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What do you get?

Transmission of pneumococcal pneumonia.

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ABSTRACT

Streptococcus pneumoniae is a polysaccharide encapsulated bacterium responsible for the majority of cases of community acquired pneumonia. The upper respiratory tract of children becomes colonized with pneumococci early in life, from the first weeks of life up to 18 months. Factors which influence timing of colonization include geographical localization, socio-economic circumstances, and household conditions.

Pneumococcal pneumonia to a degree is a seasonal disease, peaking in the winter months. One of the epidemiological determinants is that viral infections (in particular influenza) predispose for pneumococcal pneumonia. The infectious nature of pneumococcal pneumonia was underscored during the COVID-19 pandemic. Due to societal restrictions imposed (face masks, social distancing) the incidence of invasive pneumococcal disease (IPD) dropped, and returned to pre-COVID-19 numbers after lifting of the restrictions.

There are 100 different *S. pneumoniae* serotypes, based on differences in the capsular polysaccharide. Introduction of protein conjugated polysaccharide vaccines (PCV) has reduced the incidence of IPD in children. Because children are the reservoir for other risk groups, in particular the elderly, introduction of PCV has indirectly also reduced the burden of IPD in latter risk group. The first generation of PCV consisted of the seven most prevalent pneumococcal serotypes. After implementation, replacement colonization of the upper respiratory tract with non-vaccine serotypes was observed and also replacement disease. Upcoming 24-valent PCVs will have a much broader coverage, but whether replacement disease now has been eliminated remains to be seen.

Introduction

"What do you get when you kiss a girl?" is a line from the Burt Bacharach song *I'll never fall in love again*. The answer to this open question is in the next line of the song: "You get enough germs to catch pneumonia". What makes this song unique in the context of pneumonia is that it is the only song which emphasizes the infectious nature of the disease. In 1968, the opening night of the musical *Promises promises* was already advertised, but it still lacked a catchy song to end the first episode before the interval. The producer pushed Bacharach, who was admitted to the hospital with pneumonia, to finish the song in a hurry, which he did. Apart from *I'll never fall in love again*, all other popular music songs about pneumonia infer that you can get pneumonia by standing in the rain and/or cold[1].

While pneumonia is a respiratory infectious disease, there is no direct evidence that it can be transmitted by kissing. *Streptococcus pneumoniae*, the bacterium responsible for the majority of cases of community acquired pneumonia, can easily be detected in saliva, either by molecular techniques or conventional bacterial cultures[2,3]. The major risk groups for community acquired pneumonia are the young (infants and toddlers up to the age of 2 years) and the old (from which age is debated, but surely from 65 years onwards). The natural reservoir for *S. pneumoniae* is the upper respiratory tract of young children, from which the bacteria can be transmitted to others, including the elderly[4]. Apart from the "what do you get" therefore also the "how do you get" is an important question. These questions, as well as the impact of vaccination, will be addressed in this review on transmission of pneumococcal pneumonia.

Methods

A weighted linear regression analysis (from week 1, 2018 to week 52, 2022) was performed to assess the effect of season as well as non-pharmaceutical interventions (i.e. the societal restrictions implemented throughout the SARS-CoV2 pandemic) on the incidence of pneumococcal diseases. Analysis was restricted to the United States. Data about invasive pneumococcal disease was available from the American Centers for Disease Control and Prevention and was used ranging from 2019 to 2024 (https://www.cdc.gov/pneumococcal/php/surveillance/index.html; Assessed June 2024). Data about the stringency index was acquired from the Oxford Coronavirus Government Response Tracker (OxCGRT) from 2020 to 2022 (https://ourworldindata.org/covid-stringency-index; Assessed June 2024). The OxCGRT project used nine metrics (school closures; workplace closures; cancellation of public events; restrictions on public gatherings; closures of public transport; stay-at-home requirements; public information campaigns; restrictions on internal movements; and international travel controls) to calculate the stringency index of multiple countries across 2020-2023.

For statistical analysis, data were tested for linearity, normal distribution of error and multicollinearity. Heteroscedasticity was present based on the results of a Breusch-Pagan test ($p < .001$). Therefore a weighted least squares analysis was conducted. The weighted data showed homoscedasticity (Breusch-Pagan test $p = 0.8805$).

Children are colonized with *S. pneumoniae* early in life

Clinical trials using conventional nasopharyngeal swabs and subsequent culturing on blood agar determined that infants 0-2 years of age are colonized with *S. pneumoniae* early in life. This age of first colonization varies among different parts of the world (Figure 1). In North America, the age of colonization ranged from 4 days to 18 months, with a mean age of acquisition of 6 months[5]. A study in Finland found that colonization by 6 months was rare and that most infants were colonized at 18 months[6]. In a different study in Finland, 9% of infants were colonized at 2 months, and a majority (43%) at 24 months[7]. In the Netherlands, 8% of infants were colonized at age 1.5 months, 31% at 6 months, and 45% at 14 months[8]. In other parts of

the world, the age of first acquisition was much lower for most infants. In Papua New Guinea, acquisition occurred as early as day 1 after birth, more than 60% of infants were colonized by 15 days, the mean age of acquisition was 17.1 days, and all were colonized within 3 months[9]. A study in the Thailand-Myanmar border region found that 76% of infants were colonized at 3 months, and 97% by 6 months[10]. In South India, 54% of children were colonized at 2 months of age, 64 % at 4 months and 70% at 6 months, respectively[11]. In Gambia, 30% were colonized by week 1, 60% were colonized by 15 days, 90% by 15 weeks, and all the infants by 4 months[12]. Another Gambian study found similar early acquisition rates, as the mean age at first acquisition was 33 days, respectively[13]. A study in Kenya found that the earliest acquisition was on day 1, 63% were colonized by 3 months, and the median age of colonization was 38.5 days[14]. In South Africa, 3% were colonized by 2 weeks, 64% at 6 months, 95 % by 260 days (8.7 months), and 98% by the first year of life[15]. The overarching trend is that colonization is positively correlated with age[5-8, 12]. However, in low-income countries, it occurs much sooner as compared to medium to high-income countries. Please note that the data cited above are national averages, and that regional or population differences may exist. Furthermore, sampling and microbiological techniques may also vary between studies.

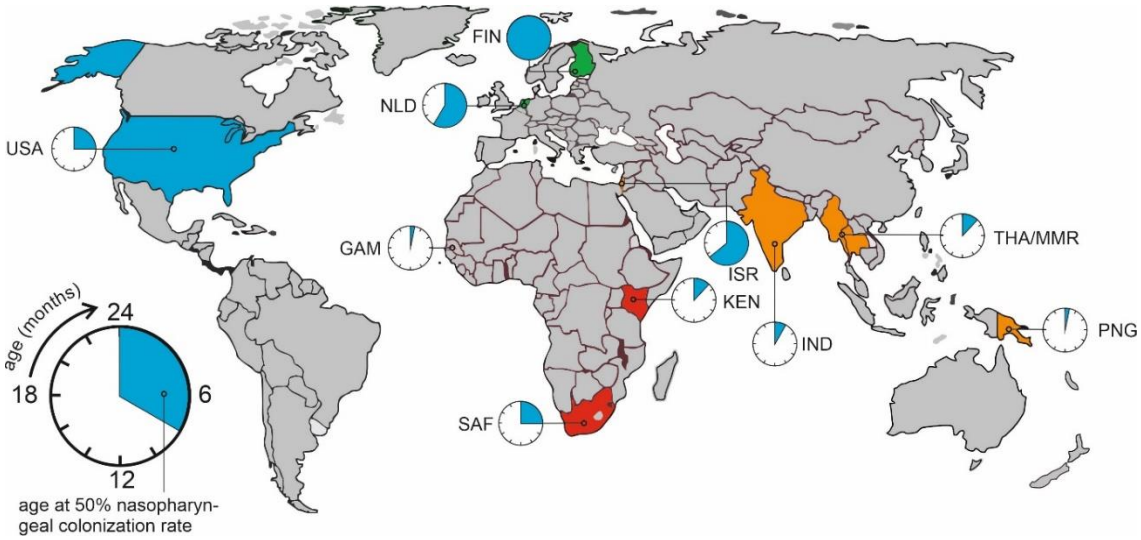

Figure 1. Time of acquisition of pneumococci in the upper respiratory tract. Shown is the age (in months) at which the at least 50% of the children are colonized with pneumococci. Countries are indicated by their alpha-3 codes (https://www.iban.com/country-codes).

Factors influencing early colonization

A number of factors contribute to earlier colonization by *S. pneumoniae*. Crowding is the most significant factor. Living in a larger family with older siblings is associated with an earlier age of first acquisition as *S. pneumoniae* is contagious within families[5,6,16,17]. Older siblings attend daycare and come into contact with other children and people, which contributes to earlier colonization[8,16,17]. Colonization could also be due to exposure of shared toys and surfaces, as pneumococci can be readily isolated from fomites such as plush toys recently manipulated by colonized children, and do not undergo desiccation on surfaces for many days [18] due to biofilm formation and catabolism of capsular polysaccharide as a carbon source [19]. Moreover, first-born children in a family have higher age at first acquisition and they acquired fewer serotypes [5]. In low-income countries, several additional socioeconomic and environmental factors could play a role in the earlier acquisition, compared to their counterparts in high income regions. These factors include maternal and secondary (household) smoking[10,11,14,17], exposure to cooking fumes[14], and home delivery[10]. Moreover, earlier age of acquisition was associated with very low educational levels (<1 year) of the mother[11].

Prevalence of different pneumococcal serotypes and carriage

There are 100 serotypes of *S. pneumoniae* documented as of 2020[20]. The serotype frequency of both colonization as well as pneumococcal disease varies in time, between age groups, geographic location and socio-economic circumstances. Gray et al. showed that serotypes 6, 14, 19, and 23, known as the pediatric serotypes, were the most prevalent ones, and they were acquired earlier and carried for longer periods (mean of 4.2 months) than other serotypes[5]. They are often carried by infants, regardless of their socio-economic circumstances[9]. The occurrence of serotypes causing infection was proportional to the rate of carriage – with serotypes 6, 14, 19, and 23 causing most infections[9]. A trend was observed in the carriage sequence - each consecutive strain was carried for a shorter period than the previous one. On average, the acquisition of a second strain took place six months following the initial one, and the acquisition of a third strain occurred three months later. Additionally, some children acquired more than one serotype[9]. In a trial by Leino et al. in Finland, serotypes 23, 19, and 6 were most common (even in family members > 5 years old). Overall, serotypes 4, 6, 9, 14, 18, 19, 23 comprised 64% of all present serotypes[6]. A Dutch study by Bogaert et al. showed that the most common serotypes were 6B, 19F, 23F, 6A, 3, 11, and 14[21]. This finding is consistent with studies from other European countries. A different Dutch study suggests that repeated pneumococcal carriage is not limited to particular serotypes, as the serotype distribution among two sampling occasions closely resembled that of those at a single sampling time[8]. As indicated above, the serotype distribution of pneumococci may vary in different geographical regions. This variability would imply the need to consider regional factors when assessing pneumococcal carriage dynamics and vaccine effectiveness. In Papua New Guinea, serotypes 6, 19, and 23 were the most prevalent. The observed pattern of carriage was that serotypes 6, 13, 15, 19, 20, 21, 22, and 29 lasted longer than 100 days[9]. Infants on the Thailand-Myanmar border showed a similar pattern, and 19F, 23F, and 6B were the dominant serotypes [10]. In Southern India, the most prevalent serotypes were 6, 9, 10, 11, 14, 15, 19, 23 and 33, which entailed 76.7% of all isolated serotypes [11]. In infants in Israel, the carriage trend showed that there was a lower risk of acquisition of types 6A, 14, and 23F following prior exposure to a homologous serotype[22]. In Gambia, serotypes 4, 6A, 6B, 19F, 23F, and 35B were most prevalent, and serotypes 4, 23F, and 35B were carriers for a shorter period[13]. A study of infants in Turkey found that the carriage rate and serotype prevalence are the same as in other developed countries, but the acquisition is earlier (first two months)[23]. However, in other parts of the world, serotype prevalence in infants differed. For example, a trial in Kenya has shown that 50% of identified serotypes were not included in any current vaccine[14]. In Bangladeshi children, the predominant identified serotypes were 2, 1, 6B, 14, and 5[24]. This distribution differed from the global analysis of serotype distribution because of high frequency of serotypes 12A, 45, 18F that are not covered by any PCV vaccine[24].

Viral infections predisposing for pneumococcal infection

Coinfections play a significant role in both community-acquired and hospital-acquired pneumonia. Children under 5 and adults over 65 are particularly vulnerable. Evidence suggests that influenza alters the immune response and allows pneumococci to thrive in virus-modified environments, leading to severe lung infections[25]. In coinfections, pneumococci utilize sialic acids provided by influenza, facilitating colonization and pneumonia development through aspiration[25]. Viral infections such as influenza further promote pneumococcal colonization[25]. This is because during influenza infection, desialylation of airway epithelial cells enhances pneumococcal adhesion through galectin binding[26].

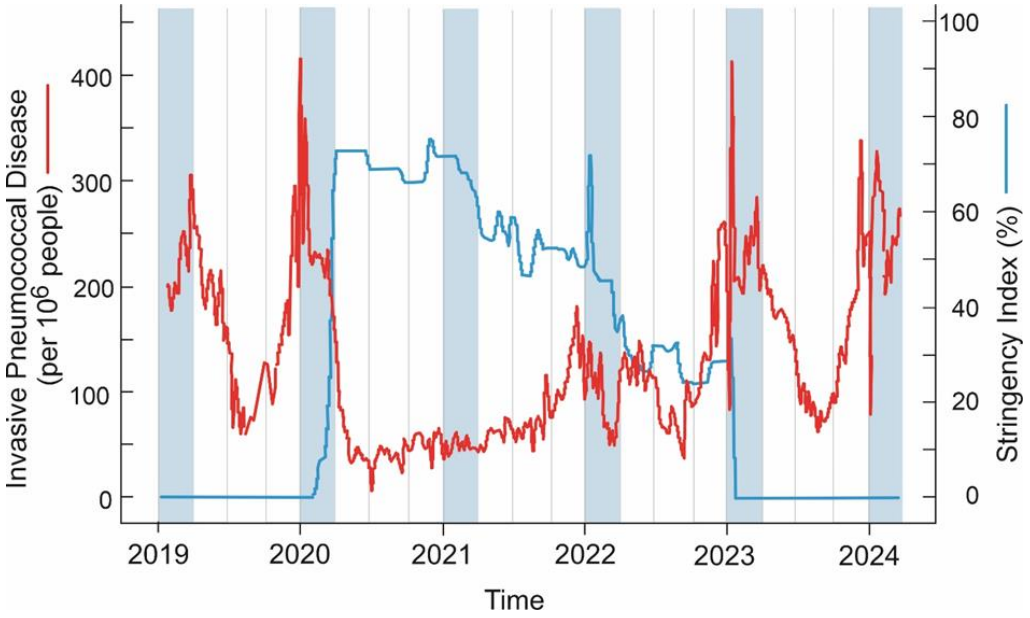

Figure 2. Seasonality of invasive pneumococcal disease and the impact of societal restrictions during COVID-19 restrictions in the USA. The incidence of invasive pneumococcal disease in shown as a red line. The stringency index (as a measure for societal restrictions) is indicated in blue Time scale from week 1of 2019 to week 10 of 2024. Winter periods (January-March) are indicated in light blue.

Seasonality of pneumococcal disease

Like many other respiratory infectious diseases, pneumococcal disease shows a clear seasonal pattern. The data in Figure 2 clearly shows a sharp increase of the frequency of invasive pneumococcal diseases during the winter period. Epidemiological factors associated with this pattern are lower temperatures and higher relative humidity during the winter, with people staying indoors more. Because, as discussed above, viral infections can predispose for pneumococcal infections, the seasonality of pneumococcal disease could closely follow that of influenza[26]. It is also suggested that the immune system would function suboptimal during the winter, potentially related to vitamin D levels.

Apart from environmental conditions, also a number of public holidays with close transgenerational family contacts (Thanksgiving, Christmas, New Year) take place during the winter season on the Northern hemisphere. However, in the Southern hemisphere pneumococcal infections peak in June-August, not during the November-December holiday season[27].

Societal restrictions during COVID-19 had impact on seasonality and incidence of pneumococcal infections

A unique opportunity to study the importance of physical contact for the transfer of *S. pneumoniae* arose when societal restrictions were implemented during the COVID-19 pandemic. These interventions included the closing of schools, wearing of face masks and social distancing, all of which reduce person-to-person contact[28]. Specifically the closure of schools highlights, again, the importance of children in the spread of communicable diseases. Epidemiological observations made throughout the time in which societal restrictions were implemented showed a general worldwide decrease in both COVID-19. But for other communicable viral and bacterial respiratory diseases including *S. pneumoniae* those historical data (i.e. from the period before societal restrictions) were available and also showed a clear-cut decline in the incidence of respiratory infections[28-33]. Figure 2 shows that implementation of societal restrictions in the USA, aimed at controlling the spread of SARS-CoV-2, also reduced the incidence of invasive pneumococcal disease. Lifting of the restrictions lead to recurrence of the seasonal increase of IPD[28]. A weighted least squares regression was used to test if the stringency index significantly predicted the number of IPD cases. The overall

regression was statistically significant (R^2 = 0.4636, F(1, 207) = 178.9, p < .001. It should be noted that the direct effect of societal restrictions cannot be determined due to the multitude of factors that may contribute towards such a decline, it is likely that they played a major role in the reduction of IPD and other respiratory diseases nonetheless[34]. Thus, these observation underline the pivotal role of close physical contact in the direct or indirect transmission of *S. pneumoniae*.

Impact of pneumococcal vaccination.

The best way to manage infectious diseases is through prevention. Vaccines are the most clinical and economically efficient method for preventing illness and death attributable to pneumococcal disease[35]. The first available vaccines against pneumococcal pneumonia were based on capsular polysaccharides which trigger antibody production and opsonophagocytosis[36] (Table 1). The polysaccharide-based vaccine resulted in prevention of invasive pneumococcal infections in adult immunocompetent individuals but not in those that were immunocompromised[37]. The PPV23 vaccine showed to be less effective in the elderly population[38,39]. Moreover, the response to the PPV23 in children younger than 2 years is poor and does not confer clinical protection against disease. The reason is that vaccines purely based on capsular polysaccharides do not induce an immune response in children and elderly population[36]. The vaccine's poor effectiveness in children is attributed to the antigenic nature of the polysaccharide antigen. PS antigens are classified as type 2 T-cell independent (TI-2) antigens, which stimulate mature B cells without requiring assistance from T cells[40]. In newborns, B cells typically do not respond to most PS antigens, and responsiveness develops gradually during the early years of life[41]. Furthermore, TI-2 antigens fail to induce immunologic memory. Anti-PS antibodies generated by the vaccine exhibit low avidity, and limited isotype switching, even after repeated immunizations[42].

Table 1. Composition of pneumococcal polysaccharide and pneumococcal conjugate vaccines

Vaccine	Year of release	Pneumococcal serotypes included
PPV23	1983	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
PCV7	2000	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10	2009	PCV7 + 1, 5, 7F
PCV13	2009	PCV10 + 3, 6A, 19A
PCV15	2021	PCV13 + 22F, 33F
PCV20	2021	PCV15 + 8, 10A, 11A, 12F,15B
PCV24	2024	PCV20 + 2, 9N, 17F, 20B

PPV= pneumococcal polysaccharide vaccine; PCV= pneumococcal conjugate vaccine. The numbers indicate the number of different serotypes included in the vaccine.

By coupling the polysaccharide molecule to a protein, the issue of low immunogenic response in children can be overcome. The principle of increasing the immunogenicity by conjugation of a polysaccharide with a protein was already discovered by Oswald Avery, almost 100 years ago[43]. Conjugate vaccines result in a stronger immune response as polysaccharides being are co-expressed with carrier proteins, allowing for their interaction with the major histocompatibility complex. Consequently, this facilitates the provision of cognate $CD4^+$ T-cell help for the activation of polysaccharide-specific B-cells[36]. The first conjugate vaccine was the seven-valent conjugate vaccine (PCV7). The PCV7 showed to be highly effective in reducing pneumococcal disease

caused by vaccine-included serotypes in young children[44-46] and in elderly population[47]. Vaccination with PCV7 also resulted in a decrease in pneumococcal meningitis[48] and otitis media[44]. Furthermore, PCV7 provided cross-protection for serotype 6A infection, but not for serotypes 6C and 6D cross-protection[49].

In 2009, PCV13 was released which contained the serotype 19A and 5 other additional serotypes, as well as those included in PCV7. PCV13 provided optimal and larger coverage against pneumococcal disease than PCV7 in children (Table 1)[50,51]. PCV13 was also effective in pneumococcal disease prevention in the elderly population[52]. The development of PCVs incorporating more serotypes has continued and currently a 24-valent (PCV24) vaccine is in the stage of clinical testing in humans. The PCV24 showed to achieve higher serotype valency and enhanced immune response compared to the PCV20 in adults[53] as well as in toddlers[54]. While PCV24 has a much broader serotype coverage, for parts of the world such as China the coverage of PCV24 would still only be 64%[55].

Transmission of *S. pneumoniae* from infants to elderly and impact of vaccination

The introduction of PCV10 and PCV15 in national childhood vaccination programs has reduced the incidence of mucosal pneumococcal as well as invasive pneumococcal disease (IPD). Childhood vaccination also had an indirect effect on pneumococcal disease in the elderly. Many studies have shown the connection between introduction of pediatric PCVs and the reduction of pneumococcal disease in the elderly population[34,47,56-60]. This is explained by the fact, as discussed above, that children are generally the ecological niche of *S. pneumoniae* and thus an integral part of the transmission route of pneumococci to the elderly population[4,29]. It should be noted that, in most of these studies, only cases of IPD were included. This means that mucosal pneumococcal diseases such as CAP would not be included when assessing the benefit for the elderly population from pediatric vaccination programs. However, a study by van Werkhoven et al. in 2016 showed that IPD data sufficiently represented CAP cases when it came to assessing the involvement of elderly[62]. Therefore, it can be assumed that studies that used IPD as a measure can be considered to be representative of other pneumococcal cases too, therefore increasing the representativeness of these studies when it comes to the prevalence of *S. pneumoniae* as a whole.

Serotype replacement and replacement disease

Many studies have shown a shift in nasopharyngeal colonization patterns of *S. pneumoniae* serotypes as a result of the introduction of PCVs within a population[63-71]. All of these studies show a decrease in vaccine-type serotypes with a concomitant increase of non-vaccine serotypes which will occupy the newly available ecological niche. Such a change in colonization pattern is of importance because pneumococcal carriage precedes disease[71], and thus may result in so-called "replacement disease", pneumococcal disease caused by non-vaccine serotypes[72]. The pattern of recolonization can be of interest as it might be able to predict which pneumococcal serotypes could cause future replacement disease, and thus could be candidate serotypes to be included in next generation conjugate vaccines.

Unfortunately, the replacement serotypes are not necessarily the ones originally 'next in line' when compared to serotype prevalence pre-vaccination but rather increase in prevalence based on other factors[64,65,70]. These could include niche preference, antibiotic susceptibility and others[29].

Interesting is that, after the introduction of PCV7, serotype 19A increased in prevalence within all age groups worldwide[47,73,74]. Serotype 19A became one of the most predominant serotypes for IPD in children and elderly adults[73]. The replacement disease of serotype 19A was remarkable because serotype 19F was included in PCV7. This is in

contrast with the concept of "cross-protection" which states that serotype-specific antibodies can offer protection against serotypes within the same serogroup, although the efficacy of these cross-reacting antibodies may differ[31]. However, at the same time, a decrease in serotype 6A was observed following introduction of PCV7 (which included 6B)[69]. These observations highlight the existence of differential cross-protection between serogroups, with some serotypes offering more protection to other serotypes within the serogroup they belong to than other serotypes might. Cross-protection, or the lack thereof, and replacement disease therefore are still aspects of the "what do you get" and "how do you get" questions on transmission of pneumococcal pneumonia that still are not fully answered.

Conclusions

So what do you get with a 24-valent PCV? You will get immunity against the 24 most prevalent pneumococcal serotypes. This will provide protection against the prevalent serotypes in many parts of the world, not just Northern America and Western Europe, but probably still incomplete in (parts of) Asia. Vaccination will also prevent colonization of the upper respiratory tract with these 24 vaccine serotypes. The indirect effect of reduced colonization of young children is that transmission to the vulnerable elderly population will be reduced as well. In young, vaccinated, children, the ecological niches of the upper respiratory tract can be (and will be) repopulated with representatives of the 76 non-vaccine pneumococcal serotypes. Which serotypes that will be cannot be predicted. Neither can it be predicted whether replacement colonization would lead to replacement disease (as was the case with 19A following introduction of PCV7) in the young, and potentially also the elderly population. Close monitoring of pneumococcal carriage and disease therefore remains warranted.

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