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Pneumococcal Vaccine: 10 Years of Strategies and Challenges in Brazil

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ABSTRACT

Streptococcus pneumoniae is an important pathogen that leads to a wide range of diseases (e.g., from simple colonization to invasive pneumococcal disease) in children, adults, and individuals with underlying conditions. Conjugate vaccines have been developed against *S. pneumoniae* to stimulate effective antipneumococcal antibody and immunological memory. In Brazil, most of population uses the Unified Health System, which provides pneumococcal conjugate vaccine free of charge through campaigns. Although this strategy resulted in increased population protection, health professionals must be aware of invasive disease serotypes not covered by currently available pneumococcal conjugate vaccines and hypervirulent clones. Here, information regarding pneumococcal vaccines in the last ten years in Brazil was collected and strategies and challenges were explored.

INTRODUCTION

Pneumococcal diseases were responsible for 34,217 hospitalizations between 2004 and 2006, according to the Brazilian National Health System (SUS). Of these, 64.8% were due to pneumococcal pneumonia [1], whose etiologic agent is *Streptococcus pneumoniae* (pneumococcus).

Pneumococcus is a gram-positive, capsulated, and extracellular bacterium avid for the upper respiratory tract membrane [2], being the nasopharynx its main reservoir [3]. Nasopharyngeal carriage is an important precondition for pneumococcal diseases and plays an essential role in transmitting the bacteria [4]. Local spread can determine mucosal or non-invasive diseases, such as otitis media, sinusitis, and community-acquired pneumonia. When the bloodstream is invaded, and sterile sites are reached by pneumococcus, the disease is classified as invasive, leading to bacteremia, sepsis, meningitis, and pneumonia [3]. Major risk factors related to carrier status encompass age less than two years, exposure to crowded spaces, passive smoking, frequency of children attending day care centers, and absence of breastfeeding [5].

In 2010, the 10-valent Pneumococcal Conjugate Vaccine (PCV10) was introduced free of charge into the Brazilian National Immunization Program for children under five years old (schedule 3+1), while the 13-valent vaccine (PCV13) replaced the 7-valent vaccine (PCV7) in private clinics [6,7]. In 2016, the scheme has changed to2+1. However, the large size and socioeconomic, geographic, and climatic differences may hinder the assessment of the impact of these vaccines in the population. In this review,

we gather information regarding pneumococcal vaccines in Brazil in the last ten years and explore strategies and challenges.

DISEASE ESTIMATES

S. pneumoniae remains the etiologic agent of greatest relevance in morbidity and mortality rates in people of all ages worldwide. According to the Global Burden of Disease study, 197.5 million episodes of lower respiratory tract infections were recorded between 1990 and 2016, resulting in 1,189,937 deaths in the same period [8]. The elderly and those with underlying diseases are more likely to be contaminated [2] and, therefore, show the highest rates of hospital mortality. Conversely, the impact of *S. pneumoniae* dynamics in children still determines community infections, with those aged up to one year presenting the highest rates of pneumococcal disease (prevalence between 50% to 80% in children aged 2–3 years, decreasing until stabilizing at 5% to 10% in children over ten years of age) [1,9]. Children are the leading carrier of the bacteria, and pneumonia and bacterial meningitis are the most important clinical manifestation in this age group. Nonetheless, deaths can be easily preventable through pediatric conjugated vaccines [3].

SURVEILLANCE PROGRAMS

Surveillance is essential to timely detect epidemics, determine local disease burden, and implement proper prevention and control strategies. The Center of Bacteriology Adolfo Lutz Institute, located in São Paulo, is the reference center for the number of meningitis and pneumococcal infections in Brazil. Our country also joined the SIREVA, an international surveillance program organized by the Pan American Health Organization (PAHO) to monitor pneumonia and meningitis epidemiology [10]. Although surveillance in Brazil is based on the mandatory notification of suspected cases in the public or private healthcare systems (including healthcare units and diagnostic laboratories), pneumococcal surveillance systems are heterogeneous and have different notification rules for case definitions, data collection, and quantity and quality of laboratories [11].

PNEUMOCOCCUS SEROTYPES AND VACCINES

The distribution of pneumococcal serotypes may vary according to geographic region, time, clinical presentation, and age [12,13]. Despite the high number of pneumococcus serotypes, only a small group is responsible for many Invasive Pneumococcal Diseases (IPD), especially in children. Some of these have high resistance levels, such as serotypes 6A, 6B, 9V, 14, 15A, 19A, 19F, and 23F [14].

The introduction of pneumococcal conjugate vaccines to routine childhood vaccination impacted IPD incidence, mainly due to a decrease in vaccine-type colonization and infections [4]. The induced immunity is predominantly serotype-specific. In this sense, capsular serotypes define the epidemiological importance of disease distribution and represent the primary basis for pathogenicity and composition of multivalent conjugated vaccines [2,3]. Conjugated vaccines work through covalent binding of pneumococcal capsular polysaccharides and carrier proteins, inducing T-dependent immune response, immune memory, and long-term protection. These vaccines differ from polysaccharide vaccines due to the high immunogenicity, the anamnestic response, and the reduction of nasopharyngeal carrier rates. Considering the high morbidity and mortality rates of pneumococcal disease, children aged two months or older must be vaccinated with conjugated vaccines [15].

In 2000, the USA licensed the first PCV7, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Its introduction in the pediatric immunization schedule significantly reduced the incidence of pneumococcal diseases, both in vaccinated children and non-vaccinated individuals of other age groups. The USA further replaced PCV7 in 2009 through the PCV13, adding serotypes 1, 3, 5, 6A, 7F, and 19A [16]. In the same year, GlaxoSmithKline laboratory produced, licensed, and approved the PCV10 in several countries. PCV10 comprises capsular pneumococcal conjugates that use the non-type able Haemophilus influenzae D protein as the primary carrier, with serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F [17].

Overall, the effectiveness of PCVs in routine immunization drastically reduces IPD and nasopharynx colonization. At the same time, serotype replacement phenomena occur reddue to occupation of the nasopharyngeal niche by serotypes not included in the vaccine (non-vaccine serotypes) [18].

10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

Brazil was the first country to include PCV10 in a nationwide immunization program for all children. It was implemented in a three-dose scheme and a booster dose at 12 months. In 2016,

the vaccination schedule changed: two doses (2-4 months) in the primary regimen and a booster dose at 12 months (regimen 2+1) for children aged two months up to five years old [19].

Composition

PCV10 vaccine comprises ten pneumococcal serotypes: eight conjugated to non-type able Haemophilus influenzae protein D (1, 1 µg; 4, 3 µg; 5, 1 µg; 6B, 1 µg; 7F, 1 µg; 9V, 1 µg; 14, 1 µg; 23F,1 µg), one serotype 19F conjugated to diphtheria toxoid (19F, 3 µg), and one serotype 18C conjugated to tetanus toxoid (18C, 3 µg). The vaccine is presented in bottles (0.5 ml, without preservatives) and contains aluminum phosphate as adjuvant and sodium chloride and water for injection.

PCV10 VACCINATION COVERAGE IN BRAZIL

According to the United Nations International Children's Emergency Fund, immunization is the most cost-effective public health intervention, preventing 2 to 3 million child deaths per year worldwide [20]. The PAHO Strategic Plan 2014-2019 for member states established an expansion in vaccination coverage of approximately 94% for the hard-to-reach population of the Americas regions [21]. Specific coverage indicators were included in the 2030 agenda for sustainable development, signed in 2015 by the United Nations and 193 countries, including Brazil [22]. The Brazilian National Immunization Program (NIP) introduced PCV10 in 2010 and expanded vaccination coverage between 1991 and 2014. This can be attributed to increased primary care access, improvements in socioeconomic conditions, and income transfer programs, in which vaccination is mandatory [23]. However, in recent years, primary vaccination coverage decreased from 88.39% in 2012to 86.83% in 2019.

The concerning decrease in vaccination coverage can be related to multiple factors and requires a contextualized assessment [24], involving political and economic fragility, the false sense of security related to illness, growing anti-vaccine movement, dissemination of fake news, lack of vaccination monitoring, and financial crisis. Of these, reluctance or refusal to vaccination must be highlighted. Complacency and lack of confidence are also reasons for the growing resistance to vaccines in most countries [25]. Although vaccination programs provide direct and indirect protection against infectious diseases, low vaccination coverage is one of the ten global health threats faced by the WHO strategic plan until 2023 [26]. In 2020, the COVID-19 virus added new obstacles to this issue due to social distance and concentration of resources and efforts to control the pandemics. The reduced vaccination coverage at global and regional levels increased the risk in vulnerable and unprotected populations [27]. Pneumococcal conjugate and influenza vaccines are essential to reduce morbidity and mortality rates from respiratory diseases, especially in the current outbreak.

IMPACT OF PCV10 IN BRAZIL

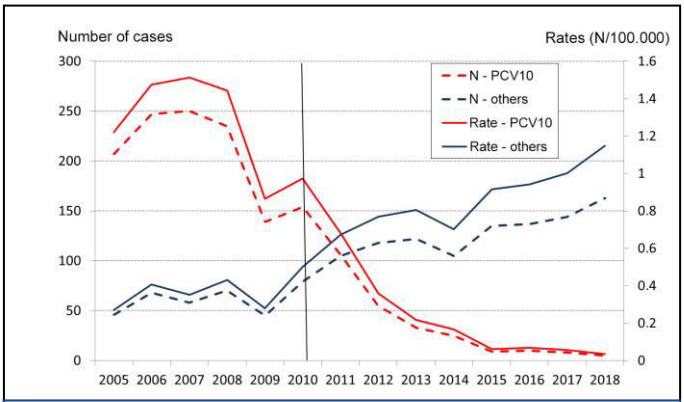

Figure 1: Number of cases and incidence estimated rates of Invasive Pneumococcal Diseases (IPD) by serotypes in Brazilian children under five years old, from 2005-2010. Source: Adolfo Lutz Institute; PCV10: vaccine serotypes, N: non-vaccine serotypes.

Both the inclusion of a high number of antigens in conjugated vaccines and low vaccination coverage represent a significant obstacle in controlling diseases associated with pneumococcus. Low vaccination coverage was observed in Brazil between 2004 and 2010 when PCV7 was available in the public health care system only for children aged <5 months and at risk of pneumococcal disease. In 2009 less than 5% of children aged <12 months had been vaccinated, which led to the introduction of the PCV10 (March 2010) [28]. After ten years of PCV10 in Brazil, clinical pneumonia and pneumonia confirmed by X-ray in children reduced 13.1 and 25.4%, respectively [29,30]. For the targeted population (children aged two months to four years old), PCV10 serotypes declined meningitis and non-meningitis cases in 83.4% and 87.4%, respectively. Conversely, diseases not covered by PCV10 serotypes, mainly the 6C and 19A, expanded after vaccine implementation [31]. Figure 1 shows the attenuated number of meningitis cases of 55.7%, 37%, and 18.8% during pre-, immediately after

(2010 to 2013), and four to five years (2014 and 2015) after PCV10 implementation, respectively. Among non-invasive diseases not related to meningitis, values were 68.3%, 37.9%, and 24.9%in the same periods, respectively. Considering non-vaccine serotypes, 6C (10%), 3 (9.8%), and 19A (9.2%) were most prevalent in patients with meningitis in 2014 and 2015, while 19A (13.4%), 3 (10.6%), 12 F (5.7%), 8 (5.5%), and 6C (4.8%) were prevalent in cases without meningitis [17]. PCV10 implementation also reduced children's hospitalizations due to pneumonia, protected nasopharyngeal pneumococcal carriers against vaccine serotypes, and reduced IPD cases in all age groups [31,32].

The Brazilian Pediatrics Society and the Brazilian Immunization Society recommend PCV13 for children aged two months due to the greater protection spectrum. From the perspective of individual protection, three doses are recommended in the first year (two, four, and six months) and a booster dose between 12 and 15 months of life [33,34]. Also, as PCV10 cross-react with 6B and 19F serotypes producing antibodies to serotypes 6A and 19A, PCV13 promotes additional immunization against serotypes 3, 6A, and 19A. PCV13 is exclusively used in 75% of 120 National Immunization Programs worldwide for the pediatric population. From 2015 to 2019, 13 countries chose to change their vaccination program from PCV10 to PCV13. In Latin America, this vaccine is available in most child immunization programs, except in Colombia, Brazil, Ecuador, and some Central American islands. Although a direct comparison between these two vaccines is limited due to evidence of heterogeneity and vaccination schemes, the latest WHO report demonstrated a significant impact of both vaccines in reducing children hospitalization, community-acquired pneumonia, and ear infections [35].

Despite both the effectiveness of PCV10 and PCV13 vaccines in direct and indirect immunization of community-dwelling individuals (guaranteeing the inclusion in immunization programs worldwide for children) and the significant reduction of IPD cases (e.g., meningitis and sepsis) ten years after implementing PCV10, colonization rates increased (19.4%) in children under 23 months-old between 2010 and 2017. Moreover, 40% of IPD cases from children < 5 years old in Brazil in 2018 were caused by serotypes not present in the PCV10, such as 19A [17,35]. Although clinical trials evaluate vaccine effectiveness before regulatory approval, indirect factors may influence the results, such as vaccination coverage rates, herd protection, serotypes replacement, and natural variation of serotypes prevalence [36,37]. For example, we can highlight the multi-resistant clone related to serotype 19A. From 1990 to 2014, 20% of nasopharyngeal and IPD samples of children and adults were not sensitive to penicillin, being the former more resistant than IPD isolates. Furthermore, a decreased number of isolates resistant to penicillin and belonging to PCV10 serotypes and a progressive trend towards isolates resistant to penicillin but not belonging to PCV10 serotypes were found [38]. A critical point for the successful implementation of a pneumococcal conjugate vaccination program is the impact on the carrier status. Disease transmission to adults may occur due to the lack of influence of cross-reactivity in the carrier status of the children [39]. Nevertheless, Brazil substantially dropped the colonization rates of PCV10 serotypes, even though serotype 19A has elevated the nasopharyngeal colonization rates of vaccinated children [29].

THE FUTURE OF PNEUMOCOCCAL VACCINES

Pneumococcal disease prevention is challenging. The development of new vaccines focused on expanding coverage for new serotypes may play an essential role in disease control. In this scenario, the following vaccines can be highlighted:

a) PCV10V from Serum Institute of India Private Limited (SIIPL), which includes ten pneumococcal serotypes and the 19A serotype;

b) PCV15 from Merck Sharp and Dhome (MSD), with the additional serotypes 22F and 33F to the PCV13;

c) PCV20, developed by Pfizer, which added 8, 10A, 11A, 12F, 15B, 22F, and 33F serotypes to PCV13.

Alternative strategies for developing pneumococcal vaccines encompass purified protein vaccines (common in several pneumococcal serotypes) and inactivated cell vaccines. Although the choice of a potential vaccine antigen is in preclinical stages, several pneumococcal vaccines remain under investigation [40-44].

CONCLUSIONS

Pneumococcal diseases are important public health problems due to their significant morbidity and mortality rates, especially

in children and the elderly. PCV10 application by the Brazilian NIP reduced disease cases, protecting unvaccinated groups through its indirect effect. Nations must be aware of the serotype replacement phenomenon and the emergence of hypervirulent clones to develop constant epidemiological surveillance and new vaccines.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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