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Review

Serotype distribution and antimicrobial susceptibility pattern in children ≤ 5 years with invasive pneumococcal disease in India – A systematic review

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ABSTRACT

Background: *Streptococcus pneumoniae* is a leading cause of childhood diseases that result in significant morbidity and mortality in India. Commercially licensed and available pneumococcal conjugate vaccines (PCVs) include ten (PCV-10) and 13 (PCV-13) pneumococcal serotypes. Vaccines with other serotype combinations are under development. Reviewing and reporting trends and distribution of pneumococcal serotypes causing invasive pneumococcal disease in India will be useful for policy making as PCV is being introduced into India's universal immunization program.

Methods: We conducted a systematic literature review of hospital based observational studies (both peer reviewed and gray literature published in English) from India available from January 1990 to December 2016. Studies that documented data on the prevalence of serotype distribution and the antimicrobial resistance pattern of *S. pneumoniae* in children ≤ 5 years of age were included.

Result: We screened a total number of 116 studies, of which 109 studies were excluded. Final analysis included seven studies. The most frequent pneumococcal serotypes causing invasive disease among children ≤ 5 years were 14, 1, 19F, 6B, 5, 6A, 9V and 23F. Serotype 14 and 19A were represented in most of the geographical regions studied in the reviewed articles. Currently available PCV formulations included 67.3–78.4% of all serotypes contributing to IPD among Indian children ≤ 5 years. Pneumococcal resistance to trimethoprim/sulfamethoxazole, erythromycin, penicillin, chloramphenicol, levofloxacin and cefotaxime was seen in 81%, 37%, 10%, 8%, 6% and 4% of all pneumococcal isolates respectively, while vancomycin resistance was not reported.

Conclusion: The present review demonstrates that up to 78.4% of reported invasive pneumococcal disease in children ≤ 5 years in India are currently caused by serotypes that are included in the available licensed PCVs. However, sentinel surveillance must be continued in representative parts of the country to assess the changing trends in distribution of pneumococcal serotypes and their implication for vaccine selection and rollout in India.

Contents

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1. Introduction

Streptococcus pneumoniae (*Spn*), is the leading cause of a wide spectrum of serious invasive diseases such as pneumonia, meningitis, febrile bacteremia and sepsis that are responsible for the life-threatening morbidity and mortality in children less than 5 years of age worldwide. Globally, the annual estimated child deaths caused by the organism ranges from 0.7 to 1 million [1]. Since 1990, the global under-five mortality rate has been reduced nearly by 50%. Nevertheless, in many developing countries, approximately 16,000 children under five years continue to die every day due to preventable causes like pneumonia, making the Sustainable Development Goal (3.2) of reducing the under-five mortality rate to as low as 25 per 1000 live births by 2030 a challenging proposition [2]. A review by O'Brien et al. suggests that 66% of the pneumococcal cases worldwide are from Asia and Africa, with the highest proportion (27%) being reported in India [3]. In 2010, the country had an estimated 0.56 million (0.49–0.64 million) episodes of severe pneumococcal pneumonia with 105 thousand (92–119 thousand) pneumococcal deaths in children under 5 years of age [4] despite high economic growth in the nation.

More than 94 immunologically distinct serotypes of pneumococci including the recently identified serotypes 6C, 6D, 11E, and 20A/20B have been described in literature [5]. However, from the epidemiological standpoint not all serotypes are equally invasive and the differences in invasive pneumococcal disease (IPD) rate and serotype distribution vary based on different age groups, geographical distribution and time period. It has been estimated that 70–80% of all invasive pneumococcal disease globally are caused by 13 serotypes that are included in the currently available and licensed pneumococcal conjugate vaccines [6]. However, one must take into account the complexity and dynamic nature of *S. pneumoniae* serotype-specific local epidemiology while considering vaccine formulations. Unlike the industrialized nations where epidemiological data on pneumococcal disease and its prevalent serotypes are routinely monitored among children $\leq$ 5 years, data from developing countries, particularly from India, are scarce with few published reports from observational multi-centre and sentinel studies. Unfortunately, data generated through these studies are often fragmented with poor geographical representation and have limited usefulness to policy makers and other stake holders. One of the major challenges to serotype prevalence studies in India has been the meagre laboratory data generated by a few centers alone [7]. This is understandable due to the complex laboratory procedures required to isolate and serotype the organism. Therefore, the existing knowledge gap is substantial.

Worldwide, the emergence of drug resistance and its rapid acceleration among *S. pneumoniae* has become a major public health concern. In developing countries, the lack of monitoring of antimicrobial resistance patterns as well as the widespread availability of antibiotics without prescription has led to inappropriate use of antibiotics. The use of vaccines and subsequent reduction in disease can help reduce antibiotic demand and use, thus curb the threat of increasing antibiotic resistance. As of March 2017, pneumococcal conjugate vaccines (PCVs) have been successfully introduced in the national immunization schedule in 139 countries including 57 Global Alliance for Vaccines and Immunization (Gavi) eligible nations. In particular, India's neighboring countries have already introduced PCV recently, such as Pakistan in 2012, Bangladesh and Nepal in 2015 [8,9]. PCV is being introduced in India this year (2017) in a phased manner, the present review is therefore timely and summarizes the available literature from India to fill-in the knowledge gaps and provide pre-PCV data that will contribute to future surveillance efforts which is necessary as nationwide coverage of PCV is achieved.

2. Materials and methods

We performed a systematic literature review of the published literature from January 1990 to December 2016 to identify articles that describe the pneumococcal serotypes and their resistance patterns from IPD cases in children ($\leq$5 years) in India. We considered this time frame for review as most of the multi-centre pneumococcal surveillance studies that included serotype data were carried out and published after1990.

2.1. Literature search

We searched the following literature databases: PubMed, Scopus, Medline via EBSCOHOST and Google Scholar, and considered studies for the review that were published in English language. Specific search terms in combination were employed to identify the articles as listed in Supplementary Table 1. The search was further supplemented by the reviews of reference lists, and bibliographies. We also contacted researchers who were known to carry out IPD surveillance and requested supplemental and

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