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Impact of COVID-19 on Pneumococcal Acute Otitis Media, Antibiotic Resistance, and Vaccination in Children

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Abstract: Streptococcus pneumoniae is the main pathogen that plays a dual role, on the one hand as an asymptomatic carrier in the nasopharyngeal mucosa and on the other hand directly responsible for triggering invasive pneumococcal infections with various important localizations, especially in the pediatric population. Thus, invasive pneumococcal infections represent one of the main causes of mortality and morbidity in children under 5 years of age. Immunization is a key preventive measure against these infections. The evolution of these infections caused by S. pneumoniae is influenced both directly and indirectly by several factors: the immunization status of the patient, the regional and seasonal distribution of pneumococcal serotypes, susceptibility to anti-biotics, the existence of viral or bacterial co-infections and the socio-economic conditions specific to each region. This review gathers the current open-access PubMed evidence on the incidence of invasive pneumococcal infections and their susceptibility to antibiotics in the 0–5 age group during and after the COVID-19 pandemic. We have chosen this association with the SARS-COV- 2 virus because this pandemic has caused major changes on all personal, social, professional, and medical levels worldwide. Both pneumococcal disease and COVID-19 have similar risk factors, and S. pneumoniae was one of the most common co-infecting agents during the COVID-19 pandemic. The attention was focused on 8 clinical trials published in the pre- and post COVID-19 period that had as main subject acute otitis media caused by Streptococcus pneumoniae in children aged 0–5 years. The studies were collected from different geographical regions, both from socio-economically developed and developing countries such as Niger, Malawi, China and Papua New Guinea, Japan, Australia, Italy, in order to have a global overview. In conclusion, the COVID-19 pandemic had a major impact on the quality of life of pediatric patients diagnosed with pneumococcal acute otitis media both in terms of non-vaccine serotypes and antimicrobial resistance.

Keywords: invasive infections, otitis, immunization, COVID-19 pandemic, pediatric population

Introduction

Respiratory tract infections (RTI) in the pediatric population are a topic of continuing interest due to increased morbidity and mortality rates and increased accessibility to medical services. These infections are usually self-limiting, but there are also cases when the clinical course is followed by some local or distant complications, short or long-term. From an etiologic point of view, the main pathogens responsible for triggering these upper and lower respiratory tract infections are bacteria, viruses, fungi, and protozoa. [1]

S. pneumoniae discovered by Professor Pasteur in 1881 is one of the most important bacterial pathogens of the respiratory tract causing invasive infections, with different localizations and a strong impact on the pediatric population. According to data from the World Health Organization, about 1 million children die annually from invasive pneumococcal diseases (IPD), mostly in developing countries. The age group most affected is under 5 years. S. pneumoniae is a Gram-positive, alpha-hemolytic, capsulated bacterium with more than 100 serotypes identified to date. Because pneumococcus has more than 100 serotypes, it represents a challenge for medical experts in vaccinology which will

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periodically require the emergence of a new pneumococcal conjugate vaccine that includes as many serotypes as possible.[2] Two types of pneumococcal vaccine are currently available worldwide: polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccine (PCV).[3] The pneumococcal polysaccharide vaccine initially comprised 14 serotypes, and later the formula was changed to 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). Pneumococcal conjugate vaccine 7 (PCV 7) was first licensed in the USA in 2000, then in 2009 it was replaced by PCV 13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). Also in 2009, pneumococcal conjugate vaccine 10 (PCV 10) became available in Europe and other countries outside the USA [6]. With the introduction of pneumococcal conjugate vaccines (PCV 7, PCV 10, PCV 13) the incidence of invasive pneumococcal diseases has been significantly reduced, especially acute otitis media, but this has also led to changes in the etiology of the disease and the serotype distribution involved. One aspect that could be improved in the future would be the reporting of these otic invasive infections through a nationally and globally standardized methodology and the wider use of surveillance systems.[4]

The most important virulence factor is the polysaccharide capsule.[5] The pneumococcal pneumococcal polysaccharide capsule has several properties to help this bacterial agent reach the site of invasion and multiply there. These properties are as follows: increased resistance to phagocytosis, prevents removal of the microorganism by the host organism, can limit autolysis and exposure to antibiotics at the same time.[6]

Streptococcus pneumoniae asymptomatically colonizes the nasopharynx in the pediatric population, but not all pneumococcal strains are equally susceptible and virulent to cause invasive disease. To determine invasive pneumococcal disease, regardless of its localization, the presence of several favorable conditions is necessary: nasopharyngeal colonization with S. pneumoniae, the presence of a susceptible and virulent serotype, and particular host factors such as immunological status, nutritional status in the first year of life, prematurity, personal pathological history of chronic diseases, but also associated bacterial or viral co-infections.[2]

One of the invasive pneumococcal infections with a significant impact on the quality of life of the patient in the pediatric population is Acute Otitis Media (AOM), which is considered to be one of the most common bacterial infections in infants and young children, 90% of children under 6 years of age present at least one episode of Acute Otitis Media in early childhood. Acute otitis media is an inflammation of the middle ear caused by an infectious pathogen that penetrates through the Eustachian tube, causing otalgia and fever as the dominant symptoms of this disease. The bacterial pathogens causing acute otitis media have a similar distribution worldwide (according to Institut National D' excellence en Sante et en services Sociaux Quebec, 2016): S. pneumoniae (40–50%), Hemophilus influenzae (30–40%), Moraxella catarrhalis (10–20%), Staphylococcus pyogenes and Staphylococcus aureus (10–20%).[1,7] Certain favorable and predisposing factors contribute to the onset of this infectious and invasive pathology: young age (less than 3 years), increased susceptibility to acute respiratory infections, community attendance, anatomical features of the skull, gastro-esophageal reflux, passive smoking, bottle or pacifier use, male sex, immune immaturity, adenoid vegetations, cold and dampness.[1,7] According to the American Academy of Pediatrics, more than 5 million cases of acute otitis media (AOM) are identified annually in children in the United States of America, which involves high health care and treatment costs, as well as the widespread use of antibiotics. Since the introduction of the pneumococcal conjugate vaccine PCV-13, the situation has changed and only 25% of cases of acute otitis media are due to Streptococcus pneumoniae. Clinical studies have shown that it takes only 4 years after the introduction of a PCV conjugate pneumococcal vaccine to reach maximum efficacy, and then the ratio is reversed and serotypes considered less aggressive and not included in the vaccine become virulent and are responsible for the occurrence of invasive pneumococcal diseases. In Romania, there are few data on the geographical circulation of pneumococcal serotypes and their antimicrobial resistance after the introduction of the pneumococcal conjugate vaccine. Pneumococcal vaccination in Romania has been introduced since October 2017 in the national immunization schedule, intended to be administered starting with the first 6 weeks of life. Two types of pneumococcal vaccine are currently available worldwide: polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccine (PCV).[3] The pneumococcal polysaccharide vaccine initially comprised 14 serotypes, and later the formula was changed to 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). PCV 7 was first licensed in the USA in 2000, then in 2009 it was replaced by PCV 13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). Also in 2009, PCV 10 became available in Europe and other countries outside the USA.[8]

With the introduction of pneumococcal conjugate vaccines (PCV 7, PCV 10, PCV 13) the incidence of invasive pneumococcal diseases has been significantly reduced, especially acute otitis media, but this has also led to changes in the etiology of the disease and the serotype distribution involved. One aspect that could be improved in the future would be the reporting of these otic invasive infections through a nationally and globally standardized methodology and the wider use of surveillance systems.[4]

The SARS virus COV 2 pandemic has led to increased mortality and morbidity rates worldwide, which required addressing new therapeutic and prevention strategies, reflecting and consolidating experience on medical action and interdisciplinary collaboration.[9] On March 11, 2020, the World Health Organization declared the COVID-19 pandemic, a multisystemic disease with complex symptoms that continues to threaten long term global health worldwide. Although children were less affected than adults, SARS-CoV-2 altered the spectrum of respiratory viruses, as well as the association with other bacterial co-infections. The most frequent viral pathogens encountered during the COVID-19 pandemic were Enterovirus, Rhinovirus and Respiratory Syncytial Virus, and S. pneumoniae as bacterial pathogens. With the introduction of restrictive and preventive measures, a massive decrease in the incidence of associated viral and bacterial pathogens was observed, but after the relaxation of the measures in 2021 things changed and a significant increase occurred.[9,10] As for the evolution of Streptococcus pneumoniae incidence during the pandemic was decreasing compared to previous years.

An important aspect that this paper aims to highlight is the trend of invasive pneumococcal diseases, especially acute otitis media during (2019–2021) and after the COVID-19 pandemic (2022–2023) in terms of case incidence, antibiotic resistance and impact of vaccination on the pediatric population.

Materials and Methods

Data Collection

Data were collected from all clinical trials that focused on invasive infections caused by S. pneumoniae in the pediatric population. Of all pneumococcal infections, the focus was only on acute otitis media diagnosed in the 0–5 age group. To perform this review, we searched the PubMed database for articles with the keywords", "Streptococcus pneumoniae child", "invasive pneumococcal infections", 'acute otitis media' to identify the most relevant articles published between 2019–2023. This period was divided into two other periods respectively, during (2019–2021) and after (2022–2023) the COVID 19 pandemic. All articles were checked by reading the full text, thus eliminating duplicates. Only articles written in English and full free text were selected, thus identifying a total of 41 clinical trials in different regions for the period 2022–2023 and 101 clinical trials for the period 2019–2021 (Figure 1). Thus from a total of 142 clinical trials, finally only 8 trials were included in this review.

Eligibility Criteria

This review was based on a set of inclusion and exclusion criteria in order to filter as well as possible all available information (Table 1).

The review focused mainly on incidence, serotype distribution, antibiotic resistance and impact of pneumococcal vaccination. We selected articles on S. pneumoniae published during the Covid 19 pandemic and postpandemic Covid 19 period that focused on acute otitis media in children. This review was conducted in accordance with ethical principles derived from the Declaration of Helsinki.

Results

During the peak of the COVID-19 pandemic (2020–2021), numerous studies were published on the SARS virus COV 2, its association with different clinical situations, with different viral or bacterial etiologic agents, and with the socio-economic context at that time. A decrease in the incidence of all invasive pneumococcal infections has been observed since that period, but this was either due to the restrictive measures implemented by the pandemic or due to the non-attendance of the pediatric population at the emergency room or family doctor's offices, many of these infections remaining underdiagnosed and not treated in outpatient clinics.

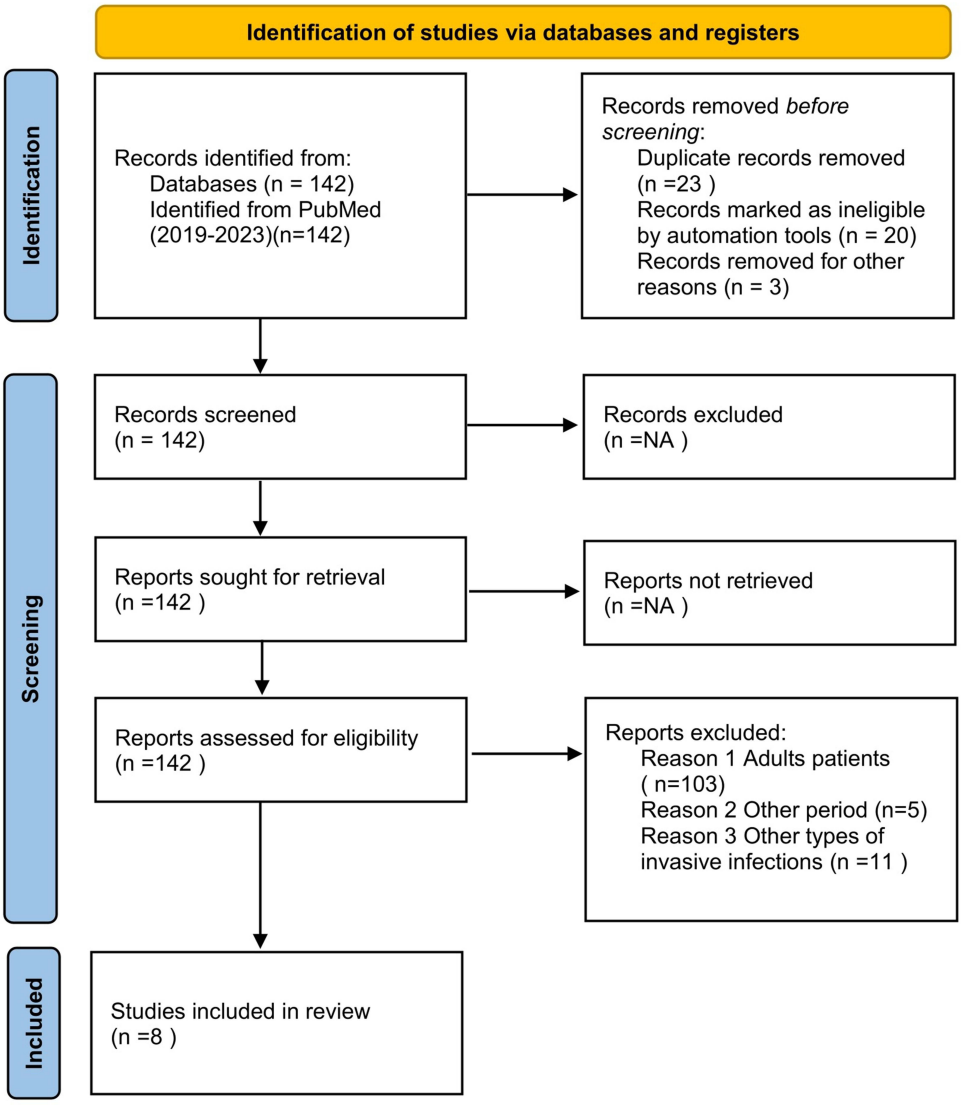

Figure 1 PRISMA flow diagram for the identification of clinical trials for acute otitis media of pneumococcal etiology in children.
Notes: Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic review. *BMJ*. 2021;372:n71.[11] Creative Commons.

Attached below is a table summarizing the results of the studies that were included in this review based on the main serotypes studied and the efficacy of the pneumococcal vaccine according to the period published (Table 2).

After the COVID 19 Pandemic

Between 2022 and 2023, we observed that attention was focused on the publication of original articles that focused on the impact of pneumococcal vaccination and the susceptibility or antibiotic resistance of this pathogen. The studies

Table 1 Inclusion/Exclusion Criteria in the Review

Inclusion Criteria	Exclusion Criteria
-Acute otitis media	-Patients over 18 years of age
-Age of patients between 0–5 years	-Other types of invasive infections
-Period 2019–2023	-Duplications
	-Articles written in other languages

Table 2 Results of the Followed Studies

First author	Tara	Project	Serotip	Endurance rate	Impact of vaccination	Published in COVID 19 pandemic	Published after pandemic COVID 19
Ashley Hazel	Niger[12]	Randomized trial	–	Azithromycin	–	–	After the pandemic
Dingase Dula, MMed	Malawi, Africa[13]	Randomized, double-blind study	6B	–	Positive	–	After the pandemic
Kai Chu	China[14]	Randomized trial	–	–	Positive, safe and efficient PCV 13	–	After the pandemic
Tilda Orami	Papua New Guinea[15]	Randomized trial	19A, 19F, 6A, 14 and 2F	Trimethoprim-Sulfamethoxazole	–	–	After the pandemic
Ghe Dai	Shuzou[16]	Retrospective study	9F, 6B, 23F, 6A and 19A	Macrolide class, Sulfamethoxazole	Benefit PCV 13	During the pandemic	–
Ataru Igarashi	Japan[17]	Review	–	–	Reducing the incidence of invasive diseases	During the pandemic	–
J Beissbarth	Australia[18]	Randomized trial	19A	–	Reduced nasopharyngeal transportation after PCV 7	During the pandemic	–
Alessandro Bondi	Piedmont, Italy[19]	Randomized trial	3,8,12F	At least two different antibiotic classes	–	During the pandemic	–

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covered both developing and developed countries such as Niger, Malawi, China, and Papua New Guinea. The distribution of both vaccine and non-vaccine serotypes was of great interest. In the following we have selected from the totality of the articles studied some of the most relevant and succinct but of real use in current medical practice.

A randomized study conducted in Niger, in rural children aged 0–36 months on the temporal trends of macrolide class resistance in rural children revealed that the prevalence of resistance to this class of antibiotics in S. pneumoniae was increased at 36 months after the initiation of mass administration of azithromycin in particular.[12]

A controlled, randomized, double-blind, double-blind, randomized controlled trial conducted in Malawi, Africa between 2021 and 2022 focused on the efficacy of the PCV 13 vaccine after its introduction in the mandatory vaccination schedule. This vaccine was introduced in 2011 in Malawi and significantly reduced invasive pneumococcal disease in vaccinated children. This study found that the effectiveness of vaccination is much lower in low-resource regions compared to high-income countries, and that carriage of vaccine pneumococci among children persists after vaccination. However, the vaccine has a protective effect.[13]

Another study conducted in China in infants and young children aimed primarily to evaluate the safety and immunogenicity of the PCV 13 vaccine to reduce invasive pneumococcal disease. This disease represents a considerable burden among the pediatric population, thus it is estimated that although deaths due to S. pneumoniae have decreased in recent years in China, acute otitis media remains one of the leading causes along with community-acquired pneumonia. PCV 13 vaccination was authorized in China in 2016. The study divided the 656 participants into 4 cohorts and tracked possible local and systemic adverse reactions after they were vaccinated with PCV 13. Most local reactions were of mild and moderate severity among which we mention local redness and warmth with onset 1–2 days after vaccination. Of the systemic events, the most reported were fever, decreased appetite, and fatigue in <10%, most of which were mild in severity. It was also found that the antibody titer after vaccination was higher among older children although they received fewer doses of vaccine compared to younger children.[14]

A study carried out in Papua New Guinea aimed to investigate the distribution of the serotypes and antibiotic resistant pneumococci after vaccination with PCV 13 or PCV 10. Children aged 1–23 months were included in the study and after being vaccinated with the 3 doses of pneumococcal conjugate vaccine, nasopharyngeal exudates were collected and it was found that the pneumococcal carriage rate was high at 89% of children at 10 months. A total of 64 different S. pneumoniae serotypes were identified. The most frequently encountered serotypes were 19A, 19F, 6A, 14, and 2F. In terms of antimicrobial susceptibility, all pneumococci that were isolated in nasopharyngeal exudates were 46% sensitive to penicillin and 40% were resistant or intermediate to trimethoprim-sulfamethoxazole. This study emphasized the need for a 20-valent vaccine to provide much broader and more effective protection against pneumococcal-inactivated diseases.[15]

A narrative review published by Dani Hall and other co-authors in June 2023 emphasized that the treatment of acute otitis media is mainly symptomatic and antibiotics do not significantly reduce otalgia in the first 24 hours, nor do they reduce the recurrence rate of otitis episodes or certain complications such as hearing loss. This review also highlighted the fact that antibiotics have certain benefits, especially in children under 2 years of age with bilateral or suppurative otitis media. Thus, the use of antibiotics should be judiciously tailored to the individual patient and his or her particularities. The National Institute for Health Care Excellence (NICE) and the American Academy of Pediatrics (AAP) recommend temporizing the administration of antibiotics in the first stage, but if the patient presents certain personal pathological particularities, clear clinical symptomatology with systemic involvement and risk of complications then the prescription of antibiotics is supported and necessary. The antibiotic of choice for acute otitis media remains amoxicillin, followed by the macrolide class and cephalosporins. The combination of amoxicillin with clavulanic acid has been found to be an effective therapeutic option in acute otitis media caused by S. pneumoniae.[20–22]

During COVID 19-Pandemic

A 2017–2018 study of children in Suzhou, China studied the distribution of pneumococcal serotypes and antimicrobial susceptibility on a total of 2446 S. pneumoniae strains. The most frequently encountered serotypes were represented by 9F, 6B, 23F, 6A, and 19A, and in terms of antibiotic resistance was represented by macrolide class, β-lactam, β-lactamine, sulfamethoxazole, clindamycin and tetracycline.[16]

A study conducted in Japan showed that since 2014 the prevalence of PCV 13 serotypes has been continuously decreasing in all age groups, and the incidence rates of invasive pneumococcal infections were 4.98–9.47/100,000 at age <4 years.[17]

A study conducted in Australia on 425 indigenous children living near the Torres Strait, diagnosed with acute otitis media, showed that S. pneumoniae is one of the pathogens responsible for this pathology along with Haemophilus influenzae, and most of them tend to develop complications at a young age (hearing loss, perforation of the eardrum, chronicization). The introduction of PCV 7 certainly led to a reduction in the carriage and serotype of invasive disease, but an increased prevalence of serotype 19 A (serotype not included in PCV 7) was subsequently observed, leading to invasive pneumococcal disease in children under 5 years of age. PCV 13 has been enrolled in the vaccination program in Australia since 2011.[18]

A study started in 2008 and continued during the COVID 19 pandemic in Piedmont, Italy, aimed primarily to assess the impact of pneumococcal vaccination and the SARS-CoV 2-virus outbreak on the antimicrobial resistance of S. pneumoniae. A total of 192 pneumococcal strains were isolated from infants and young children, of which 21.9% were resistant to Penicillin and 40.3% to Erythromycin. The study also showed that in the 0–1 year age group antibiotic resistance in this group was to at least two classes of antibiotics. The serotypes studied were 3.8 and 12 F.[19]

Since February 2020, during the COVID 19 pandemic there has been a decrease in invasive pneumococcal infections reported in an article published by Marco Peradotto and his collaborators in Piedmont, Italy. The number of these invasive infections decreased more in the adult population compared to the pediatric population, another finding of the study. However children were better protected due to the implementation of containment measures. Compared to England where the prevalence of invasive infections was sharply reduced.[23]

The incidence of Acute Middle Otitis globally seems to be 10.85%, but this percentage is difficult to establish as there is no clear reporting of this pathology at the country level.

The American Pediatric Association recommends that the duration of antibiotic treatment in children under 2 years of age or those with perforated eardrum should be 10 days, and in older children, the recommended treatment period is 7 days.[24]

Regarding the distribution and incidence of cases of invasive pneumococcal diseases at the level of the Children's Emergency Clinical Hospital "Sf. Ioan" in Galati, Romania in 2020, which corresponds to the COVID-19 era, a dramatic decrease in the number of cases was observed compared to the pre or post COVID-19 period. A total of 23 cases of infections caused by S. pneumoniae were recorded, represented schematically in the table below. (Table 3)

Compared to the previous year, pre COVID-19, the number of cases of invasive pneumococcal infections recorded was 100 pediatric patients. (Figure 2)

In Romania, there are few data on the geographical circulation of pneumococcal sero-types and their antimicrobial resistance after the introduction of the pneumococcal conjugate vaccine. Pneumococcal vaccination in Romania has been introduced since October 2017 in the national immunization schedule, intended to be administered starting with the first 6 weeks of life.

Table 3 Incidence of Invasive Pneumococcal Infections in 2020

Diagnostic	Number of Cases
Acute pharyngotonsillitis (Nasopharyngeal colonization)	4
Bilateral acute otitis medium	4
Acute otitis medium UD	3
Acute otitis medium US	2
Acute pneumonia	10
Total	**23**

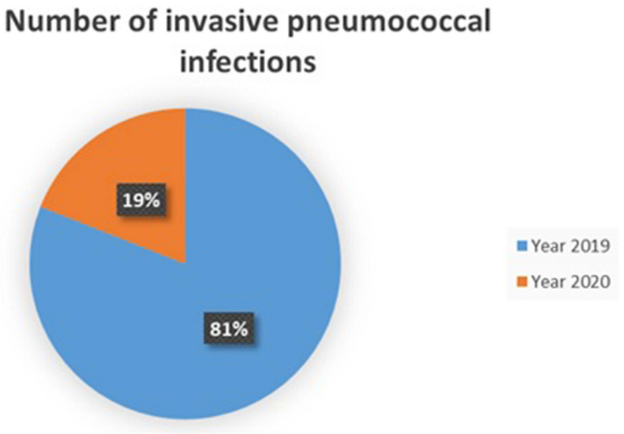

Figure 2 Distribution of cases of invasive infections caused by S. pneumoniae during 2019–2020.

Discussion

An important aspect to take into account is the World Health Organization's recommendation to include the pneumococcal conjugate vaccine in global vaccination programs, with the main goal of reducing these invasive pneumococcal infections. By 2020, only 148 countries had implemented this vaccine in their national immunization schedules, and in recent years non-vaccine serotypes have been found to be responsible for the increased incidence of these invasive pneumococcal infections and increased antibiotic resistance. The most virulent serotypes are 22F and 33F.[25] Clinical studies have shown that it takes only 4 years after the introduction of a PCV conjugate pneumococcal vaccine to reach maximum efficacy, and then the ratio is reversed and serotypes considered less aggressive and not included in the vaccine become virulent and are responsible for the occurrence of invasive pneumococcal diseases.[2] The World Health Organization found that for vaccination to be effective, national immunization coverage should be 95%. However, routine immunization with PCV 13 has been shown to significantly reduce pneumococcal bacteremia by 95%.[26]

It has also been found that populations with limited access to health care, developing countries, and which have not included pneumococcal vaccination in their immunization schedule are the most prone to develop invasive infections, namely acute otitis media, and consequently the occurrence of complications. Long term complications include hearing loss, which improves substantially after about 1 year, but also certain vestibular problems that affect the quality of life of pediatric patients.[27] Other implications that pneumococcal vaccination and the implementation of national immunization programs for invasive pneumococcal infections may have are: decreased costs of prolonged hospitalization and access to uninterrupted school education.[26]

Although pneumococcal conjugate vaccines have been available worldwide for some time, it has been found that 43% of children still do not have access to them because they live in low-income, underdeveloped countries or have not yet implemented the vaccine in the mandatory immunization schedule. This in fact represents a barrier to access to health services, with a negative impact on the pediatric patient in particular.[28,29] Examples are the low-income countries mentioned above in the detailed studies such as those in Africa (Niger, Malawi) which are among the least developed countries in the world, due to the fact that they are landlocked, always need external aid to cover the minimum necessary in various fields of activity and have a high infant mortality rate due to poor health conditions. Another country that falls into the same category of underdeveloped countries is Papua New Guinea, similar to those in Africa whose economies are based more on agriculture. At the opposite pole are countries, which are more economically and politically powerful such as Japan, China, Italy where the infant mortality rate is very low (2 cases per 1000 births). We have chosen to detail both underdeveloped and highly developed countries in order to have a richer overview from both perspectives.[30–34]

There are certain aspects that negatively influence the therapeutic management of invasive pneumococcal infections, especially acute otitis media, namely: incorrect diagnoses, unnecessary and empiric use of antibiotics, and increased antimicrobial resistance. Yue Li and coworkers exposed in a systematic review the antimicrobial resistance of Streptococcus pneumoniae in Chinese children from 2017–2024. Another aspect followed was the distribution of

serotypes that varied by geographic region and strain type. The most implicated serotypes in the development of invasive pneumococcal diseases were represented by 19F, 19A, 6B, 14, 6A and 23F. The highest pneumococcal resistance was recorded for macrolide class of antibiotics (erythromycin, azithromycin) in the percentage of 93.73%.[35] A study conducted in Morocco between 2017–2018 in children showed increased pneumococcal resistance to amoxicillin and cefotaxime in first place, and erythromycin in third place, in contrast to the study presented above.[36] For example in South Africa, 41% of pneumococcal strains isolated from community children were resistant to cotrimoxazole. In conclusion, the antimicrobial resistance of Streptococcus pneumoniae also differs worldwide depending on geographic region.[37]

Another aspect to monitor is the long-term effect of pneumococcal conjugate vaccines on the incidence of S. pneumoniae-induced disease. For example, a study conducted in Zambia in children under 5 years of age showed a reduction in the incidence of pneumococcal meningitis 6 years after the introduction of PCV 10 vaccine. In The Gambia, a study of 342 subjects showed an 80% reduction in the incidence of invasive pneumococcal disease after implementation of the pneumococcal vaccine.[38]

Vaccination is one way to prevent antibiotic resistance. Antibiotic resistance is another chapter with multiple medical and socio-economic implications for the patient. Antibiotic resistance is a major public health problem that has become increasingly common in recent years. According to data from the Centers for Disease Control and Prevention (CDC), more than 2.8 million infections caused by antibiotic resistance occur each year in the United States. This is a rather worrying fact for the medical world. According to data from the literature in 2015, the majority of antibiotics prescribed in outpatient clinics were for acute respiratory infections, 30% of which were unnecessary in the absence of paraclinical investigations. An essential recommendation in the fight against antibiotic resistance is that of collaboration between medical specialists from different medical branches and correct patient information. Vaccination is therefore one of the preventive measures against antibiotic resistance, which can of course be complemented by other preventive measures.[39,40] Although several types of pneumococcal vaccine have emerged over the years, attempting to include the most aggressive serotypes, this challenge of serotype replacement has always been an ongoing struggle. Hence the need to develop constantly updated public health strategies for this branch of the pneumococcal vaccine. Continuous surveillance of serotype distribution and the development of new vaccines accordingly are necessary to ensure the effectiveness of preventive measures against pneumococcal infections in the pediatric population. A study published by Khalid Zerouali and his colleagues in Moroccan children highlighted this issue, highlighting the lack of efficacy of PCV 13 vaccine against non-vaccine serotypes 3 and 19.[41] Vaccination is one of the most effective methods of prevention but it always needs to be updated and improved in order to keep up with all the modifications and changes generated by both the bacterial agent and certain external factors (COVID 19 pandemic).

The COVID-19 pandemic, a much-discussed topic in recent years, represented a turning point in the evolution of all medical pathologies. The imprint of the pandemic was also placed on invasive pneumococcal infections in the pediatric population bringing both advantages and disadvantages. Although strict population isolation measures were imposed, precisely to limit infection with SARS-CoV 2, and involvement with other pathogens, nasopharyngeal colonization with Streptococcus pneumoniae continued to persist during the pandemic in countries such as Vietnam, Israel.[42–44] The impact of the COVID-19 restrictions on health has been a major one both in terms of access to healthcare and mental health. Particularly in low-income and developing countries, the effects have been felt more acutely by people at risk of poverty. Due to the measures imposed by the pandemic through quarantine and home isolation, certain infectious diseases that could be prevented by vaccination (eg rubella, measles, chicken pox, invasive pneumococcal infections, etc) were limited. This was, however, a positive aspect of the pandemic in decreasing the incidence and number of cases of infectious diseases globally. A negative aspect of these restrictions has been the impact on chronic non-communicable diseases, as the prevention, diagnosis and treatment of these diseases have changed and the access to health services for the sick has been limited. Thus the COVID-19 pandemic has brought both advantages and disadvantages, especially in the medical sector.[29,45–47]

Strengths and Limitations

This review aimed to highlight several strengths but also some limitations. Among the strengths, we enumerate the large number of studies that have been published in the PubMed database and have been read and analyzed one by one to select the most important information and thus we could form an overview of the evolution of this invasive infection in the pediatric population after the peak of the COVID 19 pandemic. Another strong point is represented by the personal contribution to this review, namely the study at St. John's Emergency Hospital for Children, Galati, Romania on the post COVID-19 evolution of invasive infections caused by S. pneumoniae in the age group 1 to 5 years. Until now, no study has been conducted in this region on this topic of medical interest, or at least we have not found anywhere on any medical platform.

One of the limitations of this review is that the focus has been on the age group 0 to 5 years. Another limitation is the lack of clinical trials on the subject of this review after the COVID-19 pandemic in certain countries, for example, Romania.

It is very important to have a national registry of these invasive pneumococcal infections for each country, especially for those countries that have already included pneumococcal vaccine in the mandatory immunization schedule.

Another limitation would be represented by the lack of multicenter studies that could provide more information on this topic useful for diagnostic and treatment management.

Conclusion

The introduction of pneumococcal conjugate vaccines in immunization schedules in various countries has greatly reduced the incidence of invasive Streptococcus pneumoniae infections in the pediatric population, especially in young children. However, it has been found in various clinical studies that these invasive infections are mostly caused by non-vaccine serotypes. Of the non-vaccine serotypes most common and also mentioned in the studies in this review were 19A, 19F, 6A, 14 and 2F. Social distancing during the COVID-19 pandemic had a beneficial effect on the pediatric population, decreasing the incidence of respiratory tract infections, especially acute otitis media. Thus comparing the two periods pre and post COVID-19, SARS-CoV-2 has dramatically changed the evolution of invasive infections, the lifestyle and activities of the pediatric population, and the medical approach of the specialists in the field. The focus on S. pneumoniae incidence, distribution of vaccine and non-vaccine serotypes, antimicrobial susceptibility to antibiotics, and pneumococcal vaccination all contribute to combat and prevent these invasive infections with an impact on the quality of life of the pediatric patient. The need for future research directions and the publication of new updated studies on the circulation of pneumococcal invasive disease serotypes and pneumococcal antimicrobial resistance will help to decrease the incidence of pneumococcal invasive disease and to implement more effective preventive measures. The knowledge of antibiotic resistance is a strength in the therapeutic management of pneumococcal infections, helping medical specialists to make the right medical decisions. One of the findings of the studies presented in the review was resistance to the macrolide class of antibiotics. On the other hand, the global impact of these invasive pneumococcal infections in underdeveloped countries will only have negative effects on the pediatric population, increasing infant mortality rates.

Abbreviations

RTI, Respiratory tract infections; IPD, Invasive pneumococcal diseases; AOM, Acute otitis media; PCV, Pneumococcal conjugate vaccine; PPSV, Polysaccharide vaccine; PCV 7, Pneumococcal conjugate 7 vaccine; PCV 10, Pneumococcal conjugate 10 vaccine; PCV 13, Pneumococcal conjugate 13 vaccine.

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The authors report no conflicts of interest in this work.

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