

## EDITORIAL

### Maternal immunization

It is estimated that 1.5 million neonates die of infection each year throughout the world, almost all in developing countries (1). This is equivalent to approximately 4000 deaths each day. Between 40% and 60% of the estimated 4-5 million deaths from pneumonia among children in developing countries occur during the first 6 months of life (2) and these deaths are generally associated with bacterial disease, in particular *Streptococcus pneumoniae* and *Haemophilus influenzae* (3). For this reason there has been an increasing interest in maternal immunization as a possible way of preventing the large number of deaths in early childhood.

Long before active immunization was available for prevention of infectious diseases it was noted that young infants were protected from illnesses such as diphtheria, poliomyelitis, scarlet fever and measles but were not protected from others such as tetanus and pneumococcal disease (4). The possibility of passive immunization of the fetus and neonate through active immunization of the mother is an attractive approach towards prevention of diseases such as neonatal tetanus and group B streptococcal infection which occur too early in life for immunization of neonates to be beneficial. Maternal immunization might also protect young infants against other bacterial diseases at a time when the immune system is still insufficiently developed to respond adequately to bacterial polysaccharide vaccines.

#### Principles of maternal immunization

##### Immune response to different antigens

Maternal immunization can protect the young infant by increasing the amount of specific IgG transferred across the placenta, a process which begins in the first trimester and increases substantially during the last trimester (5). Transfer occurs by binding of immunoglobulin to Fc receptors on the membrane of trophoblasts in the placenta followed by receptor-mediated endocytosis and active

transport (6). IgG1 is preferentially transferred across the placenta compared to IgG2 because of binding specificity and affinity of the Fc receptor (7). Protein antigens such as tetanus toxoid induce a thymus-dependent (TD) immune response and IgG1 is the main IgG subclass produced (7,8) while polysaccharide antigens such as pneumococcal and group B streptococcus (GBS) vaccines are thymus-independent (TI) (9,10) and induce mainly an IgG2 response. Thus, higher concentrations of protective IgG antibodies would be transferred to the fetus following maternal immunization with TD antigens than with TI antigens. When polysaccharide is conjugated to protein, the response changes to a TD response, thereby inducing higher antibody titres than with polysaccharide alone (10,11). Protein-conjugate polysaccharide vaccines also reduce upper respiratory tract (URT) carriage of specific infectious agents (12,13), thereby reducing the exposure of infants to these infections.

##### Protection through breastmilk

Immunization of pregnant women may also protect infants through the secretory IgA present in colostrum and breastmilk, which may prevent attachment of microorganisms to mucosal membranes (14) and hence URT colonization. Breastmilk IgA is thought to be produced as a result of antigen-committed cells from Peyer's patches being transported to the mammary glands and secreting IgA there and also by transfer of serum IgA dimers to milk (15,16). In one study, pregnant women immunized with *Haemophilus influenzae* type b (Hib) polysaccharide (polyribosyl ribitol phosphate: PRP) had antibody titres in their colostrum more than 20-fold higher than those observed in nonimmunized women and antibody titres remained high in offspring of immunized women for 3-6 months after birth (17).

##### Variation in response to maternal immunization between populations

Protection afforded by maternal immunization may vary between populations

and under different environmental conditions. For example, cord:maternal serum ratios of anti-tetanus antibody titres have been found to be lower in Gabonese women living in Africa than in Gabonese women living in France (18). The investigators proposed that this difference might be due to high maternal total IgG levels saturating the specific IgG transport receptors on the placenta, reducing the specific IgG that is being transferred. High total IgG levels are common in developing countries as a consequence of constant exposure to parasites and infectious agents and may explain the rapid decline in maternal antibodies in young infants in developing countries (18,19). To compensate for less transfer of specific IgG and the rapid decline of maternal antibodies in infants in developing countries, higher levels of specific IgG may need to be achieved with maternal immunization than in developed countries in order to provide adequate protection of infants.

### **Safety of maternal immunization**

In order to move forward with studies of maternal immunization it is essential to ensure that vaccines under consideration are safe for mothers and infants. To date there is no evidence that maternal immunization with various protein or polysaccharide vaccines is teratogenic to the fetus (20-29). There has been concern that maternal immunization could reduce the response to subsequent immunization of offspring or that offspring may become immunologically tolerant to the antigen in question. Alterations in the infant's immunological response could be due to transfer of high levels of maternal antibody, transfer of vaccine antigen or transfer of maternal anti-idiotypic antibody (30). There have been occasional reports of possible immune tolerance following immunization of young infants but there has been no clear evidence of impaired immune response following maternal immunization (4,30). Infants of mothers vaccinated with meningococcal vaccine had responses to the vaccine at 6 months of age that were indistinguishable from infants of unvaccinated mothers (25). There has been no evidence of immune suppression or tolerance following maternal vaccination with tetanus toxoid (27) or with either the polysaccharide or conjugate Hib vaccines (28,29,31). Nevertheless one

must proceed cautiously in future trials: sample sizes must be adequate to detect potential deleterious effects and there must be very careful monitoring for any adverse events during trials.

Another consideration is the possible interaction between different vaccines given during pregnancy. In The Gambia, immunization with tetanus toxoid vaccine 1-5 weeks before maternal immunization with conjugate Hib vaccine was associated with a reduced anti-PRP antibody response; this may be an example of carrier-mediated suppression (29,32). Responses were higher when the two vaccines were given simultaneously, which would, in any case, be more practicable.

### **Prevention of specific infectious diseases through maternal immunization**

From the above it is clear that an ideal vaccine to be used in a maternal immunization program must be safe for mother and child, should require just a single dose, should quickly induce high levels of IgG1 in serum and IgA in breastmilk and should protect the infant until active immunization can afford protection or until the child is no longer at risk. Ideally a single dose should also protect subsequent offspring.

There are diseases affecting young infants in both developed and developing countries which might be prevented by maternal immunization. In developed countries, group B streptococcus (GBS) is a leading cause of morbidity in young infants and studies suggest that maternal immunization could protect young infants against this disease (33). Maternal immunization may also help prevent disease due to *Neisseria meningitidis* (25), respiratory syncytial virus (34) and influenza virus (26).

In developing countries maternal immunization is being used widely for the prevention of neonatal tetanus and is being investigated for prevention of disease caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) in view of the enormous burden of illness from these pathogens in young infants. The pneumococcus accounts for a much higher proportion of disease than Hib in the first three

months of life (35) and should therefore be the first priority for future studies of maternal immunization.

### *Clostridium tetani*

Protection against neonatal tetanus by maternal immunization was an important breakthrough in reducing infant mortality, as in the past neonatal tetanus was a major cause of mortality in developing countries, including Papua New Guinea (PNG) (20,21). After a successful maternal immunization trial of tetanus toxoid in East Sepik Province of PNG, WHO recommended that pregnant women throughout the developing world be vaccinated with tetanus toxoid vaccine. With complete coverage of pregnant women, neonatal tetanus can be eliminated (21,36).

### *Streptococcus pneumoniae*

Adults respond well to pneumococcal polysaccharide vaccines (23,37). A controlled trial of pneumococcal polysaccharide vaccine in PNG showed a 44% reduction in mortality from pneumonia in vaccinated adults compared to a control group (23). Pregnant women were also immunized during this trial if pregnancy was not physically apparent. There was no evidence of deleterious outcomes in mothers who received pneumococcal vaccine or in their offspring. The morbidity rate from acute lower respiratory infections (ALRIs) was significantly lower in children aged less than 18 months at the time that their mothers had received pneumococcal vaccine than in those children of the same age whose mothers had received placebo. Most of the children were not in utero at the time of maternal vaccination; since breastfeeding was universal, it is therefore likely that maternal immunization afforded protection against ALRI morbidity through breastmilk.

The 23-valent pneumococcal polysaccharide vaccine has been given to pregnant women in Bangladesh (22) and The Gambia (24). In the small numbers of women included in these two studies the vaccine appeared to be safe to both mothers and children. Pregnant women in both countries responded well to the vaccine, although the magnitude of the response to vaccination varied between serotypes. Approximately half the concentration of

serotype-specific IgG in mothers at the time of delivery was transferred to their infants (22,24). Hence the concentration of antibody in newborns seems to be directly proportional to the concentration of antibody in mothers at the time of delivery. It is therefore important to achieve high enough levels of specific antibody during the last trimester of pregnancy to ensure that infants receive substantial protection in the early months of life. However, it is noteworthy that in The Gambia cord:maternal ratios of pneumococcal serotype-specific antibody were negatively correlated with maternal antibody titres, suggesting a possible process of saturation of the transfer system and also a mechanism of optimal transfer of antibody when maternal antibody titres are low (24).

In Bangladesh serum IgG antibody concentrations for serotypes 6B and 19F were 2-3-fold higher up to 5 months of age in offspring of mothers given pneumococcal polysaccharide vaccine than in offspring of mothers who had not received pneumococcal vaccine (22). The median half-life of passive antibody was approximately 35 days. Specific IgA to serotype 19F in colostrum was 7 times higher in vaccinated women than in the control group and remained at least 3 times higher in the breastmilk of vaccinated women than in breastmilk of women in the control group for a further 5 months (22). This was not the case for serotype 6B.

The infants of vaccinated mothers in The Gambia (24) had 2-3-fold higher levels of pneumococcal antibody to serotypes 1, 5, 14 and 19F than infants in the control group, but for most serotypes this difference lasted only 2-3 months. A 2-fold difference in antibody titres was maintained to age 4-5 months for serotype 14 only. The less promising results in The Gambia than in Bangladesh could be associated with malaria parasitaemia, which reduced women's response to pneumococcal vaccine and transfer of specific antibody across the placenta to the fetus (24). However, the Gambian study did find a lower incidence of pneumonia and otitis media in children of mothers who had received pneumococcal vaccine than in the control group (4 versus 10 cases).

Preliminary results of a recent study of pneumococcal maternal immunization in PNG

also show that approximately half the concentration of serotype-specific IgG found in mothers is transferred to their infants (38,39). After birth, antibody titres to all serotypes tested (types 5, 7F, 14 and 23F) fell rapidly but for serotypes 14 and 23F remained approximately two-fold higher up to 4-6 months of age in the vaccine than in the control group. It is noteworthy that antibody titres to serotype 2 were low in mothers and hence also in their offspring, which may in part explain why serotype 2 is such a common cause of invasive disease in young Papua New Guinean children (40,41).

Trials with protein-conjugate pneumococcal vaccines are also being considered to achieve higher specific IgG levels than with pneumococcal polysaccharide vaccine and to stimulate T-cell memory. Conjugate vaccines may be less reactogenic, may result in better affinity of antibody and are not likely to result in tolerance. However, it is unlikely that more than 12 serotypes would be included in conjugate vaccines.

### ***Haemophilus influenzae* type b**

The prevention of Hib disease in young infants by maternal immunization was initially investigated using polysaccharide Hib vaccines (31,42): anti-PRP antibody levels were higher in offspring of vaccinated mothers than in control groups from birth to at least the age of 6 months. Studies of protein-conjugate Hib vaccines in the USA have found substantially higher levels of anti-PRP antibody titres in women immunized with conjugate vaccines and in their offspring up to the age of 6 months than in those immunized with polysaccharide Hib vaccines or in unimmunized women and their offspring (28,43). In The Gambia, anti-PRP antibody titres were higher up to the age of 2 months in offspring of women given conjugate Hib vaccine during pregnancy than in offspring of unvaccinated women (29). At age 2 months all the Gambian children in the study received conjugate Hib vaccine. None of the studies to date have shown any evidence of serious adverse effects to mothers or infants. There was no evidence of tolerance either in Gambian children given conjugate Hib vaccine at 2, 3 and 4 months of age (29) or in North American children immunized at age 6 months or more (28). In The Gambia it was noted that

the response was best in women who were in their first or second pregnancy, that the cord:maternal ratios were higher when conjugate Hib vaccine was given earlier in pregnancy and that maternal infection with malaria resulted in a poorer antibody response (29).

Englund et al. estimated that vaccination of pregnant North American women with conjugate Hib vaccine would protect infants up to 4-6 months of age (43) while in the Gambian study it was estimated that maternal immunization might prevent half the cases not prevented by infant immunization alone at 2, 3 and 4 months of age (29).

### **Conclusions**

Evidence to date suggests that maternal immunization should be considered a viable strategy to protect young infants from infectious diseases. However, evaluation and implementation of maternal immunization programs, other than for the prevention of neonatal tetanus, have been slow for ethical, legal and financial reasons. First and foremost, manufacturers, parents and health professionals must be convinced of the safety of maternal immunization. Manufacturers are hesitant to recommend vaccination in pregnancy for fear of litigation. Safety will only be determined through large-scale efficacy trials in which there would be very close intensive monitoring and thorough investigation of all adverse events. Inevitably, such trials will be expensive and therefore donor agencies must provide adequate funds for this purpose. In view of the very high disease burden, prevention of pneumococcal disease must be the top priority for evaluation of maternal immunization in developing countries; and the possibility of administering several vaccines in a single dose needs to be investigated.

Children at greatest risk may not be protected if access and utilization of antenatal services is not optimal. Currently only 45% of pregnant women are receiving tetanus toxoid (44). WHO is working towards improving coverage of maternal tetanus immunization in developing countries. The introduction of new vaccines through antenatal services must be achievable with minimum additional effort and will, hopefully, offer the much-needed

protection against infectious diseases in very young infants.

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