Background

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.

Methods

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&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.

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 $IRR_{PCVHPVC} = IRR_{PCV} * IRR_{HPVC}$.

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 (Figure 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 (Figure 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 (Figure 2). We predict that HPVC could prevent 67.5% and 85.5% of childhood IPD in the low and high-income settings respectively. If given in combination with PCV, this impact could be increased to about 85% and 95% in the low and high-income settings respectively.

Discussion

National PCV infancy programmes have substantially reduced the pneumococcal disease burden. In particular in high income settings, much of that reduction can be attributed to indirect protection by limiting VT transmission. While vaccine candidates that do not prevent pneumococcal carriage will not induce such indirect protection, they may protect against disease from all pneumococci and will not cause serotype replacement. We show here that such candidate vaccine, if found highly protective against disease and given early in infancy can have similar or even superior impact among young children compared with PCVs. However, in high income settings the majority of the population impact of PCVs stems from the prevention of adult and elderly disease. Hence, HPVC use in such settings is likely to only achieve a small fraction of PCV's population impact.

Vaccines that target all pneumococci at once are designed with the ultimate goal to prevent the majority if not all pneumococcal disease. Pneumococcal vaccines that do not limit transmission will not achieve such goal. In fact, we show that even at high coverage and at high clinical efficacy they are likely to offer comparable population impact only in those settings where much of the pneumococcal disease burden is concentrated in young children. However, these settings are typically low income settings which also would benefit most from a major advantage of HPVC: they may be manufactured at a fraction of the costs of PCVs. In the near future many low income countries will need to take over the full costs of their pneumococcal vaccine programmes which are currently mainly paid for by Gavi, the Vaccine Alliance [14]. To continue PCV use some would need to more than double their current vaccine budget. An option to reduce pneumococcal vaccine costs

while sustaining similar impact could be the decisive factor for programme sustainability in these settings [15].

Unless supplemented by additional vaccination programmes, settings with a high disease burden in older individuals, like most high income countries, likely favour the indirect effects of the infant PCV programme over the added protection of HPVC in young children. In those settings a combined PCV and HPVC approach may offer an alternative use for HPVC. HPVCs can further reduce the residual childhood burden of pneumococcal disease and hence counter-act serotype replacement following PCV use. However, we estimate that combined PCV and HPVC use in the two high income settings may only prevent an additional 1-3% of all pneumococcal IPD and as a result would only achieve a similar cost-effectiveness profile to PCVs if HPVC can be used to immunise children at less than 5% of PCV costs.

Conducting a phase III trial with targeted clinical efficacy of about 90% for a vaccine that was found not to protect against pneumococcal carriage may need a leap of faith. In consolation though, aiming to detect only high efficacy comes with the advantage that it reduces the required sample size and, if successful, may offer a key tool for prevention of pneumococcal disease in low income settings. A further caveat is that the vaccine candidate will need to demonstrate that it protects not only against the most severe disease but also against non-bacteraemic pneumonia and otits media which substantially contribute to the pneumococcal disease burden.

In conclusion, the success of PCVs has set a high benchmark for future pneumococcal vaccines. However, a vaccine against all pneumococci with high clinical efficacy and a moderate duration of protection given to young infants could help sustain or even further reduce the pneumococcal childhood disease burden in low income countries and at more sustainable costs, even if it fails to induce indirect protection.

Declaration of interest

Dr. Flasche has nothing to disclose.

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Figure 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.

Figure 2: The proportion of IPD cases averted in children by either PCV a hypothetical vaccine (HPVC) or their combined use.

Table 1: Overview of observed PCV impact across age groups in two low and two high income countries with good IPD surveillance (sites). The incidence rate ratios (RR) in all instances refer to ecological analyses of the population impact of the current PCV infant immunisation programme in comparison to no vaccination.

Setting	Product in use	Age group	Cases before PCV	PCV RR	reference
Gambia	PCV13	2-11m	81	0.45	[10]
		12-23m	71	0.45	
		2-4y	9	0.44	
		5-14y	37	0.84	
		15+y	40	0.41	
Kenya	PCV10	<1y	27	0.40	[9]
		1-5y	61	0.32	
		6-14y	17	0.45	
		15-20y	1	0.60	
		21-49y	11	0.99	
		50y+	11	0.49	
Netherlands	PCV10	<2y	75	0.15	[11]
		2-4y	25	0.35	
		5-17y	22	0.74	
		18-49y	197	0.77	
		50-64y	273	0.88	
		65y+	717	0.75	
E&W	PCV13	<2y	710	0.23	[12]
		2-4y	319	0.26	
		5-14y	319	0.23	
		15-44y	1839	0.31	
		45-64y	2390	0.44	
		65y+	3045	0.6	