Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

# The scope for pneumococcal vaccines that do not prevent transmission

Stefan Flasche

*Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK*

ARTICLE INFO

*Article history:*
Received 31 August 2017
Accepted 23 September 2017
Available online xxxx

*Keywords:*
S. pneumoniae
Vaccine
Replacement
Herd protection

ABSTRACT

The pneumococcal vaccine pipeline holds candidates developed with the aim to prevent the majority if not all pneumococcal disease. Herd protection is a critical component of the overall impact of current pneumococcal conjugate vaccines (PCVs) and is a prerequisite for disease elimination through an infant vaccination programme. We assessed the scope of a hypothetical pneumococcal vaccine candidate (HPVC) with high clinical efficacy against all pneumococci but that fails to induce such indirect protection. We found that, despite a lack of impact on unvaccinated individuals, HPVC use in infancy may offer similar or superior impact among young children if compared to current PCVs. Hence, it could provide a more affordable alternative to PCVs in particular in settings where most pneumococcal disease is concentrated in children.



## 1. Introduction

Pneumococcal conjugate vaccines (PCVs) have now been included into most national childhood immunisation programmes worldwide [1], primarily to reduce morbidity and mortality during childhood [2]. A striking feature of national PCV infant immunisation programmes, however, has been the added benefit of herd protection [3,4] which has led to near elimination of vaccine serotype (VT) disease within a few years after PCV introduction [5]. This indirect benefit is particularly relevant in high income settings where a substantial proportion of vaccine preventable pneumococcal disease occurs among older individuals.

PCVs, however, only target a small subset of the more than 90 pneumococcal serotypes. Hence, PCV use created an ecological niche that was instantaneously filled by untargeted serotypes (serotype replacement) [6], and mitigated some of the their impact [5]. To circumvent the problem of replacement disease, several vaccine candidates are being developed. Some aim to expand the serotype coverage of current PCVs to serotypes that are the primary cause of replacement disease. Other approaches, including whole cell vaccines and common protein vaccines, aim at capsule-independent protection against all pneumococci [7], either to be used in combination with PCVs or as an alternative. A benefit of candidates without a PCV component is that those avoid the costly conjugation process. Hence, they can improve affordability of pneumococcal vaccines which is of much concern to many low and middle income countries in particular.

In a recent phase II trial the most advanced of those vaccine candidates, a PCV combined with pneumolysin toxoid and pneumococcal histidine triad protein D, failed to demonstrate any efficacy against carriage of serotypes not targeted by the PCV [8]. In particular for candidates in the pneumococcal vaccine pipeline that do not include a PCV component this raises a strategic question: "can a pneumococcal vaccine that only provides direct protection offset the lack of indirect protection with the benefit of additional direct protection against serotypes untargeted by current PCVs?"

In the following we assess the scope of pneumococcal vaccines that target the whole species and act to reduce disease risk but do not affect transmission.

## 2. Methods

### 2.1. Data

Currently two PCV formulations are available, a 13-valent PCV (PCV13) and a 10-valent PCV (PCV10) that targets a subset of PCV13's serotypes. We selected a convenience sample of four sites with robust surveillance for invasive pneumococcal disease (IPD) spanning at least 3 years before PCV introduction to at least 3 years after introduction. We selected Kilifi, Kenya [9] to represent a low-income PCV10 setting, the Gambia as a low income PCV13 setting [10], the Netherlands as a high income PCV10 setting [11] and England and Wales (E&W) as a high income PCV13 setting [12]. For each setting age-stratified incidence risk ratios ($IRR_{PCV}$) for all serotype IPD incidence during PCV10 or PCV13 use in comparison with pre PCV were extracted. In the Gambia, the Netherlands and

*E-mail address:* Stefan.Flasche@lshtm.ac.uk

https://doi.org/10.1016/j.vaccine.2017.09.073
0264-410X/

E&W the seven valent PCV (PCV7) had been in use before the current formulation. For both the Gambia and E&W the IRRs of PCV13 use in comparison with no vaccination were reported. For the Netherlands we multiplied reported IRRs to obtain the IRR of 3 years post PCV10 to early post PCV10 to pre PCV10 to pre PCV7. For Kilifi, Kenya we calculated the IRR based on reported 2008–2010 IPD incidence before PCVs and 2011–2015 incidence during PCV use.

### 2.2. Analyses

Clearly, a vaccine against all pneumococcal serotypes that does not limit transmission will need high clinical efficacy and a reasonable duration of vaccine protection to be competitive. We compared the impact of PCVs to the potential impact of a hypothetical pneumococcal vaccine candidate (HPVC) that acts to reduce the risk for IPD caused by any serotype by 90% for 5 years after vaccination and to lose its protective effect immediately thereafter. Based on typical DTP3 vaccine coverage in low and high income countries [13] we assumed that such vaccine can be administered to immunise 75% and 95% of young infants in low and high income settings respectively. The predicted impact of HPVC was calculated as $IRR_{HPVC} = 1 - (\text{vaccine efficacy} * \text{vaccine coverage})$ for all age bands including children up to 5 years old. The predicted impact of combined use of PCV and HPVC was calculated as $IRR_{PCVHPVC} = IRR_{PCV} * IRR_{HPVC}$.

## 3. Results

Low and high income countries differ substantially in which age groups contribute most to the overall burden of pneumococcal disease, in parts a result of differences in their demographic profile and life expectancy. Before the introduction of PCV in Kenya and the Gambia over 60% of IPD cases were reported among children younger than 5 years old. In contrast, IPD in children of that age in E&W and the Netherlands only accounted for less than 15% of all IPD (Fig. 1 and Table 1). Consequently, among all IPD cases averted through PCVs use less than 25% and more than 75% have been averted among <5 year old children from the two high and the two low income countries respectively.

We estimate that in Kenya and the Gambia the HPVC could prevent 44% and 47% of all IPD while in E&W and the Netherlands it could only prevent 10% and 6%. In comparison, PCV was reported to prevent only slightly more IPD cases than that in the two low income settings, however, substantially more in the two high income settings (Fig. 1). If assessed against the impact of routine PCV use against all IPD we find that use of a combined PCV and HPVC vaccine would add little impact in the two high income settings while it may offer substantial additional protection in the two low income countries.

When focussing on the impact in young children HPVC compares more favourably. In all four settings we predict that HPVC would be superior, if compared to the observed impact of PCV on IPD in young children (Fig. 2). We predict that HPVC could prevent 67.5% and 85.5% of childhood IPD in the low and high-income

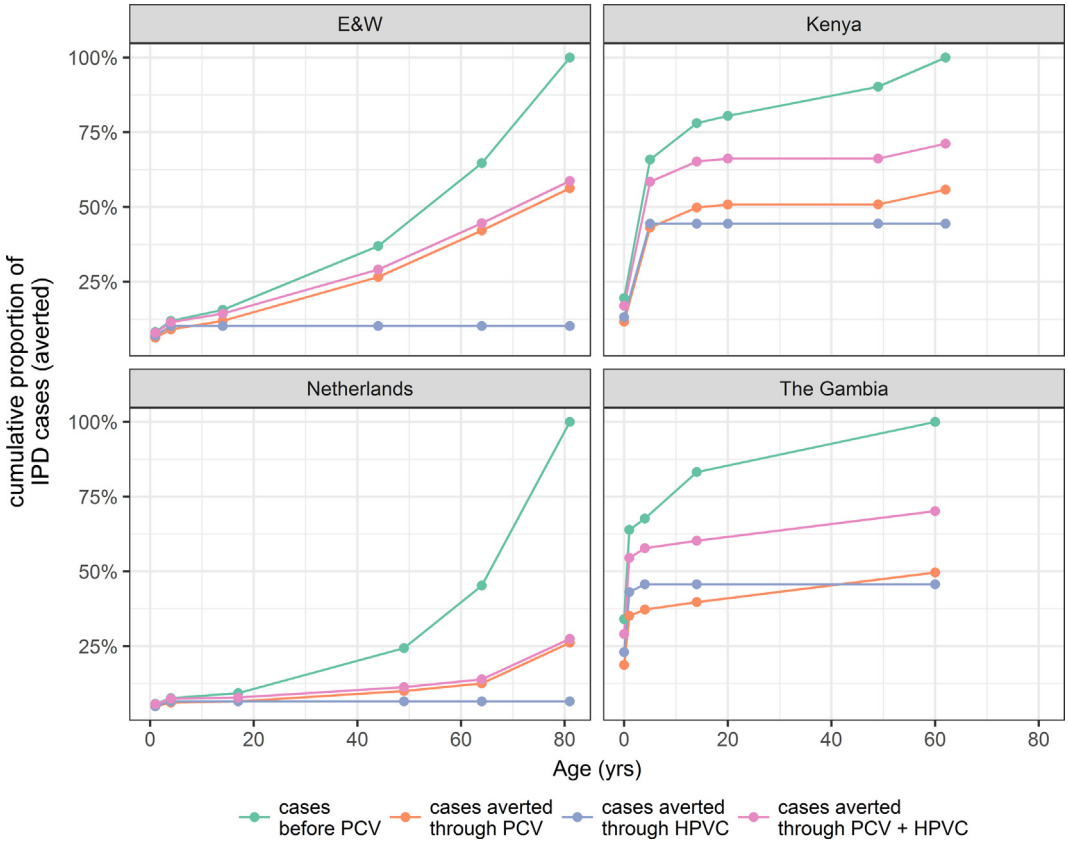


**Fig. 1.** Cumulative age distribution of the proportion of IPD cases and IPD cases averted by either PCV, a hypothetical vaccine (HPVC) or their combined use. The impact of PCVs refers to the observed impact of PCV 13, 10, 10 and 13 in Gambia, Kenya, Netherlands and the UK in comparison to no vaccination. The hypothetical vaccine is assumed to be delivered to 75% of young infants and offer no indirect protection but 90% protection against all IPD for 5 years.

Please cite this article in press as: Flasche S. The scope for pneumococcal vaccines that do not prevent transmission. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.09.073