The evidence for using conjugate vaccines to protect HIV-infected children against pneumococcal disease

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Pneumococcal conjugate vaccines (PCVs) are a potentially useful complement to existing treatment strategies in HIV-infected children, for whom pneumococcal infections are common and serious. This Review summarises available data on the burden of pneumococcal disease and the safety and efficacy of PCVs in HIV-infected children. The data demonstrate that children with HIV have significantly increased risk of pneumococcal disease compared with uninfected children; the serotypes included in currently licensed or near-licensure conjugate vaccines include most serotypes that cause invasive pneumococcal disease (IPD) in HIV-infected children and adults; PCVs provide substantial protection against IPD and clinical pneumonia when given to HIV-infected infants; and HIV-infected adults gain an indirect benefit when children in the community are vaccinated. PCV should be considered as an important intervention for improving the lives of HIV-infected children.

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Introduction

As a result of humoral immune dysfunction, children with HIV are at high risk of bacterial infections compared with uninfected children.[1–3] In the USA, among HIV-infected children, serious bacterial infections occur five times more frequently than other opportunistic infections, such as herpes zoster, disseminated mycobacterial infections, *Pneumocystis jirovecii* pneumonia, and oesophageal candidiasis.[4–6] Moreover, serious bacterial infections occur throughout all stages of HIV disease.[7] In particular, individuals with HIV have a risk of bacterial pneumonia up to 25-fold higher than HIV-uninfected people;[8] *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia and is prominent among all serious bacterial infections in this population.[4–6,8–27]

WHO estimates that between 700 000 and 1 million children die of pneumococcal disease every year, most in the developing world.[28] In countries where pneumococcal conjugate vaccine (PCV) has been routinely used in infancy, rates of invasive pneumococcal disease (IPD) have reduced by up to 75% in children and up to 29% in adults.[29,30] However, in areas of the world with a substantial burden of HIV infection, the incidence of IPD may be increasing.[31,32] Therefore, strategies to reduce the burden of IPD in children and adults with HIV are clearly needed. We review the existing evidence on pneumococcal disease risk and the effects of pneumococcal conjugate vaccination in HIV-infected people to determine whether a policy for routine PCV use in areas with a substantial burden of HIV infection should be advised.

Burden of pneumococcal disease in HIV-infected people

Many parts of the world have surveillance systems for the identification of IPD, defined as isolation of *S pneumoniae* from a normally sterile site. However, in resource-poor countries, accurate information on the burden of serious pneumococcal infections is often unavailable. Children with invasive disease may not present to medical attention, clinical specimens for culture may not be collected, culture facilities may not be available, and culture yield may be limited by antibiotic pretreatment. Even where comprehensive surveillance systems are established, the true burden of pneumococcal disease is much greater than that estimated by invasive disease surveillance. Non-bacteraemic pneumococcal pneumonia is estimated to be at least ten-fold more common than IPD.[33–37] Therefore, surveillance IPD estimates, particularly in the developing world, will typically underestimate the true scope of severe pneumococcal infection. Bacteraemia may be more common in HIV-infected people with pneumococcal pneumonia than among HIV-uninfected people,[1,38] and studies that report on pneumococcal disease in patients with advanced HIV infection only might not accurately represent the burden of invasive disease in all patients with HIV infection.

In 16 studies from Africa and the USA, the incidence of IPD, pneumococcal bacteraemia, bacteraemic pneumococcal pneumonia, or meningitis in children infected with HIV ranged from 183 to 18 500 episodes of invasive disease per 100 000 child-years, a nine-fold to 43-fold increase in IPD compared with HIV-uninfected children (table 1).[4,6,14,17,18,20,23,39–47] Children with HIV infection are also up to eight times more likely to have multiple episodes of IPD than children without HIV infection.[48,49]

30 studies from Africa, Europe, Australia, Asia, and the USA reported incidence rates for HIV-infected adults with IPD, pneumococcal bacteraemia, pneumococcal meningitis, bacteraemic pneumococcal pneumonia, or pneumococcal pneumonia (table 2).[7,10,24,38,43,50–74] IPD incidence rates among HIV-infected adults also vary, with estimates ranging between 197 and 5700 per 100 000 person-years. Adults with HIV infection have IPD rates that are between six and 324 times higher than rates of their HIV-uninfected counterparts. Recurrent disease, most of which represents reinfection, is also five to nine times more common in adults with HIV infection than those without.[49,61,70,75–77]

	Study location	Years of surveillance	Age-group	Proportion on antiretroviral therapy	Outcome	Incidence rates (per 100 000 person-years)	Increase in risk of IPD in HIV-infected compared with HIV-uninfected individuals
The National Institute of Child Health and Human Development (1991)[20]	Multicentre, USA	..	0–12 years	39% initiated zidovudine after study entry	Pneumococcal bacteraemia or meningitis	4132	No HIV-negative comparison group
Andiman et al (1994)[4]	New Haven, USA	1985–91	0–6 years	..	IPD*	12 240	9·2-fold *vs* HIV-negative children born to HIV-positive mothers
Farley et al (1994)[39]	Baltimore, USA	1986–92	0–36 months	..	IPD*	11 300	12·6-fold *vs* HIV-negative children born to HIV-positive mothers and mothers at risk for HIV infection
Peters et al (1994)[40]	New York, USA	1981–91	0–10 years	84% on ART, none on HAART	Pneumococcal bacteraemia	11 429‡	No HIV-negative comparison group
Spector et al (1994)[23]	Multicentre, USA	1988–92	3 months to 12 years	100% on zidovudine	Serious pneumococcal infection†	3690	No HIV-negative comparison group
Andiman et al (1996)[41]	New Haven, USA	1994–95	0–8 months to 14 years	..	Pneumococcal bacteraemia and/or meningitis	5640	No HIV-negative comparison group
Mao et al (1996)[42]	Massachusetts, USA	1983–94	0–7 years	44% on ART	IPD*	6100	No HIV-negative comparison group
Jones et al (1998)[43]	Soweto, South Africa	1996	<2 years	..	IPD*	1844	36·9-fold increase over HIV-negative children aged <2 years
Lichenstein et al (1998)[34]	Baltimore, USA	1986–93	0–36 months	..	Pneumococcal bacteraemia	9400	No HIV-negative comparison group
Madhi et al (2000)[44]	Johannesburg, South Africa	1997–99	<12 years	None	IPD*	3036 in children <2 years	41·7-fold (95% CI 26·5–65·6)
Madhi et al (2000)[17]	Soweto, South Africa	1997–98	2–60 months	None	Bacteraemic severe lower respiratory tract infection	1233	RR 42·9 (95% CI 20·7–90·2)
Dankner et al (2001)[6]	Multicentre, USA	1988–98	Varied; from birth to age 21 years	Majority on ART; none on HAART	Pneumococcal bacteraemia	2280	No HIV-negative comparison group
Madhi et al (2001)[18]	Soweto, South Africa	1997–99	<12 years	None	Meningitis	1541 in children <1 year and 885 in children <2 years	RR 40·4 for *S pneumoniae* meningitis (95% CI 17·7–92·2)
Hughes et al (2005)[45]	Multicentre, USA	1995–2000	3 months to 19 years	79–84% on ART; with CDC indication for *Pneumocystis jirovecii* pneumonia prophylaxis§	Pneumococcal bacteraemia	1494–1648	No HIV-negative comparison group
Nachman et al (2005)[46]	Multicentre, USA	1999–2003	2–21 years	100% on ART; 89% on HAART; CD4 percentage ≥20% for age ≥6 years and ≥25% for age 2–6 years	Pneumococcal bacteraemia	183	No HIV-negative comparison group
Laufer et al (2006)[47]	Blantyre, Malawi	2002–2003	2–15 years; most with symptomatic infection	None	Pneumococcal bacteraemia	18 500	No HIV-negative comparison group

..=not reported. ART=antiretroviral therapy. HAART=highly active antiretroviral therapy. CDC=US Centers for Disease Control and Prevention. IPD=invasive pneumococcal disease. RR=risk ratio. *Invasive pneumococcal disease defined as identification of *Streptococcus pneumoniae* from a normally sterile site. †Serious pneumococcal infection defined as bacteraemia, meningitis, pneumonia, osteomyelitis, septic arthritis, and deep abscess with confirmation of pneumococcus as pathogen (method not specified). ‡The incidence of pneumococcal bacteraemia declined to 0 after introduction of penicillin prophylaxis in this cohort. §CDC indication refers to all children less than 1-year-old; for children aged 1–5 years, CD4-cell count <500 per μL or CD4 percentage <15%; for children aged 6 years or more, CD4-cell count <200 per μL or CD4 percentage <15%; or any previous history of *Pneumocystis jirovecii* pneumonia.

Table 1: **Burden of IPD in HIV-infected children**

Impact of HAART on burden of pneumococcal disease in HIV-infected people

The introduction of highly active antiretroviral therapy (HAART) has brought about marked improvements of morbidity and mortality in HIV-infected people. HAART may also be expected to reduce pneumococcal disease burden, through improvements in immune function and through reduced rates of pneumococcal colonisation.[78] In developed countries, epidemiological studies have identified two to three-fold reductions in IPD rates among adults during the HAART era (1996–97 to the present). The incidence of pneumococcal bacteraemia in Spain has declined from 2410 to 820 per 100 000 HIV-positive adults since the introduction of HAART.[69] Similarly, among AIDS patients in San Francisco, the IPD rate declined from 1060 to 420 cases per 100 000 between 1994 and 1997.[61] A US multicentre study also showed a substantial decline in IPD among patients with

AIDS (1094 to 467 cases per 100 000) between 1995 and 2000, a time when overall IPD rates in the USA were stable, although IPD rates were still 35 times higher in HIV-infected than uninfected adults.[70] In cohort and case control studies, the use of HAART is associated with 30–63% reductions in the risk of IPD,[63,69,72,79] although declines were not significant in all studies.

No studies have directly reported the impact of HAART on paediatric IPD rates. By contrast with adults, one paediatric study found no association between HAART use and pneumococcal colonisation.[80] However, epidemiological studies have shown a five-fold reduction in overall pneumonia incidence (from 11·1 to 2·15 per 100 person-years; p<0·001),[81] a nine-fold reduction in incidence of bacteraemia (from 3·3 to 0·35 per 100 person-years; p<0·001),[81] and a substantial reduction in hospital admissions for pneumonia[82] in children between the pre-HAART and HAART eras. Additionally, the lowest reported IPD rate in HIV-infected children was from a study in the USA done in children on HAART who had reconstituted immune systems;[46] however, the rate in these children remained substantially higher than that reported in a contemporary US surveillance programme.[30]

Although introduction of HAART in the developing world will reduce IPD rates, the burden of IPD among HIV-infected children is likely to remain substantially higher than among those uninfected, even with the use of HAART. A reduction in rates of IPD in resource-limited settings will further depend on the availability of HAART, the ability to identify HIV-infected children, and the ability to deliver HAART to them.

Mortality in HIV-infected individuals with pneumococcal disease

In ten studies, mortality from IPD in children infected with HIV ranged between zero and 23·3% (webtable 1), with case fatality rates similar to those among HIV-uninfected children (0–15·2%).[4,14,18,19,25,42–44,83,84] However, in these studies, differences between HIV-infected and HIV-uninfected individuals with respect to age and other comorbidities (eg, liver disease, nephrotic syndrome, malnutrition, etc) make strict comparisons of mortality between these groups difficult. HIV-associated mortality was higher in Jamaica and Africa than in the USA. In a South African study, there was a significant trend for higher mortality in HIV-infected children with more advanced HIV disease (p=0·002),[44] although data on other potential confounding variables, such as use of antiretroviral therapy or co-trimoxazole prophylaxis, were lacking.

In 30 studies from the USA, Europe, and Africa, case fatality rates in HIV-infected adults with IPD ranged from zero to 33% (webtable 2);[2,7,11,32,38,43,51–53,55,57,59–61,68,69,75,85–97] and mortality was as high as 57% for adults with AIDS and bacteraemic pneumococcal pneumonia.[87] Where patients were stratified by clinical status, patients with AIDS had far higher mortality (10–57%) than those with HIV infection but not AIDS (0–7%).[53,61,87,93]

In 14 studies that directly compared mortality between HIV-infected and HIV-uninfected individuals, more studies found higher mortality among patients without HIV infection than with HIV infection, although many of these differences were not significant.[11,32,38,43,57,59,69,75,86,88,90,91,94,95] The proportion of HIV-infected individuals with advanced HIV disease might affect this relation; three studies stratified HIV-infected adults into those that had AIDS and those that did not; in these studies, patients with AIDS had the highest mortality, but patients with HIV infection and not AIDS had lower mortality than patients without HIV infection.[53,61,87]

Univariate comparisons between HIV-infected and uninfected adults are limited by differences in age and the presence of other comorbidities, and studies were often too small to do adjusted analyses.[43,53,59,69,95] Two studies, however, lend support to the hypothesis that differences in age and other comorbidities may effect differences in mortality between HIV-infected and HIV-uninfected adults. In the first study, HIV-uninfected patients were stratified by the presence or absence of a vaccine indication; those adults without HIV infection and without a vaccine indication had a lower mortality than patients with HIV infection, with or without AIDS.[93] A second study found a higher mortality in HIV-infected patients in the HAART era (1997–2002) than in the pre-HAART era (1986–96). The investigators postulated that the later era had a higher mortality because the HIV-infected population was older with more comorbidities.[69] Only one study assessed the relation between HAART use and mortality; in an unadjusted analysis HIV-infected people using HAART had a higher but not significant increase in mortality compared with those not using HAART, which the authors speculate may have been caused by a heightened inflammatory response.[68]

See Online for webtable 1

Proportion of IPD in HIV-infected people caused by the conjugate vaccine serotypes

Since PCVs only protect against disease caused by serotypes included in the vaccine, it is important to compare the serotypes in the vaccine to those causing disease locally. The currently licensed seven-valent conjugate vaccine includes capsular polysaccharides from seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). Other vaccine candidates evaluated include five-valent (serotypes 6B, 14, 18C, 19F, and 23F), nine-valent (seven-valent plus serotypes 1 and 5), ten-valent (nine-valent plus serotype 7F), 11-valent (ten-valent plus serotype 3), and 13-valent (11-valent plus serotypes 19A and 6A) formulations.

Only the five, seven, and nine-valent vaccines have been used in studies in HIV-infected children. Before considering the data, there are several important limitations to understand—for example, some studies report only serogroup information, which may

See Online for webtable 2

overestimate true vaccine coverage. Additionally, data from Asia and Latin America are lacking. In general, the proportion of disease caused by vaccine serotypes in Asia is lower than in the USA, Europe, and Africa, particularly when the vaccine does not include serotypes 1 and 5.[98]

Eight studies from South Africa and the USA reported on serotype/serogroup coverage of isolates causing invasive disease in children with HIV infection (webtable 3).[18,31,41–44,99,100] In the USA, seven-valent conjugate vaccine included 85–93% of invasive isolates among HIV-infected children, and in South Africa, the nine-valent vaccine comprised 83–91% of invasive isolates among HIV-infected children (figure). No significant differences were noted in these proportions between HIV-infected and uninfected children. No studies have reported on the impact of HAART on serotype distribution.

In ten studies from South Africa, Spain, and the USA, a broader distribution of serotypes cause invasive disease in adults than children, so conjugate vaccine coverage of invasive isolates is lower among adults (17–66%, webtable 4).[32,43,59,61,69,89,99,101–103] However, most of the identified studies found that adults with HIV infection have a similar or higher relative burden (and a higher absolute burden) of IPD caused by isolates that are included in the conjugate vaccines compared with HIV-uninfected adults (figure). Increased antibiotic use among HIV-infected adults might select for this phenomenon, since antibiotic resistance is seen more commonly among the so-called

See **Online** for webtable 3 and webtable 4

	Study location	Years of surveillance	Population and age-group	Proportion on antiretroviral therapy	Outcome	Incidence rates (per 100 000 person-years)	Increase in risk of IPD in HIV-infected compared with HIV-uninfected individuals
Simberkoff et al (1984)[50]	New York, USA	1982–83	Adult (VA) with AIDS	..	Pneumococcal pneumonia* and pneumococcal bacteraemia	9500 (pneumococcal pneumonia); 5700 (pneumococcal bacteraemia)	16·3-fold over non-AIDS hospital inpatients for pneumococcal bacteraemia
Polsky et al (1986)[51]	New York, USA	1979–85	AIDS only	..	Pneumococcal pneumonia*	1790	..
Witt et al (1987)[24]	Boston, USA	1983–85	Adult (21–47 years) with AIDS or AIDS-related complex	..	Pneumococcal pneumonia* and pneumococcal bacteraemia	4510 (pneumococcal pneumonia); 2260 (pneumococcal bacteraemia)	..
Selwyn et al (1988)[52]	New York, USA	1985–86	HIV-infected IDUs without AIDS	..	Pneumococcal pneumonia*	3500	Ten-fold increased risk compared with HIV-negative drug users
Redd et al (1990)[53]	San Francisco, USA	1983–87	20–55 years with AIDS	..	Pneumococcal bacteraemia	940	..
Schuchat et al (1991)[54]	New Jersey, USA	1986	25–44 years with AIDS or pre-AIDS	..	IPD†	1070 (AIDS); 530 (pre-AIDS)	324-fold and 148-fold increases over general population aged 25–44 years for AIDS and pre-AIDS respectively
Garcia-Leoni et al (1992)[38]	Madrid, Spain	1998–90	≥14 years	..	Pneumococcal pneumonia* and bacteraemic pneumococcal pneumonia	590 (pneumococcal pneumonia); 430 (bacteraemic pneumococcal pneumonia)	6·8-fold for pneumococcal pneumonia; 13·9-fold for bacteraemic pneumococcal pneumonia
Meyer et al (1994)[55]	Copenhagen, Denmark	1988–92	Adult	..	Pneumococcal bacteraemia	200 (HIV-positive without AIDS); 2000 (AIDS)	18·2-fold for HIV-positive without AIDS; 182 for AIDS patients
Boschini et al (1996)[10]	San Patrignano, Italy	1991–94	Adult former IDUs	..	Pneumococcal pneumonia*	1864	Relative risk 16·2 (95% CI 5·9–44·6)
Gilks et al (1996)[7]	Nairobi, Kenya	1989–92	Female sex workers	None	Probable‡ and definite† IPD	4250	Relative risk 17·8 (95% CI 2·5–126·5)
Plouffe et al (1996)[56]	Ohio, USA	1991–94	18–64 years	..	Pneumococcal bacteraemia	401 (95% CI 182–883; by inference)	Relative risk 41·8 (95% CI 19·0–92·0)
Almirante et al (1998)[57]	Barcelona, Spain	1985–97	>14 years	..	Pneumococcal meningitis	41·9	..
Jones et al (1998)[43]	Soweto, South Africa	1996	18–40 years	..	Pneumococcal bacteraemia	197	8·2-fold in adults aged 20–39 years
Pastor et al (1998)[58]	Dallas, USA	1995	All ages	..	IPD†	587 (95% CI 397–829)	OR 29 (95% CI 20–41)
Feldman et al (1999)[59]	Johannesburg, South Africa	..	Hospital inpatient adults 15–40 years	..	Bacteraemic pneumococcal pneumonia	..	6·2-fold
French et al (2000)[60]	Entebbe, Uganda	1995–98	≥15 years; patients in pneumococcal polysaccharide vaccine trial	..	IPD†	1680–2980 (higher rate among those receiving vaccine)	..

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Nuorti et al (2000)[61]	San Francisco, USA	1994–97	18–64 years; AIDS only	..	IPD†	802·9	Rate ratio 51·3 (95% CI 40·3–65·3) AIDS *vs* non-HIV; age and ethnicity adjusted rate ratio 46·0 (95% CI 36·0–58·9)
Attia et al (2001)[62]	Abidjan, Côte d'Ivoire	1996–98	≥18 years	..	Severe bacterial infection with *S pneumoniae* isolated from blood, CSF, urine, or stool (not specified)	589	..
Dworkin et al (2001)[63]	Multicentre, USA	1990–98	≥13 years	60% of person-time on ART; 7·4% of person-time on HAART	Pneumococcal disease§	820	..
Dworkin et al (2001)[64]	Multicentre, USA	1990–99	≥13 years; CD4-cell count ≤200 cells per μL	..	IPD†	780	..
Pierce and Hoy (2001)[65]	Melbourne, Australia	1996–2000	..	..	Probable‡ and definite† IPD with pneumonia	190	...
Allen et al (2003)[66]	London, UK	1996–2002	..	..	Pneumococcal pneumonia*	675	..
Hung et al (2004)[67]	Taipei, Taiwan	2000–02	≥15 years	92·6% had initiated HAART	Bacteraemic pneumococcal pneumonia	397	..
Jordano et al (2004)[68]	Barcelona, Spain	1996–2002	≥16 years	..	IPD†	677	59·9-fold increase
Grau et al (2005)[69]	Barcelona, Spain	1986–96; 1997–2002	Adult	..	Pneumococcal bacteraemia	2410 (1986–96); 820 (1997–2002)	..
Heffernan et al (2005)[70]	Multicentre, USA	1995–2000	18–64 years; AIDS only	..	IPD†	1094 (1995–96); 467 (1999–2000)	80-fold (1995–96); 35-fold (1999–2000)
Kyaw et al (2005)[71]	Multicentre, USA	1999–2000	≥18 years	..	IPD†	422·9	Relative risk 48·4 (95% CI 24·8–94·6)
Barry et al (2006)[72]	Baltimore, USA	1990–2003	Adult	34% of controls on HAART	Pneumococcal bacteraemia	379	..
Kohli et al (2006)[73]	Multicentre, USA	1993–2000	Women ages 16–55 years without AIDS at enrolment	46% on HAART	Bacteraemic pneumococcal pneumonia	672	..
Le Moing (2006)[74]	Multicentre, France	1997–2001	Patients initiated on protease-containing regimen	100% had initiated HAART	Pneumococcal pneumonia*	248	..

..=not reported. IDUs=injection drug users. CSF=cerebrospinal fluid. IPD=invasive pneumococcal disease. OR=odds ratio. VA=Veterans Administration Hospital. *Pneumococcal pneumonia generally defined as patients in whom *S pneumoniae* was identified by respiratory culture or Gram stain, and/or blood culture with clinical and radiographical findings consistent with pneumonia. †IPD defined as identification of *S pneumoniae* from a normally sterile site. ‡Probable pneumococcal disease was defined as *S pneumoniae* isolation from sputum, pus, or pernasal swab with clinical and radiological evidence of acute disease. §Pneumococcal disease defined as physician-diagnosed pneumonia, meningitis, bacteraemia, sepsis, endocarditis, pleural effusion, or joint infection for which *S pneumoniae* was identified as the causal agent (method of identification not recorded).

Table 2: **Burden of IPD in HIV-infected adults**

paediatric serotypes. Additionally, HIV-infected women in South Africa are more likely to develop invasive disease with paediatric serotypes or serogroups than HIV-infected men, possibly because of women's closer proximity to small children.[101] These findings provide a foundation for the hypothesis that routine conjugate vaccination of children might reduce pneumococcal disease burden for the HIV-infected adult members of their families and community. No study looked at the effect of HAART on serotype distribution in HIV-infected adults; however, a study spanning the pre-HAART and HAART eras found no change in serotype distribution over time.[69]

Safety of PCVs in HIV-infected children

Five different PCVs have undergone phase III trials in seven diverse settings—Czech Republic, California (USA), southwestern USA, Finland, South Africa, The Gambia, and the Philippines.[104–110] Since 2000, the seven-valent vaccine has been licensed in more than 70 countries and given routinely to more than 30 million children. Whereas rates of fever and local reactions following seven-valent PCV are generally higher than for other vaccines, most reactions are minor and self-limiting.[111] Post-licensure safety surveillance in the USA has shown that the proportion of serious reports after PCV administration is no different than with other currently licensed vaccines (1·9 serious events per 100 000 doses).[112]

Five studies from the USA and South Africa characterise the safety of PCV specifically among HIV-infected children.[108,113–116] One study compared pneumococcal polysaccharide vaccination to conjugate vaccination in

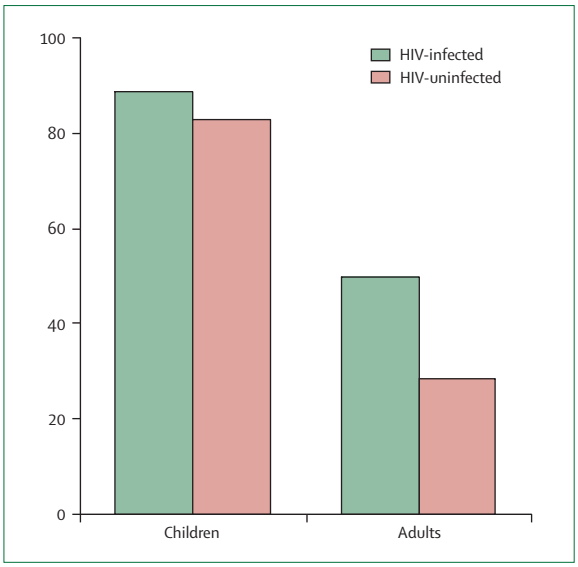

Figure: **Median percentage of paediatric isolates in invasive pneumococcal strains infecting children and adults**
Definition of pediatric isolates varies by study; refer to text and webtable 3 and webtable 4 for details.

children older than 2 years of age and found no difference in adverse reactions including fever, tenderness, erythema, and induration.[113] A separate study in HIV-infected children older than 2 years found a 7% rate (15 of 225 patients) of grade 3 or higher adverse reactions, most of which were local reactions, with no life-threatening adverse events.[116] A study comparing PCV administration among HIV-infected and uninfected children younger than 2 years of age also found no significant differences in local or systemic reactions.[114] Of the 52 vaccine doses given to 18 HIV-infected children, erythema occurred after four (8%) vaccinations, induration after five (10%), tenderness after seven (13%), and fever after seven (13%).[114] A study comparing PCV with placebo in HIV-infected children less than 2 years of age also found no significant differences in local or systemic reactions between placebo and PCV.[115] Severe acute reactions (fever, induration, and limited leg movement), all of which were self-limiting, were more common in children with symptomatic HIV infection than in those who had asymptomatic HIV infection.[115]

Although the studies were small and not powered to identify rare adverse events, the available data suggest that PCV is well tolerated in HIV-infected children with an acceptable level of local reactions. Additionally, although not designed to assess safety in children with HIV, an efficacy study involving more than 39 000 children, of whom more than 2500 were estimated to be HIV positive, found the conjugate vaccine to be well tolerated compared with placebo.[108] A higher rate of asthma was seen in vaccine recipients in this study; however, the HIV-specific rate of asthma was not reported.[108]

Overall, other vaccinations in HIV-infected people have not resulted in sustained increases in viral load, decreases in CD4-cell counts, or disease progression,[117] although ongoing vigilance is warranted, since a pneumococcal polysaccharide vaccine trial in HIV-infected adults in the developing world showed a paradoxically increased rate of pneumonia among vaccine recipients.[60] 5-year follow-up of HIV-infected children enrolled in a South African efficacy study found a lower CD4 percentage among PCV recipients compared with placebo recipients (12·6% *vs* 16·1%, p=0·04) and a non-significant difference in mean CD4-cell counts (493 cells per µL *vs* 627 cells per µL, p=0·15).[118] No studies in children have reported on the effect of PCV on viral load; two studies in HIV-infected adults found no short-term or long-term increases in viral load after conjugate vaccine administration.[119,120]

Immunogenicity of PCVs in HIV-infected children

To address a lack of uniformity in immunological endpoints, a WHO expert panel summarised ELISA data from three clinical efficacy studies[105,106,108] and estimated that an antibody concentration of 0·35 µg/mL aggregated across the serotypes correlated with clinical efficacy against IPD.[121] No consensus correlate of immunity has been determined for non-invasive pneumococcal disease, nor is there consensus on a concentration estimate that correlates with clinical efficacy in children infected with HIV.

Nine studies from Greece, South Africa, Spain, and the USA report on the immunogenicity of PCV in HIV-infected children (table 3).[113–116,118,122–125] The studies varied substantially with respect to the immunological endpoints studied, the clinical disease stage of the children undergoing vaccination, and the proportion of children taking HAART, making direct comparisons between studies difficult. Overall, however, PCV is shown to be immunogenic in HIV-infected children, albeit less so than in HIV-uninfected children. These studies all assessed PCV using the CRM carrier protein; vaccines with different conjugate technology might yield different results.

In six studies that compared responses between HIV-infected and uninfected children, the proportions of HIV-infected children (most of whom were not on antiretroviral therapy) reaching predefined IgG concentrations or fold-increases in IgG concentration were up to 39% lower than for children without HIV infection; these differences were significant in four of the six studies.[113,118,122,123] In three studies in which a substantial proportion of children were taking antiretroviral drugs, two studies showed no difference in antibody response according to disease severity,[115,125] whereas one found that antibody response correlated with higher screening CD4 percentage and lower viral load at entry.[116] The only study that examined the effect of HAART on quantitative antibody response to PCV found a significant positive association (p=0·03) between antibody concentration and duration of HAART.[116] Among children not on

	Study location	Age-group	Vaccine and schedule	Serological endpoint	Proportion of HIV-positive patients meeting serological endpoint (%)	Proportion achieving four-fold rise in GMC (%)	Proportion of HIV-negative patients meeting serological endpoint	Relation with HAART, disease stage, or CD4-cell count	Proportion of children on HAART
King et al (1996)[113]	Baltimore, USA	2–19 years	Five-valent; one-dose vaccine	Four-fold rise GMC (five serotypes pooled)	60%*	60%*	79% achieved four-fold GMC rise*	No correlation with CD4-cell count or CD4 percentage or HIV classification	..
King et al (1997)[114]	Baltimore, USA	6–23 months	Five-valent; three doses, each separated by 2 months	Proportion of titres >1·0 μg/mL (five serotypes pooled)	78% (1 month after third vaccination)†	..	88% had GMC >1·0 μg/mL†	Antibody responses good regardless of CD4-cell count	..
King et al (1998)[122]	Baltimore, USA	6–23 months	Five-valent; three doses each separated by 2 months	Proportion of titres >1·0 μg/mL (five serotypes pooled)	46% (8 months after third vaccination)‡	..	61% had GMC >1·0 μg/mL‡	No significant difference with respect to HIV disease status in absolute GMC or percent drop in antibody concentration	..
Nachman et al (2003)[115]	Multicentre, USA	Enrolled at 2–6 months	Seven-valent; three doses each separated by 2 months, booster at 15 months	Four-fold rise GMC; proportion of titres >0·15 μg/mL and >0·50 μg/mL (seven serotypes analysed separately)	>95% achieved 0·15 μg/mL and 80% achieved 0·5 μg/mL after third dose	88–100% achieved four-fold rise after third dose; 39–72% achieved four-fold rise with booster	No HIV-negative comparison group	Asymptomatic and symptomatic children did equally well	71% on ART at start; 51% on HAART at end of study
Madhi et al (2005)[123]	Soweto, South Africa	Enrolled at 6 weeks	Nine-valent; given at 6, 10, and 14 weeks of age	Proportion of titres >0·35 μg/mL (nine serotypes pooled)	63–93% (1 month after third vaccination)§	..	79–100% had GMC >0·35 μg/mL§	Children with AIDS had lower GMCs than children with mild or asymptomatic disease	None
Spoulou et al (2005)[124]	Athens, Greece	20–163 months (median 128 months)	Seven-valent; given at 0, 1, and 12 months of the study	Mean GMC after 12-month booster (four serotypes reported separately)	Moderate rise in mean GMC not consistent with anamnestic response¶	..	Significant rise in mean GMC after booster ($p<0·01$)¶	..	79% on HAART at start of trials; 100% on HAART by 12-month dose
Tarrago et al (2005)[125]	Madrid, Spain	>2 years, all participants had received pneumococcal polysaccharide vaccine before enrolment	Seven-valent; two doses separated by 2 months	Two-fold rise in OPA and ELISA for each of three serotypes analsed separately; frequency of conversion from negative to positive OPA	28·5–43·9% achieved two-fold rise in OPA and ELISA; 46·3–50% for conversion of negative to positive OPA	..	No HIV-negative comparison group	No correlation between vaccine response and clinical stage or CD4-cell count	100% (inclusion criterion)
Abzug et al (2006)[116]	Multicentre, USA	2 years to <19 years	Seven-valent; two doses separated by 2 months followed by PPV at 4 months	Proportion of titres >0·5 μg/mL and >1·0 μg/mL for each of four serotypes	76–96% achieved >0·5 μg/mL and 62–88% achieved >1·0 μg/mL after two doses PCV	..	No HIV-negative comparison group	Antibody responses associated with higher screening CD4 percentage, lower entry viral load, and longer duration of HAART	100% (inclusion criterion)
Madhi et al (2007)[118]	Soweto, South Africa	Enrolled at birth, followed for 6 years	Nine-valent; given at 6, 10, and 14 weeks of age, no booster	Proportion of titres ≥0·2 μg/mL and ≥0·35 μg/mL for each of seven serotypes, 5·3 years after third PCV dose	39–100% achieved ≥0·2 μg/mL and 19–81% achieved ≥0·35 μg/mL for each of seven serotypes tested	..	66–100% achieved ≥0·2 μg/mL and 44–91% achieved ≥0·35 μg/mL for each of seven serotypes tested	No difference in proportion of children achieving ≥0·2 μg/mL when stratified by CD4 percentage	26% on HAART

..=not reported. ART=antiretroviral therapy. GMC=geometric mean concentrations. HAART=highly active antiretroviral therapy. OPA=opsonophagocytic activity. PCV=pneumococcal conjugate vaccine. PPV=pneumococcal polysaccharide vaccine. *$p<0·05$ for difference in proportion achieving four-fold GMC rise in HIV-infected children compared with uninfected children. †Not significant (HIV-infected compared with uninfected). ‡$p<0·05$ for difference in proportion achieving 1·0 μg/mL in HIV-infected children compared with uninfected children. §$p<0·05$ for difference in proportions achieving 0·35 μg/mL in HIV-infected children compared with uninfected children for serotypes 1, 5, 18C, and 23F. Functional antibody titres also higher in HIV-uninfected children (see text). ¶$p<0·05$ for differences in post-booster GMC between HIV-infected and uninfected children for all serotypes tested (6B, 14, 19F, 23F).

Table 3: **Immunogenicity of pneumococcal conjugate vaccine in HIV-infected children**

antiretroviral therapy, in all but one study,[123] no correlation was seen between HIV clinical disease stage or CD4-cell count and quantitative PCV antibody response. Three studies that assessed the duration of antibody response found lower antibody concentrations in HIV-infected children 8 months, 12 months, and 5 years after the primary PCV immunisation series compared with HIV-uninfected children.[118,122,124] Further study and particular

	HIV-infected children		HIV-uninfected children	
	Absolute rate reduction*	Vaccine efficacy (95% CI)	Absolute rate reduction*	Vaccine efficacy (95% CI)
First episode of vaccine-type IPD, 2·3 years of follow-up[108]	570†	65% (24 to 86)	32†	83% (39 to 97)
First episode of vaccine-type IPD, 6·2 years of follow-up[118]	940	39% (–8 to 65)	75	78% (34 to 92)
First episode of IPD (all serotypes), 2·3 years of follow-up[108]	838†	53% (21 to 73)	19†	42% (–28 to 75)
First episode of IPD (all serotypes), 6·2 years of follow-up[118]	2250	46% (19 to 64)	38	35% (–31 to 68)
First episode of radiologically confirmed pneumonia, 2·3 years of follow-up[108]	912†	13% (–7 to 29)	100†	20% (2 to 35)
Mortality, 2·3 years of follow-up[108]	342†	6% (p=0·63)	0†	0%
Clinical diagnosis of lower respiratory tract infection, 2·3 years of follow-up[126]	2573	15% (6 to 24)	172	7% (–1 to 14)

IPD=invasive pneumococcal disease. *Absolute rate reduction reported as events prevented per 100 000 child-years. †HIV prevalence in the study population estimated to be 6·47%; denominators were calculated using this estimated prevalence and average duration of follow-up of 847·5 days in vaccinees and 847 days in placebo recipients. Absolute rate reduction calculated as difference between incidence rate among placebo recipients and incidence rate among vaccinees.

Table 4: **Efficacy of pneumococcal conjugate vaccination in HIV-infected children**

consideration will need to be given to proposals using fewer vaccine doses or withholding booster immunisations in settings where HIV is endemic.

In children without HIV infection, quantitative pneumococcal antibody concentrations correlate with both functional antibody measures (ie, opsonophagocytic activity) and clinical efficacy.[121] However, quantitative IgG assays do not always correlate with functional activity in children infected with HIV.[125] The functional activity of the pneumococcal antibodies elicited by PCV is lower in HIV-infected than HIV-uninfected children.[123] Additionally, a smaller proportion of HIV-infected children have measurable opsonophagocytic activity titres against three serotypes following PCV than children without HIV infection.[123] So far, no studies have evaluated the effect of HAART on functional antibody activity.

There is conflicting evidence as to whether children with HIV mount a T-cell-dependent booster response to PCV. Although HIV-infected children immunised as infants showed a quantitative rise in IgG concentration after booster immunisation,[115] in a separate study, HIV-infected children immunised when they were older and symptomatic did not show a rise in IgG concentration.[124] Another study in HIV-infected children did not find a quantitative rise in IgG concentrations or opsonophagocytic activity titres after a second PCV dose; however, the correlation between IgG concentration and opsonophagocytic activity titres improved after the booster, indicating a qualitative improvement in antibody function.[125] Most participants in the booster studies were on antiretroviral therapy, so extrapolating these findings to children not on antiretroviral therapy should be done with caution.

Efficacy and effectiveness of PCVs in HIV-infected children

Although immunogenicity studies provide evidence of vaccine response, there is still uncertainty regarding the immunological correlates of protection in HIV-infected children. Efficacy studies, however, provide direct evidence of protection. Of the clinical efficacy trials done so far, only a South African trial[108] measured vaccine efficacy in children infected with HIV (table 4). Overall, the vaccine provided significant protection against vaccine-type invasive disease in HIV-infected children (65% [95% CI 24–86%; p=0·006]). The point estimate of efficacy in HIV-infected children, however, was lower than that observed in HIV-uninfected children (83% [39–97%; p=0·003]). PCV was associated with a non-significant 13% (–7% to 29%) reduction in pneumonia and 6% reduction in mortality (p=0·63) in HIV-infected children; by contrast, the 20% (2–35%; p=0·03) reduction in pneumonia for HIV-negative children was significant. As suggested by the immunogenicity studies, 5-year follow-up of this study has shown a greater attenuation in the vaccine efficacy (VE) for HIV-infected children for vaccine-type IPD (VE 38·8% [–7·8% to 65·2%]) compared with non-infected children (VE 77·8% [34·4–92·5%]); although a greater efficacy against all serotype IPD was shown in HIV-infected (46·1%) versus uninfected children (35%, p<0·0001).[118]

When assessing the public-health impact of pneumococcal conjugate vaccination, however, it is useful to consider the efficacy of the vaccine in absolute terms, (ie, in cases prevented per 1000 children vaccinated), not just in relative terms (eg, vaccine efficacy that expresses relative risks for disease as a proportion). An intervention with a "lower" vaccine efficacy (expressed as a proportion) may confer a more significant net health benefit (expressed as cases prevented per 1000 vaccinated) than an intervention with a "higher" efficacy, if the illness prevented by the former is quite common. In this respect, absolute rate reductions provide a more meaningful measure of disease burden prevented than vaccine efficacy.

Such absolute rate reductions were demonstrated in the South African trial by using different definitions of pneumonia.[126] Whereas the point estimate for vaccine efficacy for HIV-infected children was higher for

bacteraemic pneumococcal pneumonia (45% [1–70%]) than for a clinical diagnosis of lower respiratory tract infection (15% [6–24%]), the vaccine attributable rate reduction was much greater for clinical lower respiratory tract infections (2573 cases prevented per 100 000 child-years versus 483 episodes of bacteraemic pneumococcal pneumonia prevented per 100 000 child-years), because clinical pneumonia is several times more frequent than bacteraemic pneumococcal pneumonia.[126] Similarly, whereas vaccine efficacy against vaccine-type IPD is lower in HIV-infected than non-infected children, the impact of vaccination is higher for HIV-infected children because the disease burden is so much greater. In the South African trial, the vaccine attributable rate reduction in clinical lower respiratory infections was almost 15 times greater for HIV-infected children than for uninfected children (2573 *vs* 172 cases prevented per 100 000 child-years of observation)[126] and at 6 years of follow-up, the vaccine attributable rate reduction in IPD was 59 times higher for HIV-infected children than for uninfected children (2250 *vs* 38 cases prevented per 100 000 child-years).[118]

Indirect effects of pneumococcal disease

PCVs reduce the prevalence of vaccine-type pneumococcal carriage in vaccinated children. This effect in turn reduces the likelihood that vaccine-type pneumococci will be transmitted from vaccinated children to unvaccinated contacts, providing the basis for herd immunity. Nasopharyngeal colonisation studies have found higher rates of pneumococcal carriage in adults who live with young children[127] than in adults who do not, and epidemiological studies have identified an association between risk of IPD in adults and contact with young children.[128] Declines in vaccine-type pneumococcal colonisation have been seen among non-immunised adults—for example, in Alaskan natives, the proportion of adult pneumococcal carriers with vaccine-type colonisation decreased from 28% to 4·5% (78 of 275 carriers to 17 of 377 carriers) after introduction of PCV in children aged under 5 years.[129]

An indirect effect on invasive disease has been seen in countries where conjugate vaccination strategies have been widely implemented in children aged under 5 years. In the USA, rates of vaccine-type IPD declined by 62% among people aged 5 years and older between 1998–99 and 2003.[29] In Canada, there was a 62·7% decline in vaccine-type invasive disease in adults over 65 years between 1998–2001 and 2004.[130] In absolute terms, more cases of vaccine-type IPD were prevented in the USA among individuals 5 years and older than among the population targeted for vaccination (20 459 *vs* 9140 cases).[29] An additional benefit of PCV has been the reduction of pneumococcal disease caused by antibiotic-resistant strains, many of which are included in the conjugate vaccine.[131]

The impact of vaccination on pneumococcal transmission and colonisation in communities burdened with substantial rates of HIV infection is less clearly understood. Most studies indicate that the prevalence of pneumococcal colonisation is similar among HIV-infected and HIV-uninfected children and adults.[2,132–134] The duration of colonisation, however, may be longer in HIV-infected individuals.[132] In settings with a high burden of HIV, the magnitude of the indirect benefit from conjugate vaccination of children to HIV-infected adult members of the community may be diminished because of an expanded role of older HIV-infected children and adults in pneumococcal transmission, and because of reduced mucosal immunogenicity of PCV in children with HIV, although data on these points are lacking.

However, adults in the USA aged 18–64 years with HIV/AIDS have shown an indirect benefit of conjugate vaccination since it was introduced in children in 2000. Between 1998–99 and 2003, the overall rate of IPD declined by 19% and vaccine-type invasive disease declined by 62% in this group.[135] When analysed separately by race and sex, the decline in vaccine-type IPD was shown to be significant in HIV-infected black men and women and non-Hispanic white men, although the declines for white women and Hispanic men and women did not reach significance. Non-significant reductions in disease caused by antibiotic-resistant strains were also seen, a potentially important finding in a population with greater antibiotic exposure.[135]

Effects of serotype replacement on the benefits of PCVs in HIV-infected people

In addition to reducing vaccine-type IPD among the non-immunised, the prevention of vaccine-type colonisation in immunised children is also associated with an increase in the prevalence of colonisation with non-vaccine serotypes.[136–138] This association raises the question of whether the immunological pressure of widespread vaccination will lead to large increases in disease caused by non-vaccine serotypes.

In the USA, surveillance data since 1994 show that increases in the rate of non-vaccine serotype invasive disease have occurred, attenuating the overall impact of vaccination; however, the increase in non-vaccine type disease was small compared with the overall decline in disease.[139] Specifically, when comparing rates in 2003 to pre-vaccine era rates, non-vaccine serotype IPD cases increased by approximately 4700 cases whereas vaccine-serotype IPD decreased by 29 600 cases annually.[29] The number of HIV-infected children with IPD in a US multicentre IPD surveillance programme sponsored by the Centers for Disease Control and Prevention (CDC) is too small to draw any conclusions with respect to serotype replacement among this group (Whitney C, CDC, Atlanta, GA; personal communication). Long-term follow-up among children in the South African efficacy trial showed a non-significant 27% (–80·2 to 70·6%) increase in non-vaccine serotype IPD in vaccinated HIV-infected children compared with unvaccinated HIV-infected children; this still compares favourably to the

75% (–17·8 to 94·7; p=0·11) difference (also not significant) among uninfected participants.[118]

Among 18–64-year-old HIV-infected adults in the USA, serotype replacement has reduced the indirect benefit of conjugate vaccination, with a 44% increase in non-vaccine-type invasive disease.[135] Serotype replacement disease was not seen among HIV-infected white men; therefore, the percent IPD rate reduction was lower among black men compared with white men.[135] However, because black men with HIV had higher baseline rates of IPD, more cases were still prevented in black men than in white men.[135] In defining implications for future pneumococcal disease risk, ongoing surveillance will be crucial to determine if these trends (particularly with respect to serotype replacement disease among HIV-infected people) will continue or plateau.

Cost-effectiveness of pneumococcal conjugate vaccination for HIV-infected children

Many studies in the developed world have been done to determine the cost-effectiveness of routine implementation of PCV in various settings. These studies often used different assumptions about vaccine cost and different models of effectiveness, therefore arriving at different conclusions. Most cost-effectiveness analyses did not consider the reductions in IPD in the non-vaccinated, the magnitude of which is at least as great as the direct benefit to vaccinees, nor did they consider the impact of pneumococcal conjugate vaccination on replacement disease or non-invasive disease such as pneumonia. Analyses of cost-effectiveness might therefore change when these effects are better understood. For example, when herd effects were included in an analysis in the USA, the cost of PCV per year of life saved decreased from US$112 000 to $7500.[140]

One study that did a cost-effectiveness analysis for implementation of pneumococcal conjugate vaccination in the developing world found a cost of $56–112 per life-year saved.[141] Based on a cost less than the per-capita gross national product per year of life saved, the study concluded that the vaccine would be cost-effective. Another study that incorporated more recent efficacy data from The Gambia identified a cost of $100 per disability-adjusted life year averted at a vaccine cost of $5 per dose; vaccination was projected to be highly cost effective in 68 of 72 countries eligible for support from the Global Alliance for Vaccines and Immunization.[142] However, neither of these studies considered the economic impact of non-fatal disease or the effects of herd immunity in their analyses, suggesting that the true cost-effectiveness profile may be even more favourable. No studies have been published that attempt to specifically define the cost-effectiveness of PCV in settings with a high burden of HIV infection.

Discussion

This Review shows that the incidence of pneumococcal disease in HIV-infected people might be up to 320 times higher than in HIV-uninfected people; an elevated risk was shown in all studies that compared rates directly to HIV-negative people. Although HAART may reduce pneumococcal disease, IPD rates still remain high even after the introduction of HAART.[46,61,70] The effect of co-trimoxazole prophylaxis on pneumococcal disease risk is less clear,[16,63,64,79,143,144] though any benefit is modest at best.

Two important findings emerge from a review of the serotypes that cause pneumococcal disease among HIV-infected people. First, the serotypes that cause invasive disease are similar among HIV-infected and HIV-uninfected children; therefore, a vaccination programme for all children will include the serotypes important for prevention of disease in HIV-infected children. Second, adults with HIV infection have a similar or greater relative burden (and a greater absolute burden) of IPD caused by serotypes that are included in PCVs than adults without HIV infection. This finding suggests that widespread childhood immunisation might lead to important health benefits for HIV-infected adults through herd immunity. Although these findings are consistent across the studies reviewed, additional data from other geographical settings would further strengthen this evidence base. The bulk of the current data on disease burden and vaccine impact are from the USA and South Africa only.

The South African efficacy trial provides important data to show the potential health impact of vaccination. When measured in absolute terms, the benefits of pneumococcal conjugate vaccination are greatest among those children infected with HIV. However, the safety, immunogenicity, and efficacy data stemming from this trial also indicate a need to continue to monitor the long-term impact of

Search strategy and selection criteria

Data for this Review were identified by searching PubMed using combinations of the following search terms: "pneumococcus", "pneumococcal", "*Streptococcus pneumoniae*", "conjugate pneumococcal vaccine", "HIV", "human immunodeficiency virus", "AIDS", and "acquired immunodeficiency syndrome". Only English language articles were reviewed and no date restrictions were set in these searches. Additionally, articles were identified through reference lists of relevant papers and from the authors' own files. Articles were included if they provided data for HIV-infected individuals on pneumococcal disease burden (including incidence rates of disease and comparisons with HIV-uninfected individuals), case fatality rate, capsular serotype distribution, PCV safety, immunogenicity including quantitative and qualitative assays, vaccine efficacy, absolute disease reduction caused by vaccination, or indirect effects of vaccination on pneumococcal disease burden. For IPD disease burden, serotype distribution, and rates of absolute disease reduction, data were abstracted from the published articles and if needed, used to calculate uniform comparative measures.

vaccination among HIV-infected children, since vaccinated children had a lower mean CD4 percentage at 5 years than their unvaccinated peers, and because the vaccine response, although protective, does appear to be less in HIV-infected children. Special consideration should also be given to the role of booster immunisation in HIV-infected children.

In the USA, routine use of PCV in infants has led to an indirect effect among HIV-infected adults, with significant declines in vaccine-type invasive disease; in absolute numbers the benefit to adults may be greater than to children. The magnitude of serotype replacement disease, which will likely attenuate some of the direct and indirect benefits to HIV-infected individuals, remains unknown, although given the notable disease burden, a substantial benefit is still expected.

Conclusion

In resource-poor countries, the introduction of HAART is expected to reduce the pneumococcal disease burden caused by all serotypes. In view of its safety and efficacy profiles, and the urgency to improve the health of HIV-infected children and adults, we propose that PCV should be considered as an important complement to HAART. Since many HIV-infected children in resource-poor settings have not been identified, the best approach would be to vaccinate all infants in these areas. This approach would be programmatically simple, albeit expensive. Routine immunisation would also maximise the potential direct and indirect benefits to the entire community, including older HIV-infected children and adults. Where it is possible, IPD surveillance should continue to assess the impact of pneumococcal conjugate vaccination on disease burden and serotype replacement in settings with a substantial degree of HIV infection.

Conflicts of interest

KLOB has received research funding and honoraria from Wyeth Pharmaceuticals. ENJ has been a consultant for Wyeth Pharmaceuticals. All other authors declare that they have no conflicts of interest.

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