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Pneumococcal conjugate vaccines: what do we know and what do we need?

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Abstract

Pneumococcal disease is complex with many disease manifestations. *Streptococcus pneumoniae* causes a variety of illnesses, from acute otitis media to clinical pneumonia and invasive pneumococcal disease (IPD). Immunization is among the most successful and cost-effective means of controlling pneumococcal disease. Pneumococcal conjugate vaccines (PCVs) have been approved for use in children aged up to 9 years since 2000; to date, widespread global uptake of PCVs has not yet been achieved. The heptavalent pneumococcal conjugate vaccine (PCV7) is the only PCV with large-scale controlled trials demonstrating efficacy and documented effectiveness across various disease manifestations. The benefits of including PCV7 in national immunization programmes include decreased infant mortality, reduced vaccine serotype IPD, minimized racial and social disparities in rates of incidence of pneumococcal disease, reduced disease due to nonsusceptible serotypes, reduction in pneumonia and AOM and indirect effects (herd immunity).

Keywords: pneumococcal conjugate vaccines, invasive pneumococcal disease, otitis media

Abbreviated title: Pneumococcal Conjugate Vaccines

1. 1. Pneumococcal Conjugate Vaccines: What We Know

Pneumococcal disease is complex with many disease manifestations. *Streptococcus pneumoniae* causes a variety of illnesses, from acute otitis media (AOM) and clinical pneumonia to invasive pneumococcal diseases (IPDs), including meningitis, bacteremia, osteomyelitis, and septic arthritis. *S. pneumoniae,* commonly found in the nose and throat of healthy individuals, can cause serious infections in susceptible populations, particularly children aged <5 years and older adults, as well as persons who are immunocompromised [1].

Lower respiratory tract infections (LRTIs) ranked third in a list of the 20 leading causes of death worldwide in 2004 [2]. In 2005, the World Health Organization (WHO) estimated that 1.6 million deaths annually are attributable to pneumococcal disease (Fig. 1); about half of these are children [3]. Globally, pneumonia and LRTIs comprise the second most common cause of illness and LRTIs are the leading cause of burden of disease at 94.5 million (6.2% of total) disability-adjusted life years (DALYs) worldwide [2]. Approximately 156 million new episodes of childhood

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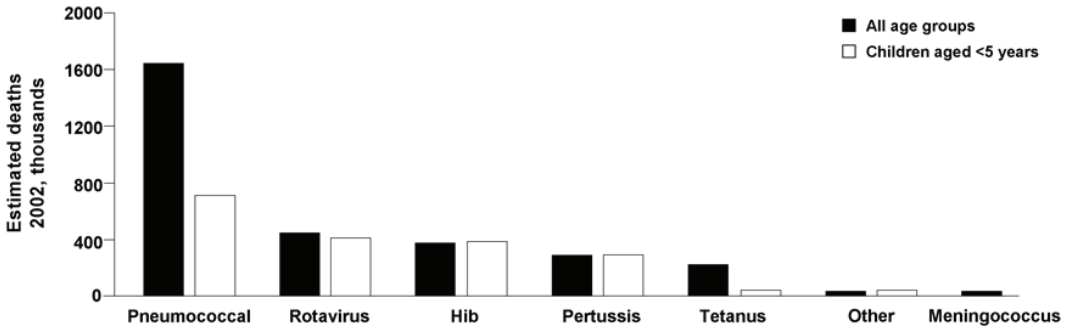

Fig. 1. The World Health Organization estimates 1.6 million deaths attributable to pneumococcal disease occur annually; about half of these are in children [3].

clinical pneumonia occurred in 2000—more than 95% of them in developing countries (Fig. 2) [4]. Of all pneumonia cases occurring in these countries, 7% to 13%, or approximately 11 to 20 million cases, are severe enough to require hospitalization [5].

In the developed world, the incidence of IPD varies by age and geography, disproportionately affecting young children and older adults [6–11]. In the United States, prior to the implementation of a widespread paediatric vaccination programme with the seven-valent pneumococcal conjugate vaccine (PCV7; Prevenar®, Wyeth Pharmaceuticals Inc., Philadelphia, PA) containing capsular polysaccharides from pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to the carrier protein cross-reactive material $(CRM)_{197}$, the combined rate of IPD for children aged ≤1 year (from 1997–1999) was estimated to be 352.5 cases per 100,000 population, declining to a low of 4.4 cases for those aged 5 to 17 years and again rising through middle age to an average of 61.2 cases for those aged ≥65 years [9–11].

Reported incidences of paediatric IPD across Europe vary widely, and considerable variation is seen even within countries and regions. A systematic review conducted by McIntosh et al. in 2005 of countries in the European Union, as well as Switzerland and Norway, found reported rates of paediatric IPD ranging from 5.9 to as high as 174 per 100,000 children aged <2 years [12]. Factors confounding the ability to capture the true burden of IPD include the pre-emptive use of antibiotic therapy, disparities in practices, inconsistencies in reporting methodology, and a lack of active, integrated surveillance systems [12,13].

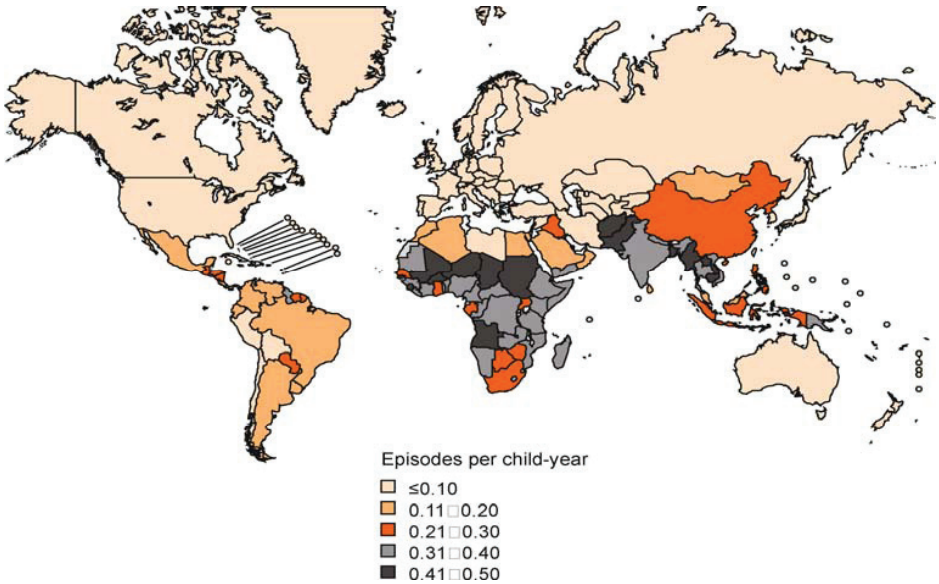

Fig. 2. Worldwide, about 156 million new episodes of childhood clinical pneumonia occurred in 2000, more than 95% of them in developing countries. Used with permission [4].

1.1. Vaccines reduce childhood mortality due to pneumonia

According to the United Nations Children's Fund and the WHO, preventing children from developing pneumonia is essential for reducing child mortality. In addition to promoting adequate nutrition (including breast-feeding and zinc intake), key prevention measures include raising immunization rates and reducing indoor air pollution. Although many pathogens can be responsible, the main bacterial causes of clinical pneumonia in developing countries are S. pneumoniae and Haemophilus influenzae type b (Hib). Three vaccines have the potential to reduce childhood mortality by reducing the incidence of bacterial pneumonia: 1) the pneumococcal conjugate vaccine (PCV); 2) the Hib vaccine; and 3) the measles vaccine, which reduces the incidence of pneumonia caused by serious complications from measles [14]. Pneumococcal diseases account for almost one in five deaths in children aged <5 years worldwide [14], and cause substantial mortality in people aged >65 years [15]. However, in most parts of the world, pneumococcal vaccines are not yet available to a substantial number of children [3]. Unlike the Hib and measles vaccines, widespread global uptake of PCV has not yet been achieved, resulting in significant mortality from vaccine-preventable disease (Fig. 1) [3].

1.2. PCV7 uptake

PCV7 was approved in the United States in February 2000 for children aged between 6 weeks and 9 years, and in the European Union in 2001 for children aged between 2 months and 5 years, in a three-dose, primary-series regimen given at 2, 4, and 6 months followed by a booster dose at 12 to 15 months (a 3+1 schedule) [16–18]. Catch-up schedules and recommendations for vaccination of children at high risk for IPD have also been published [16,19]. PCV7 is currently recommended for all children aged <5 years. PCV7 is the only PCV recommended for children aged >2 years and is the only PCV with large-scale controlled clinical trials demonstrating efficacy and documented effectiveness across various disease manifestations (Table 1) [20–25].

Since approval, more than 235 million doses of PCV7 have been distributed in over 90 countries, and as of May 2009, PCV7 had been incorporated into the national immunization programmes (NIPs) of 36 countries (Wyeth, Data on file). In Europe, 24 (75%) of the 32 countries belonging to a European surveillance network for vaccine-preventable infectious diseases (EUVAC.NET) had adopted policies to implement PCV7 into their NIPs as of January 2009. Seven of these countries offer PCV7 to at-risk groups only [26].

The WHO recommends that inclusion of PCV should be a priority in NIPs of all countries and a high priority in countries where mortality among children aged <5 years is >50/1000 live births or where the child mortality rate is >50,000 deaths annually. In addition, the WHO recommends that countries with a high prevalence of human immunodeficiency virus (HIV) prioritize the introduction of PCV7 and develop policies to target populations with a high prevalence of other predisposing underlying diseases such as sickle cell anemia [15].

Table 1

Efficacy Studies of cross-reactive material (CRM)-conjugate pneumococcal vaccines (PCV7/9v-CRM).

Disease	Study
IPD	US: Northern California Kaiser Permanente (PCV7) [20]
	US: Native Americans [25]
	The Gambia (9v-CRM) [21]
	South Africa (9v-CRM) [23]
Pneumonia	US: Northern California Kaiser Permanente (PCV7) [20]
	The Gambia (9v-CRM) [21]
	South Africa (9v-CRM) [23]
AOM	US: Native Americans [22]
	Finland: PCV7 [24]

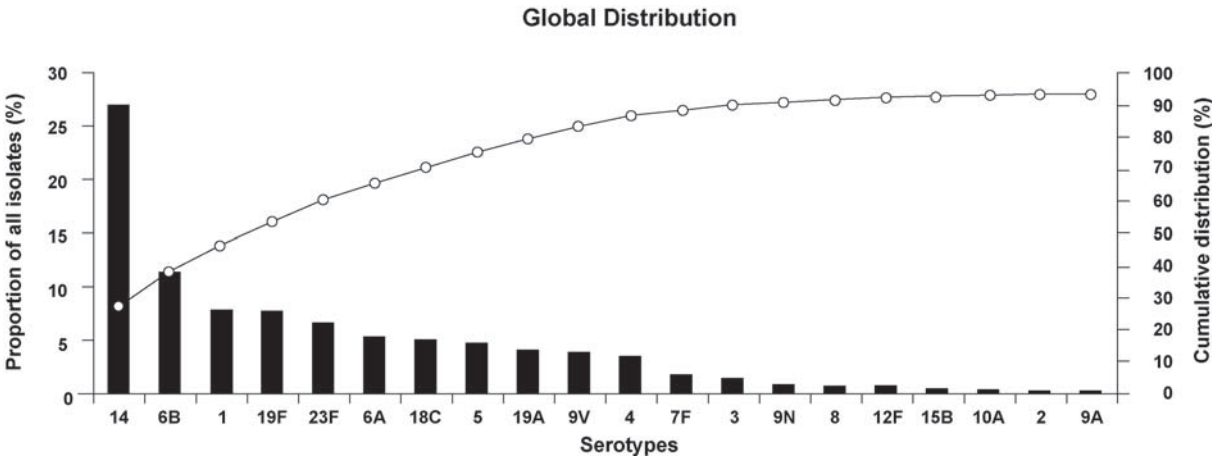

Fig. 3. Proportionate and cumulative serotype distribution of invasive disease-causing pneumococcal isolates among children aged <5 years, globally [31].

A recent analysis performed by the WHO suggested that implementation of PCV at a coverage rate equivalent to that of diphtheria-tetanus-pertussis vaccination could prevent 262,000 deaths per year in children aged 3 to 29 months in the 72 developing countries eligible for support from the Global Alliance on Vaccines and Immunization (GAVI). If every child were vaccinated using the proposed schedule, up to 407,000 deaths would be prevented each year [15]. In 2008, the Centers for Disease Control and Prevention (CDC) estimated that global use of PCV would help prevent an estimated 5.4 to 7.7 million deaths among children by 2030. The use of PCVs has been shown to be cost-effective in preventing childhood mortality in GAVI-eligible countries [27,28].

1.3. Causes of pneumococcal diseases by serotype

While 91 immunologically distinct serotypes of *S. pneumoniae* have been recognized [29], the seven most common global serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) account for approximately 58% to 66% of all serotypes underlying IPD, and 13 serotypes account for >80% of all pneumococcal isolates reported (Fig. 3) [30–32]. Serotype 14 is the most commonly identified isolate from both blood and cerebrospinal fluid in both pneumonia and meningitis cases, and is the most common isolate among children aged <5 years in all regions except Asia. Serotype 1 is more commonly isolated from pneumonia cases, particularly among children aged 2 to 5 years, and is equally widespread as serotype 14 in Asia [31]. Serotypes 1 and 5 are ranked among the top three serotypes in the GAVI-eligible countries, but do not rank within the top six serotypes in North America, Europe, or Oceania. In North America and Oceania, serotypes 18C, 4, and 9V are ranked higher than in the other regions [30].

The proportionate and cumulative distribution of serotypes causing IPD among children aged <5 years globally (as of July 31, 2007) is illustrated in Fig. 3 [31]. There are substantial geographic variations in PCV7 serotype coverage, with the highest rates (80%–90%) reported in the United States, Canada, and Australia, followed by decreasing coverage in Europe and Africa (70%–75%), Latin America (~65%), and Asia (~50%) [33]. The lower coverage rate in South Asia, particularly India and Bangladesh, is due possibly to a paucity of data, the surveillance system methodology, and the higher prevalence of nonvaccine serotypes 1 and 5 in that region. A recent report by the GAVI PneumoADIP (Pneumococcal vaccines Accelerated Development and Introduction Plan) estimated that PCV7 includes 54% to 75% of serotypes causing pneumococcal disease in children aged <5 years in all regions [31].

2. Global Impact of PCV7 on IPD

2.1. Overall impact

PCV7 has demonstrated effectiveness in countries using either a series of three primary doses in infancy followed by a booster dose in the second year of life (3+1), or an alternative schedule of two primary doses followed by a

booster (2+1), as part of a routine paediatric immunization programme (Table 2) [34–40]. Effectiveness ranges from a 56% reduction in Germany 1 year following the NIP to a 98% reduction of vaccine serotype (VST) IPD in the target population in the United States [41,42]. Effectiveness data demonstrating the impact of alternative dosing schedules for the reduction of IPD, otitis media (OM), and pneumonia are now available from the United Kingdom [6,36], Norway [37], Quebec [34, 43], Belgium [38], and Italy [39,40] (Table 2) [35–48]. Effectiveness against VST IPD in a 2+1 regimen ranged from 74% (Norway) to 99% (Quebec, Canada) following the second dose [37,43].

Table 2

PCV7 Effectiveness (vaccine-type IPD).

Country	Effectiveness*
3+1 Schedule (3 primary doses plus booster)	
United States [41]	–98%[a]
Alberta, Canada [44]	–93%
Belgium[b] [38]	–86%
France [45]	–80%[c]
Netherlands [46]	–70% (aged <1 year)
Germany [42]	–56%
Spain [47]	–40% –64% (aged <1 year)
2+1 Schedule (2 primary doses plus booster unless otherwise noted)	
Quebec, Canada [43]	–99%[d] –100%
British Columbia, Canada [35]	–89% <1 year –60% aged <5 years
United Kingdom/Wales [36]	–84%[d]
Norway [37]	–74%
Australia (3+0 with booster for high-risk groups only) [48]	–90%
Italy [39,40]	–71%[e]

*Aged <2 years, unless stated otherwise.
[a] Aged <5 years.
[b]Belgium adopted a 2+1 schedule in January 2007.
[c] Meningitis.
[d]Primary series only (2 doses). Effectiveness following a booster dose given at ≥12 months was 100%.
[e]Pneumococcal pneumonia only.

2.2. Reduction in vaccine serotype disease

Introduction of PCV7 has dramatically reduced VST disease in vaccinated infants and children [34,36,37,41,47,49–58]. Since the introduction of PCV7 in the United States, the rates of PCV7-serotype IPD have dropped among children aged <5 years from about 80 cases per 100,000 population in 1998 to less than 1 case per 100,000 population in 2007 (Fig. 4) [59]. A matched case-control study conducted by the CDC showed that effectiveness against VST disease was 96% (95% CI, 93–98) and 81% (95% CI, 57–92) in healthy children or children with comorbidity, respectively, who received at least one dose of PCV7. Vaccine effectiveness was similar for different pneumococcal syndromes: bacteremia (95%; 95% CI, 89–98) and bacteremic pneumonia (98%; 95% CI, 89–99) [57].

Other industrialized countries have experienced similar results following inclusion of PCV7 into their NIPs, as shown in Table 2 [35–48]. The range of vaccine impact on IPD reflects the geographical variations in pneumococcal

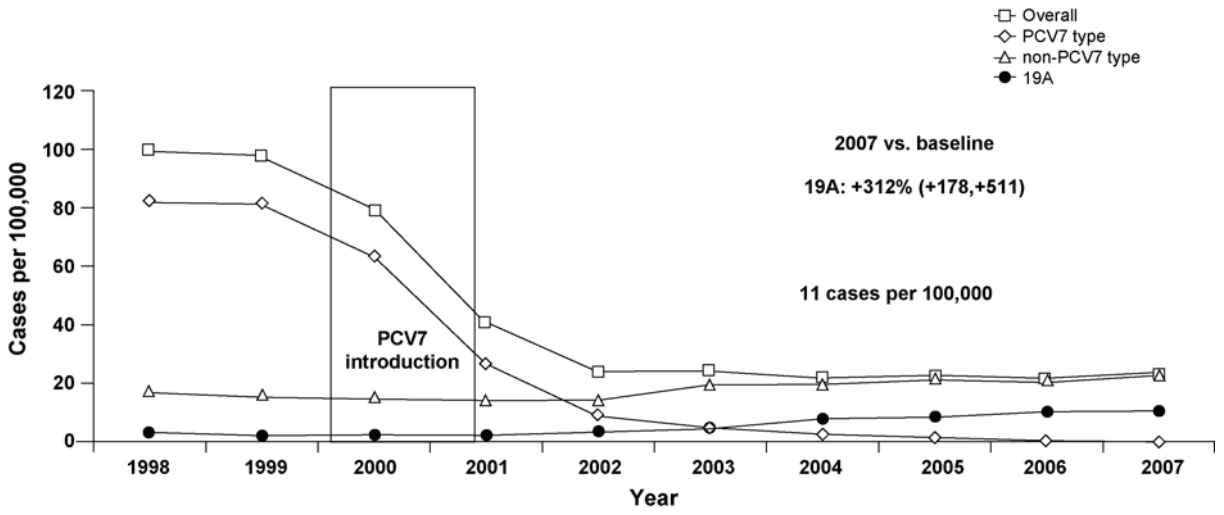

Fig. 4. Rates of IPD among children aged <5 years, 1998–2007 [59].

serotype distribution discussed earlier, as well as the rate of vaccine uptake, completion of dosing schedules, and the prevalence of HIV infection and other chronic illnesses [27].

2.3. Efficacy of a nine-valent CRM-PCV against IPD and pneumonia

Although several emerging and developing countries have implemented vaccination with PCV7, effectiveness data for these countries are not yet available. Efficacy data are available from two pivotal placebo-controlled studies which followed an Expanded Program on Immunization vaccination schedule of 6,10, and 14 weeks and used an investigational nine-valent CRM pneumococcal conjugated vaccine that includes the seven serotypes in PCV7 plus serotypes 1 and 5. In the Gambia, the nine-valent CRM PCV prevented 16% of all-cause mortality compared with controls and was highly effective against IPD, with efficacy rates of 77% (95% CI, 51–90) against IPD caused by VSTs and 50% (95% CI, 21–69) against disease caused by all serotypes. In addition, the nine-valent CRM PCV reduced the incidence of the first episode of radiologically confirmed pneumonia versus controls by 37% (95% CI, 27–45) [21]. The study in South Africa demonstrated a reduction in the incidence of the first episode of VST IPD in infants by 83% versus controls (95% CI, 39–97) and the first episode of radiologically confirmed alveolar consolidation by 20% versus controls (95% CI, 2–35) in non-HIV infected children [23]. This study also established the efficacy of this nine-valent CRM PCV in HIV-infected infants who have a higher burden of disease. The South African cohort was assessed for long-term immunogenicity by extending hospital-based surveillance for all-cause hospitalization of children who participated in the pivotal efficacy study from 2.3 to 6.16 years. At 6.16 years of follow-up, vaccine efficacy against serotype-specific IPD persisted in children who were not infected with HIV (77.8% [95% CI, 34.4–92.5] compared with 83% [95% CI, 39–97] after 2.3 years of follow-up). VST efficacy in HIV-infected children went from 65% to 38.8% (95% CI, -7.8–65.2). These data suggest that a booster dose of PCV7 may not be required in children who are not infected with HIV, as there was no waning of immunity or reduction of protection for VST IPD beyond 2.3 years of follow-up. Conversely, the booster dose of PCV7 may have greater benefit than the primary series in HIV-infected children [60].

2.4. Reduction of mortality

In the United States, national data document a substantial decrease in IPD mortality (defined as any deaths for which the underlying cause of death indicated pneumococcal meningitis or pneumococcal septicemia as contributory causes) in children aged <2 years following introduction of PCV7 [55]. Vaccination with PCV7 resulted in a significant reduction in child mortality from IPD in the first year (rate ratio, 0.39 [95% CI, 0.26–0.50])

[55]. It is important to note that prior to availability of PCV7, almost 70% of reported childhood IPD deaths occurred in children aged >6 months [55], underscoring the importance of three doses of PCV7 in the first 6 months of life as recommended by the American Academy of Pediatrics Committee on Infectious Diseases [16]. Notably, a study based in Olmsted County, Minnesota reported an 83% reduction (odds ratio [OR], 0.17 [95% CI, 0.05–0.55]) in the overall case-fatality rate for IPD, with the greatest decreases in adults aged ≥65 years (86%; OR, 0.14 [95% CI, 0.03–0.68]) and in patients with invasive pneumonia (78%; OR, 0.22 [95% CI, 0.07–0.72]) [61].

2.5. Minimization of racial and social disparities

Widespread introduction of PCV7 appears to have the potential to eliminate racial disparities in the incidence of IPD. In the United States, studies have shown that African-Americans, Native Alaskans, and Native Americans are at an increased risk for IPD compared with Caucasians, and Caucasians had a lower incidence of IPD than African-Americans prior to PCV licensure [62–65]. In 2002, following implementation of a PCV programme in the United States, there was a 75.8% decrease in episodes of IPD among Caucasians and an 83.1% decrease among African-Americans. Among children aged <2 years, the gap in rates between the races was narrowed to nonsignificance [66,67]. In persons aged >2 years, the rates in African-Americans, while reduced, remained significantly higher than seen in Caucasians, but the gap narrowed considerably [66]. Vaccine coverage rates for African-Americans lagged behind those for Caucasians [67]. IPD rates among African-American adults aged 18 to 34 years, excluding HIV-infected patients, remained 4.2 times higher than rates observed in Caucasians [66]. However, the rate of IPD among African-Americans aged >65 years is much lower than that seen in elderly Caucasians, accounting for only 17% of the total cases in the African-American population versus 50% of cases in the Caucasian population [66]. Reductions in IPD were also noted among persons of Hispanic descent; the incidence of IPD fell from 13.6 per 100,000 in 1998–1999 to 10.5 per 100,000 population in 2002. For Hispanic children aged <5 years, IPD rates fell below the targets set for Healthy People 2010 [66].

It is important to point out that children aged <2 years in the Native Alaskan population have rates of IPD two to three times that of the general US population. Following the introduction of PCV7 for routine use in 2000, the rate of IPD in children aged <2 years declined from 403.2 cases per 100,000 population to 134.3 cases per 100,000 population in 2001–2003 (P<0.001), a 67% reduction [68]. During this period, VST IPD incidence declined by 92%, with no significant change in rates for nonvaccine type IPD. Overall, the incidence of VST disease declined by 96% from the prevaccine period to 2004–2006. However, while the incidence of VST IPD declined by 54% from 2001–2003 to 2004–2006, the incidence of IPD overall increased by 82%, with an increase of 130% for IPD due to nonvaccine serotypes, primarily 3, 6A, 7F, and 19A; there was no disease due to serotypes 1 and 5. In contrast, in non-Native Alaskan children, there was no significant increase in nonvaccine serotype IPD during this period [68].

2.6. Reduction of antibiotic resistance

Five of the serotypes included in PCV7 account for most of the antimicrobial-resistant pneumococcal infections. In view of the increasing prevalence of drug-resistant pneumococci causing invasive disease, a vaccine that reduces both invasive disease and the circulation of pathogenic, potentially drug-resistant serotypes is of major public health value.

The rates of IPD caused by penicillin-nonsusceptible (PNS) strains as well as strains not susceptible to multiple antibiotics fell by 57% (95% CI, 55–58) from 1999–2004 following the introduction of PCV7 in the United States. The reduction was most dramatic among children aged <2 years (81% decrease; 95% CI, 80–82), but disease caused by PNS strains also fell by 49% (95% CI, 46–51) among persons aged ≥65 years (Fig. 5) [69], providing evidence of decreased transmission among nonvaccinated individuals.

3. Impact of PCV7 on Noninvasive Pneumococcal Disease

3.1. Pneumonia

Three large randomized trials have demonstrated the efficacy of PCVs against pneumonia [21,23,49]. In the randomized, controlled, phase 3 trial of PCV7 (the Kaiser Permanente trial), PCV7 reduced the incidence of

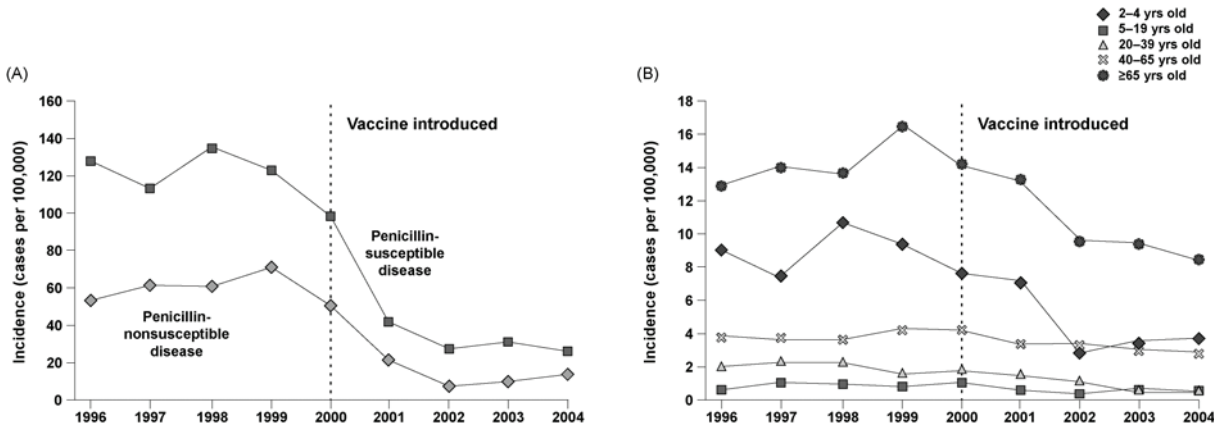

Fig. 5. Penicillin-nonsusceptible strains among persons aged <2 years (A) and 2 to ≥65 years (B). Used with permission. Copyright © 2006 Massachusetts Medical Society. All rights reserved [69].

radiograph-positive pneumonia by 23.4% (95% CI, 5.2–38.1) in children aged <2 years [49]. In addition, in the randomized trials conducted in The Gambia and South Africa, the investigational nine-valent PCV had 37% (95% CI, 27–45) efficacy against the first episode of radiologically confirmed pneumonia [21] and 20% (95% CI, 2–35) efficacy against radiologically confirmed pneumonia among children without HIV [23].

The effectiveness of PCV7 in reducing hospitalization rates due to pneumonia following the introduction of PCV7 has been demonstrated in studies based on large population databases in the United States and Quebec, Canada [34,70–72]. Among children aged <2 years in the United States, rates of all-cause pneumonia hospitalization fell from an average annualized (1997–1999) rate of 1250 per 100,000 children prior to the introduction of PCV7 to 910 per 100,000 children in 2005 and 810 per 100,000 children in 2006, representing reductions of 27% and 35%, respectively [70]. The observed rate of all-cause pneumonia hospitalization did not change significantly among children aged 2 to 4 years in this study, but the hospitalization rate for non-pneumonia acute respiratory infections declined significantly from 2810 per 100,000 during the baseline period to 2190 per 100,000 in 2006 (relative risk, 0.8) [70]. Similar outcomes were reported in two other studies based in the United States [71,72]. The first evaluated data from the Nationwide Inpatient Sample database, a data set comprising approximately 20% of all US hospital admissions from 1997–2004 [71]. Hospitalization rates for all-cause pneumonia and pneumococcal pneumonia declined by 39% (95% CI, 22–52) and 65% (95% CI, 47–77), respectively, among children aged <2 years, and by 17% (95% CI, -3–34) and 73% (95% CI, 53–85), respectively, in children aged 2 to 4 years [71]. The second study, which evaluated data from employer health insurance databases from 48 states and the District of Columbia from 1997–2004, reported 52.4% and 57.6% declines in the hospitalization rate for all-cause pneumonia and pneumococcal pneumonia, respectively, in children aged <2 years [72]. A study based in Quebec, Canada reported a 13% decrease in admissions for all-cause pneumonia following implementation of a 3+1 dose programme for high-risk children in 2002 and a universal 2+1 programme in 2004. The reductions were most marked (69.4%–72.3%) for admissions for lobar pneumonia [34].

3.2. Acute otitis media

Studies published in the pre-PCV7 era demonstrated that OM caused by *S. pneumoniae* is more likely to present with severe signs and symptoms, less likely to resolve spontaneously, and more likely to result in complicated disease compared with OM caused by other bacterial pathogens [73–75]. Randomized trials have demonstrated efficacy of PCV7 against AOM [20,24,76,77]. In the Finnish Otitis Media (FINOM) study, the efficacy of PCV7 was 6% (95% CI, -4–16) against AOM from any cause, 57% (95% CI, 44–67) against episodes of VST AOM, and 16% (95% CI, -6–35) against recurrent AOM [24]. In the Kaiser Permanente trial, the efficacy of PCV7 was 7% (95% CI, 4.1–9.7) against OM episodes, 8.9% (95% CI, 5.8–11.8) against OM visits, 9.3% (95% CI, 3.0–115.1) to 22.8% (95% CI, 6.7–36.2) against frequent OM, and 20.1% (95% CI, 1.5–35.2) against ventilatory tube placement [20]. In a community-randomized trial among Navaho and White Mountain Apache children, the efficacy of PCV7

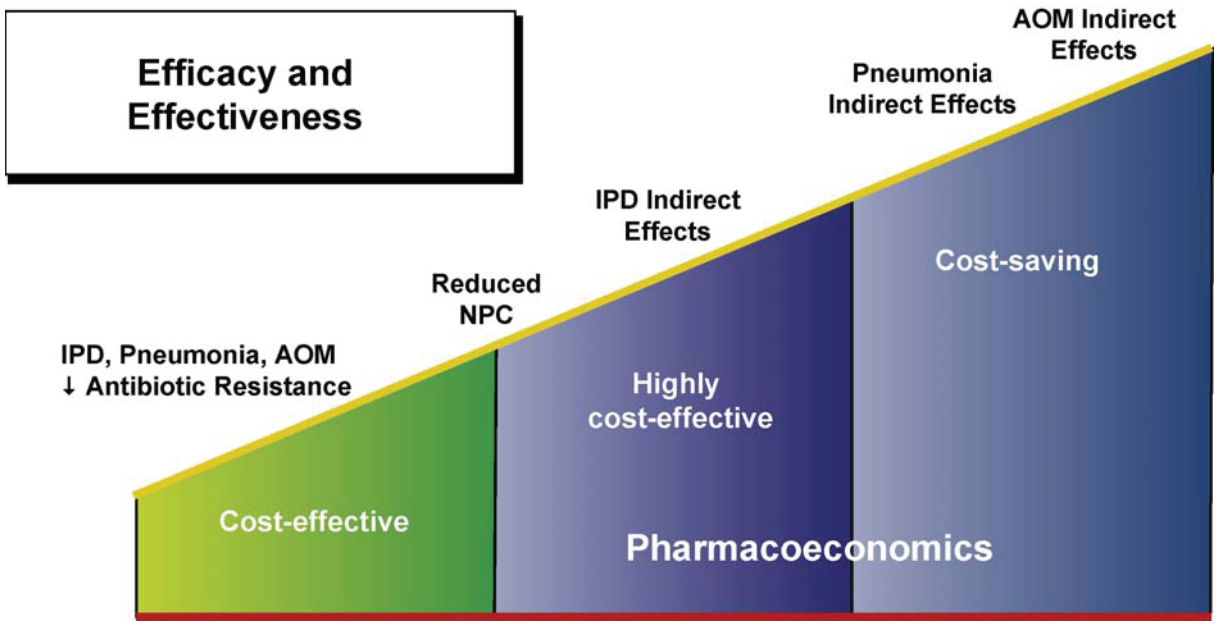

Fig. 6. Cost-effectiveness of pneumococcal vaccination with CRM-based PCVs increases as indirect effects spread to unvaccinated population.

was not significant against AOM (-0.1%; 95% CI, -20.8–17.1) or severe OM (5.1%; 95% CI, -51.5–40.6), but was greater against pressure-equalizing tube (PET) insertion (28.3%; 95% CI, -225.3–84.2) [22].

More recent effectiveness studies conducted during the era of routine and widespread use of PCV7 have demonstrated greater reductions against overall AOM-related visits, recurrent AOM, PET insertions, and other sequelae of AOM compared with the efficacy reported in the FINOM study [24,78,79]. One study reported 17% and 28% reductions in frequent OM and 16% and 23% reductions in PET insertions from 1998–1999 to 2004 in children aged <2 years who were enrolled in managed care programs in Tennessee and New York, respectively [78]. A study based in Australia demonstrated 23%, 16%, and 6% reductions of episodes of myringotomy with ventilation tube insertion in children aged <1, 1, and 2 years, respectively, from 1998 to 2007 [79]. In addition, two studies based in the United States reported declines in outpatient visits for AOM in children aged <2 years following the introduction of PCV7 in the United States [80,81]. The first study, using data from two national healthcare surveys, reported a 20% (95% CI, 2–38) decline in outpatient visits for AOM from 1994–1999 to 2002–2003 [80]. The second study, using data from a large health insurance database covering 48 states and the District of Columbia, reported a 42.7% (95% CI, 42.4–43.1) decline in ambulatory visits for AOM and a 41.9% decline in the number of antibiotic prescriptions for AOM from 1997 to 2004 [81].

4. Impact of PCV7 on nasopharyngeal colonization by vaccine serotypes

Transmission of pneumococcal disease is driven by asymptomatic carriage of pneumococci. Therefore, it is essential to understand the changing dynamics of nasopharyngeal (NP) carriage in communities in which PCV7 is used widely. It is generally accepted that an important effect of PCV7 is the near eradication of VSTs within the nasopharynx, which is followed by replacement by nonvaccine serotypes [82–84]. Overall, the proportion of pneumococci may remain the same or slightly decrease. This phenomenon of ‘replacement colonization’ may be impacted by the rapidity of introduction of PCV and vaccine coverage levels within a population [68]. This noted reduction in NP colonization and interruption of transmission of VSTs has been associated with indirect (herd) effects in the unvaccinated population, as demonstrated in studies showing that NP carriage of VSTs is reduced among unvaccinated members of families with vaccinated individuals [85–87].

5. Indirect (Herd) Immunity in the Community

As a result of decreased transmission of VST strains of pneumococcus from younger, vaccinated children, nonimmunized children and adults have also had decreased incidence of IPD (a phenomenon known as "indirect immunity" or "herd immunity") [15,56,88]. The reduction in disease burden in PCV7-vaccinated populations has been shown to extend to the unvaccinated due to decreased transmission. In 2003, more than twice as many cases of VST IPD were prevented indirectly as were averted directly [58]. This herd immunity is particularly important, because the incidence and mortality rates of pneumococcal disease are high in older adults [64].

Since PCV7 introduction into the recommended infant immunization schedule, the impact on invasive disease caused by VSTs has been profound; reductions have been documented not only in the age group for which the vaccine is indicated (direct effect), but also in unvaccinated persons (indirect effect), highlighting the considerable benefits of routine pediatric use of this vaccine [53,54,58,66,67,85,89–91]. The effectiveness of vaccination programmes extends beyond the immediate reductions in IPD, pneumonia, AOM, and antibiotic resistance in the vaccinated population (Fig. 6). Rates of IPD in infants aged 0 to 90 days, too young to receive pneumococcal vaccination, decreased in eight states following initiation of PCV7, providing evidence of herd immunity in this population secondary to decreased NP transmission of pneumococci from vaccinated to unvaccinated individuals [54]. Data from the Active Bacterial Core Surveillance of the CDC indicated decreases in the rates of IPD in adults in communities where young children had received PCV7 (Fig. 7). In the United States, an estimated 69% of all prevented cases of IPD were attributed to this indirect effect [58]. Similar effects have been reported for adults with other pneumococcal syndromes, particularly pneumonia. The previously described study using the Nationwide Inpatient Sample database showed declines in rates of hospitalization for pneumonia in all adult age groups [71]. These declines were significant only in the group aged 18 to 39 years, with 26% (95% CI, 4–43; P=0.021) and 30% (95% CI, 9–47; P=0.008) reductions in all-cause pneumonia hospitalization and pneumococcal pneumonia hospitalizations, respectively. These reductions are most likely due to the indirect effect on patients in this age group who are parents of immunized children [71].

6. Health Economics

PCV7 vaccination programs are generally well within widely accepted thresholds for cost-effectiveness [92], and more recent data indicate that PCV7 may, in fact, be cost-saving when indirect effects are taken into consideration (Wyeth, Data on file) [93].

Three studies have examined the cost-effectiveness of PCV7 against pneumococcal disease in the United States (Wyeth, Data on file) [94,95]. A study on the cost-effectiveness of PCV7 published soon after licensure in the United States estimated that routine vaccination with PCV7 would result in $757 million (1997 US dollars) saved annually, not including costs of vaccine doses and administration; cost-effectiveness estimates ranged from net savings for vaccine costs less than $46 per dose to $80,000 per life-year saved for vaccine costs of $58 (1997 US dollars) per dose [94]. This model did not incorporate estimated benefits from indirect effects. In contrast, a study on the cost-effectiveness of PCV7 5 years after its introduction compared to no vaccination estimated that PCV7 was cost-effective, with a cost of $7500 per life-year saved when including indirect effects related only to IPD [95]. When indirect effects of hospitalized pneumonia were included, the vaccine was cost-saving. An update to this model that includes 7 years of data and indirect protection against both IPD and hospitalized pneumonia estimates that PCV7 saves approximately $10 billion in medical care costs over the 7-year time horizon (Wyeth, Data on file).

Globally, cost-effectiveness studies of PCV7 vaccination programmes have been published for several countries, covering regions including North America, Europe, Australia, Latin America, and the developing world [28,96–101]. Models that include indirect effects range from being cost-saving to costing €60,000 per life-year saved, from the societal perspective. While cost-effectiveness results vary across studies, indirect effects appear to have a dramatic effect, bringing cost-effectiveness ratios within accepted thresholds for adoption [92], including cost-saving.

Isaacman and colleagues reviewed the literature published between January 2000 and October 2006 on cost-effectiveness analyses of PCV7 vaccination and identified 16 studies that met their inclusion criteria [102]. They found that many of the economic models used similar assumptions: four doses of vaccine administered, 10-year model timeline, 10 years of vaccine protection, and costs and benefits discounted at 3% per year. In terms of vaccine

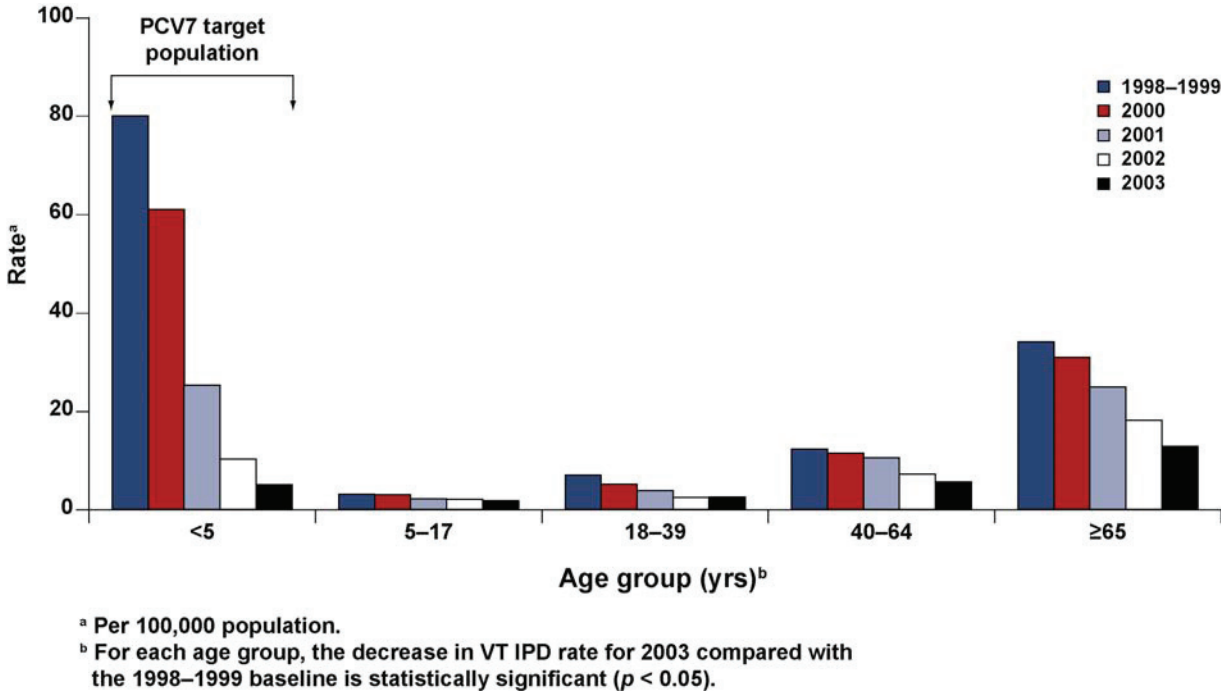

Fig. 7. Rate of vaccine-type IPD before and after introduction of PCV7, by age group and year — Active Bacterial Core surveillance, United States, 1998–2003 [58].

efficacy, they identified the following assumptions: 5.8% to 7.0% against all-cause OM; 17.7% against radiological-confirmed pneumonia; 4.3% to 6.0% against all-cause clinical pneumonia; and 89.1% to 97.4% against IPD. Most models used the CDC estimates of indirect effects on disease rates: 32% decrease in persons aged 20 to 39 years; 8% decrease in those aged 40 to 64 years; and 18% decrease in those aged ≥65 years [56,102]. The results of these studies varied considerably, with the adjusted break-even costs ranging from €12.56 to €72.71 from the societal perspective, and from €5.24 to €38.18 from the payer perspective. In this analysis, the authors noted that studies that included the indirect effects of disease reported much more favorable cost-effectiveness than those that did not include indirect effects [102]. This is consistent with the conclusions of other cost-effectiveness studies [58,72,89,94,99].

Models generated using the WHO 2007 analysis suggest that pneumococcal vaccination at a coverage rate equivalent to that of diphtheria-tetanus-pertussis vaccination could prevent 262,000 deaths per year in children aged 3 to 29 months in these countries at a net cost of €532 million or €63.50 per DALY averted (2008 mid-year exchange rate). This model, which used a cost of 5 international dollars per vaccine dose, was projected to be highly cost-effective in 68 of the 72 countries under consideration [15], even without accounting for indirect effects. A decision-analytic model developed to assess the public health and economic impact of PCV7 in the context of an influenza pandemic in the United States estimated that the use of PCV7 could potentially result in savings of $7 billion over a period of 1 year after accounting for vaccine costs, suggesting an important role for pneumococcal vaccination in influenza pandemic preparedness [103].

7. Safety

The safety profile of PCV7 was established prior to licensure from the results of a clinical study involving more than 18,000 infants and children who received PCV7 at 2, 4, 6, and 12 to 15 months of age [20]; subsequently, the safety profile of the vaccine was further evaluated in the course of a large post-marketing safety study including more than 162,000 vaccinated children [104]. This analysis did not suggest any new safety consideration that would alter the risk-benefit balance of the vaccine and demonstrated the favorable safety profile of PCV7. To date, global

surveillance of spontaneously reported adverse events to the manufacturer, after more than 235 million doses distributed, has confirmed these findings. Additionally, there have been evaluations of the safety profile of PCV7 by the US Food and Drug Administration (FDA), the CDC [105], and the World Health Organization [106]. In both pre- and post-licensure studies, the majority of adverse events were mild and limited in duration; the most common events were localized injection site reactions, fever, irritability, rashes, urticaria, and vasodilation [20,105,106]. The WHO Global Advisory Committee on Vaccine Safety assessed the safety of PCV7 in November 2006 and concluded that the safety data on PCV7 were consistent with those reported in previous studies; the committee confirmed the favorable safety and tolerability profile of PCV7 [15].

8. What We Need

PCV7 was designed to be a public health tool to prevent the morbidity and mortality associated with pneumococcal disease. To date, outcomes of vaccination programs with PCV7 have surpassed expectations beyond the reduction of IPD, and now include important clinical outcomes of reduction of pneumonia, mortality, reduction of NP colonization, and the resultant indirect or herd immunity. Important serotypes with global relevance such as 1, 3, 5, 6A, 7F, and 19A need to be covered by next-generation vaccines. These six serotypes represent 50% to 65% and 15% to 60% of the current IPD cases occurring among children targeted for vaccination in the United States and Europe, respectively [30–32].

The inclusion of serotype 19A in newer formulations of PCV is important in light of IPD surveillance data indicating an increase in this serotype in both PCV7-vaccinated and unvaccinated populations. In the United States, serotype 19A has emerged as an important pathogen implicated in antibiotic-resistant infections [59,107]. Increases in infections due to serotype 19A have also been noted in South Korea [108] and in the Bedouin population of southern Israel [109]. The emergence of multidrug-resistant strains of serotype 19A underscores the importance of circumventing IPD infections due to this serotype by including it in vaccine formulations.

In addition to providing immunogenicity equal to PCV7, any new vaccine must meet WHO antibody threshold concentrations of 0.35 μg/mL one month after a three dose primary series [110], demonstrate a favorable safety profile [110], and be effective in 3+1 and alternative 2+1 dosing schedules with other concomitantly administered vaccines [15]. It will be important to assess extended-valent PCVs' effects on NP carriage, since this will be crucial to expanding the indirect benefits of these vaccines.

9. Looking Ahead

A 10-valent PCV (PCV10) has recently been licensed. It includes serotypes 1, 5, and 7F, in addition to the serotypes in PCV7 [111]. A pivotal trial of PCV10 designed to assess noninferiority compared with PCV7, based on the percentage of infants achieving an antibody threshold of 0.20 μg/mL 1 month after the primary series, demonstrated that noninferiority was met for PCV10 for all but two common serotypes (6B and 23F) [112]. PCV7 elicited statistically significantly higher antibody geometric mean concentrations than PCV10 for all seven common serotypes following the primary series, and for five of the seven common serotypes following the booster dose [112]. Although the clinical relevance of these observations is unknown, it is clear that immunogenicity is a key to the effectiveness of PCVs. Prevention of noninvasive pneumococcal disease and prevention of new acquisition of NP colonization by VSTs is likely to require higher anticapsular immunoglobulin G concentrations than that required for the prevention of IPD [113–115]. Similarly, although reference standards (correlates of protection) for the prevention of noninvasive disease and NP colonization by VSTs have not been established [110,116], it is believed that serological correlates will be higher than those required for IPD [116].

Wyeth Pharmaceuticals' 13-valent PCV (PCV13; with serotypes 1, 3, 5, 6A, 7F, and 19A in addition to the seven serotypes included in PCV7) is built on the scientific foundation of PCV7, and is currently being evaluated by regulatory authorities in several countries. The FDA granted fast-track designation to PCV13 in May 2008, and the company completed its US filing for paediatric use of the vaccine in March 2009. PCV13 was recently approved in Chile. PCV13 will provide the broadest coverage of any PCV. Wyeth is seeking a paediatric indication for active immunization against IPD, pneumonia, and OM caused by serotypes included in the vaccine [117]. The PneumoADIP will work with GAVI-eligible countries to determine the most appropriate vaccine strategy for each country and provide support, including surveillance programmes, as developing nations introduce these PCVs into

their NIPs [27]. There is an acute need for such initiatives, and they will play a significant role in the prevention of pneumococcal disease around the world.

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