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Original Article

Impact of pneumococcal conjugate vaccines (PCV) on pneumonia, the forgotten killer of children

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ABSTRACT

Pneumococcus contributes to nearly 50% of severe cases of pneumonia and pneumonia deaths. This article presents a literature review of the impact of the pneumococcal vaccines namely PCV7, PCV10 and PCV13 on community acquired pneumonia (CAP). It appears that the quantum of reduction of CAP is much better with PCV13 than PCV10 in several countries. However, inclusion of either vaccine in the national immunisation programme in developing countries has the potential to save 0.3–0.5 million deaths and 7–8 million episodes of severe CAP.

1. Introduction

Recent World Health Organization (WHO) estimates for 2015 show that the global child mortality rate in 2015 was 42.5 per 1000 live births and hence MDG 4 goal of reducing child mortality by two thirds from 90 per 1000 live births in 1990 to 30 per 1000 live births by 2015 could not be achieved.[1] WHO estimates that in 2015 5.9 million children under the age of five died world over of which 4.4 million were from Africa and South East Asia alone.[1] India is ranked 48th in the list of countries with child mortality of 47.7 per 1000 live births.[1] Besides all causes of neonatal mortality put together as the number one cause of under-five deaths, pneumonia and diarrhea are the two leading individual causes of child mortality in that order.[1]

Pneumonia has been stressed upon as the forgotten killer of children by UNICEF and WHO.[2] Globally in 2015, 13% of under-five deaths were caused by pneumonia, which would mean nearly 0.76 million deaths.[1] There occur nearly 120 million episodes of pneumonia per year in children of which 12% or nearly 14 million episodes are severe pneumonia.[3] As per State of World's Children 2015 report, parents of 65% of children with signs of pneumonia seek health care and only 35% are prescribed antimicrobials world over.[4] Pneumococcal diseases are a major cause of childhood morbidity and mortality, especially severe pneumonia as is discussed by various authors in this special issue of pneumococcal disease. Pneumococcus contributes to nearly 50% of severe cases of pneumonia and pneumonia deaths.[2] Three pronged strategy to prevent pneumonia burden is adopted by WHO that is (a) Protect by breast-feeding, proper complimentary feeding, zinc, vitamin A supplements, prevention of indoor and outdoor pollution, avoidance of overcrowding and hand hygiene; (b) Prevent by using vaccines such as PCV, hib, pertussis and measles; and (c) Treat with antibiotics, oxygen, oral zinc and community based treatment of pneumonia.[5] Use of PCV stands out as a single most effective strategy to reduce pneumonia morbidity and mortality that can piggy back on the success of childhood vaccination program and show rapid results. If developing countries like India have to introduce PCV in the national program it will be not for its impact on invasive pneumococcal disease (IPD) alone but mainly for its role in prevention of hospitalization or deaths due to community acquired pneumonia (CAP) which are almost 100 times more common than IPD. In this paper we will discuss further the impact of PCV on pneumonia.

We have three commercial PCVs launched so far, PCV7 (Prevenar7) from Wyeth (now Pfizer), PCV10 (Synflorix) from GSK and PCV13 (Prevenar13) from Wyeth-Pfizer. PCV7 was introduced in the NIP in US in 2000 after a highly successful pivotal RCT in children below 2 years in NCKP, USA; and subsequently licensed and used in NIP in several other countries.[6] There was a need to include some more serotypes which were important cause of pneumococcal diseases in countries other than US, especially developing countries, to make it a global vaccine. Besides serotype 19A was not cross protected by PCV7 and the incidence of 19A IPD increased in all age groups in US and other

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countries after using PCV7 in NIP.[7] Accordingly six additional serotypes (serotypes 1, 3, 5, 6A, 7F and 19A) were including in PCV7 to make it PCV13, which has virtually replaced PCV7 world over. Both PCV7 and PCV13 have CRM as the carrier protein. GSK first invented PCV11 which had 4 additional serotypes other than in PCV7 namely serotypes 1, 3, 5 and 7F with protein D as the carrier protein for all 11 serotypes which underwent a RCT against acute otitis media (the POET trial) in Check republic.[8] As serotype type 3 was found to be non-boostable and as incidence of type 3 AOM did not decrease (and in fact it increased) in vaccinees as compared to placebo, type 3 was dropped subsequently, and GSK made PCV10 as the commercial vaccine. However, PCV10 has 3 different carrier proteins i.e. protein D, tetanus toxoid, and diphtheria toxoid. PCV13 has replaced PCV7 in most countries, and hence for all practical purpose we now have two PCVs i.e. PCV13 and PCV10 that protect against pneumococcal diseases. Besides the difference in the carrier protein, there are three additional serotypes (serotype 3, 6A, 19A) in PCV13, which are important causes of pneumococcal diseases world over. These vaccines have a major role to play in reducing child morbidity and mortality, especially that caused by pneumonia. PCV7 had undergone field efficacy trials, whereas both PCV10 and PCV13 did not undergo any field efficacy RCT and were licensed based on non-inferiority to PCV7 in separate pivotal immunogenicity trials. Hence it was mandatory for both PCV10 and PCV13 to show effectiveness post their use in NIP in various countries.

2. Impact of PCV7 on community acquired pneumonia (CAP) (mainly consolidated CAP as proven on X ray chest using WHO definition)

PCV7 and PCV9 with addition of serotypes 1 and 5 (an experimental vaccine) had shown moderate efficacy against all cause CAP hospitalization in children below 2 years of age in three double blind randomized controlled trials (RCT). In a RCT done in US the hospitalization for X-ray proven all cause CAP decreased by 30% (95% CI 11–46) with PCV7 used in 2-4-6-15 month schedule in children <2 years of age.[9] In another RCT done in South Africa PCV9, an experimental vaccine, used in EPI schedule of 6-10-14 weeks without any booster, reduced the X-ray proven all cause CAP hospitalization by 25% (95% CI 4–41) in HIV non-infected children <2 years of age in per protocol analysis.[10] PCV9 was also tried in the Gambia in EPI schedule without booster and it decreased X-ray proven all cause CAP hospitalization in <2 years old children by 37% (95% CI 23–46) and all cause infant mortality fell by 16% (95% CI 3–28) prompting WHO to recommend PCV vaccines in all developing countries with significant pneumonia and child death burden.[11] PCV7 was then introduced in the National Immunization Program (NIP) in several countries and many researchers have looked at effectiveness of PCV7 post NIP against all cause CAP hospitalization. In US looking at impact of PCV7 on health care utilization for pneumonia in children <2 years of age the effectiveness was found to be 52.4% against all cause CAP hospitalization and 41.1% against ambulatory visit for all cause CAP in 2004 as compared to pre-PCV7 baseline (1997–1999) and sustained decline of 43.2% (95% CI 34.9–51.6) in all cause CAP hospitalization in children <2 years of age over 7–9 years since the introduction of PCV7 in NIP.[12,13] Similar data are available from several other countries using PCV7 in the NIP.

3. Impact of PCV13 or PCV7/PCV13 on community acquired pneumonia (CAP) (mainly consolidated CAP as proven on X ray chest using WHO definition)

Since its use in the National Immunization Programs (NIP) in various countries we now have significant effectiveness data with PCV13 against all cause CAP.

A study in Tennessee, USA looked at impact of PCV7/PCV13 on hospitalization for all cause CAP in children below the age of 2 years after their sequential introduction in NIP with PCV7 introduced in 2000 followed by transition to PCV13 in 2010.[14] They compared the trends of such hospitalization in pre-PCV period (1990–1999) with trends post PCV7/PCV13 period (2001–2012). There was a massive 72% reduction in all cause CAP hospitalization as a combined effect of PCV7 and PCV13 and 27% reduction post PCV13 as compared to PCV7 era.

A similar study was done in France to look at the impact of PCV13 on emergency department visit and or hospitalization for all cause CAP for <2 years old children.[15] The Pediatric Infectious Diseases Group of the French Pediatric Society has established an active surveillance network of CAP in pediatric emergency departments (PEDs) of 8 hospitals across France representing 10% of all pediatric emergency cases seen in France since 2009. The data were compiled for children 1 month to 15 years old on X-ray confirmed pneumonia for pre-PCV13 year (2009–2010 when PCV7 was in use) and post-PCV13 year (2011–2012). The results showed that PCV13 led to 31.8% reduction in CAP cases in <2 years old, 42.2% reduction in those with CAP and CRP >120 mg/dL, 52.7% reduction if they had associated pleural effusion, 62.5% reduction in pneumococcal CAP and 75% reduction in CAP caused by 6 additional serotypes that are there in PCV13 but not in PCV7. All these reductions were statistically significant.

Israel introduced PCV in NIP in July 2009 and transitioned to PCV13 in November 2010. There is an ongoing prospective population based study in Southern Israel looking at utilization of hospitals either emergency care or hospitalization for X ray proven CAP (Alveolar CAP, A-CAP) in children <5 years of age. Analysis of data from 2002 to 2013 was done to look at effectiveness of PCV7 and subsequently PCV13 by comparing monthly A-CAP hospitalization rates per 1000 children for three time periods; pre-PCV years (2002–2008), post-PCV7 (2010–2011) and post-PCV13 years (2012–2013).[16] Results showed that vaccine effectiveness in <5 years old children overall was 13% (95% CI 5–21) with PCV7 compared to pre-PCV years, 47% (95% CI 41–52) with PCV13 compared to pre-PCV years and 38% (95% CI 32–44) with PCV13 when compared to PCV7 years. For all the vaccine periods the reductions were more for emergency visits than hospitalizations for A-CAP.

Argentina is a high income country from Latin America and uses PCV13 in 2 + 1 schedule since January 2012 with 2 dose catch of 12–24 months old. Prospective surveillance was undertaken to see impact of PCV13 on CAP burden in the Pilar region of Argentina, where coverage of the vaccine was high at 87.6% for 1st dose and 61.3% for 3rd dose. Post PCV13 (2012–2013) data on X-ray confirmed consolidated CAP incidence (based on cases reported from 3 major hospitals in Pilar region) was compared to same during Pre-PCV years (2003–2005). The results showed that PCV13 led to 39.6% reduction in CAP incidence in <5 years old overall, 44.6% reduction in 1–12 months old and 57.9% reduction in 12–24 months old.[17]

Nicaragua in 2010 became the first developing country to introduce PCV13 in NIP using 3 + 0 EPI schedule at 6-10-14 weeks. Data on health care visits for CAP was collected from all 107 public health facilities in León, Nicaragua between 2008 and 2012.[18] Rates of hospitalization and ambulatory visits for CAP and infant mortality were compared during the pre-PCV years (2008–2010) and post-PCV13 years (2011–2012) for children up to 15 years of age of which only children <2 years of age were eligible to receive PCV13. Results showed that the PCV13 effectiveness against CAP hospitalization was 33% (95% CI 25–31) in <1 year old and 26% (95% CI 19–37) for 1–2 years old. The infant mortality fell by 33% (95% CI 20–43). The vaccine effectiveness in 2–4 years old was 27% (95% CI 19–34) and 5–15 years old was 19% (95% CI 10–28)