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INFECTIOUS DISEASE EPIDEMIOLOGY (A REINGOLD, SECTION EDITOR)

Changing Epidemiology of Pneumococcal Disease in the Era of Conjugate Vaccines

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Abstract Pneumococcal disease is a major cause of illness and death in the young, the elderly, and those with certain medical conditions. Pneumococcal conjugate vaccines are changing both the epidemiology of pneumococcal disease and disease burden. Conjugate vaccines were first licensed in 2000 for use in young children; second generation conjugates covering more serotypes became available in 2009 and are now part of the routine infant immunization programs of most countries around the world. When part of a routine program, conjugate vaccines not only prevent disease in the targeted age group but also in unvaccinated children and adults because of reduced pneumococcal transmission. Measurement of these direct and indirect benefits of immunization programs has illustrated how young children serve as the primary reservoir of pneumococci in the community. Clinical trials of pneumococcal conjugate vaccines have proven to be an effective method for eliciting the proportion of disease syndromes like pneumonia that is caused by pneumococci or pneumococcal and viral co-infections. While these highly successful vaccines are introduced into more places, surveillance programs are monitoring for signs of any increase in disease caused by serotypes the vaccines are not designed to prevent.

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Introduction

The pneumococcus has been recognized as an important cause of serious infections and deaths since it was first identified in 1881 [1]. Over time, the risk of serious pneumococcal disease has dropped with general improvements in health, and the discovery of antibiotics, in particular penicillin, changed the outcome for patients with pneumococcal disease. Vaccines based on pneumococcus' polysaccharide capsule were first introduced in 1977 for broad use in adults in the USA, and this vaccine design has been shown to prevent bloodstream infections in adults [2]. In high-income settings, where most of the population has ready access to high-quality healthcare, deaths from pneumococcal disease occur primarily in older adults [3].

According to WHO estimates, however, pneumococcal disease kills nearly 500,000 children a year [4], with the vast majority of deaths occurring in children <1 year of age in developing countries. In addition, young children have high rates of pneumonia, otitis media, and other pneumococcal infections, and between 40–90 % of children will have pneumococcus in their nasopharynx even when not ill [5]. Because children this young do not respond well to pure polysaccharide vaccines, researchers spent years trying to develop a more immunogenic product to try to reduce pneumococcal disease burden in children. When this product—pneumococcal conjugate vaccine—was finally available in 2000, the epidemiology of pneumococcal disease changed radically in places that first adopted it, and public health leaders became hopeful that large reductions in disease burden and deaths might now be possible worldwide [6].

Pneumococcal Conjugate Vaccines

Pneumococcal conjugate vaccines are constructed of a protein carrier biochemically attached (conjugated) to a particular pneumococcal polysaccharide capsule. Pneumococcus has more than 90 different serotypes, defined based on the polysaccharide structure. The first licensed vaccine included antigens targeting 7 serotypes (Prevnar, Wyeth Lederle Vaccines/Pfizer); the USA became the first country to use the vaccine in 2000 [7]. In 2009, the 7-valent vaccine was replaced by a design targeting 13 serotypes (Prevnar13, Pfizer), and a second manufacturer licensed a 10-valent formulation (Synflorix, GSK vaccines). The vaccines were initially licensed only for use in infants and young children; the 13-valent vaccine was later licensed for older children and adults in some countries.

Before introduction, pneumococcal conjugate vaccines were tested in several clinical trials (Table 1). The first included nearly 38,000 children enrolled in a health system in the USA, randomizing them to receive either 4 doses of 7-valent pneumococcal conjugate vaccine or a control vaccine; the researchers found 97 % efficacy against invasive disease (infections with pneumococcus found in blood, CSF, or other typically sterile body fluids), 30 % reduction in pneumonia with consolidation seen on Xray, and 7 % reduction in clinical otitis media episodes [8–10]. Later trials in Africa using a 3-dose schedule [11, 13], in the USA among Native Americans [12], and in Finland with the 10-valent product [15] also found good efficacy against a range of endpoints; an 11-valent formulation with less clear efficacy tested in the Philippines [14] was never licensed.

The South African trial was notable for testing a 3-dose schedule of a 9-valent vaccine among children with and without HIV infection; the point estimate for efficacy against invasive disease was higher among those without HIV, and protection against pneumonia was only demonstrated for those without HIV infection [11]. In the Gambia, vaccine was efficacious against the typical pneumococcal endpoints; in addition, researchers demonstrated a 16 % reduction in deaths from any cause and a 15 % reduction in hospitalizations, illustrating the contribution of undiagnosed pneumococcal disease to severe infections in that setting [13]. In Finland, a community-randomized trial demonstrated efficacy for both 3- and 4-dose schedules [15]. While the clinical trials demonstrated very promising efficacy against disease endpoints, they also showed that pneumococcal conjugate vaccines prevented acquisition of pneumococcus in the nasopharynx [19]. This effect on carriage would later prove to be the most powerful driver of impact on disease burden.

Demand for 7-valent pneumococcal conjugate vaccine increased quickly after the early clinical trials, but supply limitations initially restricted introductions. When the 13- and 10-valent formulations that covered more serotypes were licensed and supply improved, policy makers in many countries moved quickly to develop immunization policies. By 2014, pneumococcal conjugate vaccines were used in routine infant immunization programs in most countries (Fig. 1). The vaccines' relatively high cost compared to other routinely used vaccines remains a challenge to vaccine introduction in the remaining countries; vaccine cost is a particular barrier in lower middle income countries, those countries with a per capita income too high to qualify for support from the Gavi Alliance [21]. Pneumococcal conjugate vaccines have also been slower to roll out in parts of Asia, where disease burden has less clearly been demonstrated than in Africa and elsewhere.

Effect of Pneumococcal Conjugate Vaccine Use on Pneumococcal Epidemiology

Risk of pneumococcal disease is linked strongly with age, with the highest disease incidence in infants and young children, low incidence in older children and young adults, and increasing incidence with increasing age (Fig. 2) [22–24]. Certain ethnic groups have been shown to have higher disease rates (e.g., Alaska Natives, Australian aboriginals) than the general population [25], and in the USA those of black race have disease rates about twice those of white persons [26]. Measured rates of culture-confirmed pneumococcal disease often differ between countries, largely because of differences in clinical practice with collection of samples for culture [27]. However, rates of pneumonia and culture-confirmed pneumococcal disease in low-income populations with active surveillance typically report disease rates higher than what is reported from high-income countries. Host factors, such as underlying illnesses, can also profoundly affect disease rates. Adults with chronic conditions such as lung disease or diabetes have rates 2–5 times those of healthy adults the same age, while those with immunosuppressive conditions such as HIV infection can have rates >50 times those of healthy persons [28, 29]. Among adults <65 years of age who develop invasive pneumococcal disease, nearly all have either an underlying health problem or are smokers [30].

Introduction of pneumococcal conjugate vaccines for infants has had a profound effect on the epidemiology of pneumococcus. In the USA, rates of invasive pneumococcal disease caused by all serotypes among children <2 years fell from about 180 cases/100,000 population before conjugate vaccine became available to about 35/100,000 in 2009 (9 years after 7-valent vaccine introduction) and 15/100,000 in 2013 (3 years after 13-valent vaccine introduction; Fig. 2) [22–24]. By 2007, diseases caused by serotypes targeted by the 7-valent vaccine were rare [31]. The pneumococcal vaccine program also reduced the burden of several other pneumococcal syndromes, including meningitis [32], pneumonia hospitalizations [33, 34], and infections resistant to antibiotics [35]. Rates of disease caused by vaccine serotypes fell markedly in children of

Table 1 Results from randomized and controlled clinical trials of efficacy of pneumococcal conjugate vaccine in infants and adults against selected clinical endpoints. Results listed are from per protocol analyses unless otherwise stated

Reference	Population	Number of subjects	Pneumococcal vaccine used	Outcome	Efficacy, % (95 % CI)
Black [8–10]	Infants, California	37,868	7-valent (Wyeth)	Invasive disease, vaccine types	97 (83, 99)
				Pneumonia, Xray confirmed, clinical reading	20 (4.4, 34)
				Pneumonia, Xray confirmed, WHO protocol readings	30 (11, 46)
				Acute otitis media episodes	7.0 (4.1, 9.7)
Klugman [11]	Infants, South Africa	39,836	9-valent (Wyeth)	Pneumonia with alveolar consolidation, HIV−	20 (2, 35)
				Invasive disease, vaccine types, HIV−	83 (39, 97)
				Invasive disease, vaccine types, HIV+	65 (24, 86)
				Invasive disease, penicillin resistant	67 (19, 88)
O'Brien [12][a]	Navajo and Apache <2 years	8292	7-valent (Wyeth)	Invasive disease, vaccine types, per protocol	77 (−9.4, 95)
				Invasive disease, vaccine types, intent-to-treat	83 (21, 96)
Cutts [13]	Infants, The Gambia	17,437	9-valent (Wyeth)	Pneumonia, Xray confirmed	37 (27, 45)
				Invasive disease, vaccine types	77 (51, 90)
				All-cause admissions	15 (7, 21)
				Mortality	16 (3, 28)
Lucero [14]	Children 3–24 months, The Philippines	12,191	11-valent (Aventis)	Pneumonia, Xray confirmed	23 (−1.1, 41)
Palmu [15][a]	Children <18 months, Finland	47, 369	10-valent (GSK)	Invasive disease, vaccine types, 3 primary doses plus a booster	100 (83, 100)
				Invasive disease, vaccine types, 2 primary doses plus a booster	92 (58, 100)
Tregnaghi [16]	Children 6–16 weeks, Latin America	23,738	10-valent (GSK)	Likely bacterial pneumonia (either Xray confirmed, WHO protocol reading, or other infiltrate with C-reactive protein ≥40 μg/ml)	22 (7.7, 34)
French [17]	HIV+ adults with previous invasive disease, Malawi	496	7-valent (Wyeth)	Invasive disease, vaccine types, HIV+	74 (30, 90)
Bonten [18]	Adults ≥65 years, The Netherlands	84,496	13-valent (Pfizer)	Pneumonia, vaccine-type	46 (22, 63)
				Invasive disease, vaccine types	75 (41, 91)

[a] These two clinical trials were community randomized; all others used individual randomization

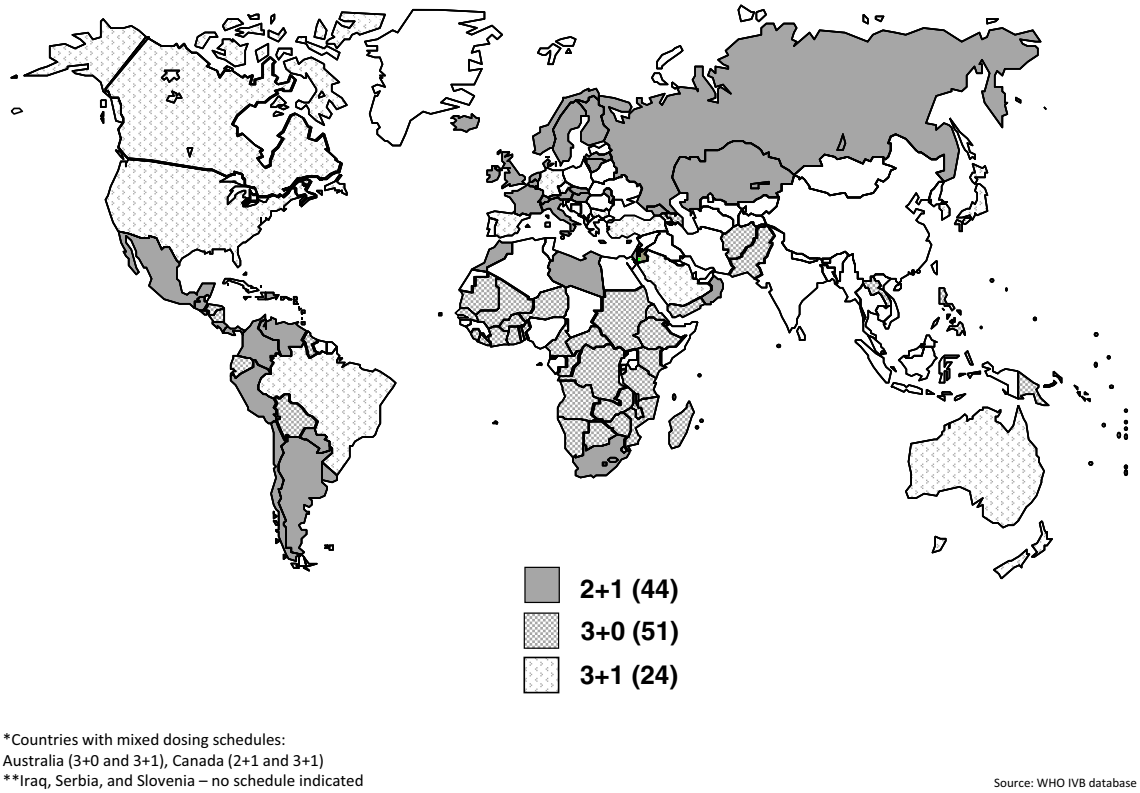

Fig. 1 Countries using pneumococcal conjugate vaccines in their infant immunization schedules as of 31 December 2014 by dosing schedule [20]

all races, leading to similarly low rates among both white and black children [26].

Results similar to those seen in the USA were later seen elsewhere in many high-income settings, such as the UK [36], Australia [37], and Israel [38] (Table 2). Importantly, data from Israel showed large decreases in pneumonia and otitis media following 13-valent vaccine introduction; vaccine impact is more difficult to measure for these syndromes than for invasive disease because pneumococcus is only one of the many possible etiologies for pneumonia and otitis media [43•, 44]. The measured reductions in these syndromes were larger than had been documented in earlier clinical trials of lower-valent vaccines, perhaps in part due to the additional antigens, indirect effects, or prevention of recurrent infections. Results from low- and middle-income countries, which introduced pneumococcal conjugate vaccines somewhat later than

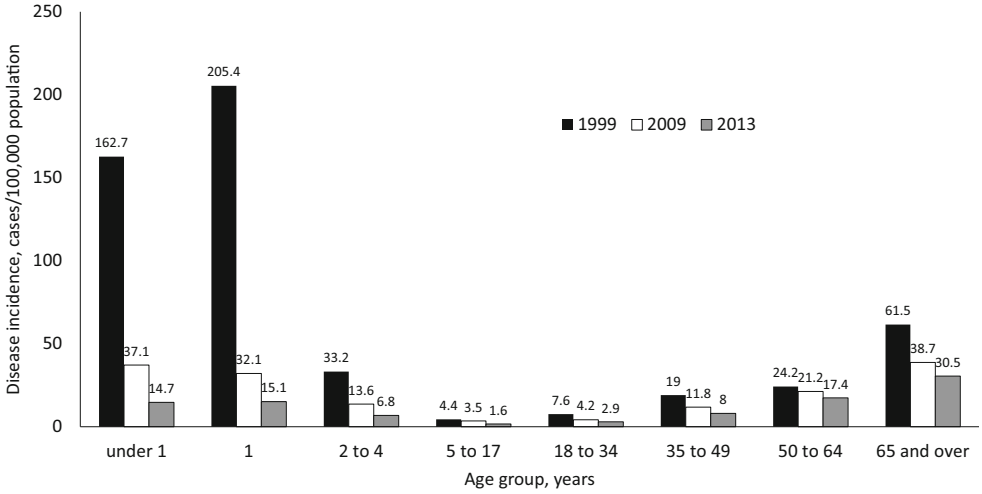

Fig. 2 Incidence (cases/years) of invasive pneumococcal disease in the USA by age group before pneumococcal conjugate vaccine use (1999), 9 years after 7-valent conjugate vaccine introduction (2009), and 3 years after introduction of 13-valent pneumococcal conjugate vaccine for infants (2013) [22–24]

Table 2 Selected reports of the impact of routine use of pneumococcal conjugate vaccines on disease in infants and young children

Reference	Population	Data source	Vaccine product and national schedule	Disease outcome evaluated	Baseline rate (years)	Post-immunization rate (years)	Percent reduction (%)
Moore [39]	10 US sites, children <5 years	Active Bacterial Core surveillance (ABCs)	7-valent (2000–2009) then 13-valent (2010-2013); 3 primary doses + booster	Invasive disease, 13-valent vaccine serotypes	91/100,000 (1998–1999)	1.8 (2013)	98
Miller [40]	England and Wales, children <2 years	National electronic reporting	7-valent; 2 primary doses + booster	Invasive disease, 7-valent vaccine types	41/100,000 (2000–2006)	0.9/100,000 (2009–2010)	98
Waight [36]	England and Wales, children <2 years	National electronic reporting	7-valent (2006–2009) then 13-valent (2010–2013); 2 primary doses + booster	Invasive disease, 13-valent vaccine serotypes	14/100,000 (2008–2010)[a]	1.8/100,000 (2013–2014)	87
Lowbridge [37]	Sydney area, Australia,children <5 years	New South Wales surveillance	7-valent; 3 primary doses (no booster)	Invasive disease, vaccine serotypes	57/100,000 (1998–2004)	1.8 (2008–2010)	97
Von Gottberg [41•]	South Africa	National surveillance (GERMS-SA)	7-valent (2009) then 13-valent (2011); 2 primary doses + booster	Invasive disease, 13-valent vaccine serotypes	46/100,000 (2005–2008)	7.5/100,000 (2012)	84
Griffin [34]	USA,children <2 years	Nationwide Inpatient Sample	7-valent; 3 primary doses + booster	Pneumonia hospitalizations by ICD-9-CM code	1274/100,000 (1997–1999)	723/100,000 (2007–2009)	43
Simonsen [42]	USA, children <2 years	IMS Charge Data (500 US hospitals)	13-valent; 3 primary doses + booster	Pneumonia hospitalizations by ICD-9-CM code	799/100,000 (2007–2009)[a]	665/100,000 (2011–2012)	21
Greenberg [43•]	Negev District, Israel, children <5 years	Prospective surveillance, Soroka University Medical Center	7-valent (2009–2010) and 13-valent (2010–2013); 2 primary doses + booster	WHO protocol Xray confirmed pneumonia hospitalizations	8.7/1000 (2002–2008)	5.6/1000 (2012–2013)	32
Ben-Shimol [44]	Negev District, Israel, children <2 years	Prospective surveillance, Soroka University Medical Center	7-valent (2010–2011) and 13-valent (2012–2013); 2 primary doses + booster	Otitis media with vaccine-type pneumococcus isolated from middle ear fluid	6.6/1000 (2004–2010)	0.5/1000 (2012–2013)	92

[a] This baseline estimate was after the 7-valent vaccine had been in use for several years

many high-income countries, are now becoming available. South Africa was the first country in Africa to introduce pneumococcal conjugate vaccine; in their setting, pneumococcal disease rates have fallen among children both because of pneumococcal vaccine use and also because of highly effective programs to prevent mother-to-child transmission of HIV infection [41•]. In Brazil, early results indicated reductions in pneumonia hospitalizations in several states [45]. In Kilifi district, Kenya, invasive infections caused by vaccine serotypes became rare quickly after the introduction of 10-valent vaccine [46].

One of the surprising findings from the early years following introduction of pneumococcal conjugate vaccine in the USA was the speed at which disease rates fell, in particular because vaccine shortages between 2001 and 2004 meant that many children went unvaccinated or missed doses [47]. The rapid drop in disease rates indicated that the pneumococcal conjugate vaccine program was preventing disease not only in children who received vaccine but in unvaccinated children through reduced transmission of vaccine-type strains—so called indirect or herd effects. While health officials had been hopeful that indirect effects would enhance the overall impact of the pneumococcal immunization program, the magnitude of these effects was larger than expected and indicated that, at least in a high-income setting, young children were the primary reservoir for pneumococci. Models later suggested that the conjugate vaccine's ability to prevent acquisition of vaccine-serotype pneumococci in the nasopharynx was the primary driver of vaccine impact in a population, more so than the vaccines' ability to prevent disease [48].

The indirect effects noted among children extended to preventing disease among infants too young to be vaccinated [49] and to adults. In the USA, disease rates began to fall among adults shortly after the effect was first seen in children [47]. By 7 years after use of 7-valent pneumococcal conjugate vaccine began, rates of invasive disease caused by all serotypes among adults age 65 years and older had fallen by 37 %, including a 92 % reduction in vaccine-serotype disease [31]. Disease rates fell further after introduction of the 13-valent vaccine [50]. A significant reduction in pneumonia hospitalizations was also seen among adults [33, 34, 42]. In the USA, the indirect benefits generated by vaccinating infants, in particular the large reductions seen in pneumococcal disease among adults, have been the primary driver of favorable cost-effectiveness estimates of pneumococcal conjugate vaccine [51].

Vaccination among children has led to similar results in many different populations. In contrast, the striking indirect effects measured among adults in the general US population have not been seen in all populations. No overall benefit was seen among Navajo or Alaska Native older adults, for example. In these populations, conjugate vaccine serotypes only accounted for a small proportion of all disease in the pre-vaccine era [52]. While data on pneumococcal disease among adults are limited from developing countries, results from South Africa show a robust reduction in disease among adults both with and without HIV infection following roll-out of their infant vaccination program [41•].

One concern following pneumococcal conjugate vaccine introduction was that non-vaccine serotypes would simply take over and cause more disease—so called replacement disease—once vaccination removed vaccine serotypes from circulation. This replacement concern was based on results of carriage studies that repeatedly demonstrated that pneumococcal conjugate vaccination does not reduce the overall amount of pneumococci in the nasopharynx; vaccination simply changes the serotypes found in the nasopharynx from vaccine serotypes to non-vaccine serotypes [19]. Replacement disease did in fact occur following the 7-valent vaccine introduction; the first report of significant replacement disease came from surveillance among Alaska Natives [53]. The non-vaccine serotype most commonly noted among those increasing in frequency was serotype 19A; in the USA and elsewhere, a highly antibiotic-resistant 19A strain emerged from a lineage that in the past typically expressed serotype 19F (a vaccine serotype) but that had picked up genetic material allowing it to "switch" its capsule, perhaps as a result of selective pressure induced by widespread vaccination [54]. An assessment of serotype replacement that analyzed data from 21 surveillance systems found that while most detected an increase in non-vaccine serotype invasive disease following the 7-valent vaccine introduction, overall net vaccine program effects were good because reductions in vaccine-serotype disease were greater than increases in non-vaccine serotype disease [55•]. Whether substantial replacement disease will occur following introduction of the second generation conjugate vaccines that cover more serotypes than the 7-valent formulation remains unclear given its relatively recent introductions.

Remaining Questions

In spite of decades of study of the pneumococcus, its epidemiology, and measures to prevent pneumococcal disease, some important questions remain.

What is the Real Burden of Pneumococcal Disease? Current global estimates of pneumococcal disease are based on very limited data. While pneumococcus is relatively difficult to grow in the laboratory, a larger challenge to identifying pneumococcus and therefore estimating burden is the difficulty of getting clinical specimens that will yield pneumococcus from ill patients. Samples of blood and cerebrospinal fluid are collected and cultured for pneumococcus for severely ill patients; however, antibiotics that kill pneumococcus are often given before specimens are collected, lowering the sensitivity

of such tests. In addition, collecting specimens from the site of pneumococcal infection—like deep in the lung—is often impossible. A urine assay is useful for the diagnosis of pneumonia in adults; the assay is not recommended for children however as it can be positive in children who are not ill but carrying pneumococcus in their throats [56]. Because of the limited diagnostic options, some have used indirect markers of pneumococcal infection like C-reactive protein as measures of likely pneumococcal infection [16]. A recent US pneumonia etiology study conducted after many years of routine pneumococcal conjugate vaccine use found few pneumococcal infections, which may in part be because of limited diagnostic options as well as benefit of vaccination [57•, 58].

The pneumococcal conjugate vaccine trials have provided some insight about pneumococcal disease burden, with the proportion of syndromes like pneumonia that was prevented by vaccine providing a minimum estimate of the proportion caused by pneumococcus. The trial in South Africa also provided additional information about the ability of pneumococcus to join forces with viral infections to cause disease. In this trial, vaccinated children had 31 % fewer respiratory infections in which a viral etiology was confirmed by PCR [59]. In a recent US study of pneumonia etiology, 70 % of children and 30 % of adults with confirmed pneumococcal infections had at least one other potentially pathogenic virus detected in the upper respiratory tract [57•, 58]. Therefore, estimates of pneumococcal disease burden should account for infections that occur in conjunction with other organisms.

How do We most Efficiently Use Pneumococcal Conjugate Vaccines Among Children? The World Health Organization recommends pneumococcal conjugate vaccine for routine use in infant immunization programs globally [60], and an increasing number of countries are introducing the vaccine each year. Conjugate vaccines are available at reduced prices for low-income countries, but even these prices are a strain to some immunization program budgets. In addition, programmatic changes such as the move from the oral live polio vaccine to the intramuscular inactivated form have resulted in concern about a growing number of injections at each visit. As a result, investigations into whether a 2-dose schedule is adequate to maintain control of pneumococcal disease transmission are beginning [61]. Given the high prevalence of colonization among older children and adults in some low-income settings compared to high-income settings [62], a reduced-dose schedule may work in some populations and not others. The need for a booster dose at around 1 year of age and whether vaccination of older children (i.e., catch up campaigns) are a cost-efficient means for disease control are also being evaluated.

Should Adults Receive Pneumococcal Conjugate Vaccine? Two clinical trials have demonstrated the efficacy of pneumococcal conjugate vaccines when used in adults. In the first, conducted among adults with HIV infection in Malawi who already had an episode of invasive pneumococcal disease, a 7-valent formulation was 74 % efficacious at reducing invasive disease caused by vaccine serotypes [17]. In the Netherlands, a study of over 80,000 adults age 65 and older found that the 13-valent conjugate vaccine reduced invasive disease caused by vaccine serotypes by 75 % and vaccine-serotype pneumococcal pneumonia by 46 % [18]. These results suggest that conjugate vaccines would be beneficial when used routinely among adults. On the other hand, pneumococcal conjugate vaccine use among infants has done much to prevent disease in adults through reduced transmission of vaccine-type strains, suggesting that vaccination of adults may not be needed because of the low burden of disease caused by vaccine serotypes in a setting with a mature infant immunization program.

Following the Netherlands trial, the US Advisory Committee on Immunization Practices (ACIP) reviewed evidence on whether the 13-valent vaccine should be recommended for all adults age 65 years and older; the Committee had previously recommended the use of the vaccine among adults with immunocompromising conditions [63]. Cost-effectiveness calculations that assumed the reduction in adult disease would follow the pattern seen after the 7-valent vaccine was introduced suggested that routine vaccination of older adults would be cost-effective for a limited number of years [63]. ACIP voted for the use of the 13-valent vaccine for all older adults but added a recommendation to review the policy in 2018 to determine its ongoing usefulness [64].

In low-income settings, large outbreaks of meningitis caused by pneumococcus serotype 1 have been reported from Ghana [65] and Burkina Faso [66]. In both outbreaks, most meningitis cases occurred among adults. Both countries are now using conjugate vaccines for routine vaccination of infants. Whether infant immunization can prevent serotype 1 epidemics is unclear, however. The epidemiology of serotype 1 disease differs from that of most other pneumococcal serotypes, so vaccinating infants alone may not interrupt transmission [67]. If an epidemic were to recur, vaccination of older children and adults could be considered as part of disease control measures.

Will Non-vaccine Serotypes Take Over? Significant replacement disease was seen following routine use of the 7-valent pneumococcal conjugate vaccine in several populations [55•]. Whether substantial replacement disease will occur following introduction of the second generation conjugate vaccines remains an open question, however, some 4 to 5 years after these vaccines were introduced in high-income settings. With over 90 different pneumococcal serotypes capable of causing disease, the fact that vaccines covering so few serotypes can have such an overall beneficial effect is remarkable;

these limited-serotype vaccines work because pneumococcal serotypes differ substantially in their invasiveness or ability to cause disease rather than stay in the nasopharynx [68]. Of particular concern as a potential hotbed of replacement disease is South Asia, where some sites report a higher proportion of disease at baseline caused by non-vaccine serotypes than in other regions. In Bangladesh before vaccine introduction less than half of meningitis episodes were caused by vaccine serotypes [69]. Ongoing surveillance will be important for detecting possible replacement strains and, if detected, evaluating their genetic origin.

Conclusion

Pneumococci are part of our normal flora, only causing disease when they wander outside their normal niche of the nasopharynx, perhaps tempted by a new viral infection. The epidemiology of pneumococcal disease shows that, while anyone can get a pneumococcal infection, the most vulnerable are those that have weak immune systems—the very young who have not yet developed antibodies, the elderly whose antibodies may have forgotten what they once knew, and those with immunosuppressing conditions such as HIV infection. In addition, factors that may encourage pneumococci to wander from their nasopharyngeal niche—like smoking—can increase disease risk.

The availability and introduction of pneumococcal conjugate vaccines have taught us much about the epidemiology of pneumococcal disease, such as how young children serve as the reservoir for pneumococci in a community. If a program vaccinates children and prevents the most invasive pneumococcal strains from circulating, both vaccinated children and unvaccinated persons in the community will have less disease. Pneumococcal conjugate vaccines are an important part of a comprehensive global strategy to reduce pneumonia and diarrhea deaths among children <5 years of age [70••]. The challenge now is to facilitate vaccine introduction into those countries that have not yet developed a policy for routine use and to sustain vaccine programs in places where funding for vaccine purchase is limited.

While pneumococcal conjugate vaccines are still not available everywhere, they are already making a big impact where they are being used. In the USA alone, estimates suggest that nearly 400,000 cases of invasive disease and about 30,000 deaths were prevented during the first 12 years of the conjugate vaccine program [50]. The 7-valent vaccine prevented about 131,000–168,000 hospitalizations for pneumonia per year in the USA [33, 34]. In addition, researchers are pushing for better products even though the existing conjugate vaccines are highly effective. New pneumococcal vaccines are being evaluated that could potentially cost less to produce and cover the majority of pneumococcal serotypes by targeting conserved antigens; conjugate vaccines targeting more serotypes are also under evaluation. Conjugate vaccines have markedly changed pneumococcal disease burden and epidemiology. Ongoing study of pneumococcal epidemiology in a variety of settings will help policy makers with tough decisions as new vaccines become available or existing vaccines need to be supported in the face of an increasing number of competing budget demands.

Compliance with Ethical Standards

Conflict of Interest Cynthia Whitney declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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