Title

Maternal and neonatal pneumococcal vaccination - where are we now?

Abstract

Pneumococcus is a significant pathogen in neonates and in early infancy, particularly as a cause of invasive disease in sub-Saharan Africa where nasopharyngeal carriage rates are also exceptionally high. The pneumococcal-conjugate vaccines have now been rolled out in many high income settings and an increasing number of low and middle income countries. They have been highly effective at preventing vaccine serotype disease in infants. However, a window of susceptibility remains prior to the first vaccination at around six weeks of age. This paper summarizes the data available on both maternal and neonatal vaccination to prevent disease in newborns and early infancy and considers the key challenges and next steps for research in the field

Keywords

Streptococcus pneumoniae; pneumococcus; maternal vaccination; neonatal vaccination; 23-valent pneumococcal polysaccharide vaccine; pneumococcal conjugate vaccine; safety; immunogenicity; nasopharyngeal carriage

Introduction

The last decade has witnessed important reductions in under-five mortality [1]. Despite this, most countries have fallen short of the rate of reduction required to meet Millennium Development Goal 4, which called for a two-third reduction in under-five mortality by 2015 [1]. Seventy percent of under-five mortality occurs in those under the age of one and of these, 40% occurs in neonates. Globally, nearly half of all deaths in children under-five years of age happen in sub-Saharan Africa with a further one third of deaths occurring in south Asia [1]. Consequently, as we move into the new post-2015 sustainable development agenda, child survival strategies that aim to reduce mortality in early infancy in low and middle income countries, have some of the greatest potential for life saving impact [2, 3]. Within sustainable development goal three, related directly to health, the aim is to reduce neonatal mortality to an absolute value of 12 per 1000 live births or fewer, irrespective of the starting rate in 2015. This goal reinforces the need for logistically feasible and economically viable strategies targeting disease in this age group [4].

Pneumococcal carriage and disease in early infancy

Streptococcus pneumoniae (pneumococcus) is a leading cause of childhood disease worldwide. Recent estimates suggest it is responsible for around 11% of all deaths in children less than five years of age and that over half of these deaths occur in Africa with up to a further quarter occurring in Southeast Asia [5].

Infants, particularly in low-income setting, become rapidly colonized with bacteria in the nasopharynx. Data from The Gambia indicate that over 80% of infants will be colonized with the bacteria over the first two months of life [6, 7]. Similarly, over 50% colonization has been reported at two months of age in South India; around 70% by the age of three months in a study undertaken in Bangladesh [8, 9]; and close to 100% in indigenous infants in Australia by three to four months of age [10]

Colonization is an immediate precursor to disease [11], and in settings with high colonization rates in early life, disease is likely to follow. Reflecting this, a recent systematic review indicated that the pneumococcus was responsible for 16.5% (95% CI: 13.5-20.1) of cases of community acquired neonatal sepsis in sub-Saharan Africa and was second only to *Staphylococcus aureus* in this setting. Furthermore, across all low and middle income countries the bacteria was responsible for 31.8% (95%CI: 18.1 - 45.6) of community acquired neonatal sepsis in infants between two and three months of age making it the most common invasive pathogen in this age group by a significant margin [12]. A recent review of bacterial isolates from cerebrospinal fluid (CSF) taken from infants under two months of age with suspected meningitis in Malawi identified the pneumococcus in 21.7% of samples taken in the first week of life. Pneumococcus was second only to Group B streptococcus over this period. Beyond the first week of life, 41.9% of CSF isolates were identified as pneumococcus [13]. A comparable study aiming to identify the aetiology of invasive infection in Gambian infants over the first three months of life reported that 47% of cases of culture-proven meningitis were caused by pneumococcus [14]. Finally, an association has also been demonstrated, in indigenous Australian infants, between the nasopharyngeal pneumococcal carriage and the occurrence of chronic suppurative ear infections [10]; a condition which is also reported with variable prevalence in sub-Saharan Africa and South and East Asia [15]. Once established, as early as the first two or three months of life in this indigenous infant population, the infection is associated with prolonged morbidity, including educational disadvantage, throughout childhood [10, 16, 17]. Of note, there are

currently limited data on the overall burden of disease from countries such as China and India which have large populations under five years of age; much less on the burden of disease in early infancy in these countries. Consequently, certain figures are necessarily estimations [5]. In addition, the sole reliance on culture in the studies reviewed above will tend to under-estimate the frequency of pneumococcal infection in settings in which oral antibiotic use is widespread without prescription. Importantly, the data reviewed above are taken from a period before the established use of the pneumococcal conjugate vaccines (PCV) in low and middle income settings. These vaccines have had significant impact not only on pneumococcal disease caused by serotypes in the vaccine but also on pneumococcal carriage of vaccine serotypes which will now be considered.

Indirect protection from pneumococcal-conjugate vaccines in early infancy

Pneumococcal-conjugate vaccines are currently recommended by the WHO within the Expanded Programme on Immunization (EPI) schedule according to either a '3+0' schedule administered at around six, 10 and 14 weeks of age or a '2+1' schedule with two doses given starting at around the same age, followed by a booster dose at between nine and 15 months [18, 19]. In either case, infants are not directly protected against pneumococcal disease - as a result of active immunization - until approximately two weeks after the primary schedule has been completed. During introduction of PCV into National Immunization Programmes the '3+0' schedule may be preferable in those settings in which disease incidence peaks in infancy and where vaccine coverage is relatively poor beyond the infant primary series. The '2+1' schedule may be more suited to those settings with a later peak of disease, as observed in higher income countries, and may offer enhanced or more sustained protection against certain serotypes [20]. Nonetheless, both schedules have been implemented to good effect and any differences between them are likely to be limited once programs are established [20].

The indirect effects of PCV vaccine introduction on individuals too old to have been vaccinated within EPI, have been demonstrated for vaccine-type (VT) invasive pneumococcal disease (IPD), VT nasopharyngeal carriage as well as for clinical pneumonia [21]. These effects have now been documented in high income and subsequently also in middle and low income countries including in sub-Saharan Africa [21-27].

Herd protection against IPD in newborns, prior to the age of first vaccination, has also been demonstrated in high income settings [24, 25]. A prospective, population-based study was conducted in the United States, examining the rates of invasive pneumococcal disease (IPD) in infants between 0 and 90 days of age, before and after the introduction of the seven-valent pneumococcal conjugate vaccine into the routine programme. At the time of introduction, the vaccine was recommended as a three dose schedule, starting at two months, for those under the age of six months, with two doses being recommended for those between six and 24 months. A booster dose of the vaccine at between 12 and 15 months was also recommended for infants who were under 12 months at the time of the primary series [28]. In the subsequent study, the rates of IPD in infants under 90 days of age fell from 11.8 per 100 000 live births in the pre-vaccination era to 7.2 per 100 000 live births in the post-vaccination era. When examining IPD caused by VT pneumococci alone, the equivalent figures were 7.3 per 100 000 in the pre-vaccination era compared to 2.4 per 100 000 in the post vaccination era. Nonetheless, 40% of IPD in infants aged under 90 days of age continued to be caused by VT pneumococci 4 years after introduction of PCV7 in a '3 + 1' schedule which included a catch-up campaign [24]. In a comparable study undertaken in the UK, the overall incidence rate of IPD in infants under 90 days of age showed a non-significant decline following vaccine

introduction. Seven-valent VT isolates accounted for 44% of IPD in this age group in the pre-vaccination era, falling to 10.3% three to four years following vaccine introduction which again included a catch-up campaign targeting all those under two-years of age [25].

At present, there are no published data examining the effects of PCV introduction on IPD in early infancy from middle or low income settings. However, a study undertaken within a trial of a nine-valent pneumococcal conjugate vaccine in The Gambia examined VT pneumococcal carriage in the younger siblings (average age three months) of vaccine and placebo recipients and found no differences in the carriage rates between the two groups (VT carriage prevalence 35.3% and 37.1% in the younger siblings of those in the vaccine and placebo groups respectively (Risk Ratio (95% CI): 0.95 (0.78 - 1.16)) [29]. Similarly, a study nested within a phase 3, community-randomized, efficacy trial undertaken within the Navajo and White Mountain Apache Indian communities in North America did not find differences in the VT colonization of two month old infants from communities in which the seven-valent PCV had been introduced compared to control communities [30].

Whether these early data will translate into an ongoing burden of disease in early infancy in low income settings, once programmatic delivery is well established, remains to be seen. Nonetheless, the epidemiology of the pneumococcus is very different in many low and middle income countries, from observations in those high income countries where the vaccines were first introduced. For example, in the Gambia, pneumococcal carriage remains high into adulthood - providing a continued reservoir for potential transmission to young infants. It is uncertain yet whether an adult pool of carriage will be reduced sufficiently by infant immunization to halt potential transmission. In a cluster-randomized trial undertaken across villages in a rural part of The Gambia, vaccinating all children between two and 30 months of age reduced the carriage of VT pneumococcal serotypes in infants of less than two months of age by only around 10% - to 38%. In contrast, additionally vaccinating older children and adults reduced carriage to 17% - a reduction of around 30% - confirming older children and adults as an important source for transmission to infants [31]. Consistent with this finding, recent modeling data from The Gambia suggest carriage of serotypes included within the 13-valent vaccine will continue at a level of between 25 and 40% - even assuming 100% coverage over a 20 year period. The same model predicts rapid VT elimination in all age groups in the UK, even at 80% coverage, highlighting the fundamental difference in transmission dynamics between these settings [32].

Finally, any indirect protection which may be generated in infants is unlikely to impact on all serotypes equally. Highly invasive strains such as serotypes 1 and 5 are rarely carried and hence may be less susceptible to indirect effects while causing a disproportionate amount of disease in Africa [33]. In The Gambia, data collected since the 13-valent PCV (PCV13) was introduced, demonstrate that serotypes 1 and 5 alone have continued to cause a significant proportion of IPD in infants below 5 months of age [34]. Thus, even if modest indirect protection against carriage is generated, it seems unlikely to entirely address invasive disease in this age group.

Therefore, in summary, despite the increasingly widespread roll out of PCV within the infant EPI schedule of low and middle income countries and the associated herd protection the vaccines induce, a burden of disease related to VT pneumococcus in early infancy may persist and vaccination of pregnant women (maternal) and neonates therefore warrants ongoing consideration.

Pneumococcal vaccine use to prevent disease in early infancy

Maternal vaccination

There has been a recent renaissance of interest in the use of maternal immunization as a way to protect neonates and in some cases expectant mothers from infectious diseases prominent in either group. Pathogens targeted include not only tetanus but also pertussis, influenza, and an increasing range of other agents causing morbidity and mortality these populations [35]. However, the approach is not a new one. Trials examining the administration of the 23-valent pneumococcal polysaccharide vaccine to expectant mothers have already been undertaken in high income as well as in low and middle income countries and in widely distributed geographic areas (Table 1). None of the studies reported any safety concerns related to the vaccine administered during pregnancy and reported a low level of local or systemic reactogenicity overall.

Polysaccharide vaccines do not generally prevent colonization of the nasopharynx - even in the vaccine recipient (i.e. in this case the mother) [36]. This represents one of their major disadvantages over the polysaccharide-conjugate vaccines (e.g. Prevenar13™ and Synflorix™). In addition, the antibodies generated by polysaccharide vaccines tend to be less efficiently transferred across the placenta than those generated by protein vaccines, including conjugate vaccines [37, 38]. This may reflect the predominate induction of IgG2 - the isotype for which active transport is least efficient - by the T-cell independent polysaccharides. In contrast, IgG1 is the predominant IgG isotype generated with T-cell help and is most efficiently transported across the placenta [39-42]. However, of note, the only trial which has directly examined the transfer of the pneumococcal serotype 19F-specific in comparison to tetanus toxoid-specific IgG, IgG1 and IgG2 reported a consistently lower placental transfer for the polysaccharide-specific antibodies irrespective of whether total IgG or the IgG1 or IgG2 isotypes were examined [43]. In this study the cord/maternal antibody ratio was above one only when tetanus toxoid-specific IgG1 was examined, indicating an apparent inefficiency of antibody transport across the placenta for polysaccharides-specific antibodies in general, at least in this context [12]. This finding is supported by the other studies which have examined the phenomenon and have consistently reported transfer ratios of less than one for pneumococcal polysaccharide-specific IgG (Table 1). In contrast, studies examining the transfer of protein-specific IgG report transfer ratios ranging from 1.3 to 1.6 for pertussis, (according to pertussis antigen examined), 1.6 for diphtheria toxoid and between 1.4 and 1.7 for tetanus toxoid [37, 38].

Despite the relative inefficiency of antibody transfer across the placenta, those studies which have examined the polysaccharide-specific IgG levels in the infant at delivery or prior to infant vaccination have generally reported higher antibody levels in the infants of mothers vaccinated during pregnancy compared to controls [43-47]. The half life of polysaccharide-specific antibody in the infant is subsequently variable and appears study- (or context) as well as pneumococcal serotype dependent. The latter may reflect differences in the predominant isotypes generated against individual polysaccharides, although there is little data examining this in the context of pneumococcal vaccination. Some studies demonstrate antibody persistence above control at 5 months while in other studies the infants of vaccinated and control mothers are essentially indistinguishable based on serological measures within three to four months [43, 46-48]. The only study to estimate the time for the polysaccharide-specific antibody concentration to fall below the 0.35μg/mL correlate of protection was conducted in an HIV positive maternal population. This study reported geometric mean concentrations (GMC) above the

threshold for a period of 0.6 months from birth for serotype 3 as compared to 2.0 and 2.7 months for serotype 5 and serotype 6B respectively [49].

Four trials have also reported the effects of maternal pneumococcal polysaccharide vaccination on breast milk IgA. In each case, the level of polysaccharide-specific IgA was higher in the breast milk in vaccinated compared to control mothers. Levels returned towards baseline by around six months in each case although with some variation in the exact time of sampling [16, 43, 47, 50]. Given the primary site of pneumococcal colonization in the nasopharynx, antibodies delivered in this way may reasonably be expected to provide local protection although there are no data to examine this directly.

Three trials have reported pneumococcal nasopharyngeal colonization rates in infants born to mothers vaccinated with a 23-valent pneumococcal polysaccharide vaccine during pregnancy compared to controls. In a study conducted in the United States, nasal washes were undertaken on infants between two and 15 months of age although an average of only 1.6 washes per child were obtained over this period and the time points are unclear. At 2 months of age, no infants born to mothers who had been vaccinated and only eight percent of infant (3/36) who were born to mothers in the control group were colonized with pneumococcus (difference non-significant). At 16 months the equivalent figures were 16.6 percent (3/18) and 50 percent (19/38) ($p=0.021$). No significant differences were detected in serotype distribution, a reflection of the low number of isolates overall. The apparent difference in colonization at 16 months is difficult to reconcile with the rates on antibody decay reported. The GMC to the four serotypes tested had returned to baseline before seven months [47]. Two additional studies have reported overall pneumococcal colonization rates in infants at three and six months. A study undertaken in Bangladesh reported that 50 percent of the infants were colonized with pneumococcus by three months and three-quarters by six months but these figures were unaffected by maternal polysaccharide vaccination [43]. A Brazilian study reported that around 17 percent of infants were colonized at 3 months and by six months between 26 and 27 percent had carried the bacteria although again maternal vaccination did not alter the total pneumococcal carriage rates and serotype specific carriage was not reported [51]

Pneumococcal disease outcomes (including meningitis, pneumonia, otitis media and mortality from acute lower respiratory infections) were reported in three trials but no significant differences were detected reflecting the small sample sizes and hence low event rates in each case [46, 47, 52].

The effect of maternal vaccination or maternally-derived antibodies on the subsequent response of the infant to their routine pneumococcal-conjugate vaccines is a further important consideration. A single maternal vaccination trial, using the 23-valent pneumococcal polysaccharide vaccine, has examined this directly [48]. However, in this trial the subsequent born infants received a dose of the polysaccharide rather than the polysaccharide-conjugate vaccine at either seven or seventeen weeks. Use of a polysaccharide vaccine in this way would no longer be recommended due to the poor immunogenicity and hyporesponsiveness associated with these vaccines in this age group; thus the findings must be interpreted with extreme caution [53]. For four of the six serotypes examined, neither the infants of the control (unvaccinated) nor of the vaccinated mothers made a two-fold rise in GMC following vaccination. For the two remaining serotypes high pre-vaccination GMC continued fall despite vaccination at seven weeks although a small number of infants did have a two-fold rise in antibody concentrations. Infants vaccinated at seventeen weeks, who had pre-vaccination

antibody concentrations close to that of the infants of unvaccinated mothers, made more reliable responses overall and ultimately ended up with higher GMC than either the control or early vaccination groups. Consequently, some inhibitory effect of maternal antibodies is suggested [48]. A trial examining the use of a neonatal dose of the polysaccharide-conjugate vaccines, which will subsequently be described, also examined the relationship between the polysaccharide-specific GMC in cord blood and at 18 weeks in infants - following three doses of the same vaccine. This trial reported a significant inverse relationship between the GMC at these two time-points, suggesting an inhibitory effect of maternal antibodies on the infant responses to the primary series [54].

A Cochrane systematic review, updated most recently early in 2015, reviewed the data available regarding the potential role of pneumococcal vaccination during pregnancy in preventing infant infection. Reflecting the sizes of the trials and their inconsistent findings, the review concluded that 'There is insufficient evidence to assess whether pneumococcal vaccination in pregnancy could reduce infant infections' [55].

A single, randomized trial conducted in the United States between November 2000 and March 2003, although only published at the end of 2014 and hence absent from the systematic review cited above, examined the effects of maternal vaccination with an unlicensed nine-valent pneumococcal conjugate vaccine at 30 to 35 weeks gestation (n=74), and is the only study thus far to describe maternal vaccination with a PCV. Expectant mothers in the control group of the same trial (n=78) received a placebo injection of normal saline at the same time-point. The trial examined pneumococcal antibody transfer across the placenta and also the responses of the infants to routine vaccination with the seven-valent PCV at two, four, six and 12 months. Data on the occurrence of otitis media in infants over the first 12 months of life were also extracted retrospectively from the records of the primary care provider. No information regarding the cause of the otitis media or on rates of pneumococcal carriage was collected. The vaccine was reported to be well tolerated by maternal and infant participants. Cord blood antibody concentration in the infants born to mothers who had been vaccinated with the nine-valent vaccine were between 3.0 and 22.8 fold higher according to serotypes than in infants born to mothers in the unvaccinated control group. The mean antibody concentration increased in both groups following the vaccine administered to infants at six and 12 months with a vigorous anamnestic response occurring in both groups following the pneumococcal conjugate vaccine 12 month booster. Nonetheless, the final mean concentrations were lower for all the serotypes included in the seven-valent vaccine at seven months and for four of the seven serotypes at 13 months in the maternal vaccination group. The paper did not report seroprotection rates although the mean concentrations for all serotypes were at least three-fold above the 0.35ug/mL widely used correlate at seven months and at least 10-fold above the same cut off at 13 months irrespective of group.

Based on clinical findings documented during visits to family physicians, the study reported higher rates of otitis media over the first six months of life in the infants of those mothers who had received the conjugate vaccine during pregnancy than in the placebo group (32% in the vaccine group and 16% in the placebo group, $p = 0.03$). No difference in the proportion of infants diagnosed with otitis media between six and 12 months was noted (58% in the vaccine group and 56% in the placebo group, $p = 0.87$). The age at which the first episode of acute otitis media occurred was also significantly lower in the maternal vaccination group (15 days) compared to the control group (114 days). Of note, a sibling history of grommet insertion and a history of upper respiratory tract infections were more strongly associated with otitis media than the group into

which a mother had been randomized ($p<0.01$ and $p<0.001$ respectively). Furthermore, although the trial was reported to be double-blind, mothers were asked at six months which vaccine they thought they had received and their response also had a borderline association with otitis media rates ($p=0.09$) making blinded nature of the results somewhat difficult to interpret and they should therefore be interpreted with caution. No other disease endpoints were described [56].

Finally, the PneuMum trial group has recently reported the results of a randomized controlled trial examining the impact of maternal 23-valent pneumococcal polysaccharide vaccination on middle ear disease amongst indigenous infants in the Northern Territory of Australia [16]. The trial enrolled a total of 227 eligible women who were randomized, in equal number into one of three groups. The first received a dose of the 23-valent vaccine at 30 to 36 weeks gestation; the second a dose of the same vaccine within 72 hours of delivery; the third (control) group was not vaccinated as part of the trial. The trial's co-primary endpoints were the point prevalence of middle ear disease and the point prevalence of 23-valent vaccine-type pneumococcal carriage in the infants at seven months. The trial was not blinded although an independent assessor confirmed or refuted the diagnosis of middle ear disease made by an un-blinded research nurse. The independent assessor was blinded to both group and to the diagnosis of the research nurse thus reducing although not removing any bias associated with the assessment. Although the trial met the recruitment targets set, power was reported to be compromised due to the lower than expected rates of middle ear disease and nasopharyngeal carriage in the control infants.

The trial demonstrated no impact of maternal vaccination on either of the primary endpoints. Vaccine efficacy against ear disease at seven months was 13% (95% CI -12% to 31%) and against carriage was 30% (95% CI -35% to 64%) at the same time point. A *post hoc* analysis was undertaken to look at concurrent ear disease and carriage of the pneumococcal serotypes present in the 23-valent vaccine plus vaccine-related serotype 6A (as a surrogate for ear disease caused by these vaccine types). The vaccine efficacy against this exploratory, derived endpoint was 51% (-2% to 76%) in the maternal vaccination group. In contrast, there was no evidence of comparable efficacy when looking at the association between ear disease and carriage of other pneumococcal serotypes or other bacteria (non-typeable *Haemophilus influenzae* or *Moraxella catarrhalis*) suggesting a genuine, albeit only borderline significant result [16].

Neonatal vaccination

Two trials have been published assessing the effects of a neonatal dose of the 7 valent pneumococcal conjugate vaccine [54, 57]. In the first trial, undertaken in Kenya, 300 neonates were randomized in equal number, to receive the seven valent vaccine at either birth, 10 and 14 weeks or according to the routine EPI schedule at six, 10 and 14 weeks. The study reported no significant difference in the solicited or un-solicited safety events between the two groups. At 18 weeks, four weeks following the completion of the infant schedule in both groups, there was no difference between groups in terms of the proportion of infants who had an antibody concentration above a protective threshold of $\geq$0.35µg/mL. However, when a more conservative threshold of $\geq$ 1.0µg/mL was used the respective percentages for three (4, 18C, 19F) of the seven serotypes were lower in the neonatal vaccination group. For four (4, 9V, 18C, 19F) of the seven vaccine serotypes the GMC were also lower in the neonatal vaccination group compared to the routine group at the same point. In contrast, the mean avidity indices were significantly higher for three of the four serotypes tested (4, 6B, 19F) in the neonatal compared to

the control group reflecting, presumably, the longer duration over which affinity maturation had occurred following the dose of the vaccine at birth [54].

At 36 weeks, 20 weeks following the primary schedule, there was no difference in the percentage of infants with an antibody concentration above either the 0.35µg/mL or 1.0µg/mL comparing the two groups although the serotype 4 GMC remained lower and the serotype 19F avidity index remained higher in the neonatal compared to the control group [54].

The study reported no evidence of immunological tolerance resulting from the administration of the seven-valent vaccine at birth, as judged by the comparable response to a booster pneumococcal conjugate vaccine given at 36 weeks [54].

Carriage was measured only at 18 and 36 weeks in this study. No significant differences in carriage were detected between groups at either point although, in keeping with the difference in the GMC between the two groups, the VT carriage tended to be higher and the non-vaccine type (NVT) carriage lower in the neonatal group at both time points [54].

In the second trial, undertaken in Papua New Guinea, 318 infants were randomized into one of three groups to receive PCV7 according to a birth, one and two month (neonatal) schedule or a one, two and three month (infant) schedule. The third group did not receive the vaccine (control). A low level of local reactogenicity was reported overall although the levels were higher in the infant group compared to neonatal group. There were no differences in the illness episodes or serious adverse events captured across the groups. At two months of age, the GMC were significantly higher in the neonatal group than in the infant group (following two doses and one dose of PCV7 respectively) for four (4, 9V, 18C, 19F) of the seven VT in PCV7. By four months, following three doses of the vaccine in both groups the situation had reversed and the GMC were significantly higher for all serotypes in the infant group than in the neonatal group (one and two months after the third doses of the vaccine respectively). Both the neonatal and the infant groups responded to a subsequent challenge with a pneumococcal polysaccharide vaccine at nine months, generating comparable anamnestic responses. The fold-rise in GMC was significantly greater in the vaccinated groups than in the control group for all serotypes following the neonatal schedule and for five of the seven serotypes following the infant schedule suggesting at least comparable memory induction between the two regimens and further supporting the absence of tolerance following vaccination in newborns [57].

Expert commentary

The pneumococcal vaccine field has continued to evolve since the pneumococcal conjugate vaccines were licensed and first introduced into routine infant immunization schedules. Initial introduction in high income countries has now been followed by routine use in many low and middle income countries, thanks to WHO endorsement and GAVI purchasing with 126 countries using PCV to date. Geographical differences in pneumococcal epidemiology, dominant carriage and disease-causing serotypes and prevalence of nasopharyngeal carriage in different age groups has meant that the impact of PCV in diverse settings has not been uniform.

Contributing factors to diverse outcomes have included the presence of a catch up campaign targeting children too old to have been vaccinated according to the routine schedule, largely implemented only in high income countries. Different vaccination schedules, including two or three infant priming doses with or without a booster dose have also been used and variable levels of vaccine coverage within the target age groups

have been achieved. All of these factors have complicated the analysis of optimal strategies for PCV introduction and maintenance of control of VT disease. Consequently, a significant volume of work both in the form of clinical trials and post-introduction disease surveillance continues.

Indirect protection has played an important role in the demonstrated effectiveness of the pneumococcal conjugate vaccines so far and has impacted on disease, not only in older children and adults, but also in infants too young to have been vaccinated. Such effects have predominantly been seen in high income countries where PCV coverage has been high, a booster dose of PCV in the second year of life has been used and where carriage is relatively low and largely confined to infants less than 5 years of age. While infants are the predominant reservoir of carriage and the source of spread in many high income countries, a significant level of carriage in adults in countries across sub-Saharan Africa means that they are an important reservoir that is potentially less effectively addressed by the infant schedule.

Although data are relatively sparse, as a consequence, the level of indirect protection offered to newborns and infants appears to be lower in low income setting with high rates of pneumococcal carriage in early infancy as well as a reservoir of carriage in older children and adults and incomplete vaccine coverage. In addition, certain pneumococcal serotypes, including serotypes 1 and 5 cause a disproportionate amount of invasive disease in sub-Saharan Africa, are rarely carried, and hence likely to be less adequately controlled by indirect protection. For this reason, the opportunities offered by both maternal and neonatal pneumococcal vaccination in low income settings warrant further consideration while ongoing data on carriage and disease is generated and other vaccination schedules are also explored.

Unfortunately sample sizes and endpoints used have precluded any definitive evaluation of 23-valent pneumococcal polysaccharide vaccine in pregnancy. The added value of the 23-valent vaccine, in terms of its extended serotype coverage, will be eroded as the valency of the conjugate vaccines continues to increase. In addition, maternal immunization with a conjugate rather than a polysaccharide vaccine may result in higher antibody concentrations in the infant reflecting both the higher antibody concentrations generated in the mother and the higher antibody transfer ratio of the isotypes generated. On this basis it is unlikely that further trials with the polysaccharide vaccine, as would be required before implementation was considered, will be warranted.

Assuming an ongoing burden of disease, maternal immunization with PCV has the potential to prevent infection and perhaps carriage, over the first few months of life. Maternal vaccination may also facilitate the future use of the two-dose and potentially one-dose infant priming schedules which are now being explored, by providing protection in early life when one dose may be insufficient for direct protection. However, the potential for interference with infant PCV responses in the face of high maternally transferred antibody needs to be borne in mind and any potential biological effect of these reduced responses evaluated. Further research dissecting underlying immune mechanisms which might interfere with effector function or long term memory may also be required.

In order to proceed with maternal or neonatal vaccination, definitive maternal and infant safety data, alongside information on immunogenicity, carriage and, where possible, other efficacy endpoints must be generated. Evaluating serotype-specific interference between maternal antibodies and the subsequent response of the infant to the same conjugate vaccine will also be critical. The effect of carrier protein (CRM_{197}) specific

antibodies on the infant responses also needs to be assessed. Finally, any interference with the likely co-administered vaccines (tetanus toxoid in mothers, hepatitis B, BCG and the oral poliovirus vaccine in infants) needs to be established. Such data is required from low income settings were a future maternal vaccination strategy may be appropriate and trials to address these questions are already underway (Clintrials.gov NCT02628886) or are in the planning stage.

Neonatal vaccination is an alternative approach which does not suffer from the potential drawback of high levels of maternal antibody which may impact on the subsequent response to the infant priming schedule. However, the protection, in this case, is delayed and relies on an effective response to the conjugate vaccine at birth. The delivery of the vaccine at this point has been shown to be safe and immunogenic and does not appear to compromise the potential long term protection the vaccines generate, at least if considering the response to a booster vaccination given at nine months. In order to proceed with such a strategy, given the assessment of disease endpoints is no longer feasible, convincing immunogenicity and carriage data is likely to be required on a background of a clearly documented burden of disease.

Five year view

Within the next five years the potential utility of both maternal and newborn pneumococcal conjugate vaccination is likely to become much clearer. The level of indirect protection from infant immunization delivered according to the EPI schedule in low-income, high-carriage settings over the initial months of life is likely to be established as programmes become embedded. Nonetheless, schedule changes, particularly in low-income settings, are likely to mean that questions with this regard remain.

Trials underway or planned are expected to provide definitive safety data on maternal pneumococcal conjugate vaccination and further strengthen the existing data set related to newborn vaccination, although the safety profile of the latter is already supportive. Further information on immunogenicity and carriage endpoint for both schedules will similarly be available and it is expected that the data set which thus exists will provide sufficient information to guide policy or decisions regarding large scale impact studies. In addition, there is currently a significant level of interest in alternative pneumococcal protein-based vaccines, with or without conjugated polysaccharides. It is hoped that the next five years will bring significant progress in this area which could also impact on the questions related to maternal and neonatal pneumococcal vaccination. It is unlikely that any such vaccine would gain traction in the absence of clear indirect effects, at least when considering programmatic use. However, the indirect protection may not be consistent across age groups, reflecting the complexities of pneumococcal epidemiology and the current lack of protein-based correlates of protection against disease or carriage. Thus within five years, new questions related to the role of maternal and newborn pneumococcal vaccination are also likely to have been generated while existing questions are addressed.

Key issues

- Pneumococcus is a significant pathogen in newborns and in early infancy, particularly in sub-Saharan Africa.
- The seven, 10 and 13-valent pneumococcal-conjugate vaccines have been highly effective at preventing infection and carriage of the included pneumococcal serotypes in infants and children following their rollout in high, middle and low income countries.

- Due to differences in pneumococcal epidemiology the indirect protection seen in newborns in high income settings are unlikely to be translated consistently into low income countries and residual disease in early life seems likely to persist in the absence of additional interventions
- Numerous trials of maternal vaccination with the 23-valent pneumococcal polysaccharide vaccines have been undertaken but a recent systemic review concluded that based on these trials there was insufficient evidence to determine a role for maternal pneumococcal vaccination in pregnancy
- A single trial has been reported from the US using a nine-valent conjugate vaccine in pregnant women. High levels of antibody transfer were reported but the infants in the maternal vaccination group had a higher level of acute otitis media than those in the control group. Data in this paper is important but may need to be interpreted with some caution
- Two trials have examined neonatal vaccination with a seven valent conjugate vaccine. In both the safety profile was reassuring and good responses to the vaccine administered at birth were documented.
- Further clinical trials are currently underway or being planned to examine both maternal and neonatal pneumococcal-conjugate vaccination in low-income settings

Table 1: Trials of maternal pneumococcal vaccination

	Vaccine	Control	Population	Gestation at vaccination	Outcomes reported					Ref
					Safety	Serological	Carriage	Disease	Other	
The Gambia 1991 - 1992	23-valent Pn PS vaccine	Men A and C PS vaccine	150 pregnant women randomized: 75 vaccine 75 control Mean age: 22 years	Mean time between vaccination and delivery: 6.3 weeks Mean estimated gestation at vaccination: 38 weeks	No significant side-effects recorded in vaccinated women No apparent differences in maternal deaths, still births, infant deaths - small number of events	Serotypes tested: 1, 3, 5, 6B, 14, 19F Higher cord blood Pn PS IgG in vaccinated compared to controls for 4 of 5 serotypes tested Cord/Maternal IgG ratio between 0.24 to 0.52 according to Pn PS and group Rapid Pn PS IgG decline in infants - levels comparable between vaccine and control groups by 2 to 4 months. Reduced Pn PS IgG responses associated with malaria parasitaemia at the time of vaccination for 2 of 6 serotypes tested	Not tested	Small number of events. No apparent differences in diseases outcomes (meningitis, pneumonia, otitis media)	Significantly higher colostrum and breast milk secretory IgA concentrations and avidity indices (type 6B, 6B and 14 to 6 months; type 19F to 4 months) in vaccine compared to control mothers	[46, 50, 58]
Papua New Guinea 1991 - 1994	23-valent Pn PS vaccine	Not vaccinated	437 pregnant women 235 Vaccine 202 Control	Mean interval from vaccination to delivery was 8.5 weeks	No difference in the number of still births in vaccinated mothers compared to background population. No other safety concerns described	Serotypes tested: 5, 7F, 14, 23F Significant increase in GMC to 3 of 4 serotypes tested (no increase in serotype 7F) 1.4 to 2.7 fold rise in concentration across the 3 serotypes in mothers Mean cord/maternal IgG ratio 0.57 across all serotypes tested GMC significantly higher in maternal and cord blood samples in vaccinated compared to controls at delivery Infant GMC significantly higher in vaccinated compared to control groups to 30-59 days (type 5, 7F, 23F) and 119 days (type 14) Infants in both vaccine and control groups responded to a dose of the 23-valent Pn PS vaccine given at 8 to 9 months of age. No significant differences between groups. 3.1 to 7.5 fold rise in antibody concentrations according to group and serotype	Not reported	Mortality from acute lower respiratory infections reported to be lower in vaccine group compared to controls (17 versus 30 per 1000 live-births) but numbers of events low (4 and 6 events respectively)		[52]

Philippines 1994 - 1995	23-valent Pn PS vaccine + Hib-TT conjugate vaccine + TT vaccine	TT vaccine alone	160 pregnant women randomized, open label 106 vaccine 54 control Mean age: 26.8 years	Mean time between vaccination and delivery: 10.9 weeks Mean gestation at vaccination: 27.3 weeks	Local and systemic adverse events in keeping with those expected No pregnancy or infant outcome data reported.	Serotypes tested: 1, 5, 6B, 14, 18C, 19F Significant increases in GMC for the 6 serotypes tested. Mean 5.4 fold rise in vaccinated mothers Pn PS IgG in cord blood 2.9 to 5.7 times higher in vaccine than in control group. 89% of Pn PS IgG levels in cord blood samples > 0.35ug/mL in vaccinated group compared to 57% in control group Cord/Maternal IgG ratio estimated to be between 0.52 and 0.88 for the 6 serotypes tested No correlation between gestation in weeks at time of vaccination and cord blood antibody concentrations	Not tested	Not reported		[44, 45]
	Infants vaccinated with 23-valent Pn PS vaccine at 7 or 17 weeks	Infants vaccinated with 23-valent Pn PS vaccine at 7 weeks				Serotypes tested: 1, 5, 6B, 14, 18C, 19F Infants of vaccinated mothers had a higher Pn PS IgG GMC at 7 weeks compared to infants born to mothers in control group 23% (type 1) and 6% (type 5) of infants born to vaccinated mothers had a 2 fold rise in Pn PS IgG compared to 63% and (type 1) and 28% (type 5) of infants born to mothers in control group. Post-vaccination Pn PS IgG higher in infants born to vaccinated mothers reflecting ongoing effects of maternal antibodies at 12 weeks No responses above declining maternal antibodies to 6B, 14, 18C and 19F				[48]
United States 1995 - 1996	23-valent Pn PS vaccine	Hib-CRM_{197} conjugate vaccine	60 pregnant women randomized, double blinded: 20 vaccine 40 control Mean age: 30.2 (vaccine) 31.6 (control)	Mean time between vaccination and delivery: 43.6 days (vaccine) 44.0 days (control) Mean gestation at vaccination: 33.3 weeks 33.0 weeks	No SAE likely to be attributed to the vaccine in mothers No still births or infant deaths No significant differences in the rates of adverse events between vaccine and control group	Serotypes tested: 6B, 14, 19F, 23F Pn PS IgG, IgG1 and OPA significantly higher in vaccine compared to controls at deliver for 4 of 4 serotypes tested Pn PS IgG2 significantly higher in vaccine compared to control group for 2 of 4 serotypes tested Cord/Maternal IgG mean ratio for 4 serotypes tested 0.89 Higher cord blood IgG for 4 of 4 serotypes tested in vaccine compared to control groups. Persistence to 2 and 6 months dependent on Pn serotype and IgG isotype tested.	Higher colonisation in the infants of control compared to vaccinated mothers in nasal washes taken at between 2 and 15 months of age.	Not reported	Significantly higher breast milk IgA in vaccinated compared to control mothers at 2 months Significantly higher breast milk IgG in vaccinated compared to control mothers at 2 months for 2 of the 4 serotypes tested	[47]

United States 2000 - 2003	9-valent Pn PS-CRM_{197} conjugate vaccine	Saline placebo	152 pregnant women 74 Vaccine 78 Control	Vaccinated at 30 to 35 weeks gestation	Vaccine well tolerated by maternal and infant participant	Serotypes tested: 4, 6B, 9V, 14, 18C, 19F, 23F (plus 1 and 5 in 9-valent vaccine) Significantly higher maternal GMC to 7 serotypes in 7-valent PS-CRM_{197} conjugate vaccine comparing vaccine versus control groups Significantly higher cord blood GMC to 7 serotypes in 7-valent PS-CRM_{197} conjugate vaccine comparing vaccine versus control groups GMC inferior in the vaccine group compared to the control group at 7 months (one month after third dose of the 7-valent vaccine) for 7 of 7 serotypes GMC inferior in the vaccine group compared to the control group at 7 months (one month after fourth (booster) dose of the 7-valent vaccine) for 4 of 7 serotypes GMC higher in infants born to mothers in vaccine compared to control groups at 6 and 7 months for serotypes 1 and 5 (in 9 valent vaccine received by mothers but not in 7 valent vaccine received by infants)	Not reported	First episode of acute otitis media (AOM) occurred at 15 days in vaccine group compared to 114 days in control group AOM and otitis media (OM) free rates over the first six months significant higher in control group (AOM 89% versus 74%; OM 85% versus 68%) The apparent effect was lost after 6 months		[56]
Bangladesh 2004 - 2005	23-valent Pn PS vaccine	Inactivated influenza vaccine*	340 pregnant women, randomized, double-blind 168 Vaccine 172 Control	Mean interval between vaccination and birth 56 days in vaccine group, 54 days in control group	No difference in the number of pregnancy outcomes or severe adverse events between the mothers in the vaccine and control groups Minor local and systemic reactogenicity only	Serotypes tested: 4, 6B, 9V, 14, 19F, 18C, 23F, 1, 5 At delivery 86.4 to 100.0% of mothers in the vaccine group and 30.0 to 96.5% of mothers in the control group had Pn PS IgG concentrations of >0.35µg/mL, dependent on serotype At 12 months post-delivery 86.7 to 100.0% of mothers in the vaccine group and 55.0 to 100.0% of mothers in the control group had Pn PS IgG concentrations of >0.35µg/mL according to serotype.	Not reported	Not reported		[59, 60]
Brazil 2005 - 2006	23-valent Pn PS vaccine	Not vaccinated	150 pregnant women, randomized, open label 45 Vaccine 47 Control 47 Vaccine (following delivery) (11 exclusions)	Vaccinated at 30 to 34 weeks gestation Vaccinated following delivery	No significant relationship between vaccination use and premature labour Minimal local or systemic reactions to the vaccine	Not reported	No difference in pneumococcal colonization rates up to 6 months of ages. Non-significant differences in serotypes carried - small number of events overall	No difference in acute respiratory infections or antibiotic use between birth and 6 months of ages in infants		[51, 61]
Brazil Dates not provided	23-valent Pn PS vaccine	No control group included	46 pregnant HIV positive women 45 on anti-retroviral treatment	Vaccinated at 32 to 34 weeks gestation, mean 33 weeks Median interval between vaccination and birth 40 days (range 21 to 78 days)	No serious adverse reactions attributable or possible attributable to the vaccine were observed. Minimal reactogenicity No still births or infant deaths 2 infants vertically infected with HIV	Serotypes tested: 1, 3, 5, 6B, 9V, 14 Significant increases in GMC to 5 of 6 serotypes tested (no increase in serotype 3 titres) 1.5 to 2.9 fold rise in concentrations across the 5 serotypes in mothers Strong correlation between maternal and infant IgG concentrations. Pearson's correlation coefficient 0.767 to 0.931. Infant/maternal IgG ratios 0.459 (type 9V) to 0.718 (type 3) Time for GMC to fall to 0.35µg/mL in infants ranged from 0.6 months (type 3) to 2.7 months (type 6B).	Not reported	Not reported		[49]

Bangladesh Dates not provided	23-valent Pn PS vaccine	Men A, C, W, Y PS vaccine	70 pregnant women, randomized, double blinded 36 vaccine 34 control	Mean time between vaccination and delivery: 7 weeks Mean gestation at vaccination: 32 weeks	Vaccines well tolerated in both groups with a profile of local reactions as expected No differences in number of low birth weight (<2.5kg) or premature (<37 week) infants between vaccine and control groups. 2 full term unrelated still births in the vaccine group No congenital defects or serious illnesses noted in any infant up to 22 weeks of age.	Serotypes tested: 6B, 19F Significantly higher GMC in vaccine compared to control mothers at delivery (13.8 and 17.4 compared to 5.3 and 4.7µg/mL for 6B and 19F respectively) Maternal and cord blood Pn PS IgG concentrations highly correlated. Spearman coefficients 0.81 and 0.90 for type 6B and 19F respectively. Cord/Maternal IgG mean ratio 0.56 (type 6B) and 0.59 (type 19F) Cord/Maternal IgG1 mean ratio 0.88 (type 19F) and 1.20 (tetanus toxoid) Cord/Maternal IgG2 mean ratio 0.45 (type 19F) and 0.80 (tetanus toxoid) Infants in vaccine group had GMC 2 to 3 fold higher for 6B and 19F up to 22 weeks postnatal age.	Half of infants colonised by 3 months and three quarters by 6 months with no differences between groups. VT not reported separately	Not reported	Breast milk IgA 3x higher in colostrum of vaccinated mothers - falling to undetectable levels by 2 weeks (6B) Breast milk IgA 7x higher in colostrum of vaccinated mothers - remaining at least 3x higher up to 5 months (19A)	[43]
Australia - Indigenous Population, Northern Territory	23-valent Pn PS vaccine	Not vaccinated or 23-valent Pn PS vaccine given to mother within 72 hours of delivery	227 pregnant women randomized, mothers not blinded. Investigators incompletely blinded for disease endpoint 75 vaccine in pregnancy 75 vaccine given to mother at birth 77 control Median age 23 to 25 years	Median time between vaccination and delivery 6 weeks Range 1 to 10 weeks Inter-quartile range 4 to 6 weeks Median gestation at deliver 39 weeks in all groups Note that 84 to 89% of infants had received $\geq$ 2 doses of the 7 valent Prevenar™ vaccine of the 10-valent Synflorix™ vaccine by the time of the 7 month primary endpoint assessments	Low local and systemic reactogenicity following vaccination in pregnancy Median birth weight 3.2 - 3.4kg No differences in: Low birth weight (<2.5kg) - 5 to 9% Prematurity (<37 weeks) - 3 to 9% Special/Intensive Care admission - 19 to 21%	Higher cord blood antibody IgG GMC in mothers vaccinated in pregnancy compared to control mothers or mothers vaccinated at delivery (19A, 15B, 33F, 10A shown) Indistinguishable by 7 months for vaccine types in 23-valent but not 7 or 10 valent vaccine Infant immunogenicity data to be reported separately	23-valent vaccine-type pneumococcal carriage at 7 months Controls: 17/66 (26%) Maternal vaccination group: 12/67 (18%) VE 30% (-34 to 64) Birth vaccination group: 12/66 (18%) VE 29% (-36 to 63) No carriage differences at 1 or 2 months of age either.	Ear disease Controls: 47/66 (71%) Maternal vaccination group: 42/67 (63%) VE 12% (-12 to 31) Birth vaccination group: 50/66 (76%) VE -6% (-31 to 13)	Breast milk IgA GMC in mothers vaccinated in pregnancy > mothers vaccinated at delivery > control mothers Differences persist at 7 months (19A, 15B, 33F, 10A shown)	[16]

Pn - pneumococcal; PS = polysaccharide; IgA - Immunoglobulin A; IgG - Immunoglobulin G; VT - vaccine-type; NVT - non-vaccine type; Hib - *H.influenzae* type b; Men A - meningococcal serogroup A; TT - tetanus toxoid; GMC - geometric mean concentrations; OPA - opsonophagocytic activity; VE - vaccine efficacy (1- risk ratio) with 95% confidence intervals *study conducted to assess influenza vaccine

Table 2: Trials of neonatal pneumococcal vaccination

	Vaccine	Neonatal group	Control group	Outcomes reported					Ref
				Safety	**Serological**	**Carriage**	**Disease**	**Other**	
Kenya 2004 - 2007	7-valent Pn PS-CRM_{197} conjugate	150 infants vaccinated at 0, 10 and 14 weeks of age	150 infants vaccinated at 6, 10 and 14 weeks of age	No significant differences in fever or local reactogenicity between groups No significant differences in adverse event or serious adverse event rate One death, judged unrelated to vaccination, occurred in each group	Serotypes tested: 4, 6B, 9V, 14, 18C, 19F, 27F (serotypes incorporated into 7 valent vaccine). At 18 weeks (4 weeks post primary schedule): • There was no significant difference in the percentage of infants with Pn PS IgG $\geq$ 0.35µg/mL (87 - 99% for neonatal group compared to 92 - 100% for control group). • There were significant differences in the percentage of infants with Pn PS IgG $\geq$ 1.0µg/mL for 3 of 7 serotypes (serotypes 4, 18C, 19F) in the neonatal compared to the control group • GMC were significantly lower for 4 of 7 serotypes (serotypes 4, 9V, 18C, 19F) in neonatal group compared to control group. • The geometric mean avidity indices was significantly higher for 3 of 4 serotypes tested (serotype 4, 6B, 19F) compared to the control group • There was a significant downward trend in the GMC at 18 weeks moving from the highest quintile of cord blood GMC to the lowest quintile (serotypes 6B, 9V, 14 and 19F in control group and serotypes 6B 14 and 23F in neonatal group) - inhibitory effect of maternal antibodies At 36 weeks (20 weeks post primary schedule): • There was no difference in the percentage of infants with Pn PS IgG $\geq$ 0.35ug/mL (56 - 92% for neonatal group compared to 60 to 95% for control group). • There were no significant differences in the percentage of infants with Pn PS IgG $\geq$ 1.0µg/mL in the neonatal compared to the control group • GMC remained significantly lower for 1 of 7 serotypes (serotype 4) in neonatal group compared to control group. • The geometric mean avidity indices remained significantly higher for 1 of 4 serotypes tested (serotype 19F) compared to control group • There were no significant differences in the response to a booster of either a 7 valent Pn PS-CRM_{197} conjugate vaccine or a 23-valent Pn PS vaccine between the two groups	There were no significant differences in VT or NVT carriage at either 18 or 36 weeks Total VT carriage prevalence was higher in the neonatal group at 18 (p=0.28) and 36 weeks (p=0.07) Total NVT carriage prevalence was higher in the control group at 18 (p=0.25) and 36 weeks (p=0.08)	Not reported		[54]
Papua New Guinea 2005 - 2007	7-valent Pn PS-CRM_{197} conjugate	101 infants vaccinated at 0 1 and 2 months of age	105 infants vaccinated at 1, 2 and 3 months of age (106 infants not vaccinated)	No serious reactions within 1 hour of vaccination in any group. Lower levels of local reactogenicity in neonatal compare to vaccinated control group No significant differences in SAE rate between the three groups	Serotypes tested: 4, 6B, 9V, 14, 18C, 19F, 27F (plus 2, 5 and 7F NVT) At birth: • 90.2 to 100% of infants had a Pn PS IgG $\geq$ 0.35µg/mL and 70.7 to 97.7% of infants had a Pn PS IgG $\geq$ 1.0µg/mL according to serotype At 2 months (following 2 vaccination in the neonatal group and 1 vaccination in the control group) • 80.9 to 100.0% to infants in the neonatal group compared to 71.0 to 97.8% of infants in the control group had a Pn PS IgG $\geq$ 0.35µg/mL. Percentages higher in the neonatal group for all serotypes At 4 months (following 3 vaccinations in both groups) • 71.8 to 98.8% of infants in the neonatal group compared to 88.9 to 100% of infants in the control group had a Pn PS IgG $\geq$ 0.35µg/mL. Percentages higher in the control group for all serotypes Infants in both the neonatal and control groups responded to a dose of the 23-valent Pn PS vaccine with a mean 6.4 fold rise in Pn PS IgG compared to a 1.9 fold rise in the unvaccinated infants taken to indicate the induction of PS-specific B-cell memory by both the neonatal and the control schedule. No significant differences in IgG rise between the neonatal and the control schedule.		No significant differences in acute lower respiratory infection rate between groups No significant differences in the rates of IPD between groups (n=7 in total)		[57]

Pn - pneumococcal; PS = polysaccharide; IgA - Immunoglobulin A; IgG - Immunoglobulin G; VT - vaccine-type; NVT - non-vaccine type; Hib - *H.influenzae* type b; Men A - meningococcal serogroup A; TT - tetanus toxoid; GMC - geometric mean concentrations; OPA - opsonophagocytic activity; *study conducted to assess influenza vaccine

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