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Maternal immunisation 1

Maternal immunisation: a worldwide landscape analysis

[A: title edited to be more descriptive and explanatory]

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Maternal immunisation has the potential to substantially reduce morbidity and mortality from infectious diseases after birth. The success of tetanus, influenza, and pertussis immunisation during pregnancy has led to consideration of additional maternal immunisation strategies to prevent group B streptococcus [A: We avoid using abbreviations when possible, particularly for disease and drug names] and respiratory syncytial virus infections, among others. However, many gaps in knowledge regarding the immunobiology of maternal immunisation prevent the optimal design and application of this successful public health intervention. Therefore, we did an innovative landscape analysis to identify research priorities. Key topics were delineated through review of the published literature, consultation with vaccine developers and regulatory agencies, and a collaborative workshop that gathered experts across several maternal immunisation initiatives—group B streptococcus, respiratory syncytial virus, pertussis, and influenza. Finally, a global online survey prioritised the identified knowledge gaps on the basis of expert opinion about their importance and relevance. Here we present the results of this worldwide landscape analysis and discuss the identified research gaps.

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This is the first in a **Series** of three papers about maternal immunisation

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Introduction

Failure to improve survival in neonates by 2035 could lead to an estimated 116 million preventable stillbirths or neonatal deaths, 99 million survivors with disability, and millions more with a lifelong increased risk for non-communicable diseases.[1] The underlying causes for the 2·6 million stillbirths per year are largely unknown, but roughly 20% of the 2·9 million annual neonatal deaths are thought to be due to infection.[1] The transfer of antibodies from pregnant women to their offspring is profoundly important for the health and survival of neonates and young infants, particularly because it reduces the risk of severe infections. Unfortunately, not all pregnant women have protective concentrations of antibodies against pathogens that affect their offspring.

The strategy of maternal immunisation to enhance protection of young infants is rapidly gaining support from both the public and health professionals.[2] Factors contributing to this momentum include the global reduction in neonatal tetanus as a result of maternal immunisation, the benefits of seasonal and pandemic influenza immunisation for both mother and infant, and the positive effect of maternal immunisation on pertussis outbreaks. These factors are also stimulating commercial development of new vaccines against additional threats, such as group B streptococcus and respiratory syncytial virus.

In recognition of the need to enhance the science of maternal immunisation, the Bill & Melinda Gates Foundation commissioned the authors of this Series paper to do a landscape analysis of the immunobiology that underpins successful vaccination during pregnancy. The scope of the analysis included all relevant immunobiological issues in general terms and as applied to immunisation against pertussis, influenza, group B streptococcus, and respiratory syncytial virus specifically. We aimed to identify differences that might exist between pregnant women in low-income and middle-income countries (LMICs) and those in high-income countries that could affect the success of maternal immunisation programmes. We used an innovative approach to identify and prioritise the current knowledge gaps to inform future studies.

Here we describe the methods and the results of this effort and discuss the identified research gaps in immunobiology of maternal immunisation that can be generalised across pathogens. The two companion papers in this Series [Editor: Add references for the following two papers in this Series here when details are known] discuss research gaps specific to individual pathogens. Other crucially important aspects of maternal immunisation, including safety, public perception, and integration into existing global immunisation programmes, are outside the scope of this Series, but are discussed in another publication that summarises the outcome of a series of meetings sponsored by the National Institutes of Health.[3]

Landscape review process and prioritization of knowledge gaps

We used an innovative multistage review process to best capture the state of knowledge about maternal immunisation. The appendix provides a detailed description of the methods used and the results of the analysis. Briefly, an international team of ten recognised experts did a scoping review of the English literature published since 2000 [A: Please provide month and date here (eg, Jan 1?)]. The experts summarised the state of

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Panel: Top 20 knowledge gaps and Likert scores identified by the online survey

Immunisation during pregnancy
- Effect of vaccine antigen type on maternal responses (Likert score 4·1)
- Effect of health conditions on maternal immune responses (Likert score 4·2)

Transplacental transfer of antibodies
- Effect of timing of vaccination during pregnancy on net transfer (Likert score 4·4)
- Effect of antigen type on maternal responses and transferability (Likert score 4·1)
- Effect of complications during pregnancy on antibody transfer (Likert score 4·0)

Protection of fetus and newborn infant
- Effect of maternal immunisation regimen on cord titres (Likert score 4·3)
- Effect of maternal immunisation regimen on infant responses (Likert score 4·3)
- Clinical relevance of interference with active immunisation (Likert score 4·3)
- Effect of maternal antibodies on effector and memory B-cell responses of infants (Likert score 4·0)
- Modulation of breastmilk immune components by immunisation (Likert score 4·2)

Pertussis vaccination
- Correlates of protection against colonisation, disease, and death (Likert score 4·4)
- Requirement for multiple pertussis antigens, role of pertussis toxin (Likert score 4·2)
- Reactogenicity of repeated doses of tetanus, diphtheria, acellular pertussis vaccine in sequential pregnancies (Likert score 4·0)

Group B streptococcal vaccine
- Correlates of protection against colonisation, disease, outcomes (Likert score 4·5)
- Serotype specific immunogenicity, transfer, and protection (Likert score 4·3)
- Effect of serotype on correlates of protection (Likert score 4·0)
- Effect of carrier proteins on responses of infants to vaccination (Likert score 4·0)

Respiratory syncytial virus vaccine
- Correlates of protection against infant disease and death (Likert score 4·6)
- Protection against lower respiratory infection and disease (Likert score 4·6)
- Impact of pre-existing immunity on maternal responses (Likert score 4·0)

Likert scores were assigned by use of a 5 point scale. A score of 4 indicates high importance and a score of 5 (the maximum score) indicates very high importance.

knowledge pertaining to their assigned area, including assessments of the gaps in understanding about the biology of the immunisation process. The team met at a collaborative workshop in Vancouver (BC, Canada) to share their assessments with 26 additional international experts who commented critically on the presentations. More than 100 knowledge gaps were identified through this process, attesting to the underdevelopment of the underlying science of maternal immunisation. To ensure that deliberation was sufficiently broad and issues affecting translation were addressed, further consultations were held with leaders of maternal vaccine development programmes at three major vaccine companies and with representatives of two major regulatory agencies (the US Food and Drug Administration and the European Medicines Agency) who freely shared their insights into the knowledge gaps and challenges.

To prioritise the identified knowledge gaps, topics deemed most relevant during the collaborative workshop were included in an online survey completed by nearly 200 [A: Can the exact number of experts be provided?] content experts from the global maternal immunisation community. Respondents rated the importance of each knowledge gap; the results were consistent among respondents, including industry representatives, academic researchers, and national immunisation policy makers. The panel [A: Table I has been converted to a Panel, in line with our house style] shows the top 20 knowledge gaps; each gap was rated as 4 or more on the 5 point Likert scale (high to very high importance). To prepare this Series, we integrated and summarised the information gathered from each step of the multistage review process [A: correct as edited?].

General considerations regarding maternal immunisation strategies

When considering the four disease targets for maternal immunisation included in the landscape analysis (pertussis, influenza, group B streptococcus, and respiratory syncytial virus), it is striking that no two vaccine programmes are alike (table), and that different strategies are likely to be needed for each disease, which could make the production of a combined vaccine challenging. To focus on the immunobiology of maternal immunisation, contextual differences such as maternal disease risk, infant disease burden, global epidemiology, and microbial diversity will not be discussed further in this paper.

The common goal among maternal vaccination programmes is temporary protection of the young infant against severe illness and death by ensuring sufficient and timely transfer of protective antibodies from the mother. This passive protection should persist until the infant is no longer at high risk of disease (eg, 3 months of age for group B streptococcus disease) or until protection can be achieved by active infant immunisation (eg, pertussis). Protection of the infant might also be achieved indirectly

by reducing carriage or disease in the mother, which subsequently reduces transmission of pathogens to the infant (eg, group B streptococcus, pertussis). Whether or not protection of the mother against disease is also required is another important factor in determining the timing of maternal immunisation. For example, in the case of influenza immunisation early during pregnancy might be the favoured strategy to protect both the pregnant woman and neonate. Additionally, immunisation before pregnancy might have the benefit of preventing infections that could have harmful effects on a developing fetus. However, understanding of optimal maternal immunisation for any target is limited by the scarcity of defined correlates of protection for young infants. Without a validated measure of protection, it will be difficult to compare results of studies in different settings or to improve vaccines or immunisation regimens by use of serological criteria.

Immunisation during pregnancy relies on the capacity of the pregnant woman to mount appropriate primary or secondary antibody responses, depending on whether the pathogen has been encountered before pregnancy. The notion that pregnancy is associated with the induction of various immunoregulatory mechanisms that are essential for the survival of the fetus suggests that antibody responses to vaccines might be different in pregnant women compared with non-pregnant women. Vaccine responses might be further influenced by complications affecting pregnant women, such as chronic infections. Optimal protection of the young infant is considered to rely on the effective transfer of maternal immunity through the placenta and the persistence of this passive immunity for the duration of infant exposure to the particular pathogen. Additional protection might be provided by transfer of immunity via breastmilk. However, the relative contributions of breastmilk and serum antibodies to infant protection will be difficult to define, but are important to understand, especially for infants born prematurely with restricted transplacental transfer of antibodies. These passively transferred maternal immune factors can further influence active immunity induced in the infant by natural infection or immunisation. Experts at the collaborative workshop identified 68 knowledge gaps related to the effect of pregnancy on vaccine responses, the transfer of maternal immunity to the infant, and infant immunity (appendix). The panel presents the top ten of these knowledge gaps deemed most relevant in the online survey.

	Pertussis	Influenza	Group B streptococcus	Respiratory syncytial virus
Maternal disease risk	+	+++	++	+
Infant mortality	++	+	+++	++
Infant disease frequency	+ (cyclic*)	++	+	+++
Disease seasonality	✓	✓	×	✓
Microbial diversity	+	++	++	+
Licensed vaccine available	✓	✓	×	×
Maternal booster response expected†	✓	Quasi [A1]‡	Not assumed	✓
Passive protection of infant	✓	✓	✓	✓
Maternal to cord antibody ratio	1·1–1·9	0·7–1·0	0·7–0·8	1·0
Antibody half-life (days)	36–40	40–50	30–44	36–79
Infant vaccination	✓	³6 months	×	(✓)§
Correlate of protection	×	Quasi [A1]¶	×	×
Functional immunoassay	×	✓	?‖	✓
Competing control option	×	×	✓**	✓††

*Increased disease incidence usually occurs every 3–4 years. †Via previous vaccination or infection. ‡Previous vaccination or infection will lead to partial protection due to virus evolution. §Monoclonal antibody administered to high-risk infants during respiratory syncytial virus season. ¶Correlates of protection based on haemagglutinin inhibition assay or microneutralisation titres have not been validated in young infants and are not based on maternal immunisation. ‖Bacterial killing in an opsonophagocytic assay has been suggested as a possible correlate of protection. **Intrapartum antibiotic prophylaxis has reduced the incidence of early onset group B streptococcus neonatal sepsis. ††Monoclonal antibodies administered to high risk infants during respiratory syncytial virus season reduces rates of hospital admission. [A1: Please explain what is meant by Quasi in this context] [A: Please describe in the legend what the symbols +, ++, +++, ? in the table mean for clarity]

Table: **Targets of maternal immunisation**

Effect of pregnancy on vaccine responses

Pregnancy and B lymphocytes

Studies indicate that pregnancy influences B cells and antigen-presenting cells; no studies have assessed the potential effect on follicular helper T cells.

Oestrogen and pregnancy reduce B-cell lymphopoiesis in mice.[4] Reductions in the number of circulating B cells have likewise have been shown in pregnant women, but the potential effect on antibody responses to primary immunisation is unknown.[5–7] Some studies[8–10] have shown an effect of pregnancy on memory B-cell subsets, but no consistent evidence has yet emerged. Additionally, the potential effect of pregnancy on other B-cell subsets, including transitional or marginal zone B cells, remains to be assessed. In populations living in LMICs, chronic exposure to microbial antigens, such as *Plasmodium falciparum*, induces high numbers of circulating atypical memory B cells.[8,9] Because these memory cells have a reduced capacity to produce immunoglobulins, their increased numbers could hamper the immune response on subsequent challenge [A: Is this suitable instead of 'recall immunisation'?] in both pregnant and non-pregnant women living in LMICs.

Pregnancy and immunoglobulins

Studies assessing the influence of hormones on B-cell functions support the notion that pregnancy might affect the production of immunoglobulins. Oestrogen increases the production of IgG by human B cells.[11] Additionally, activated human B cells upregulate the expression of the prolactin receptor, and prolactin further decreases the threshold of B-cell activation.[12] In mice, oestrogen also upregulates the expression of the activation-induced deaminase—the enzyme that initiates somatic hypermutation and class switch recombination of immunoglobulins.[13] By contrast, serum IgG concentrations are

See Online for appendix

lower in pregnant than in non-pregnant women in both LMICs and high-income countries.[14,15] The mechanism involved is unclear, but could, at least partly, be due to haemodilution. Pregnancy is also associated with modifications in IgG glycosylation.[16]

IgG are glycoproteins that carry N-glycans at both the Fc and Fab segments, which modulate their effector functions.[17] In pregnancy, IgG antibodies have increased sialylation and decreased N-acetylglucosamine bisection of both Fc and Fab fragments, and increased galactosylation of Fc fragments.[16] Although the functional consequences of Fab fragment glycosylation remain unclear, sialylation and galactosylation of Fc fragments have been associated with decreased inflammation and were suggested to be involved in the remission of rheumatoid arthritis associated with pregnancy.[18,19] The potential implications of the anti-inflammatory properties of maternal IgG on immune homoeostasis and antimicrobial defenses in the fetus and newborn baby have not been determined. Surprisingly, IgGs of different antigen specificity have different glycosylation profiles and this profile is modified after recent antigen exposure.[20] Moreover, IgG glycosylation patterns are different in populations living in high-income countries and LMICs.[20] Studies are needed to establish the effect of pregnancy on the glycosylation and effector functions of vaccine-induced IgG.

Pregnancy and antigen-presenting cells

Pregnancy is associated with changes in the numbers and phenotypes of antigen-presenting cells. The number of myeloid dendritic cells increases in the first trimester of pregnancy and decreases in the third trimester as pregnancy progresses to reach similar cell counts as in non-pregnant women.[21,22] By contrast, the number of plasmacytoid dendritic cells is reduced during the third trimester of pregnancy.[23] Myeloid dendritic cells and plasmacytoid dendritic cells were shown to express higher concentrations of toll-like receptors in pregnant women than in non-pregnant women.[24] Several differences exist between antigen-presenting cells from women and men that are induced by sex hormones and could therefore be relevant to pregnancy.[25] Modifications of antigen-presenting cells are likely to be important for successful pregnancy, but the potential effect on vaccine responses have not been determined.

Pregnancy and vaccine response

The effect of pregnancy and sex hormones on B cells and antigen-presenting cells suggests a possible influence on antibody responses to vaccines. This potential is indirectly supported by the observation that the magnitude of antibody responses to many vaccines is often higher in women than men.[25] However, most studies of pregnant women that showed potent vaccine immunogenicity did not include a comparison group of non-pregnant women.[26–29] A few controlled studies have been done, but only in small populations. Some studies reported similar responses to seasonal influenza vaccines in pregnant and non-pregnant women, whereas others detected differences in titres or seroconversion rates.[30–34] Factors responsible for the discrepancies between studies might include differences in tested vaccines and participant characteristics. The results of two controlled studies **[A: Please provide references for the two studies immediately after their mention]** done in high-income countries showed similar antibody responses to tetanus, diphtheria, acellular pertussis vaccine (Tdap) immunisation in pregnant and non-pregnant women, whereas two other studies in LMICs reported no effect of pregnancy on the response to tetanus immunisation.[35–38]

In 2016, the immunogenicity of a conjugated group B streptococcus vaccine was studied in South Africa.[39] Although the responses were not compared between pregnant and non-pregnant women, the vaccine was immunogenic in both groups. Whether the gestational stage of pregnancy affects responses to vaccines has not been extensively studied. Similar antibody responses to seasonal and pandemic influenza vaccination were observed throughout pregnancy in two studies **[A: Please provide references for the two studies immediately after their mention]**, whereas seroconversion rates with a seasonal influenza vaccine were higher during the third trimester than during the first and second trimesters **[A: comparator correct as added?]** in one study.[27,31,40] The effect of pregnancy on the quality of antibody responses to vaccines remains largely uncharacterised. Conflicting results on the avidity of antibodies following pertussis immunisation during early pregnancy compared with late in pregnancy have been obtained in small-scale studies.[41,42]

The persistence of antibodies after maternal immunisation will influence the optimum timing of immunisation and the requirement to repeat immunisation during consecutive pregnancies; however, little information about this topic is available. Antibody decay following immunisation with adjuvant pandemic influenza vaccine was similar in pregnant and non-pregnant women.[33] Pertussis immunisation has been recommended during the second or early third trimester of pregnancy to achieve sufficiently high titres of antibodies close to delivery.[x1] **[A: To maintain style, the journal reference provided has been added to the reference list—see x1, the references will be renumbered accordingly]**. This recommendation was challenged by a 2016 study,[43] which showed higher titres of cord-blood antibodies following pertussis immunisation during the second trimester of pregnancy than during the third trimester, suggesting cumulative transfer of antibodies.

Innate immune responses after maternal immunisation have not been explored. One study **[A: Please provide a reference for this study directly after first mention]** reported similar plasma concentrations of inflammatory cytokines in pregnant and non-pregnant women following seasonal influenza immunisation. This result accords with the similar or even lower reactogenicity

observed in pregnant women following influenza immunisation.[44,45]

Influence of maternal factors on vaccine responses

Most studies reported no significant effect [A: We reserve the use of significant for instances of clinical or statistical significance. Is this the case here, or should 'substantial' 'relevant' eg, be used instead?] of maternal age, parity, socioeconomic status, or bodyweight on antibody response to vaccines during pregnancy.[46–48] However, parity was associated with reduced antibody responses to *Haemophilus influenzae* type b conjugate vaccine in The Gambia and with heightened responses to pertussis toxin in Belgium.[49,50] This finding could be particularly important in LMICs, where high-order multiparity is more common than in high-income countries [A: comparator correct as added?]. Some studies suggested a small effect [A: correct as rephrased?] of nutrition on vaccine responses during pregnancy.[51,52]

Whether obesity affects immune response to vaccination in pregnancy is poorly understood because obese women (body-mass index >30 kg/m²) are typically excluded from clinical trials. Little information is available about the possible differences in vaccine immunogenicity between LMICs and high-income countries resulting from health conditions of the mother. One study[35] reported that *P falciparum* parasitaemia had no effect at the time of immunisation on antibody response to tetanus toxoid. However, HIV infection impairs responses to vaccines. In South Africa, pregnant women with HIV have lower seroconversion rates after seasonal influenza vaccination than do uninfected pregnant women, but antibody half-life and vaccine efficacy are similar between the two groups.[53,54] HIV infection was also associated with lower immunogenicity of a glycoconjugate group B streptococcus vaccine in pregnant women in South Africa.[55] The effect of helminth infection on vaccine responses during pregnancy has not been systematically analysed.[56] [A: Summary paragraphs have been deleted to increase flow and readability]

Transfer of maternal immunity through the placenta

IgG transfer and preterm birth

IgG is the only antibody that is directly transferred across the placenta.[57] A 2015 study[58] indicated that other maternal immunoglobulins can be transported to the fetus when complexed with IgG. IgG antibodies are actively transported through the placenta by the neonatal Fc receptor (FcRn), and possibly by additional receptors that have not yet been identified.[59,60] The FcRn is expressed by syncytiotrophoblasts covering the surface of the chorionic villi, and transports IgG by transcytosis into the fetal circulation. Although the FcRn is expressed and functional in the placenta from the first trimester, most of the antibody transfer occurs after 28 weeks' gestation.[61,62] Preterm birth is therefore an important factor that restricts the transfer of maternal immunity through the placenta and might affect the transport of IgG1 more than IgG2.[63–66]

Preterm birth occurs in 5–18% of pregnancies globally and is a leading contributor to infant morbidity and mortality. In a 2012 systematic analysis,[67] over 60% of all preterm births were estimated to occur in sub-Saharan Africa and south Asia (>9 million of roughly 15 million births per year globally). At 28–33 weeks' gestation, fetal–maternal antibody ratios are typically 0·5–0·6 compared with 1·0 or higher at full term. Thus, transfer of maternal antibody could afford some potential protection even in prematurely born babies if their antibody concentrations were elevated by previous immunisation.[66]

Factors influencing IgG transfer

The rate of IgG transfer through the placenta is influenced by several factors, including IgG subclass, antigen specificity, and chronic maternal infections. IgG subclasses are transcytosed at different rates, with IgG1 being most actively transferred, followed by IgG4, IgG3, and IgG2.[59,68,69] IgG3 allotypes have different affinity for FcRn and this results in differential transfer ratios.[69] It is puzzling that antibodies of different antigen specificities are transported at different rates across the placenta, resulting in different maternal to cord-blood antibody ratios.[70–72] Reported cord-blood to maternal ratios range from 1·9 for pertussis to 0·7 for group B streptococcus, with influenza ranging between 0·7 and 1·0.[26,53,73–75] These differences might be partly related to the differences in IgG subclass proportions, as protein antigens generally induce IgG1 and IgG3 subclasses, whereas polysaccharide antigens induce mainly IgG2 antibodies, but this hypothesis has not been systematically examined.[57,72]

Whether or not the structure of maternal IgG influences placental transfer beyond subclasses has not been clearly established. Two studies[76,77] have suggested that high avidity antibodies can be transferred preferentially across the placenta. Previously, studies also suggested a preferential transfer of hypergalactosylated IgG, but this theory was not supported by a more recent study that used more advanced technologies, which showed that Fc galactosylation had no effect on IgG transfer.[78,79]

Chronic maternal infections and hypergammaglobulinaemia have a profound effect on maternal antibody transfer.[66] Reduced transfer of IgG is observed in women with hypergammaglobulinaemia, a condition that might be associated with the saturation of FcRn.[80–82] Hypergammaglobulinaemia and the denudation of syncytiotrophoblasts from chorionic villi could also be involved in the reduced transfer of IgG associated with placental malaria.[66,81] A 2016 study[83] in Papua New Guinea indicated an association between reduced transfer of respiratory syncytial virus-specific IgG and hypergammaglobulinaemia, but not with placental malaria itself. Maternal HIV infection also results in a reduction of maternal IgG transfer.[82,84–86] Intriguingly, the effect

of chronic maternal infections and hypergammaglobulinaemia seems to depend on the subclass and antigen specificity of IgG. In a study[85] in South Africa, maternal HIV infection was associated with reduced transfer of naturally acquired group B streptococcus-specific IgG1, but not IgG2. In a study[81] in The Gambia, maternal hypergammaglobulinaemia was found to be associated with impaired transfer of total IgG1 and IgG2, but not IgG3 and IgG4, and with a reduced transfer of IgG against pathogens, but not vaccine antigens. [A: Summary paragraph has been deleted to increase flow and readability.]

Transfer of maternal immunity through breastfeeding

The importance of breastmilk in postnatal life is highlighted by the strong correlation between breastfeeding and the profound reduction in risks of infection and infection-associated mortality in infancy.[87,88] However, only one study [A: Please reference this study at first mention] assessed the role of breastfeeding in protection against an infectious pathogen after maternal immunisation. In Bangladesh, exclusive breastfeeding was associated with a decrease in the number of episodes of respiratory illness with fever in children born to mothers immunised against influenza during pregnancy.[89] Prevention of infectious diseases by breastfeeding is thought to be due to the strengthening of gastrointestinal and respiratory mucosal immunity via improvement of the function of the epithelial barrier through the high content of growth factors in breastmilk, and by transference of antimicrobial factors, such as lactoferrin and lysozyme, and microbial antigen-specific immunity (figure 1). Thus, maternal immunisation might modulate antigen-specific immune factors in breastmilk and promote antigen-specific immune responses in infants.

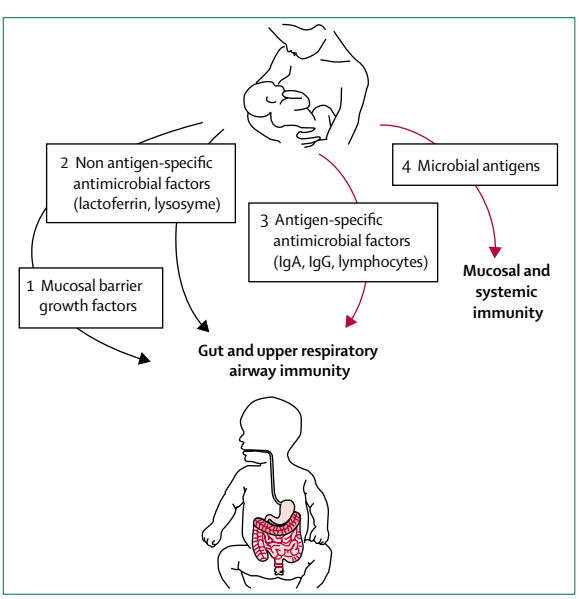

***Figure 1*: Transfer of maternal immunity through breastfeeding**
Microbe-non-specific immunity (blue) is promoted by breastmilk through growth factors that improve the function of the epithelial barrier (1) and antimicrobial molecules (2). Microbe-specific immunity (red) is provided by antigen-specific maternal IgA and IgG and lymphocytes (3). Breastmilk also contains antigens and attenuated microbes that can stimulate infant immunity (4). Maternal vaccination could improve prevention of infectious disease in breastfed children by increasing the concentration of antigen-specific antimicrobial factors and microbial antigens in breastmilk.

Breastmilk IgA

Breastmilk secretory IgA antibodies are specific for various common intestinal and respiratory pathogens as a result of the selective migration of B cells originating from the mucosal membranes to the mammary gland.[90] Therefore, concentrations of secretory IgA should be higher when induced by mucosal immunisation than by systemic immunisation, as observed following HIV immunisation of lactating Rhesus macaques.[91] The antimicrobial properties of secretory IgA depend on the inhibition of pathogen adherence to, and invasion of, mucosal epithelia, the neutralisation of pathogens and toxins, the transfer of antigens across the mucosal barrier, and the stimulation of low-level inflammation.[92] The stimulation of low-level inflammation [A: correct as edited?] has been mainly described in mice [A: Please provide a reference]. Some studies[90,93,94] in humans have demonstrated the transport of breastmilk IgA into the circulation of breastfed mature and premature newborn babies. In LMICs, where prematurity and gut mucosal inflammation are common, IgA transport to neonatal circulation might be increased and prolonged and could therefore be particularly beneficial. By contrast, breastmilk IgA could have a negative effect on the response to mucosal vaccines, but this finding remains controversial.[95,96]

Several studies[97] showed increased concentrations of antigen-specific IgA in breastmilk following maternal immunisation against influenza, pertussis, respiratory syncytial virus, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. The amount of breastmilk and magnitude of secretory IgA responses against a consensus HIV envelope protein have been associated with the reduced risk of postnatal transmission of HIV in Malawi [A: Please provide a reference]. This observation highlights the need for development of maternal vaccination strategies that increase the concentration of [A: ok as edited?] HIV-1 envelope-specific breastmilk IgA to reduce mother-to-child HIV transmission.[98] Importantly, maternal conditions that are known to negatively affect transplacental transfer of IgG do not affect IgA transfer through breastmilk. Prematurity increases the transfer of growth and immune factors, particularly IgA, in colostrum and milk.[99,100] Furthermore, the concentration of total and pathogen-specific IgA in breastmilk is not affected by maternal HIV infection or by malnutrition.[101–04]

Breastmilk IgG

Breastmilk IgG originates from serum via FcRn transport and from resident B lymphocytes.[105] The total IgG concentration in breastmilk is about 10% of the IgA concentration, but tends to increase with duration of breastfeeding.[100,106,107] Increased concentrations of antigen-specific IgG are detected in breastmilk following immunisation against respiratory syncytial virus and pneumococcus, and following natural infection with group B streptococcus, rotavirus, and HIV.[96,108,109] Evidence of a protective role of breastmilk IgG was shown in studies of HIV infection, whereby IgG had higher neutralising activity than IgA, mediated antibody-dependent cellular cytotoxicity, and was inversely correlated with the risk of HIV transmission.[109] Breastmilk IgG was also inversely correlated with human cytomegalovirus load, suggesting a protective role against human cytomegalovirus transmission.[110] However, the role of breastmilk IgG in the defense against other pathogens has not been studied.

Experiments in mice suggest that breastmilk IgG can cross the gut barrier through FcRn and can thereby promote the transport of IgG–antigen immune complexes and stimulate immune response to antigens and pathogens.[60,111–14] Whether this process occurs in human beings is unknown.

Breastmilk leucocytes

Breastmilk contains neutrophils, macrophages, and lymphocytes.[115] Common infections increase the number of total leucocytes in breastmilk, but whether similar changes occur after immunisation is unknown.[116] Breastmilk B lymphocytes are IgG-producing memory cells. The antigen specificity of these lymphocytes was demonstrated in the context of HIV infection.[105] Similarly, HIV-specific CD4 and CD8 T lymphocytes were detected in breastmilk and might contribute to virus control through inflammatory cytokines and cytotoxicity.[117,118] Studies[93,119,120] suggest that CD4 T cells in breastmilk might be transferred to human neonates and induce transient specific cellular immunity.

Transfer of microbial antigens through breastmilk

Although pathogens can be detected in breastmilk after maternal infection, transmission to the offspring is not commonly observed, with notable exceptions, including HIV, human cytomegalovirus, and human T-cell lymphotropic virus 1.[121] The evidence suggests that breastmilk immunity can prevent pathogen transmission. Additionally, studies[102,122] suggest that exposure to pathogens through breastmilk induces immune responses in infants independently of transmission. Exposure to HIV-containing breastmilk is associated with the induction of mucosal IgG and IgA responses and with systemic cell-mediated immune responses in uninfected infants. Similarly, *Vibrio cholera* can be transferred through breastmilk and induce either disease or colonisation associated with specific IgG responses in infants.[123] These observations suggest that breastfeeding can promote immunity to pathogens in infants by transmitting pathogens that are attenuated by maternal immune responses or transfer of pathogen antigens.

Studies[124] indicate that a similar process occurs following immunisation of lactating women with the live attenuated rubella vaccine. Studies in mice[125] have shown that the intrinsic adjuvant properties of antigens and the concentration of IgG and amount of vitamin A in breastmilk are crucial factors in the induction of effector immune responses in the offspring. **[A: Summary paragraph has been deleted to increase flow and readability]**

Maternal immunisation and infant immunity

Placental transfer of maternal antibodies is expected to protect the infant from disease. However, a specific concentration of antibody (the presumed correlate of protection) has to be reached to provide clinical protection and this concentration needs to be maintained until the infant is no longer at risk, or is protected by active immunisation. How long maternal antibodies persist above the protective concentrations in the infant is a function of the concentration of the antibody in the newborn baby at birth and the antibody half-life ($t_{1/2}$). Thus, the transplacental transfer and decay kinetics of maternal IgG in the infant are key determinants of the duration of protection. However, high concentrations of maternal antibodies present at the time of infant vaccination might also interfere with the immune response of the infant to the respective vaccine. Maternal immunisation can have effects on the fetus and newborn infant beyond passive protection.

Prevention of infection and disease

The distribution of serum antibodies beyond the bloodstream of the neonate or infant is not well defined, but could restrict what is achievable in terms of mucosal protection. For example, little IgG is detectable in saliva of young infants until the teeth erupt,[126] making sterilising immunity against respiratory pathogens unlikely. A more readily achievable objective would be the minimisation of invasive disease severity rather than prevention of portal of entry infection and colonisation, as emphasised by the failure of various preparations of pertussis immunoglobulin to prevent colonisation (and subsequent invasive infection) in human beings and animal models.[127–129] The observed effectiveness of maternal pertussis immunisation in preventing infant disease represents an important advancement.[130] If the benefit of maternal immunisation is largely attributable to minimisation of disease severity such encounters could result in passive and active immunity **[A: Correct as edited?]**, with active immunity following attenuated natural infection.[131]

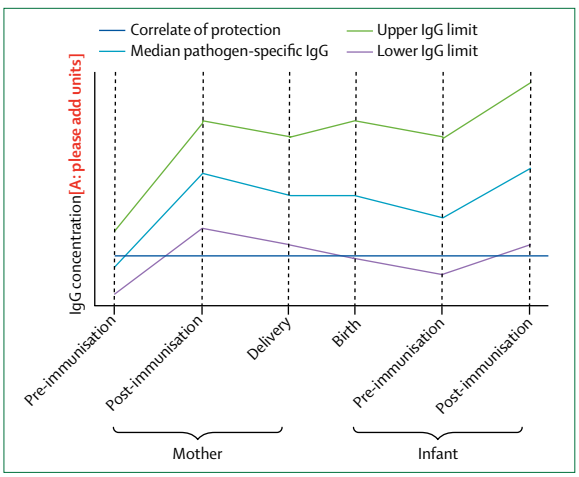

***Figure 2*: Influence of maternal immunisation on infant IgG before and after vaccination**

[A: First two sentences have been removed, as this information can be shown in the figure itself using a key.] In the absence of maternal immunisation, maternal IgG concentrations are low and could be below the correlate of protection. An ideal vaccine would raise this IgG concentration such that even the lower end of the range would be above the correlate of protection, and would remain above the correlate of protection until delivery, which would depend on the initial response to vaccination and the timing between immunisation and delivery. The infant IgG concentration at birth will depend on placental health, gestation, and antibody-specific factors. The concentration of transferred maternal IgG will decrease until the infant receives additional protection via direct immunisation, and the rate of decrease will vary between pathogens and between individuals. Ideally, maternal vaccination would ensure the IgG concentration is above the correlate of protection until infant immunisation, which will depend on the initial IgG concentration at birth and the interval until infant immunisation, creating a so-called window of susceptibility when the IgG concentration falls below the correlate of protection. Following infant immunisation, the IgG concentration will rise again, and the extent of this would be influenced by any interference caused by the presence of maternal IgG.

Maternal antibody decay in infants

The $t_{1/2}$ of IgG differs by subclass and is not a fixed entity, but is directly proportional to the total IgG concentration. This mechanism is called the concentration–catabolism effect, whereby IgG catabolism is accelerated in individuals with increased IgG concentrations and, conversely, reduced in individuals with a low serum IgG concentration.[132] The molecular mechanisms underlying the differences in $t_{1/2}$ of the various IgG subclasses and the concentration–catabolism effect centre around FcRn.[59,60]

Subclass and structural modifications of IgG have a profound effect on the interaction with FcRn, and thus $t_{1/2}$. For example, IgG3 allotypes have different affinity for the FcRn, which results in different $t_{1/2}$.[69] Furthermore, aglycosylated human IgG1 has a considerably shorter $t_{1/2}$ (62 h) than the glycosylated form (153 h).[132] Glycosylation of maternal antibodies is modified during pregnancy,[16,133] but how this relates to $t_{1/2}$ in the infant is not known. Moreover, studies suggest that the $t_{1/2}$ of IgG in infants varies depending on the antigen specificity of the antibodies and between populations. For example, reported $t_{1/2}$ in the infant of maternal antibodies specific for pertussis antigens is roughly 30–40 days, for tetanus roughly 50 days, but for group B streptococcus roughly 60 days.[29,134,135] The $t_{1/2}$ of maternal antibodies of a given specificity can also vary substantially between populations; however, whether this variability involves differences in IgG subclass or other structural differences has not been delineated.[136–38]

Interference with infant immunisation

The presence of maternal antibodies to a particular vaccine antigen has been reported to reduce antibody generation following vaccination of the infant with the same antigen,[139–41] a process known as interference. Maternal antibodies not only affect concentrations of antibodies produced by the infant, but can also influence their quality (strength of antigen binding or avidity).[141,142] Priming of T-cell responses to vaccines does not seem to be affected by passive antibodies and this probably contributes to the good response to booster doses.[139,140] The key factors influencing interference are antigen-specific maternal antibody titres at the time of infant immunisation, and the antigen content (including dose) of the infant vaccine schedule.

For pertussis, maternally-derived antibodies interfere with antibody responses to whole-cell vaccines in the infant, but less so to acellular vaccines.[37,50,143–47] Whether the improved response to acellular versus whole-cell vaccine among infants with higher antecedent titres of pertussis toxin **[A: Correct as defined?]** is due to higher antigen load in the acellular product or to the absence of other components of the whole-cell vaccine in the acellular product has not been determined.[148] In view of the fact that the current lead candidates for a maternal group B streptococcus vaccine are tetanus toxoid or CRM197 (non-toxic mutant of diphtheria toxin) conjugate polysaccharide vaccines, it is worth noting that infants born to mothers with high titres of anti-tetanus toxoid immunised with *Haemophilius influenza* type b vaccine conjugated with tetanus toxoid have reduced anti-group B streptococcus responses, but infants immunised with haemophilus b conjugate **[A: Is this the correct definition for HbOC?]** (CRM197) had no interference.[149–51] Although several mechanisms have been proposed, the molecular and cellular basis of the interference remains incompletely understood.[139,140]

Influence of maternal immunisation beyond passive immunity

Following influenza vaccination during pregnancy, anti-human influenza haemagglutinin **[A: correct as added?]** could be detected in 38·5% of cord-blood specimens, and anti-matrix protein IgM antibodies could be detected 40·0%.[152] Because IgM does not cross the placenta, this finding suggests an active adaptive B-cell response in the fetus. This hypothesis was further corroborated by the detection of human influenza haemagglutinin-specific T-cell responses in some newborn babies of immunised women with synthetic peptide-human leucocyte antigen

multimers [A: Please provide a reference]. Similarly, earlier studies[153,154] of tetanus vaccination during pregnancy reported detection of anti-toxoid IgM in sera of some infants. Because vaccines can have immune modulatory effects in postnatal life beyond initiating antigen-specific adaptive responses (ie, non-specific effects[155]) immunisation during pregnancy could also have non-specific effects not only in the mother, but also in the fetus or newborn baby. To our knowledge, this notion has not been systematically investigated. However, MF59-adjuvanted influenza vaccination during pregnancy led to an altered cytokine production profile in the nasal mucosa of 4-week-old infants from vaccinated versus unvaccinated mothers.[156] The clinical relevance of these unexpected findings (active in-utero immune response and non-specific effects on the newborn baby after maternal immunisation) is unclear. [A: Summary paragraph has been deleted to increase flow and readability]

Conclusion

The passive transfer of maternal immunity is considered central to antimicrobial defenses in early life (figure 2 [A: Please move this figure citation to earlier in the paper, rather that readers reaching the end of the paper before seeing this informative graph]). The proposed mechanisms centre around active transport of maternal IgG through the placenta providing systemic immunity during the first months after birth until the infant actively acquires immunity through exposure to pathogens or vaccines. The immune components of breastmilk can provide longer-term immunity at the mucosal level and could also contribute to the development of infant immunity at the systemic level.

Although maternal immunisation is an effective strategy to increase antimicrobial immunity in early life, many knowledge gaps remain in the understanding of vaccine responses during pregnancy, the transfer and persistence of maternal immunity in infants, and the interactions between maternal antibodies and the infant immune system. In this landscape analysis, we prioritised gaps of particular relevance to the development of new vaccines for pregnant women and to the implementation of maternal immunisation worldwide [A: Don't need to refer to the panel again in this section of concluding remarks]. Addressing these knowledge gaps [A: edit OK?] offers the potential to further improve this important public health intervention, and will require immunological studies of existing vaccines administered to pregnant women and the inclusion of immunological endpoints in the clinical studies of vaccines under development.

Contributors

AM, DWS, and TRK developed and managed the landscape analysis, and synthesised the information. AM, VV, LP, and TRK led the literature review on the immunobiology of maternal immunisation. MG and GB provided major administrative support and participated in the synthesis of the information. AM, MS, ND, VV, LP, CEJ, SAH, KME, PH, PJO, DWS, and TRK contributed to the literature review and synthesis. AM, MS, VV, MG, DWS, and TRK drafted the initial manuscript and all authors contributed to the final version of the manuscript.

Declaration of interests

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