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Review

Impact of the introduction of the pneumococcal conjugate vaccine in the Brazilian routine childhood national immunization program☆

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ABSTRACT

Brazil introduced the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, *Synflorix*™, GSK Vaccines) in the routine childhood immunization program in 2010 with a 3+1 schedule (with catch-up for children <2 years-old). This review represents the first analysis of the overall impact of a second-generation pneumococcal conjugate vaccine on nasopharyngeal carriage and all the major pneumococcal disease manifestations in a single, pneumococcal conjugate vaccine-naïve, developing country. A total of 15 published articles and 13 congress abstracts were included in the analysis. In children <5 years-old, studies showed a positive impact of PHiD-CV on the incidence of vaccine-type and any-type invasive pneumococcal disease (including decreases in pneumococcal meningitis morbidity and mortality), on pneumonia incidence and mortality, and on otitis media. Nasopharyngeal carriage of vaccine-type and any-type pneumococci decreased after the primary doses, with no early signs of replacement with other pathogens. Finally, herd protection against vaccine-type invasive pneumococcal disease and pneumonia in unvaccinated subjects was shown in some studies for some age groups. In conclusion, pneumococcal disease decreased after the introduction of PHiD-CV into the Brazilian national immunization program. Further follow-up is needed to evaluate the long-term overall impact of PHiD-CV in the Brazilian population.

1. Introduction

The diseases caused by *Streptococcus pneumoniae* are a leading cause of morbidity and mortality in children <5 years-old worldwide, especially in developing countries [1–4]. Pneumococcal diseases range from life-threatening invasive pneumococcal diseases (IPD) such as meningitis, bacteremia, and bacteremic pneumonia, to the less serious but more frequent non-invasive pneumonia and acute otitis media (AOM) [1].

Brazil is a large, upper middle-income country composed of five regions with different climatic, demographic, and socioeconomic characteristics. It has a mixed ethnic population of approximately 200 million with approximately 3 million births per year [5,6]. Brazil was the first country in Latin America to introduce the 10-valent pneumococcal non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine (PHiD-CV; *Synflorix*™, GSK Vaccines) into its routine national immunization program for all children [7].

PHiD-CV contains ten capsular polysaccharides from serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, eight of them being conjugated to the cell-surface protein D from NTHi, serotype 18C conjugated to tetanus toxoid, and serotype 19F conjugated to diphtheria toxoid. Implemented between March and September 2010, the recommended vaccination schedule includes three primary doses at 2, 4, and 6 months of age followed by a booster dose at 12–15 months of age (3+1 schedule) [7]. Catch-up schedules were also set up by the Ministry of Health for older children: two primary doses and a booster at 12–15 months were recommended for infants 7–11 months-old, and one dose for children 12–23 months-old. For high-risk children, the vaccine was recommended up to 5 years of age. In 2016, reduction to a 2+1 schedule (2 and 4 months of age, and booster at 12 months of age) was put in place [8].

Abbreviations: AOM, acute otitis media; CI, confidence interval; CVE, Centro de Vigilância Epidemiológica; IAL, Instituto Adolfo Lutz; IPD, invasive pneumococcal disease; NS, statistically non-significant; NTHi, non-typeable *Haemophilus influenzae*; NVT, non-vaccine type; PCV, pneumococcal conjugate vaccine; PHiD-CV, pneumococcal *Haemophilus influenzae* protein D conjugate vaccine; PM, pneumococcal meningitis; RCTs, randomized controlled trials; SINAN, Notifiable Diseases Information System; VE, vaccine effectiveness; VT, vaccine-type.

☆ *Trademarks*: Synflorix is a trademark of the GSK group of companies. Prevenar/Prevnar is a trademark of Pfizer/Wyeth LLC.

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Brazil has a national surveillance system of meningitis through the Notifiable Diseases Information System (SINAN for *Sistema de Informação de Agravos de Notificação*) and the national reference laboratory for meningitis and pneumococcal infections (IAL for *Instituto Adolfo Lutz*, São Paulo). The municipalities or states also have the possibility to register morbidity and mortality data for other non-mandatory pneumococcal diseases via the unified health system. Thus, 5 years after the introduction of PHiD-CV, Brazil offers an opportunity to measure the impact of the vaccine on pneumococcal disease in a large pediatric population in a country with high vaccine coverage and available surveillance systems [9,10].

In this review, we examined the impact of PHiD-CV introduction in the Brazilian national immunization program on IPD, pneumonia, AOM, and nasopharyngeal carriage. We also examined herd protection in unvaccinated age groups.

2. Methods

2.1. Search strategy and selection criteria

We conducted a search of the literature in three different online databases (PubMed, Embase, and SciELO) to identify reports of studies investigating the possible effects of PHiD-CV

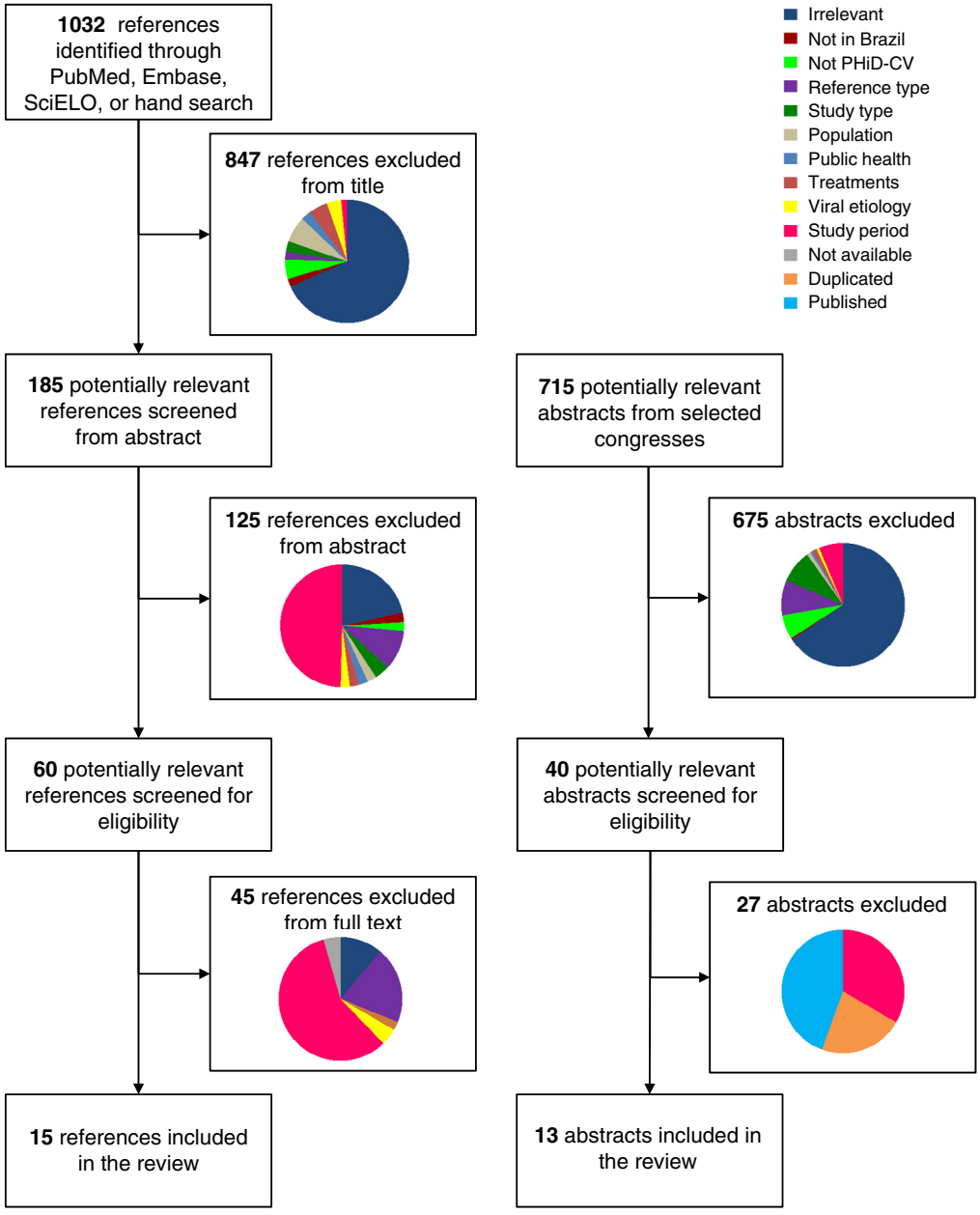

Fig. 1. Flow chart of the articles and congress abstracts evaluated for inclusion in the review. Reasons for exclusions were: irrelevance (studies not analyzing *Streptococcus pneumoniae*, pneumococcal diseases, or topic-related diseases), not in Brazil (studies performed in other countries), not PHiD-CV (studies of vaccines other than PHiD-CV), reference type (case reports, reviews, editorials, or comments), study type (animal studies, in vitro studies, models, or vaccine immunogenicity or safety studies), population (studies conducted among populations with chronic diseases not representative of the general population or, for topic-related diseases, in too-old populations), public health (public health programs or recommendations, cost-effectiveness or health economics studies), treatments (studies evaluating treatments such as antibiotics), viral etiology (studies of virus etiology only), study period (studies conducted only before or after PHiD-CV introduction or whose analysis period was unspecified), not available (full text not available), duplicated (studies presented several times), and published (congress abstracts whose results were also described in a published article included in the analysis).

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