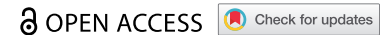



REVIEW



Vaccine strategies to reduce the burden of pneumococcal disease in HIV-infected adults in Africa.

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ABSTRACT

Introduction: *Streptococcus pneumoniae* is the leading cause of invasive bacterial disease, globally. Despite antiretroviral therapy, adults infected with human immunodeficiency virus (HIV) are also at high risk of pneumococcal carriage and disease. Pneumococcal conjugate vaccines (PCVs) provide effective protection against vaccine serotype (VT) carriage and disease in children, and have been introduced worldwide, including most HIV-affected low- and middle-income countries. Unlike high-income countries, the circulation of VT persists in the PCV era in some low-income countries and results in a continued high burden of pneumococcal disease in HIV-infected adults. Moreover, no routine vaccination that directly protects HIV-infected adults in such settings has been implemented.

Areas covered: Nonsystematic review on the pneumococcal burden in HIV-infected adults and vaccine strategies to reduce this burden.

Expert opinion: We propose and discuss the relative merit of changing the infant PCV program to use (1a) a two prime plus booster dose schedule, (1b) a two prime plus booster dose schedule with an additional booster dose at school entry, to directly vaccinate (2a) HIV-infected adults or vaccinating (2b) HIV-infected pregnant women for direct protection, with added indirect protection to the high-risk neonates. We identify key knowledge gaps for such an evaluation and propose strategies to overcome them.

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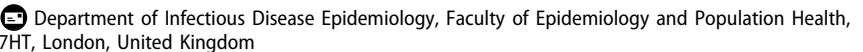
Pneumococcus; hiv; pcv; vaccination strategy

1. Introduction

Streptococcus pneumoniae is a major cause of global childhood mortality [1,2], particularly in <5 year-olds, and also causes a high burden of disease among the elderly and human immunodeficiency virus (HIV) infected adults [3–5]. In the last two decades, infant pneumococcal conjugate vaccine (PCV) programs have substantially reduced the burden of invasive pneumococcal disease (IPD) and mortality in vaccinees [2,6–13]. In contrast to high-income countries though [14,15], routine infant PCV programs in the most low-income sub-Saharan African (sSA) countries have led to a less pronounced herd effect with a continued circulation of vaccine serotypes (VT), especially in the unvaccinated adult population [12,16–20] including those with HIV infection and thus those at high risk for pneumococcal disease [21]. For instance, an over a 3.5-year study in Malawi, post-PCV VT carriage in HIV-infected adults only declined from 15.2%, 95%CI, 10.8–20.9 in survey 1 to 8.9% 95%CI 5.7–13.7 in survey 7 [20]. While the underlying reasons have not been fully established they may include a higher infection pressure as a result of more frequent human contacts and lower vaccine uptake [18].

HIV infection can substantially increase the risk of IPD among otherwise healthy older children or adults on antiretroviral therapy (ART) [5,22–24]. This is in part related to the impairment of both the cell-mediated and humoral arms of the immune system [25,26]. Capsule-specific immunoglobulin G (IgG) antibodies as well as T and B cell-mediated protein-specific responses play a central role in the control of pneumococcal colonization and infection [27–29]. However, HIV affects both T and B cell functions, resulting in the impairment of humoral responses to extracellular pathogens such as pneumococci [30–32] and control of pneumococcus at the mucosal level. ART only partially reconstitutes the immune system of HIV-infected individuals by increasing B and T-lymphocyte numbers and functionality [25,27]. Deficiencies in humoral response due to depleted or persistent defects in memory cell function persist after ART initiation and disproportionately so at the mucosal level [33,34]. Thus, HIV-infected individuals on ART remain with impaired antibody responses to natural pneumococcal infections and vaccination [35,36].

In this article, we present a review of the pneumococcal burden in HIV-infected adults in the presence of mature PCV infant programs, particularly in sub-Saharan Africa (sSA). We

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Article highlights

- Circulation of VTs persists in the PCV era in some low-income countries and results in a continued high and potentially vaccine-preventable burden of pneumococcal disease in HIV-infected adults.
- Routine pneumococcal vaccination programs for HIV-infected adults are not implemented in low-income countries.
- Mitigation of the VT-disease burden in HIV-infected adults in low-income countries may be achieved either by added direct protection or increased indirect protection from the infant program (via increased coverage or a change in vaccine schedule).
- For added direct protection both PCV and PPV are licensed and used in high-income countries. PCV is more immunogenic but also substantially more expensive and has inferior serotype coverage.
- For added indirect protection a change in infant immunization schedule to stipulate longer-lasting protection may largely mitigate the risk for vaccine-preventable pneumococcal disease in the HIV-infected.
- Both strategies will need a formal evaluation of their likely effectiveness and cost-effectiveness.

highlight four options for vaccine strategies that could be implemented to address this disease burden and discuss the key evidence gaps to enable a solution to be identified.

2. Pneumococcal burden in African HIV-infected adults

Without ART, the risk of IPD in HIV-infected adults is reported to be 30–300 times higher than in HIV-uninfected individuals, and with an about sixfold higher risk of recurrence [25,37–39]. Although ART has reduced the risk of IPD and subsequent mortality [3,40], the risk remains more than 30-fold higher than in HIV-uninfected adults [41] with an incidence of >50 cases per 100,000 person years [3,5,42]. The introduction of infant PCV programs in South Africa and Kenya has led to a further reduction in VT-IPD and pneumococcal pneumonia incidence in HIV-infected adults [9,43,44].

HIV prevalence in African adults varies widely, with Swaziland reporting the highest at 27.2% [45]. In 2017, all sSA countries reported >10% national or subnational adult HIV prevalence [45]. It has been observed that countries with suboptimal PCV herd protection and substantial residual vaccine-serotype circulation, like Malawi and Mozambique, also report a high prevalence of HIV [46]. HIV prevalence amongst children has fallen as a consequence of the effective prevention of vertical transmission of HIV and ART use [47–50]. Only a small proportion of infants are infected with HIV and are already included in the PCV infant programs. HIV prevalence remains high as a consequence of improved survival with ART in adults. Thus, a large proportion of adults at high risk of pneumococcal disease attributable to HIV infection will remain a concern in the years to come in sSA.

3. Pneumococcal vaccines in HIV-infected adults

Since the 1980s, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been approved for use in HIV-infected adults for direct protection against a wide range of serotypes, in most high-

income countries where it is reported to be safe, including in HIV-infected but otherwise healthy adults [51–54]. However, evidence of PPV23's efficacy in HIV-infected adults is somewhat controversial [53,55–60], with the suggestion of potential hyporesponsiveness in individuals with advanced immunosuppression, and a reported increase, albeit not statistically significant, in the incidence of all-cause pneumonia when given to HIV-infected Ugandan adults, not on ART [61]. Estimates of PPV23 efficacy in HIV-infected adults are highly heterogeneous which may be linked to differences in HIV viral load and ART status at the time of vaccination [25,61–64].

PCVs are more immunogenic than PPV23 in HIV-infected adults [23,65] and are highly efficacious in preventing VT-disease in HIV-uninfected children and adults [6,66]. Two formulations, a 10- and a 13-valent product, are currently in use worldwide. They have comparable effectiveness and have been licensed based on their noninferiority to a previous 7-valent formulation (PCV7) [67]. While the efficacy of PCVs against VT-disease in HIV-infected children is somewhat inferior to that of HIV-uninfected children (51% vs 77%) [6], the efficacy against carriage is similar irrespective of HIV status [68]. PCV7 has been shown to be immunogenic [69] and 74% efficacious against VT-IPD in HIV-infected adults, with the highest efficacy within the first 12 months of vaccination even in those with CD4+ count <200 cells/mm³ and with unsuppressed HIV viral load at vaccination [65,70]. Further evidence on PCV13 efficacy of 75% against VT-IPD and 72.8% against VT community-acquired pneumonia in older adults (aged ≥65 years) have been reported in the Netherlands and the United States, respectively [66,71,72].

In many high-income countries PCV is recommended for use as priming of HIV-infected adults followed by a PPV23 booster [52,73,74], which acts only against IPD. This is despite the limited PCV serotype disease incidence in these settings as a result of effective herd effects from infant PCV programs [75]. However, no such pneumococcal immunization program for HIV-infected adults exists in low-income African countries [76], where the highest disease burden exists [2]. Implementation barriers include the high costs of PCV [77] and a limited amount of evidence on effective and cost-effective vaccine strategies to address the high pneumococcal disease burden among HIV-infected adults in Africa.

4. Optimal vaccination strategies

We propose two potential approaches for reducing the disproportionate burden of pneumococcal disease in HIV-infected African adults: through (1) expanded indirect protection or (2) introduction of direct protection. For expanded protection, options include either (1a) changing the three-doses infant PCV schedule to a two prime plus boost schedule with potentially longer-lasting protection and greater herd protection against IPD in HIV-infected adults or (1b) using a three dose prime-boost strategy but with a fourth dose given as an additional booster at school entry to further enhance the duration of protection and thereby limit onward transmission. Direct protection could be achieved by (2a) vaccinating all HIV-infected adults to confer direct protection, or (2b)

vaccinating HIV-infected pregnant women which has the additional benefit of protecting the young infant via the transplacental transfer of antibody and reduced maternal exposure [Figure 1](#).

4.1. (1a) Switch from 3p+0 to 2p+1 PCV schedule to potentially increase herd protection

The World Health Organization currently recommends a three dose schedule administered either as three doses in early infancy (3p+0) or as two infant priming doses followed by a booster typically at 9–12 months (2p+1) [67]. In contrast to high-income countries, the vast majority of Africa opted for a 3p+0 schedule based on prioritization of direct protection against the high disease burden in early childhood, alignment with other routine immunizations, and concerns about potentially low booster dose coverage in a 2p+1 schedule. A notable exception is South Africa where the 2p+1 PCV schedule was introduced in 2009 with a booster dose at 9 months to align with measles vaccine dose 1 [8,9,78].

In theory, a third dose given as a booster to 9–12 month olds elicits high levels of an antibody that extend protection against VT-carriage acquisition into early or preschool age and hence further interrupt transmission in one of the key age groups for pneumococcal spread [79,80]. While trials to test this hypothesis is ongoing [81,82], there is currently no clear evidence to confirm that a 2p+1 schedule would induce superior herd protection in those African countries that have been using a 3p+0 with unsatisfactory indirect effects [67].

For now, a conclusive comparison of the differential impact of the two vaccine schedules across countries is hindered by the strong correlation between vaccine schedule and pneumococcal transmission intensity. Most high-income countries have been using 2p+1, and most African countries, typically with higher overall carriage prevalence, have been using 3p+0. Exceptions to this include South Africa introducing PCV in a 2p+1 schedule and Australia using a 3p+0 (but switching to a 2p+1 as a result of breakthrough disease in the PCV13 era) [83,84]. South Africa has experienced substantial reductions in VT-carriage and IPD in unvaccinated populations including HIV-infected adults [44]. Other low-income African countries like Malawi [16,20], Mozambique [19], and the Gambia [85] have substantially less evidence of herd immunity from their mature PCV infant programs with overall residual VT-carriage prevalence of 13.9%, 19.7%, and 11.4%, respectively [46], at a minimum third dose vaccine coverage rate of $\geq 81\%$ [20,86,87].

4.2. (1b) Switch from 3p+0 to 2p+1(+1) PCV schedule to increase herd protection

A switch from 3p+0 to a 2p+1 schedule would not have major cost implications. Also, if indeed with the addition of a booster dose herd effect can be enhanced, the impact of such schedule change extends beyond just HIV-infected adults and will benefit other unvaccinated individuals as well. However, herd immunity is the result of a complex interplay of factors including bacterial physiology, booster dose coverage, the average age of pneumococcal carriage, duration of vaccine protection








Option	Approach	New vaccine doses needed	Potential impact	Certainty of impact
1a	PCV switch from 3p+0 to 2p+1			???
1b	PCV switch from 3p+0 to 2p+1(+1)			??
2a	1 dose PCV (+ 1 PPV boost) to all HIV-infected adults			?
2b	1 dose PCV (+ 1 PPV boost) to all HIV-infected pregnant women			?

Figure 1. Schematic of potential pneumococcal vaccine strategies against invasive pneumococcal disease (IPD) in HIV-infected adults through indirect (1) and direct (2) approaches. Change the infant PCV schedule from 3p+0 to 2p+1 to enhance herd immunity against IPD in HIV-infected adults through a single booster dose (1a), change the infant PCV schedule from 3p+0 to 2p+1(+1) to enhance herd immunity against IPD in HIV-infected adults through double booster doses (1b), vaccinate HIV-infected adults for direct protection (2a), vaccinate HIV-infected pregnant women for direct protection, with some indirect protection for their neonates (2b). Option 1a will not require any additional vaccine doses as it simply rearranges the timing of the three-dose schedule. Option 1b will need additional vaccine doses equivalent to the number of 5-year-old children in a country per year (e.g. about 300,000 doses per annum for Malawi). Option 2a will need one additional dose of PCV and one of PPV for each HIV-infected adult (e.g. assuming revaccination of the 970,000 HIV-infected adults in Malawi (<http://aidsinfo.unaids.org/>) every 10 years would use about 200,000 doses per annum, although the rate of new HIV infections is lower than that). The last option 2b will need one additional dose of PCV and one of PPV for each HIV-infected pregnant women (e.g. 90,000 doses per annum for the about 45,000 HIV-infected pregnant women in Malawi each year). Options 1a and 1b are likely to have large impact because of their potential to elicit herd immunity, however, to date it is not well established that herd immunity would indeed be enhanced through a booster dose schedule (several trials are under way to assert this). Option 1b offers less uncertainty due to extra dose included. Option 2a only provides direct protection against vaccine serotypes to HIV-infected adults while 2b will see only a small subset of that vaccinated. There is limited uncertainty for the impact of the latter two strategies as PCV's efficacy is relatively well established in the two groups.

against the carriage, and social mixing patterns [88–90]. Additionally, the high average age of carriage, intense social mixing, and the waning of PCV protection against carriage (estimated half-life is 4–6 years) may imply that, in some settings, older children are a key source of pneumococcal transmission and are not fully protected in a 2p+1 schedule [91,92]. A school entry PCV booster dose may be necessary to interrupt transmission and increase herd protection [91].

4.3. (2a) Vaccinating HIV-infected adults

PCV is more immunogenic than PPV23 [23,57,65,69] and efficacious in preventing recurrent episodes of VT-IPD in HIV-infected adults [65]. As per existing recommendations in many high-income countries [51,52], a single dose of PCV followed by a PPV23 booster for expanded serotype coverage could be given to HIV-infected adults in low-income countries to prevent VT-IPD [73,74]. As PCV is efficacious in vaccinees with low CD4+ cell count [65], it could be given immediately at HIV diagnosis to increase PCV coverage [93]. Since most sSA countries have considerably high ART coverage between 65% and 85% [94], adoption of this strategy will require a carefully considered integration of the proposed HIV-infected adult pneumococcal vaccine program into the mature ART programs to achieve a similar high coverage in the midst of competing health priorities [49,50,95,96]. In order to optimize local resources, PCV/PPV23 could concurrently be given with ART to HIV-infected adults [97].

PCV-mediated protection against IPD in HIV-infected adults has been reported to wane rapidly beyond 12 months, especially in those with low CD4+ cell count [65]. Revaccination with PCV or PPV is feasible [98], but of unproven clinical value. Choosing a PPV booster repeated may seem more rational as it is a cheaper vaccine and has higher serotype coverage, but also carries theoretical risks of generating hyporesponsiveness. This approach may also have additional indirect effect benefits if a PCV + PPV strategy could be shown to reduce carriage in this population. HIV-infected adults typically have higher pneumococcal carriage prevalence than HIV-uninfected adults [99,100], and may be part of a reservoir for residual VT circulation in high HIV prevalence sSA settings. Whilst there is no substantial evidence to suggest they sustain transmission, they consequently represent a disproportionate health burden [101–103].

4.4. (2b) Vaccinating HIV-infected pregnant women

Where there are insufficient resources for targeting all HIV-infected adults, HIV-infected pregnant women could be prioritized for PCV protection. Their vaccination would come with the added benefit of indirect protection of their infant and hence would be particularly relevant in settings where the benefits of herd immunity from PCV pediatric programs are limited or neonatal acquisition of VT pneumococcal carriage commonly occurs before the infant can be directly protected by vaccination [46]. Transmission of pneumococci from HIV-infected mothers to their children has been reported [101,102], and this is also likely to be seen in infants not yet eligible for PCV vaccination; e.g. >40% of the infants in the

Gambia [104,105], and Kenya [106,107] were reported to acquire pneumococci by the age of 4 weeks. Although HIV infection is reported to reduce the efficiency of maternal antibody transfer to the infant [108], maternal vaccination may still be useful since the (reduced) transfer ratio is applied to a higher vaccine-induced anti-pneumococcal capsular IgG in pregnancy. Thus, vaccination may directly protect the mother and fetus against pneumococcal carriage and disease [105,107,109], and interrupt VT transmission between mother and neonate, thereby providing cocooning immunity during neonatal life.

Maternal PCV vaccination has been shown to be safe. No serious adverse pregnancy-associated outcomes has been reported from clinical trials where the average gestation at vaccination was between 27 and 38 weeks [110]. However, data on the IPD burden in neonates and mothers, as well as the benefits of maternal immunization from low-income countries are limited. A Cochrane systematic review highlighted that there is insufficient evidence to assess whether pneumococcal vaccination during pregnancy could reduce infant infections [110].

National antenatal programs in most low-income countries are well established, with substantial service coverage [48]. Vaccine doses along with other services could be given to HIV-infected pregnant women who attend the antenatal clinics or otherwise ART clinics.

5. Expert opinion

PCV is widely used in global infant immunization programs and has been recommended for use in HIV-infected adults in high-income countries along with a PPV23 booster dose. In parts of Africa, there is a combination of substantial residual VT circulation among adults despite mature infant PCV programs, still relatively high adult HIV prevalence, and persistent high risk of IPD in HIV-infected adults. An adapted vaccination strategy could reduce the risk of IPD in HIV-infected adults. Here, we have presented a number of options through direct and indirect vaccine protection to enable the identification of an effective way forward.

We define the optimal vaccination strategy as one that maximizes the reduction in pneumococcal disease burden in HIV-infected adults in Africa. There are of course other factors as well that may determine whether a theoretically optimal strategy is indeed programmatically feasible. Important evidence gaps exist to enable evaluation of the optimal pneumococcal vaccine strategy. It is uncertain if a 2p+1 dosing schedule will work to achieve better herd protection than a 3p+0 in settings where it has not yet been implemented, or whether an additional booster at school entry 2p+1 (+1) may be needed if protection against carriage wanes considerably in early childhood. Two cluster randomized trials in Malawi and Vietnam, in which 3p+0 and 2p+1 schedules are being compared head to head in each trial, can be used to evaluate their impact on pneumococcal carriage [81,82], and could provide crucial information on their relative merits for providing herd protection.

While PCV7 vaccine efficacy against IPD in HIV-infected adults has been previously estimated at 74% [65], efficacy

against VT-carriage is unknown. Moreover, the duration of protection against both carriage and disease in HIV-infected adults is unknown, with some evidence for the latter pointing to a rapid decline after 12 months of vaccination [65]. Data on the interaction between ART (which may improve efficacy) and PCV shows no major impact of ART [25], but since PPV23 effectiveness/efficacy against IPD is contentious [60], dosing intervals to optimize efficacy and protection remains uncertain. More importantly, it is uncertain whether, in the era of routine PCV use in infants, HIV-infected adults substantially contribute to the residual VT transmission because of their elevated rates of carriage. Despite the importance of social interactions for pneumococcal transmission [111,112], only a few social mixing pattern studies have been conducted in low-income countries [112–116]. Moreover, data on whether HIV-infected adults have differential social mixing behavior compared to HIV-uninfected adults are not available. Thus, limiting our ability to precisely quantify transmission dynamics in HIV-infected adults.

Uncertainties around the benefits of maternal immunization with PCV also need to be addressed. The efficacy of maternal vaccination in protecting the neonate from carriage acquisition and the duration of vaccine-induced protection in the newborn need to be established [105,110]. Also, there are concerns that maternal vaccination could interfere with the benefits of infant priming doses by inhibiting the antibody responses particularly when high residual concentration of maternal placentally transferred antigen-specific antibodies are present at the time of infant immunization [117,118].

Author Contributions

DT, NF, and SF conceived the idea for the manuscript. DT wrote the first manuscript draft with support from AP, OJ, KEG, NF, and SF. All authors contributed to, and approved the final draft. All authors declare that they meet the ICMJE criteria for authorship.

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