virus, and hepatitis B virus, infectious for which vaccines are routinely recommended for many adults and the elderly, too. Furthermore, children vaccination has an impact on adolescent and adult populations by altering the epidemiology of disease (the so-called herd immunity) [1].

The WHO also recommends an immunization schedule for infants, as a part of the WHO Expanded Program on Immunization [48]. In brief, at birth anti-tuberculosis BCG vaccine together with a first oral poliomyelitis vaccine (for the countries where poliomyelitis has not been controlled); at 6 weeks of age the first administration of tetanus-diphtheria-pertussis vaccine plus a dose of oral poliomyelitis vaccine, to be repeated at the age of 10 weeks and again at the age of 14 weeks. At the age of 9 months, measles vaccine together with yellow fever immunization (recommended in areas at risk for yellow fever) are scheduled, while anti-HBV immunization may be administered at birth, 6 weeks, and 14 weeks of age in countries where newborns are at risk of exposure to hepatitis B through their mothers, or at weeks 6, 10, and 14, when the above-mentioned risk is not of concern [48].

Finally, the choice of an adequate antimicrobial chemotherapy to be delivered in childhood has to take into careful account of the body weight, the body surface, and the measured or expected characteristics of drug metabolism and excretion in children compared with adults [1]. The product label (package insert) approved by the regulatory authorities for a given antimicrobial drug provides information on indications based on the available clinical trial data reviewed by the FDA (United States) and the EMA (Europe). An approved indication means that statistically adequate and well-controlled studies were conducted, reviewed, and approved by the regulatory authorities. However, accepted medical practice (i.e., when to use which antimicrobial agent for a specific infection) often includes use of drugs for indications that are not reflected in approved drug labeling. These additional indications are based on studies conducted by clinical investigators. These studies may not have been presented formally to the regulatory authorities for review. Therefore, unapproved use does not imply improper use, provided that reasonable medical evidence supports such an indication and that use of the drug is deemed to be in the best interest of the patient. The decision to prescribe a drug is the responsibility of the physician, who must weigh risks and benefits of using the drug for the specific indication. Furthermore, some antimicrobial agents with proven therapeutic benefit in adults are not approved by the FDA and/or EMA for use in pediatric patients or, more rarely, are considered contraindicated in children because of possible toxicity. For instance, drugs such as fluoroquinolones (in people younger than 18 years of age), tetracyclines (in children younger than 8 years of age), and other agents approved for use in adults may be used in special circumstances after careful, individual assessment of risks and benefits in each single case. Also formulations of a number of antimicrobial agents cannot be available or adequate for the use especially in early childhood (in particular, among the quite elevated number of antiviral drugs marketed against HIV, a few number is also easily deliverable to neonates and young children).

Questions for further research

Even taking into account of the limitations of our work (which is essentially focused on English-American and European-Italian parallel development of Pediatric Diseases and Infectious Diseases), this review may serve as a basis for a significant remind of the past, and for a future planning and resource allocations in both disciplines.

The review in brief

- Historical pathways of the development of academic and healthcare assistance in both pediatrics and Infectious Diseases are reported, with special focus on European (Italian) and English-American environments
- The relevance of Infectious Diseases in the comprehensive field of Pediatrics is underlined
- The major historical milestones of Pediatric Infectious Diseases are reported and commented
- The unmet needs in terms of academic research, healthcare assistance, and planning of clinical, therapeutic and preventive strategies especially for developing countries are presented and discussed in detail.

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