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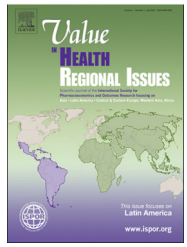

Modeling Possible Inclusion of Pneumococcal Conjugate Vaccine into the National Immunization Program for Infants in India

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ABSTRACT

Background: India is home to up to 28 million infants born annually, and yet to a large extent these children do not benefit from the protection provided by a pneumococcal conjugate vaccine (PCV) immunization program. The Government of India, with support from Gavi, The Vaccine Alliance (in short, Gavi), has committed to a pilot implementation of PCV. There are few public health impact evaluations available for India, and equally limited epidemiologic data. **Objectives:** To estimate the potential impact of an infant pneumococcal vaccination program in India. **Methods:** Using a well-established pneumococcal disease impact model parameterized with local data to the extent possible, we calculated the potential impact of introducing an infant PCV program in India. The model considered direct vaccine protection by PCV10 or PCV13, focusing on children younger than 5 years, while varying vaccine uptake according to the implementation method (i.e., state-level programs [Gavi funding] or a government-supported national immunization program [NIP]). **Results:** With state-level PCV13 programs comprising 25% uptake across the country, approximately 1.9 million cases of pneumococcal disease and approximately 77,000 deaths could be prevented annually. An NIP with PCV13 could prevent approximately 7.6 million cases of pneumococcal disease and approximately 0.3 million pneumococcal deaths annually, compared with no vaccination, considering 100% vaccine uptake. These results are likely to have underestimated the additional potential benefits of herd effects in unvaccinated children and adults. **Conclusions:** Incorporation of PCV into an Indian vaccination program for infants is predicted to have a substantially positive health impact. Gavi funding of state-level programs is an important step toward achieving the full benefits of an NIP in India.

Keywords: India, national immunization program, pneumococcal conjugate vaccine, pneumococcal diseases.

Introduction

Pneumococcal disease, although vaccine-preventable worldwide, continues to be a major cause of morbidity and mortality [1], and can result in multiple outcomes ranging from self-limiting illness, with full recovery, to sequelae or death. It can present as noninvasive pneumococcal disease (e.g., nonbacteremic pneumonia, acute otitis media [AOM], sinusitis, and bronchitis) or invasive pneumococcal disease (IPD) (e.g., meningitis, bacteremia, pneumonia, and sepsis) [2].

In 2010, up to 1.9 million children worldwide were estimated to die from pneumococcal diseases each year, mostly in low- and middle-income countries [3,4], with 66% of this burden disproportionately falling on 10 countries in Asia and Africa. In a World Health Organization (WHO) report published in 2011 inclusive of data up to 2008 for Southeast Asia, it was estimated that 99,400 children younger than 5 years ("under-five") would die because of pneumonia and 3,800 children because of meningitis; also, globally 5% of all-cause child mortality (476,000; range 333,000–529,000) in HIV-negative under-five children was because of pneumococcal (*Streptococcus pneumoniae*) infections [5]. Almost all (99.9%) child pneumonia deaths occur in developing and least developed countries, with most occurring in sub-Saharan Africa and South Asia. Of all pneumonia deaths, 47.7% occur in the least developed countries, most of which are eligible to receive support for the purchase of vaccines and improvement of their immunization programs through Gavi, The Vaccine Alliance (in short, Gavi) [6]. According to a recent estimate from 195 countries, pneumococcal pneumonia was the most common etiology of lower respiratory tract infections or deaths in under-five children, leading to an estimated 55.8% (95% uncertainty interval 32.5%–75.0%) (58.7% in India) of lower respiratory tract infections, and of 392,965 deaths (95% uncertainty interval 228,367–532,281) (82,448 deaths in India) [7].

Conflicts of interest: All the authors are employees of Pfizer.

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India presents the largest birth cohort in the world and represents 27% of the global burden of pneumococcal disease [8]. According to WHO's Child Health Epidemiology Reference Group estimates for 2010 in India, pneumonia caused 397,000 of the yearly total of 1,682,000 deaths in under-five children [9]. Considering that a pneumococcal etiology of about 5% to 35% for pneumonia has been estimated across different studies, the annual under-five mortality in India caused by pneumococcal pneumonia is estimated to range from 19,850 to 138,950 deaths per year [9].

In contrast to surveillance systems in countries where IPD is reportable and monitored by health authorities, much less is known of the burden of IPD in India. The proportion due to IPD was found to be 10.58% in Indian children hospitalized with suspected invasive bacterial disease (IBD), and 24% of all bacterial pneumonia cases were due to *S. pneumoniae* [10]. In India, pneumonia is the leading cause of death for postneonatal children, contributing about 27.5% of the total under-five mortality [11]. Data available on the incidence of acute bacterial meningitis in India are rare; a single prospective, population-based study conducted among under-five children estimated the annual burden of acute bacterial meningitis to be 53 per 100,000 [12]. Although hospital-based [13] studies highlight the prevalence of IPD among Indian children, there has been no nationally representative study of IPD incidence. Pneumonet, a 2-year-long hospital-based surveillance study, which attempted to close this knowledge gap, was conducted at three hospitals in Bengaluru, South India. The incidence of IPD in under-five children was estimated to be 17.8 cases per 100,000, with the highest burden of 49.9 cases per 100,000 among 6- to 12-month-olds [14]. The most prevalent serotypes found to cause IPD in Indian children were (in order) 6A, 6B, 1, 19F, 19A, 14, 5, 7, 9V, 33, and 17 [15,16].

Two pneumococcal conjugate vaccines (PCVs) are licensed for use in children in India. PCV13 contains poly- or oligosaccharides from 13 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, and 19A) of *S. pneumoniae*, conjugated to genetically detoxified diphtheria toxin, CRM197. A 10-valent PCV (PCV10) uses recombinant protein D, tetanus toxoid, or diphtheria toxoid as the carrier protein and contains 10 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, and 7F) of *S. pneumoniae* [17].

Although more than 90 serotypes of the pneumococcus are known, PCVs were designed to address the most predominant causes of IPD morbidity and mortality, which also tend to be the most virulent and antibiotic-resistant strains. PCVs have been shown to reduce invasive disease and noninvasive disease, as well as nasopharyngeal acquisition of vaccine serotypes [18]. On the basis of the substantial burden of pneumococcal diseases globally and the growing resistance to antibiotics, the WHO recognized in 2007 the efficacy, safety, and cost effectiveness of PCVs and recommended their inclusion in childhood national immunization programs (NIPs) [19].

With the largest birth cohort in the world, India needed inclusion of PCVs in the national childhood immunization schedule. Recently, Gavi announced that it would fund a statewide pneumococcal vaccine pilot program in India [20,21]. In view of the current situation, and in the context of only partial local epidemiology data, the present study was intended to estimate the potential impact of an infant pneumococcal vaccination program in India.

Methods

Model Structure

A well-established decision-analytic model designed in Microsoft Excel was used to estimate the potential impact of implementing an infant pneumococcal vaccination program in India with a 2 + 1 schedule [15,22,23]. To summarize, infants entered the model with or without vaccine protection, dependent on assumed vaccine uptake rate, and then could fall into one of the following mutually exclusive health states: no disease, AOM, severe pneumonia, pneumococcal bacteremia, pneumococcal meningitis, or death. The risk of disease was based on the local incidence without PCV adjusted by the effectiveness of the vaccine evaluated, which depended on local serotype coverage estimates. The model then evaluated the impact of a respective vaccination program (PCV10 or PCV13) on the basis of the number of cases averted for under-five children as well as on the associated death or sequelae prevented. Outcomes were calculated over a 1-year period considering only direct protection afforded by vaccination, occurring during a steady state.

Vaccination Program Implementation

In 2015, India's National Technical Advisory Group on Immunization recommended a phased introduction of PCV into India's NIP using a 2 + 1 dosing schedule at age 6 and 14 weeks, with a booster dose at age 9 months [24]. At the same time, the Indian Academy of Pediatrics recommends an infant pneumococcal vaccination schedule consisting of a 3 + 1 schedule at age 6, 10, and 14 weeks, followed by a booster dose to be completed between age 12 and 15 months [25].

Although the indirect effects of infant PCV programs of reducing disease in unvaccinated persons of all ages in the population are well documented, in this analysis we limited the impact to direct protection of under-five children. Because the analysis was for a steady-state year, under-five children were assumed to be previously vaccinated and directly protected by vaccination. Developed countries with well-established programs maintain national coverage rates between 80% and 95% [26]. Given the potential for variation in vaccination implementation among the large population in India, scenarios around levels of the vaccination rate (i.e., vaccine uptake) were tested including scenarios that reflect 1) regional (state-level) PCV implementation through Gavi funding (10%, 25%, or 50% national uptake) or 2) full NIP (75% or 100% national uptake).

Epidemiologic Inputs

The model was adapted using data from the published literature. The population estimate in India was based on age-specific data (for year 2011) published by the United Nations Statistics Division [27]. Pneumococcal disease data (i.e., age-specific pneumococcal disease incidence, case-fatality rates, and life expectancy data in under-five children) were collected from studies by Farooqui et al. [28] and Thomas [29]. The incidence of pneumococcal bacteremia and meningitis was calculated on the basis of the assumption that 80% of IPD cases are bacteremia and 20% are meningitis. Farooqui et al. [28] used a mathematical model to estimate the number of severe pneumonia episodes, pneumococcal pneumonia episodes, and pneumonia deaths in under-five children in India in 2010. They predicted an incidence (cases per 1000) of severe pneumonia of 30.7 and of IPD of 4.4 in under-five children [28]. Prevalence data for AOM obtained from Rupa et al. [30] were used as a proxy for incidence (Table 1).

Thomas [29] assessed the characteristics of IPD, including serotype prevalence, in six hospitals in India over a 4-year period among patients with suspected pneumonia, pyogenic meningitis, septicemia, or localized pus-forming lesions. Case-fatality rates for pneumococcal bacteremia and meningitis in under-five children were 21% and 34% (Table 1), respectively [29]. Meningitis carries a risk of neurological sequelae or hearing loss; detailed data were collected on the probability of hearing loss from a meta-analysis by McIntyre et al. [31] and on neurological sequelae due to meningitis from Pomeroy et al. [32] in children and