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IMMUNIZING IN PREGNANCY TO PROTECT THE FETUS, NEONATE AND MOTHER: BRIDGING THE GAP BETWEEN VACCINE EVIDENCE AND ADOPTION IN LOW INCOME COUNTRIES

BY

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Abstract

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By Adaeze Ogee-Nwankwo

Neonatal mortality as a share of under-5 mortality is substantial. Preterm birth, intrapartum complications and infectious diseases are the leading causes of neonatal deaths worldwide. In 2012, the neonatal mortality rate in low income countries was more than 8 times that of high income countries, signaling the need for more intensive efforts to ensure survival early in life in low income countries. Immunizing in pregnancy has the potential to avert millions of cases of disease, disability and death in mothers and neonates, and ensure good pregnancy outcomes.

Current evidence suggests that routine use of the following ten vaccines in pregnancy can have a substantial impact on the infectious disease burden in low income countries: Tdap (tetanus–diphtheria–acellular pertussis)/tetanus toxoid vaccine; inactivated influenza vaccine; *Haemophilus influenzae* type B vaccine; pneumococcal vaccine; meningococcal vaccine; hepatitis B vaccine; hepatitis E vaccine; group B streptococcal vaccine; respiratory syncytial virus vaccine; and malaria vaccine. There is variability in the availability of these vaccines, with some still in the development pipeline. Challenges that may impede routine use of these vaccines in pregnancy exist, the foremost of which is insufficient definitive evidence on their effectiveness on clinical outcomes.

There is global support and advocacy for immunizing women in pregnancy. However, there are also barriers to adoption by lower income countries. To bridge the gap between evidence and adoption, a strengthening of the evidence base has to occur; there has to be clear recommendations for routine use of these vaccines in pregnancy by WHO; the vaccine adoption decision-making processes in many low income countries has to be strengthened; and private-public partnerships that address acceptability issues related to multiple vaccine administration in pregnancy are required. Accomplishing these objectives will pave the way to adoption and eventually lead to a decrease of the global neonatal disease burden.

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List of acronyms & abbreviations

ACIP	Advisory Committee on Immunization Practices
ALRI	Acute lower respiratory illness
EOD	Early onset disease
GBS	Group B streptococcus
GNI	Gross national income
HAI	Hemagglutination inhibition
HBV	Hepatitis B virus
LAIV	Live attenuated influenza vaccine
LOD	Late onset disease
MDG	Millennium development goal
MHC	Major histocompatibility complex
MNT	Maternal and neonatal tetanus
NITAG	National Immunization Technical Advisory Group
RSV	Respiratory syncytial virus
SAGE	Strategic Advisory Group of Experts
Tdap	Tetanus-diphtheria-acellular pertussis
IIV	Inactivated influenza vaccine
TT	Tetanus toxoid
WHO	World Health Organization

PART I. Introduction

1.1. Overview

Vaccines are one of the greatest tools in the fields of public health and medicine. Their ability to elicit an immune response and induce long-term protection has led to a significant reduction in the global burden of many infectious diseases. The eradication and elimination of diseases are no longer idealistic dreams, but realities given the strategic use and effectiveness of vaccines. Smallpox, a disease responsible for millions of cases of debilitating illness and deaths around the world, was eradicated in 1979 through intensive immunization campaigns (1). Such an achievement is the basis for global health initiatives that strive to rid the world of infectious diseases, particularly those that place a disproportionate burden on children.

The Millennium Development Goal 4 calls for nations and non-governmental partners to implement measures that reduce the magnitude of under-five child mortality by two-thirds in 2015 compared to 1990 (2). While these efforts have almost halved the 1990 rate of 87 deaths per 1,000 live births, there still remains a significant burden. In 2011, 6.9 million children died mainly from preventable diseases, 43% of which were neonates (newborns) (2). Due to the facts that, 1) neonates lead in under-five deaths in all regions of the world, 2) the immune system is "immature" early in life, and 3) life-saving vaccines are generally not administered in the first month of life, it is of utmost importance that new strategies be put in

place to protect neonates. Such strategies also need to address poor pregnancy outcomes, such as preterm delivery and low birth weight, which can result from infectious diseases that are largely preventable (3).

Maternal immunization is one such strategy that can make a substantial impact on early life survival in low income countries. This paper outlines a case for immunizing pregnant women to ensure immunity against morbidity and mortality from infectious diseases, and thereby protect the fetus during gestation, and the newborn before active immunization ensues.

1.2. Background on neonatal mortality

Neonatal mortality (death within the first 28 days of life) is increasingly becoming a major public health challenge (4). The risk of dying in childhood is greatest as a neonate. About 50% of all neonatal deaths occur within the first day of life and 75% occur within the first week (5). Preterm birth, intrapartum complications and infectious diseases are the leading causes of neonatal deaths worldwide (6). Although neonatal mortality has declined from 33 per 1,000 live births in 1990 to 21 per 1,000 live births in 2012, it has increased as a share of under-5 mortality, from 36% in 1990 to 43% in 2011 (2). This signals the need for more intensive efforts to ensure survival.

The WHO African and South-East Asian regions have the largest shares of global neonatal deaths—36% and 34%, respectively—with India, Nigeria, Pakistan, China and the Democratic Republic of the Congo together capturing 53% of the burden (6,

7). This is not surprising given their large population size and modest to low economic statuses. Health outcomes are generally a factor of economic wealth, with countries in the higher economic sectors that spend more on health per capita showing more favorable health outcomes compared to those in the lower sectors.

The World Bank groups countries into 4 sectors based on gross national income (GNI) per capita. These are low income, GNI per capita of $1,035 or less; lower-middle income, GNI per capita of $1,036 - $4,085; upper-middle income, GNI per capita of $4,086 - $12,615; and high income, GNI per capita of $12,616 or more. Figure 1 shows the proportion of global neonatal deaths by income status in 2011 and figure 2 shows the time-wise burden of neonatal mortality by income group. It is apparent that those in the lower income sectors (low and lower-middle income countries) consistently have the highest burden, with rates more than double those in the higher income sectors (upper-middle and high income countries). Notably, of the 26 countries with more than 20,000 neonatal deaths in 2012, all but three countries were in the lower income sectors (7).

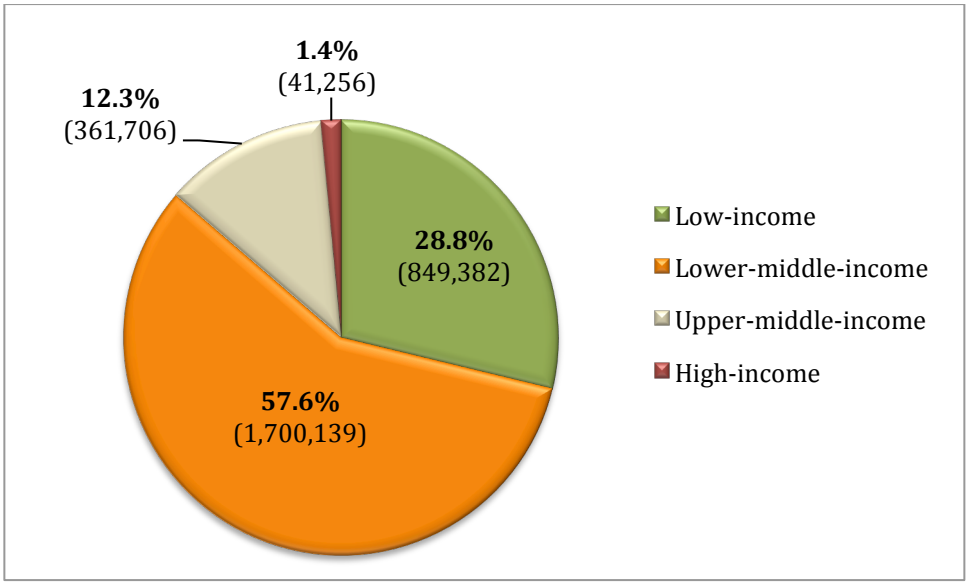


Figure 1. Global neonatal deaths (0-27 days) by income group, 2011.[1,2]

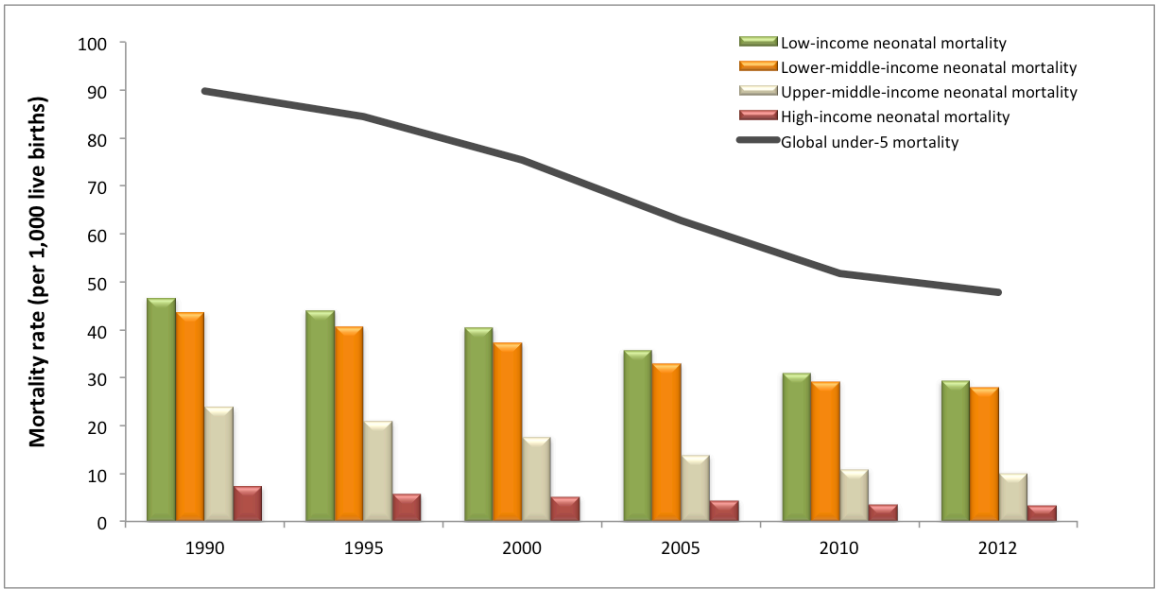


Figure 2. Neonatal mortality rate by World Bank income group: 1990 – 2012.[2]

[1] Sum of percentages is greater than 100% due to rounding.

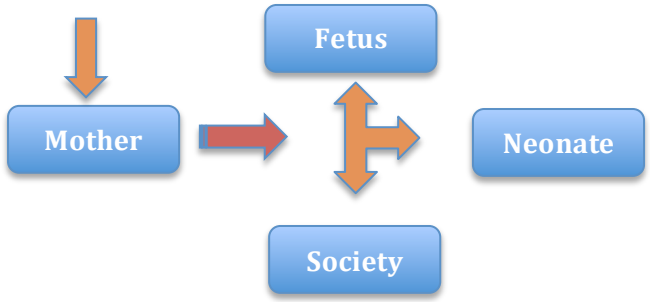
[2] [7]

1.3. Addressing neonatal mortality through maternal immunization

There is a plethora of initiatives currently addressing under-five mortality. Those that focus on infectious diseases provide monetary and technical support for interventions in low income countries. Chief among these is childhood immunization, which is a proven cost-saving intervention that ensures long-term protection for the individual and, when coverage rates are high, helps interrupt endemic transmission of pathogens (8). The majority of vaccines administered during childhood are recommended for the post-neonatal period. The Hepatitis B and bacille Calmette–Guérin vaccines are currently the only vaccines recommended by the WHO to be administered during the neonatal period (the first dose given close to birth) (9, 10).

It has been shown that newborns—at birth and for several months thereafter—possess maternal antibodies to viral and bacterial pathogens (11, 12). These antibodies can modulate the development and severity of disease, and ultimately enhance neonatal survival (13). However, mothers can only transfer antibodies to pathogens they have developed an immune response against, and the quantity of maternal antibody transferred to the neonate factors into protection early in life. This, together with protecting mothers from acquiring disease and ensuring optimal pregnancy outcomes, are the basis for maternal immunization.

1.3.1. Quadruple benefit of maternal immunization



Mother, fetus and neonate

Immunizing pregnant women can be proximally beneficial to the mother, fetus and neonate. Acquiring a vaccine-preventable disease in pregnancy can result in serious disease, complications or even death (14-16). Although natural immunity will be gained (if the mother survives), there is the possibility of sequelae and poor birth outcomes (17-19). The immunogenicity of inactivated vaccines is generally less potent than that of the actual disease-causing agents, and, with the elimination of pathogenicity, the risk to mother and fetus is low (20).

Society

Society distally benefits from this as increasing levels of immunity in the population—from immunized mothers and immune neonates—enhance herd immunity, resulting in interruption of transmission of pathogens.

1.4. The immune system: Pregnant mother, materno-fetal environment and the neonate

During pregnancy, the mother undergoes physiologic changes. She experiences non-generalized immunosuppression, specifically at the placental barrier, that ensures tolerance of the semi-allogenic fetus (21, 22). Complete immune functioning is not lost as the mother still retains immune competence to respond to pathogens she is challenged with. Still, the severity of disease can be exacerbated in pregnancy. This was evident in the increased rates of infections, complications and hospitalizations seen in pregnant women during the 2009 influenza A (H1N1) pandemic (14, 15).

The mother's response to immunization is typically similar to that of a non-pregnant adult in that, in a time-dependent manner, significant humoral transition or boosting is observed (i.e., conversion to seropositive status or ≥ 4-fold rise in titer where preexisting immunity is present) and cell-mediated immunity is gained (19, 23). Generally, antigen-specific antibodies appear within the first 10 days and peak at 30 days post-immunization. As time progresses, the circulating antibody levels wane if no exposure to the antigen occurs (20). This decrease is not necessarily symbolic of a loss of immunity as cellular immunity may still be active; and, the proportion of antibodies that remain in circulation mature in avidity and have potent neutralizing and opsonizing activities that generally surpass the serologic protective threshold when measured *in vitro* (20).

Maternal and placental circulatory systems are separate, but fetal syncytiotrophoblasts freely circulate in maternal blood owing to their lack of expression of MHC class I or II (22). Syncytiotrophoblasts mediate maternal IgG transport across the placenta through endocytosis and binding of antibodies to the neonatal Fc receptor for IgG (FcRn), followed by release into fetal circulation (24). This active transport mechanism expresses isotype preferentiality by binding to IgG1 and IgG3 more readily than other IgG subclasses (25-27). This efficiency in transfer, together with IgG1 concentrations about 9 times the level of IgG3 in serum and 3 times the half-life of IgG3, results in a higher proportion of IgG1 in fetal blood. While fetal:maternal ratios of IgG2, IgG3 and IgG4 can remain equivalent at birth, IgG1 is much higher in the fetus compared to the mother (28). Consequently, the concentration and heterogeneity of the maternal IgG population to a pathogen matters in the efficiency of antibody transport. Vaccines containing protein antigens (protein-only vaccines or conjugated polysaccharide-protein vaccines) elicit a more pronounced IgG1 response compared to those solely utilizing polysaccharide antigens, which elicit a mostly IgG2 response (27, 29). This skew in antigen subclass production can affect the total amount of IgG the fetus receives. Maternal cellular immunity is not transferred to the fetus.

A time-dependent correlation exists between gestational age and transfer of antibody across the placenta. In the first trimester, no transfer occurs; during the second trimester, between 13 - 17 weeks, transfer begins but with low amounts of antibody. At 17 – 22 weeks, the amount transferred to the fetus is about 10% of

maternal total antibody, and 50% by weeks 28 - 32. Continuing through the third trimester, increasing antibody amounts are transported to the fetus; by 33-34 weeks, maternal and fetal antibody levels are similar, and by 40 weeks (term), the fetal antibody levels exceed maternal levels (27, 29-31).

Placental integrity and infection has been shown to limit the efficiency of antibody transfer. In a study in The Gambia assessing the effects of malaria and hypergammaglobulinemia on maternal antibody transfer, researchers found that mothers with malaria-parasitized placentas, despite their high antibody levels, transferred lower levels of total IgG (and significantly reduced amounts of IgG1, IgG2 and IgG4) to their fetuses compared to those without placental malaria (32). A reason for this is syncytiotrophoblastic necrosis and the thickening of the trophoblastic basement membrane, which may result in a lowered efficiency of the FcRn receptors to transport antibodies across (32, 33). Also, elevated levels of specific and non-specific antibodies due to immune assault by the parasite leads to completion for limited FcRn receptors, thereby reducing the amount of specific antibody transferred (27, 32, 33).

HIV has also been shown to affect the efficiency of antibody transport. In a study in Kenya, Farquhar *et al* showed that high HIV viral loads at 32 weeks had a strong negative correlation with the amounts of measles antibody transferred, further emphasizing the need to control HIV viral loads during pregnancy (34). The study also showed an inverse relationship between levels of maternal HIV-1–specific gp41 antibodies and levels of measles-transferred antibodies, indicating a

similar relationship as that observed in the aforementioned study in The Gambia. High concentrations of HIV-1–specific gp41 antibodies compete for limited FcRn receptors, thus limiting the transfer of measles antibodies. Another study in Kenya focusing on placental transfer of tetanus antibody found that pregnant women with HIV and placental malaria had a 16% reduced placental transfer efficiency (ratio of cord blood to maternal antibody levels) (35). Although this study did not show a synergistic effect of maternal HIV and malaria, it is possible that their varying mechanisms of pathogenicity may contribute to a more enhanced reduction of placental transfer efficiency than their individual effect.

The neonate's immune system is "immature" and thus inefficient at deterring infections (27). The protection provided by the womb, now lost, can leave the neonate vulnerable to a host of pathogens. However, passive immunity acquired from placental-transferred and breast milk-derived maternal antibodies bridge this gap by decreasing the risk of illness as the neonate's immune system matures (30, 36-38). Neonates that are premature or are of low birth weight do not fully benefit from placental transfer. Studies have shown that premature, low birth weight, and dual premature–low birth weight neonates have lower maternal antibodies compared to term, adequate birth weight neonates (11, 12, 31, 39). Preterm birth limits the amount of antibody transferred since substantial levels are not gained until about 30 weeks of gestation. However, the closer to term the neonate is, the less of an effect this has on maternal transfer (27). Low birth weight can be

attributed to insufficient gas and nutrient transfer to the fetus due to impairment of the placenta by infection (33). This disruption most likely affects maternal antibody transfer resulting in reduced placental transfer efficiency and lower levels of antibodies at birth compared to adequate birth weight neonates.

As the neonate develops into infancy, the immune system matures. With active immunization, the dependence on maternally-acquired passive immunity shifts to self innate and adaptive immunity. There have been conflicting reports that maternal antibody interferes with the infant mounting up responses to childhood vaccines (37, 40, 41). This effect, termed "blunting" or "immune tolerance," has been attributed primarily to epitope masking, wherein maternal antibodies bind to antigens, thus preventing a B-cell response. This interference is dependent on the amount of maternal antibodies present and the concentration of antigen in the vaccine used (42).

PART II. Vaccines: Evidence of protection

This section discusses the characteristics of 10 vaccines with potential for adoption into the maternal health programs of low income countries to reduce the burden of neonatal morbidity and mortality that they disproportionately bear. The first 6 vaccines are prequalified by the WHO and are *inactivated* viral, bacterial or toxoid formulations(43, 44). The seventh is not widely available and the last 3 are still in the development pipeline.

2.1. Tdap (Tetanus–diphtheria–acellular pertussis) vaccine / TT (tetanus toxoid) vaccine

Tetanus

Tetanus, an often fatal disease in immune-naïve populations, is caused by a potent neurotoxin produced by the bacterium *Clostridium tetani* when it invades the body through contaminated objects coming in contact with broken skin (45). In the case of neonatal tetanus, unhygienic practices, such as using non-sterile objects to cut or dress the umbilical cord site result in *C. tetani* infection and probable death of the child. In the 1980's, close to 800,000 deaths were attributed to neonatal tetanus, a rate of 6.7. per 1,000 live births (46). About 90% of cases occur 3 to 14 days after birth, with case fatality rates nearing 100% if untreated and 10-60% with medical care (47). Active immunization with vaccine containing TT (the chemically-inactivated, yet immunogenic, neurotoxin) is highly effective in preventing

development of tetanus and has considerably reduced the incidence of the disease globally (20).

An observational study conducted in Papua New Guinea was the first to prove the effectiveness of TT vaccine in pregnancy. It showed the efficacy of 2 and 3 doses of tetanus immunization administered during pregnancy in significantly reducing neonatal tetanus morbidity and mortality (48). In a controlled trial in Columbia, there were no neonatal tetanus deaths in the study group of pregnant women who received 2-3 doses of TT vaccine, but the control group experienced a neonatal tetanus mortality rate of 78 per 1,000 live births (49). The vaccine was found to reduce the risk of neonatal tetanus death by 43% with 1 dose and 94 – 98% after 2 or 3 doses (47, 50). Other studies have confirmed these findings (11, 50).

Placental transfer efficiency range from 1.33 – 1.79 for tetanus antibodies (11, 12, 35). Neonates born to mothers that receive a TT vaccine in pregnancy have a higher placental transfer efficiency. In one study, the placental transfer efficiency was 0.92 when mothers were immunized while pregnant compared to 0.60 in those who were not immunized in pregnancy (35). Placental transfer efficiency was also higher in mothers who received 2 doses of TT vaccine in pregnancy compared to those who received just one dose in pregnancy (1.63 vs. 1.16) (11). Factors that affect the transfer of tetanus antibody include HIV infection, placental malaria, anemia, preterm birth, low birth weight, and malnourishment of the mother (11, 35). Maternal age, weight, and parity do not affect antibody transfer (12, 35).

Pertussis

Pertussis, also known as whooping cough, is an acute respiratory tract illness caused by the bacteria *Bordetella pertussis*. In spite of high immunization coverage, there has been a resurgence of the disease in many countries resulting in a significant global burden. There is uncertainty in pertussis burden in low income countries due to poor surveillance (51); however, it was estimated that in 2008, 95% of the 16 million cases globally occurred in these countries (52). Even in high income countries like the United States where pertussis immunization coverage is very high (greater than 95%), large outbreaks of pertussis still occur (30, 53). In 2012, the country experienced 41,880 cases and 14 deaths in infants less than 12 months of age (53). There has been a global decrease in pertussis mortality in recent years (from 195,000 in 2008 to 85,000 in 2011); however, it is still unacceptably high (7, 52).

An epidemiologic shift has occurred with pertussis in the last 20 years whereby the disease burden has shifted from children younger than 10 years to adults, adolescents, and infants less than 6 months of age (41, 54). Complications rates are highest in these infants and can include pneumonia, seizures, encephalopathy, and death, even with adequate medical care (55). Neonates are particularly vulnerable to the disease because they are below the age recommended for the first dose of pertussis-containing vaccine (6 week) and must rely on passive immunity (52, 56).

Neither vaccine-acquired nor natural immunity to pertussis is lifelong. Immunity wanes 4-12 years after immunization in infancy and 4-20 after natural disease (54). The increasing incidence of disease in older age groups is a reflection of this and the basis for recommendations to boost immunity in adolescence and adulthood through additional pertussis immunizations. Both whole cell and acellular pertussis formulations are efficacious in eliciting an immune response; however, they differ in reactogenicty in that increasing age and increasing doses are associated with adverse reactions from use of the whole cell formulation (41, 57). Acellular formulations with reduced antigen content are less reactogenic and suitable for older age groups, but efficacy correlates with the number of immunogenic pertussis antigens contained in the vaccine (41, 52).

Immunization is highly recommended in pregnant women and contacts of neonates in an effort to "cocoon" them from disease (52, 53). Cocooning is not feasible in developing countries and may prove cost-prohibitive and programmatically challenging (58). Thus, maternal immunization presents a viable option for protecting neonates from pertussis early in life as it increases the amount of pertussis-specific antibodies available for transfer to the fetus. A study by Gall *et al* done in the United States showed that immunized pregnant women responded well to booster doses in pregnancy and achieved high levels of antibodies to all pertussis antigens (pertussis toxin, pertactin, filamentous hemagglutinin and fimbriae 2/3). The study also showed that neonates of immunized pregnant women had much higher concentrations of pertussis antibodies compared to neonates of

unimmunized mothers (59). Another study followed infants of mothers immunized in pregnancy for 18 months from birth and determined that maternally-acquired antibodies (which were up to 20-fold greater than neonate from the control group) persisted at high levels when active immunization began (60).

Healy *et al*'s study comparing antibody levels in mothers immunized in the previous 2 years and mothers immunized in pregnancy found no significant difference in maternal or infant antibody levels between the two groups. They did find, however, that more infants of mothers immunized in pregnancy retained high levels of pertussis antibodies through 2 months. (61). The need for boosting in pregnancy was further emphasized by result showing that at 2 months, the levels of pertussis antibodies in infants of mothers not immunized dropped 3- 4 fold (55).

Placental transfer efficiency for antibodies to the various pertussis antigens range from 1.21- 1.86, and was highest in women immunized during pregnancy, followed by those immunized within 2 years of delivering (55, 61). In a Turkish study, preterm birth was shown to reduce placental transfer efficiency (0.68-0.72 in the preterm group compared to 1.07-1.2 in the term group) as well as the total amount of pertussis antibody at birth (31).

Tdap immunization in pregnancy

The use of TT in pregnancy is widespread, and is firmly backed by official recommendation by WHO (62). Although the WHO does not have an official recommendation on the use of Tdap in pregnancy, other notable bodies such as the United States Centers for Disease Control and Prevention (CDC) Advisory

Committee on Immunization Practices (ACIP), after considering the evidence, now recommend that women get a booster dose in each pregnancy, preferably in the third trimester between. The ideal window recommended for immunization is 27-36 weeks, as it allows for 2 weeks to mount a significant IgG response, as well as ensure maximal transfer to the fetus (53). In addition to the United States, pertussis immunization in pregnancy is practiced in the United Kingdom and Australia (63, 64).

Tdap and TT have been shown to be immunogenic in pregnant women and no serious adverse events have been associated with the vaccines (43, 54, 59-61, 65). While there is ample evidence on the safety and effectiveness of tetanus toxoid use in promoting neonatal survival, there is a less in regards to pertussis. Adequately powered studies assessing clinical endpoints following immunization with Tdap can bridge this gap.

2.2. Inactivated influenza vaccine (IIV)

Influenza is a viral respiratory disease caused by Influenza A, B or C viruses that can result in severe morbidity and mortality. Influenza pandemics such as the 1918 Spanish flu pandemic, the 1957 Asian flu pandemic, the 1968 Hong Kong flu pandemic, and most recently in 2009, the A(H1N1) pandemic, resulted in high mortality, some numbering into the millions (66). Each year, circulating strains of influenza viruses cause moderate to severe illness and death globally. The

seasonality of influenza differs by climate. Temperate regions experience widespread influenza activity during winter months while tropical climates generally experience it year-round, particularly during humid conditions (67, 68). Previous exposure to a strain of the virus may not guarantee immunity to other strains, given the propensity for the virus to antigenetically shift or drift.

Morbidity and mortality associated with influenza is significant, especially in children under the age of 5, pregnant women, the elderly and those with underlying chronic conditions—all of which are deemed high-risk groups for influenza illness (66).

Influenza burden in children

It was estimated that in 2008, 90 million cases of influenza occurred in children less than 5 years of age globally, with up to 111,500 deaths in this population (69). The contribution of influenza to the global acute lower respiratory illness (ALRI) burden in children is substantial. Influenza was associated with 20 million non-severe ALRI (respiratory difficulties with confirmed influenza infection) and 1 million severe ALRI (severe respiratory difficulties with confirmed influenza infection or that requiring hospitalization) (69). In children less than 1 year of age, the number of influenza-related episodes, ALRI and severe ALRI were 25-, 17- and 13-fold higher, respectively, in developing countries compared to developed countries (69). A retrospective study from 1974 – 1993 assessing influenza burden in children younger than 15 years of age found that children less than 6 months had

the highest rates of influenza-associated hospitalizations and outpatient visits than any other age group, during both low and high influenza seasons and between influenza seasons (70). The burden is also quite high in developing countries. In a small study in Bangladesh from 2004-2005, Henkle *et al* found the incidence of influenza in infants less than 6 months to be 31/100 (71).

Influenza burden in pregnant women

The risk of severe illness, complications and death due to influenza in pregnancy is well documented (14, 15, 19, 72, 73). Physiologic changes, such as cardiac and pulmonary alterations, and immunosuppression that occur as a result of pregnancy may exacerbate the severity of disease compared to non-pregnant women (14, 15). During the 2009 A (H1N1) pandemic, pregnant women were 7.2 times more likely to be hospitalized for influenza illness and complications compared to the non-pregnant women of child bearing age in the general population (72). Even in the absence of exacerbating conditions for influenza (such as anemia, diabetes, heart disease, renal disease, pulmonary conditions, and obesity, among others) pregnant women were more at risk for severe influenza (requiring intensive care or resulting in death) compared to non-pregnant women (14, 19, 72).

Moderate and severe influenza-associated illness occurs in all trimesters, but was shown to occur most in the third trimester, indicating a correlation with gestational age (19, 72). Poor pregnancy outcomes, such as spontaneous abortions, stillbirth, premature delivery and low birth weight, have been associated with

moderate and severe influenza in pregnancy (14, 19, 72, 74). In one study, poor neonatal outcomes requiring intensive care or death was observed in 83% of pregnant cases with severe influenza and 13% with moderate influenza (72).

Influenza immunization in pregnancy

There are four formulations of the vaccine for seasonal influenza—trivalent inactivated influenza vaccine (IIV3), quadrivalent inactivated influenza vaccine (IIV4), trivalent recombinant hemagglutinin influenza vaccine (RIV3), and quadrivalent live attenuated influenza vaccine (LAIV4) (75). Pregnancy is a contraindication for LAIV4 as there remains a theoretical risk that live vaccines can pose a threat to fetal development or survival (44, 66). There is no evidence that suggests that immunizing in pregnancy poses a threat to the fetus or neonate (43, 76). Thus, the WHO recommends that pregnant women be immunized in pregnancy during any trimester, but that infants less than 6 months should not receive the vaccine. There are also recommendations for cocooning (immunizing contacts of infants younger than 6 months) an additional strategy to create a ring of immunity around the infant (66).

Although many of the studies assessing the protective effects of maternal immunization included only healthy women, they provide overwhelming evidence that even with co-morbid conditions, some benefits can be had with immunization. Influenza immunization in pregnancy has been shown to protect both mother and child (68, 77). Pregnant women responses to immunization are no different from

those of non-pregnant recipients. The vaccine is immunogenic and induces specific antibodies to circulating influenza viruses in the mother, and this ensures adequate levels of protective antibodies are available for transport to the fetus (77-79). Placental transfer efficiency of influenza antibodies assessed in studies ranged from 0.7 to 2.8, with variability in transfer mostly due to virus strain (79, 80).

Several studies have shown that neonates of immunized mothers have higher levels of influenza-specific antibodies than neonates of unimmunized mothers (78, 81, 82). Blanchard-Rohner *et al* showed that 84-86% of neonates born to immunized mothers had seroprotective levels of antibodies at delivery (titers of 1:40 or greater as determined by the hemagglutination inhibition (HAI) assay) compared to 29-33% in those of unimmunized mothers. Neonates of immunized mothers also had antibody levels that were 7.0-8.8 times that of neonates born to unimmunized women (78). In another study, 96% of neonates of immunized mothers had seroprotective titers at birth and at 2 months; by 5 months, 81% still retained seroprotective titers (77). A similar proportion of neonates of immunized mothers with protective levels at birth was shown by Tsatsaris *et al* (79).

Schlaudecker *et al* showed that IgA levels in breast milk were higher in immunized mothers compared to the control group, even at 6 months after delivery (38). The same study determined that exclusive breastfeeding by immunized mothers within the first 6 months of infancy reduced the risk of respiratory illness and fever compared to control group. A prospective study in the United States spanning 3 influenza seasons determined that the risks of laboratory-confirmed

influenza, influenza-like illness, and hospitalization in less than 6 month old infants of immunized mothers was reduced by 41%, 39%, and 42%, respectively, compared to infants of unimmunized mothers (13).

Retrospective studies in the United States, Canada and Sweden showed that maternal influenza immunization reduces the likelihood of poor pregnancy outcomes (74, 83-85). Immunization in pregnancy was shown to reduce the odds of preterm birth by 40% with the seasonal influenza vaccine, and by 37% with the A(HINI) vaccine (74, 84). The likelihood of fetal death was reduced by 34% (83). However, there were conflicting results regarding the protective effect on small for gestational age and low birth weight in that some investigators found that immunization in pregnancy reduced the risk, while others did not (74, 83-85).

The half-life of influenza serum antibodies seems to differ with strain, but range from 33 to 83.4 days (68, 71, 77, 80). High levels of humoral and mucosal immunity lasting close to 6 months can ensure significant protection of infants until active immunization begins. According to one estimate, an effective maternal immunization program in the United States program can avert as much as 48% of influenza-associated hospitalizations in infants less than 6 months each year (82).

The impact of immunization on maternal health is noteworthy. Borse *et al* estimates that influenza immunization program in the United States with the monovalent A(H1N1) vaccine in 2009 to 2010 averted 5% of clinical cases (71,601/1,410,032), 7% of hospitalizations (446/6,481) and 7% of deaths (37/533) in pregnant women (86). There is also evidence on the impact of maternal

immunization in decreasing the risk and severity of illness and hospitalization. A randomized control trial in Bangladesh determined that maternal influenza immunization reduced the rate of febrile respiratory illnesses in infants less than 6 months of age and mothers by 36% and 29%, respectively; reduced the rate of rapid test-confirmed influenza by 63% in infants; and reduced the rates of febrile respiratory illness-associated clinic encounters by 49% (68).

The benefits gained by both mother and neonate are well documented. However, in high-income countries such as the United States, the utilization of influenza vaccine in pregnancy is not adequately high (50.5%) (87). Barriers include safety concerns, lack of facilitation by obstetric providers and cost-prohibitive factors (14). In lower-income countries, the vaccine is not routinely used due to a host of factors, the foremost being cost (19, 88).

There is considerable evidence on the safety, immunogenicity, and effectiveness of IIV use in pregnancy. However, a fair number of studies assessing these parameters have been modest in size (38, 68, 78, 79, 82). Larger studies evaluating clinical endpoints in diverse populations, including immunocompromised and chronically-ill pregnant women, are required to provide convincing evidence on the effectiveness of this intervention in fetal, neonatal and maternal health and survival.

2.3. Haemophilus influenzae type B vaccine

Haemophilus influenza (*H. influenzae*) is a bacterium that causes a spectrum of diseases, the most common of which are pneumonia, meningitis and sepsis. There are 6 recognized serotypes—a, b, c, d, e and f. Type b serotype is the most often implicated serotype in invasive *H. influenzae* diseases (89). *H. influenzae* resides in the human nasopharynx and is transmitted by aerosol droplets. Nasopharyngeal carriage rates vary due to a number of factors, such as age, immunity prevalence, and social and environmental factors (89). In children younger than 5, the incidence of *H. influenzae* disease without immunization is 1,034 per 100,000 (90). In 2000, *H. influenzae* infections resulted in 8.13 million cases of severe disease (including pneumonia, meningitis, and non-pneumonia, non-meningitis sever disease) and 371,000 deaths, 2.2% (8,100) of which were in HIV-positive children (90). Sequelae (such as hearing loss, vision alteration, seizure disorder, clinical impairment, and cognitive, behavioral and motors difficulties) occur in 7.1-40% of cases and is highest in developing countries, which also experience high incidence of *H. influenzae* disease (89, 91-93). In 2000, the largest proportion of *H. influenzae* cases worldwide occurred in South-East Asia, and in order of decreasing burden, Africa, Western Pacific, Eastern Mediterranean, the Americas and Europe (90).

Immunization is the most effective strategy against *H. influenzae* disease (89). In areas with high immunization coverage, nasopharyngeal colonization has been significantly reduced (89). Studies have shown that the incidence of *H.*

influenzae disease in pregnant women was 17-25 times that of non-pregnant women, and *H. influenzae* infection was associated with fetal loss, premature birth and stillbirth (94, 95). Among children younger than 5, the disease burden is highest in infants 4 -18 months, and lowest in those less than 2 months or those older than 2 years. Infants less than 2 months are protected by passive immunity acquired in-utero (89).

Passive immunity ensures protection early in life and can be enhanced by maternal immunization. Studies have shown that infants of immunized mothers have higher levels of *H. influenzae* antibodies at birth compared to infants of unimmunized mothers, and that these antibodies retain protective levels of *H. influenzae* antibodies at 2-6 months of age (96). In two small controlled studies, *H. influenzae* type B vaccine was shown to be immunogenic in pregnant women and no serious adverse events were reported (97, 98). Sero-conversion or a significant boost in *H. influenzae* antibody titers occurs post-immunization, although the response is dependent on the vaccine formulation (96-99). *H. influenzae* type B polysaccharide vaccine has been reported to be less immunogenic than conjugated vaccines in children and pregnant women (89, 97). This in turn can have consequences on the protection of infants in the first few months of life.

Placental transfer efficiency following immunization varied in studies (0.61 – 1.45), but was generally lower in immunized women compared to controls—a result of the vaccine formulation used and IgG isotype induced (11, 96, 97, 99). Infants of immunized mother had significantly higher total antibody levels at birth and 2

months later compared to control groups (98). Placental transfer efficiency was lower in preterm and low birth weight neonates compared to term and adequate birth weight neonates, and a negative correlation between high concentrations of mother's total IgG antibody and placental transfer efficiency was observed (11, 96, 100). Maternal underweight and malaria were found to negatively impact placental transfer efficiency (39, 96, 99). One study showed that placental transfer efficiency was highest when maternal immunization occurred greater than 28 days before delivery (97).

There have been reports that maternal *H. influenzae* antibodies inhibit infant response to immunization (37, 101, 102). However, this effect is transient and may not be clinically significant as infants still respond well to the vaccine. Kurika *et al* showed this inhibitory effect in the first does (when maternal *H. influenzae* antibodies were high), but not after the second dose (102).

A major reason impeding the routine use of *H. Influenzae* vaccine in pregnancy to benefit the newborn is that the evidence base is lacking and therefore is not sufficiently convincing. Large studies that assess the immunogenicity of the different formulations, safety in terms of fetal harm, and effectiveness in reducing the risks associated with infection are necessary.

2.4. Pneumococcal vaccine

Infection with the bacterium, *Streptococcus pneumoniae* (pneumococcus), can result in moderate disease (acute otitis media, sinusitis and bronchitis), severe disease (pneumonia, meningitis and febrile bacteremia), and death. The burden of pneumococcal disease is substantial in children less than 5 years of age, and concentrated in those less than 2 years of age (103). It was estimated that in 2000, 14.5 million episodes of severe pneumococcal disease and 826,000 deaths occurred in children less than 5 years, equivalent to 11% of total global deaths in that age group (104). Although the estimated deaths in 2008 (476,000) indicate vast improvement, the burden is still unacceptably high (103). Developing countries, particularly those in Africa and Asia, capture the vast majority of the global pneumococcal burden (103). The risk of sequelae from pneumococcal disease is more than twice that of the other leading causes of bacterial meningitis (median risk of 24.7% compared to 9.5% for *Haemophilus influenzae* and 7.2% for meningococcal meningitis) (91).

Immunization has proven to be effective at reducing pneumococcal disease in children (103). However, the vaccine is not recommended for infants less than 6 weeks. Maternal immunization is one intervention considered in the literature for its ability to provide passive immunity (29, 105). Studies assessing the 23-valent pneumococcal polysaccharide vaccine in pregnancy found it to be immunogenic and not result in serious adverse maternal or fetal events (106-112). Pregnant women experienced boosts in titers following immunization, although the magnitude of

response varied by the vaccine serotypes (106, 112, 113). Compared to the control group, mothers immunized in pregnancy had higher functional opsonic antibodies and higher breast milk IgA, which, in one study, was shown to persist at high levels at 7 months post-partum (106, 112, 113).

Infants of mothers immunized with the polysaccharide vaccine showed higher antibody levels compared to those of unimmunized mothers at birth and up to 4-6 months (110, 112). In one study, pneumococcal nasal colonization was absent in the immunized group at 2 months, whereas 8% of the unimmunized group was colonized; and at 16 months, nasal colonization rates were significantly lower in the immunized group compared to the unimmunized group (16.6% vs. 50%) (112). Placental transfer efficiency was generally less than 1 (range 0.24 to 0.8) and varied considerably across vaccine serotypes, which consequently affected the proportion of serotype-specific antibody at birth (106, 109, 112). Placental malaria, low birth weight and preterm birth significantly reduced placental transfer efficiency (11, 39, 106). A negative correlation between high concentration of maternal antibodies and placental transfer efficiency was observed in one study, and was attributed to a possible synergistic effect of FcRn receptor saturation and placental dysfunction due to malarial infection (106). Infant response to primary immunization (fold increase) negatively correlates with high antibody concentration at birth. However, this is not clinically significant as high antibody levels were achieved post-immunization (37). The significance of gestational timing of immunization is conflicting between reports, but the preponderance of data point

to later administration where higher levels of maternal antibody are available for placental transport (106, 112).

Evidence on the effectiveness of maternal immunization in reducing pneumococcal-related diseases in neonates is limited (107). Nonetheless, it has been reported that immunization in pregnancy reduced the risk of ALRI by 14% in children followed more than 3 years after birth (113). The high antibody levels at birth together with breast milk IgA transference and reduced pneumococcal nasal colonization are likely to ensure protection from pneumococcal disease during the neonatal period.

More studies are needed to properly evaluate pneumococcal immunization in pregnancy. The few studies assessing pneumococcal vaccine in pregnancy utilized the polysaccharide formulation, creating a paucity of information about the conjugate formulation. Conjugate vaccines are generally known to elicit a more robust immune response than polysaccharide vaccine, so this area requires further investigation.

2.5. Meningococcal vaccine

Neisseria meningitidis (the meningococcus) is a bacterium that typically colonizes the nasopharyngeal region asymptomatically. When it invades the body, it becomes pathogenic and causes severe disease, including meningitis, fulminant

septicemia and pneumonia (114). Nasopharyngeal carriage rates vary by age: 4-5% in childhood, 24% in adolescence and 13% in adulthood (115). Of the 13 recognized serogroups, 6 (A, B, C, W-135, X and Y) cause the vast majority of invasive meningococcal disease and have distinct regional distributions (114, 116). The global annual burden of the meningococcus is estimated to be 1.2 million cases and 135,000 deaths (116). In countries in the Americas and Europe, where meningococcal disease is endemic, incidence rates of 0.3-8.9 per 100,000 are observed (117). The African region has the highest rate of meningococcal disease, with up to 400 million people impacted annually (118). A chain of 21 countries comprising the African meningitis belt experience cyclical epidemics that can reach 1,000 cases per 100,000 (114). The epidemic that occurred in 2010 resulted in close to 23,000 cases and 2,500 deaths in 14 countries (118). Case fatality rate range from 5 to 41%, and approaches 100% in untreated cases (114, 118-121). Sequelae, such as hearing loss, vision impairments, mental retardation, and limb loss, occur in 10-20% of survivors (114-116, 119). In children less than 5 years of age, there is a 7.2% risk of at least one sequelae due to meningococcal disease (91).

In many countries, infants 1 year old or less have the highest incidence of meningococcal disease (117, 122). Incidence rates range from 1.9-88.7 per 100,000, and the case fatality rate is also quite high (9.2%) (115-117, 122). This age group also has the highest attack rate compared to any other age groups in endemic situations (114, 117). The attack rate peaks in the 3-12 month age group and it is believed that younger age groups, including neonates, are protected by maternal

antibodies acquired in utero (114). Still, severe and fatal meningococcal disease in neonates occurs, highlighting the need to enhance passive immunity (123-126). Meningococcal vaccines are highly effective at reducing carriage rates, eliminating circulating serogroups, and reducing the burden of disease in endemic settings (127-129). Thus, there is great potential to improve passive immunity by immunizing women in pregnancy.

Studies dating back to the 1970s have assessed meningococcal vaccine immunogenicity in pregnant women and their effect on neonatal immunity (130, 131). Upon immunization, the majority of pregnant women seroconverted or showed a strong boost in titer (4-7 fold) (130, 131), and elevated maternal titers persisted at 7-8 months (131). One study showed that pregnant women with malaria have reduced titers after immunization compared those without the disease (130). Placental transfer efficiency in this study was low, ranging between 0.3-0.42 (130). This can be explained by the meningococcal polysaccharide vaccine used, which is known to result in reduced transplacental transport (29). Parasitic diseases, malaria and syphilis, were shown to dampen placental transfer efficiency (130).

Studies showed that infant antibody levels were substantially higher than that of the control group and lasted 2-5 months (130, 131). At 3 months, high levels of antibodies were found to persist in the immunized group (130, 131). The trimester in which mother received the vaccine was not significantly associated

with antibody levels in infants (131, 132). Interference with active immunization was not observed when infants were immunized at 6 months (132).

The vaccine is considered not to be harmful in pregnant women as there have been no reports of maternal or fetal adverse events following usage (43, 105). Still, the evidence base is insufficient in terms of effectiveness. This most likely hinders its routine use in pregnancy. Adequately powered studies are needed to verify the safety of the vaccine and to assess clinical outcomes following immunization.

2.6. Hepatitis B vaccine

Hepatitis B virus (HBV) is a highly infectious pathogen spread through contact of parenteral and mucosal areas of the body with infected bodily fluids. Infection of the virus has two outcomes: clearance and persistence. About 87-90% of infected individuals develop immunity and clear the virus; the rest become chronic carriers of the virus and are at risk of liver cirrhosis, hepatocellular cancer, liver failure and death (9, 105, 133). It is estimated that 360 million people are chronic HBV carriers worldwide and that HBV-related diseases result in 600,000 deaths annually (9). Morbidity of HBV is significant as well. It is the causative agent in 30% of liver cirrhosis cases and 53% of hepatocellular cancer cases globally (134). About 400,000 HIV-infected people are co-infected with HBV, and this increases their risk of HBV-related diseases (9). The western pacific region has the

highest prevalence of HBV, accounting for 45% of all HBV chronic carriers globally (134).

Infants of hepatitis B e antigen (HBeAg)-positive mothers who acquire the virus vertically are 90% more likely to become chronic carriers themselves (133, 134). The risk of HBV chronicity reduces with age—infection at 1-4 years carries a 30-50% risk while the risk in adulthood is 5% (133, 134). Routine childhood immunization beginning at birth has reduced the global burden of HBV (9). Pregnancy screening for hepatitis B surface antigen (HbsAg) positivity facilitates early administration of immunoprophylaxis (consisting of HBV-specific immunoglobulin and a dose of the vaccine) to the neonate 24 hours after birth. This combination therapy given to neonates of HBeAg-positive mothers limits transmission during delivery by 85-95%, but has no impact on *in utero* transmission (135, 136). Furthermore, 34% of infants of HbeAg-positive mothers who escape transmission at birth acquire the infection in their first 6 months of life (135). Thus, ensuring mothers are immune to HBV is key, and maternal immunization is a logical approach to achieve this.

One study found that 88-97% of women responded to HBV immunization and those with per-existing immunity had significantly higher antibody titers (137). At birth, 59-66% of neonates of immunized mothers had evidence of passively-acquired immunity (137). Another study showed that HBV-specific antibody placental transfer efficiency range from 0.5 to greater than 1.5, with 84% of neonates having rates of greater than 1 (138). Maternal antibody rates declined

rapidly after the first 2 months and did not interfere with long term immunogenicity of active immunization in the infant (137, 138). The vaccine is considered not to be harmful as it is inactivated and poses little to no risk to the mother or fetus (9, 105, 139). A study assessing safety following administration of HBV-containing vaccine in pregnancy found no increased rates of adverse events to both mother and neonate (140).

However, despite there being some evidence that immunizing HBV-negative pregnant women and those with pre-existing immunity can provide protection to both the mother and infant, routine immunization in pregnancy is not practiced. One reason for this is the dearth of studies investigating the effect of immunization in pregnancy on clinical outcomes. Carrying out such studies are warranted, but may be less of a priority given the effectiveness of the infant immunization series in reducing the global burden, especially in endemic settings.

2.7. Hepatitis E vaccine

Hepatitis E virus (HEV) has a wide geographic distribution and diverse hosts, ranging from humans to animals to shellfish (141). In humans, HEV is primarily transmitted by consumption of contaminated water and food products, and through receipt of blood and organs from infected persons (141-143). Infection can be sub-clinical or clinical (141). In clinical manifestations, infection usually results in an acute, self-limiting illness that resolves within 2 months of onset (141). It can,

however, become chronic (in immunocompromised individuals), and can progress to severe liver disease and death (141, 144). Genotypes 1 and 2 are primarily found in humans, and genotypes 3 and 4 in animals, although zoonosis does occur (141). Outbreaks of HEV are typically associated with genotypes 1, 2 and 4: genotype 1 in Asia, Africa, and the Middle East; genotype 2 in Central Africa and Mexico; and genotype 4 in Asia (141, 142, 145, 146). Sporadic cases in Europe and the Americas have been attributed mostly to genotype 3, and, to a lesser extent, genotype 4 (141, 145). The burden of disease due to genotypes 1 and 2 in Africa and Asia is significant, with 20 million infections resulting in 3.4 million symptomatic cases and 70,000 deaths estimated to have occurred in 2005 (147).

HEV infection in pregnant women is more pathogenic, with an increased incidence of symptomatic illness, pregnancy complications and death (16, 141). Immune modulation and high viral loads are thought to be factors in the increased severity of disease in pregnancy (141, 148-152). The risk of hepatic encephalopathy, disseminated intravascular coagulation, and the most severe, acute liver failure, is high in this group, especially during the third trimester (16, 141, 153). Case fatality rates are high, typically around 15 - 32% but can reach up to 100% in some settings (141, 153-155). In one study in India, HEV-infected pregnant women were 2.7 times more likely to experience acute liver failure and 6 times more likely to die compared to uninfected pregnant women (156). Poor pregnancy outcomes such as fetal death, premature delivery, and stillbirth have been associated with HEV infection (16, 141, 156-158). High rates of vertical transmission also occur resulting in congenital

infection (153, 154, 157). Neonatal illnesses, such as neonatal jaundice, respiratory distress syndrome, and hepatosplenomegaly, have been reported (157, 159).

Achieving immunity pre-pregnancy or in pregnancy through immunization can presumably provide protection to both mother and neonate in developing countries as environmental measures (such as sanitation interventions) may be lacking. Of two concept vaccines that showed good efficacy in clinical trials—rHEV and HEV 239 (Hecolin), only the latter has so far been made commercially available (146, 160). In a clinical trial in Nepal, rHEV showed good efficacy of 95.5% after three doses. However, pregnant women were absent from this trial (160). The large HEV 239 clinical trial in China with 16-65 year old showed the vaccine had a 100% efficacy against HEV disease (146). The vaccine was well-tolerated and there were no serious adverse events reported (146). A subset of vaccinees showed a 4-fold or more boost in titers and close to 100% seroconversion was seen in previously seronegative individuals following immunization (146, 161). Furthermore, there was limited evidence that the vaccine—derived from HEV genotype 1—was protective against genotype 4 (146). It is plausible then that given the shared serotype by all 4 genotypes and the high efficacy, this vaccine may be capable of preventing all HEV disease, regardless of serotype cause.

An analysis of a small number of study participants who became pregnant during the course of the study showed that the vaccine produced no serious adverse event following immunization. No fetal loss occurred and in those that went on to deliver, birth outcomes were good and neonates experienced no congenital

infections (162). Baseline and post-immunization serum available for one pregnant woman that received 3 doses of the vaccine showed significant seroconversion with an antibody titer in the top quintile of antibody concentration for three-dose vaccinees (162).

Although promising results were seen in the pregnant women who were inadvertently immunized, there is a need for larger, controlled studies to assess safety of the vaccine in regards to the fetus, immunogenicity in various groups (including HIV-infected women) and clinical outcomes in neonates and pregnant women. A major challenge is the availability of the HEV 239 vaccine. It is currently only licensed in China therefore a significant part the world—particularly endemic countries—lacks access. Other vaccines are currently in development, including a norovirus-HEV combination vaccine, which has shown promising results (163).

2.8. Group B streptococcal vaccine

Streptococcus agalactiae (commonly referred to as Group B streptococcus (GBS)) emerged in the 1970s as a major cause of death during the neonatal period and early infancy (164, 165). Typically, GBS asymptomatically colonizes the gastrointestinal and genital tract of adults, and carriage rates in the rectovaginal area are about 10-30% in women of childbearing age and 25-35% in pregnant women (29, 164, 166). Carriage rates are similar in developing and developed countries with substantial GBS burden (167, 168). Of the 10 serotypes, only 5 (Ia, Ib,

II, II and V) cause 95% of infant and maternal GBS disease, which include fulminant septicemia, pneumonia and meningitis in infants; and, in mothers, urinary tract infection, amnionitis, enometritis, mastitis, and puerperal sepsis, among others (17, 23, 165). Nineteen to thirty percent of survivors suffer permanent neurological sequelae of varying degrees (164, 166, 169). Death of the infant is the extreme outcome of infection. About 2-7% and 20% of term and premature infants, respectively, die as a result of GBS disease (23, 29). Poor pregnancy outcomes (fetal loss, stillbirth and premature birth) have been associated with GBS disease (17, 164-166, 170).

GBS disease in infants less than 3 months of age has two distinct presentations: early-onset disease (EOD), which presents during the first week of life, and late-onset (LOD), which presents 7 to 89 days after birth. The global incidence for EOD and LOD were estimated to be 0.43 and 0.53 per 1,000 live births, respectively; and the case fatality rates for EOD and LOD were estimated to be 12.1% and 9.6%, respectively (171). Over 90% of EOD cases occur 12-24 hours after birth, most frequently as fulminant septicemia and pneumonia (170). Vertical transmission is often the cause of EOD and risk is associated with maternal GBS carriage (165). About 30-70% of infants born to GBS-colonized mother are themselves transiently colonized following delivery, and 1-3% develop disease (165, 166). About 3.5% of lactating mothers carry GBS in their break milk, which may be the cause of the 0.5-3% recurrence of infant GBS disease (17, 29).

Intrapartum antibiotic prophylaxis has significantly reduced the incidence of EOD, but has had little effect on LOD (23). A major risk factor identified in EOD and LOD was the paucity of maternal antibodies to GBS (166). High antibody titers to serotypes Ia, II, III and V have been recognized to confer protection from disease (23, 172). Improving maternal immunity—and, consequently, passive immunity early in life—is a viable strategy in reducing the burden of both maternal and infant GBS disease, especially in resource-poor settings where intrapartum antibiotic prophylaxis is lacking (167, 168). Furthermore, immunization is less invasive and more cost-effective than therapy and holds the potential of averting selection for antibiotic resistant GBS (23, 164)

There is currently no licensed GBS vaccine, but a number of candidates are in different stages of development (170). Vaccine trial results have shown that GBS conjugate vaccines are well-tolerated and immunogenic, eliciting greater than 4-fold increase in GBS antibody titers in vaccinees (23, 29, 173). One randomized control trial with pregnant women showed greater than 50-fold rise in titers at 4 weeks post-immunization compared to baseline levels (23). These high levels persisted at 2 months post-partum while the placebo group remained at low levels. Maternal and cord blood antibody level were correlated and the placental transfer efficiency was 0.8. (23). At 1 and 2 months, infants retained 50% and 30% of cord antibody levels, respectively (23), and showed good functionally opsonic activity (23, 173). The conjugate formulation of the vaccine was shown to be more immunogenic than the polysaccharide formulation (≥4-fold rise in 90% of conjugate vaccine recipients

compared to 50% in polysaccharide recipients); still, antibody levels for both were much higher than the placebo group (173). *In vivo* lethal challenge studies in mice showed that sera from vaccinees were protective (173).

The impact of a GBS vaccine could be substantial. It was estimated that a vaccine that induces immunity to serotypes Ia, Ib, II, II and V could prevent neonatal disease, pregnancy-associated disease, and global GBS disease in infants less than 3 months by 98%, 88% and 85%, respectively (17). Non-pregnant adults, especially the elderly and those with underlying chronic conditions, who also experience morbidity related to GBS infection will benefit from an effective vaccine (29, 164, 170).

A solid evidence base will be required before routine use of any GBS vaccine in pregnant women is adopted. Thus, large controlled studies will be necessary to verify the safety of the vaccine and its effectiveness in reducing the risks associated with GBS infection in the pregnant mother, neonate, and young infant.

2.9. Respiratory syncytial virus vaccine

Respiratory syncytial virus (RSV) is the causative agent of the vast majority of ALRI in children (174). RSV morbidity manifests as bronchiolitis, pneumonia and other acute respiratory illnesses (175). In the first year of life, more than 70% of all children are infected, and by the second year almost 100% are infected (176). The burden of RSV in children less than 5 years of age is significant. It was estimated that

in 2005, there were 33.8 million episodes of RSV-associated ALRI, 3.4 million severe RSV-associated ALRI requiring hospitalizations, and 66,000-199,000 deaths in this age group (174). The global burden is not uniform as developing countries experience more than twice the incidence of RSV-associated disease compared developed countries, and 99% of all deaths occur in developing countries (174).

Rates of hospitalization for severe RSV-associated ALRI requiring hospitalizations are highest in children less than 1 year of age (1,543-2,350/100,000 person years) compared to any other age groups 1 - ≥65 years (176-178). Infants less than 6 months have a high risk of severe outcomes following infection. One study reported a hospitalization rate of 1,195 per 100,000 person-years for infants 0-5 months (177). The high burden of RSV disease in this age group has been attributed an immature immune system and the lack of adequate antibodies to the virus (179, 180). While some studies have found associations between high maternal antibodies and reduced severity of disease, there have also been reports of no association between the two, and an increased risk of recurrent wheeze in infants (181-187). These conflicting reports bring into question the effectiveness of maternally-acquired antibodies in modifying RSV disease. However, overwhelming evidence points to some increased benefit of maternal antibodies acquired *in utero;* and there is the added benefit of passive mucosal immunity gained from breast milk (188).

There is currently no licensed RSV vaccine although a few are undergoing development. A randomized controlled trial assessing the safety and

immunogenicity of a candidate vaccine in pregnant women in their third trimester found it to elicit a response in 75% of vaccinees (of which 95% had a 4-fold rise in antibody titer). Placental transfer efficiency was greater than 1 and infants of immunized mothers had 4 times the antibody titers of the placebo group at birth, 2 and 6 months after delivery. Neutralization antibodies were modest in the vaccinees but were transferred to infants, who had higher levels than the placebo group at birth and at 2 month of age. Breast milk antibody level in the immunized group was 6-fold higher than that of the placebo group and stayed at high levels at 6 months. The vaccine was well-tolerated and subjects did not experience any adverse effects. Still, the vaccine was not considered to be sufficiently immunogenic because of the low neutralizing antibody response (179). Ensuring adequate immunogenicity in pregnant women is the foremost challenge facing the RSV vaccine.

2.10. Malaria vaccine

Malaria is a parasitic disease caused by the *Plasmodium* species. It is transmitted by female *Anopheles* mosquitoes during feeding on the host. The disease is endemic in 104 countries in Africa, Latin America and Asia. (189). An estimated 3.4 billion people are at risk of malaria worldwide and in 2012, there were 207 million cases of the disease and 627,000 deaths, 77% (482,000) of which were children under the age of 5 (189). Sub-Saharan Africa has the largest burden of any region, with 90% of all deaths occurring there (189).

Malaria in pregnancy is most often caused by *Plasmodium falciparum* (18, 190). The risk of pregnancy malaria is highest in younger women and in first pregnancy (primigravid), but decreases over successive pregnancies (multigravid) (18, 191). HIV exacerbates malaria wherein parasitic densities are higher and gavidity-dependent immunity is relatively lower compared to non-HIV infected women (190). Low pre-existing immunity can result in peripheral parasitaemia, severe anemia, cerebral malaria, pulmonary edema and death in the mother (18, 33).

Dense parasitic accumulation in placental cells leads to inflammatory cell infiltration that ultimately results in the thickening of the throphoblastic basement membrane. This consequently impairs materno-fetal gas exchange and transport of nutrients and antibodies (33). Several studies have shown the relative decrease in transplacental antibody transport in women with acute or past malaria compared to women without the disease (32, 35, 96, 130, 137). Poor fetal outcome, including spontaneous abortions, premature delivery, intrauterine growth retardation (IGR) and low birth weight, are associated with malaria infection in endemic areas (33, 191). Malaria-associated low birth weight outcomes are seen in both term and preterm neonates as a result of IGR. Mortality is high in these neonates, which make up a substantial portion of the 62,000-363,000 infant deaths in Sub-Saharan Africa annually (33). Neonates born to mothers that experience placental malaria are themselves three times more likely to suffer from anemia and twice as likely to acquire the disease (191).

Immunity to parasites has been correlated with protection from infection, increased hemoglobin levels and improved pregnancy outcomes, such as increased birth weight and term or near-term gestation (18). A vaccine that induces high levels of immunity will be beneficial to both mother and neonate. There is currently no licensed malaria vaccine, but several candidates that target the different life stages of the parasite are in development (192, 193). The most advanced of these, the RTS,S/AS01E vaccine, showed an efficacy of 35–55% in children during clinical trials in Sub-Saharan Africa (194). Modeling showed that a malaria vaccine with 85% efficacy could avert 150 million uncomplicated cases and 1.1 million deaths over the course of 10 years (195). Before malaria vaccine is routinely used in pregnancy, it must first demonstrate high immunogenicity and a good safety profile in pregnant women. Secondarily, it must prove effective at reducing the disease and poor pregnancy outcomes.

PART III. Immunizing women during pregnancy: Timing and mode of delivery

3.1. Timing of immunization

The timing of vaccine administration factors into the magnitude of maternal antibodies transferred (78). Immunizing during late adolescence or prior to pregnancy does indeed provide protection, but as studies have shown, the neonates of women immunized in pregnancy boast larger quantities of placental-transferred antibodies compared to those immunized prior to pregnancy (27).

Women should ideally be immunized in the last trimester of pregnancy, between 28 – 32 weeks to ensure optimal transfer of antibodies to the fetus (27, 29). However, special circumstances may justify earlier immunization and it may be programmatically easier to manage a recommendation that does not specify a trimester.

3.2. Antenatal care as a point of access

A large proportion of women seek antenatal care during pregnancy, although not fulfilling the recommended 4 visits recommended by WHO (Table 2). The rates of antenatal care are highest in high-income countries and lowest in the low-income countries, perhaps a reflection of economic, social or institutional barriers. Nonetheless, a significant amount of pregnant women attend at least one antenatal visit, making it a feasible avenue for delivering maternal vaccines.

Table 2. Antenatal care coverage from 2005 – 2012, by income group.[1]

Income group	At least 1 visit (%)	At least 4 visits (%)
Low income	72	37
Lower-middle income	76	53
Upper-middle income	94	80
High income	99	96

Technical knowledge of administering vaccines and counseling pregnant women on the risks and benefits of immunization already exists in antenatal clinics as a result of the maternal tetanus immunization programs. Thus, introducing new vaccines into the maternal healthcare framework in low income countries can be achieved utilizing this established practice without incurring significant costs, as would be required for development of a new delivery mechanism or an outreach immunization campaign. The drawbacks to this approach include imperfect immunization coverage owing to the proportion of women that will be missed because they do not solicit antenatal services, and those who arrive for antenatal care late in pregnancy (i.e., less than 4 weeks to delivery) may fail to provide any significant benefit to their newborn.

[1] [196]

Case study. Maternal and neonatal tetanus elimination initiative

In the late 1980s, the magnitude of neonatal mortality from tetanus quickly made the disease a global health priority. In 1989, the World Health Assembly called for the elimination of neonatal tetanus, which is defined as less than 1 per 1,000 live births at the district level (197). The maternal and neonatal tetanus (MNT) elimination initiative utilizes three strategies to accomplish its mission: promotion of clean delivery to prevent infection; surveillance for neonatal tetanus; and widespread immunization of infants and mothers. Global commitment has paid off in that the burden of neonatal tetanus has been drastically reduced from 787,000 deaths in 1988 to 4,214 reported cases in 2011. Only 25 countries remain that are yet to meet the elimination target (46).

There is widespread acceptance of tetanus immunization in pregnant women. Coverage rates remain high globally. In 2011, the proportion of newborns with passive immunity to tetanus due to maternal immunization exceeded 80% in all regions (Table 3). The fact that all countries adopted the WHO recommendation of routine maternal tetanus immunization gives hope that other vaccines capable of producing the same impact in neonatal morbidity and mortality will be considered as well (196, 197).

Table 3. Proportion of neonates protected at birth against neonatal tetanus through maternal tetanus immunization, 2011.[1]

Income group	Percentage of live births protected from neonatal tetanus (%)
Low income	82
Lower-middle income	81
Upper-middle income	86
High income	90

[1] [196] ibid.

PART IV. Policy environment and global support for maternal vaccine introduction in low income countries

It is well known that policy guides action. An area that deserves analysis is the global landscape as it relates to policy, actors and advocacy for vaccine use in pregnancy.

4.1. Policy environment

WHO serves as the global leader in recommending vaccine policy. Most countries look to WHO for advice on adoption and usage of its pre-qualified vaccines. The Strategic Advisory Group of Experts (SAGE) on immunization is the main advisory body that makes recommendations on both adult and child vaccine use worldwide. After consideration by the WHO Director-General, SAGE recommendations eventually become WHO official policy (198). Of the 6 currently available vaccines outlined above, WHO-SAGE has recommended just 2 for routine use in pregnancy.

- *Influenza* - There is a strong recommendation to use the IIV vaccine anytime in pregnancy. WHO acknowledges that immunization in pregnancy protects both mother and neonate from disease and complications. Pregnant women are also deemed the highest priority group for the vaccine (66).
- *Tdap/ TT* – Tetanus immunization is strongly recommend in pregnancy. Pregnant women and non-pregnant women of childbearing age are

encouraged to complete the immunization series. However, pertussis is currently not recommended in pregnancy to protect the newborn due to insufficient evidence on its effectiveness. The tetanus guidance does note that any tetanus-containing vaccine can be used to fulfill the tetanus recommendations (52, 62).

- *Hepatitis B* – The guidance notes that pregnancy and lactation are not contraindications for the vaccine. However, there is no strong recommendation for routine HepB use in pregnancy (9).
- *H. influenzae* type b – There is no recommendation for routine use of *H. influenzae* type b in pregnancy, although there is recognition of the protective effects of passively-acquired antibodies during the first two months of life (89).
- *Pneumococcal* – The vaccine is currently not recommended for routine use in pregnancy to protect the newborn due to insufficient evidence (103).
- *Meningococcal* – Although it is noted that meningococcal vaccine is considered safe to use in pregnant women, there is no express recommendation for its use to protect the newborn (114).

4.2. Global support and advocacy

Maternal and child health are high on the global health agenda. Similar to MDG 4, MDG 5 (target A) aims to reduce the maternal mortality ratio in 1900 by two-thirds in 2015 (2). Great effort has gone into achieving the MDG 4 and 5 targets

over the years and with the impending goal date of 2015, there is an urgency by global partners to achieve, or at least approach, the goals set (2). A seasoned approach to improving child health in low income countries has been through immunization. Since 2000, the GAVI Alliance has supported lower income countries (with GNI per capita below a certain point) financially and technically in adopting childhood vaccines that were once out of their reach due to cost. Their efforts have resulted in 440 million children gaining access to critical vaccines and averting 6 million future deaths (199). Similarly, the Measles and Rubella Initiative and the Global Polio Eradication Initiative, both consortiums of governmental and non-governmental partners, have helped bring the global burden of their respective target diseases to historic low number (200, 201). As many as 13.8 million measles deaths were averted between 2000-2012 and more than 10 million polio cases have been averted since 2000 (202, 203). While there are a number of such child-focused initiatives with substantial funding and clout, there are relatively few that address maternal health in the context of immunization during pregnancy, which can also impact neonatal health.

Influenza immunization in pregnancy garnered the attention of the GAVI Alliance following the WHO influenza vaccine policy prioritizing pregnant women. In 2013, GAVI considered adding seasonal influenza vaccine for pregnant women to its portfolio during its Vaccine Investment Strategy consultation. The vaccine case hinged on the WHO recommendation and was in line with their mission in that maternal immunization was a vehicle to protect the fetus and neonate. The impact

assessment indicated that broad adoption in 53 GAVI-supported lower income countries would avert about 210,000 maternal and infant deaths from 2015-2030. There was also the potential to shape the influenza vaccine market to ensure equity in accessing the vaccine. However, the vaccine was not added to GAVI's vaccine portfolio due to uncertainty the impact assessment as a result of limited data; year-round supply concerns; and the probability of low demand (204, 205).

Such consideration and prioritization of maternal immunization at a high level indicates support of the strategy for global implementation. GAVI has expressed intent to reconsider maternal influenza immunization following completed analysis and dissemination of results of three large Bill and Melinda Gates Foundation-sponsored studies in Nepal, Mali and South Africa assessing the maternal and neonatal health impact of the vaccine (58, 204).

The momentum created by these groups has stirred up others to support maternal immunization and create a wider advocacy base. Experts in the field of global health, medicine and development have also engaged in the discourse to hasten the implementation of routine maternal vaccines to decrease disease burdens (14, 15, 19, 29, 42, 56, 105, 166, 168, 206, 207). WHO policy is key as is evidenced by the high level support for maternal influenza immunization following its decision. A reassessment of current evidence, or even sponsorship of studies to generate convincing evidence, can facilitate wider acceptance of vaccine use in pregnancy. Finally, explicitly tying maternal immunization into the strategic

framework of MDG 4 and 5 has the potential to broaden the advocacy base for this intervention.

Part V. The road to adoption: key considerations

Adoption of new vaccines by low income countries depends on several factors and involves a number of stakeholders. The decision making process is often in view of competing interests and limited budgets. A prudent approach to vaccine adoptions involves detailed assessment of the following.

5.1. Burden of disease

Accurate knowledge of the burden of disease is the essential first step in deciding if a vaccine should be adopted. It is not enough to justify adoption based on general awareness of the disease, as competing priorities demand decision makers use rigorous means to attain the expected impact of immunization (208). This requires good surveillance that at least captures district-level disease incidence. Low income countries may not have such data available due to resource constraints in setting up disease-specific surveillance, or they may not routinely report disease-specific causes (for example, distinction between influenza-associated ALRI and RSV-associated ALRI). In such cases, regional estimates or neighboring country data may suffice in the near term (209). Still, surveillance is necessary and should be put in place to monitor the disease burden and impact of immunization (210-212).

5.2. Broad evidence of vaccine impact

Available vaccines supported by WHO have undergone rigorous evaluation and pre-qualification exercises before they are licensed for use. Tdap, IIV, *H.*

influenzae type b, Hepatitis B, pneumococcal and meningococcal vaccines have not been linked to any serious adverse event in pregnant women as shown above. Still, there may be a need to confirm the safety, immunogenicity and effectiveness of the vaccine in pregnant populations or a variety of populations to alleviate concerns that positive results seen in pre-licensure studies conducted in developed country will be different. Factors such as HIV, malaria and malnutrition, which may be endemic in these population, can affect vaccine effectiveness (32, 35, 99, 213). Thus, in-country trials may be justified, particularly in these specific settings or subpopulations.

Conducting such trials for each vaccine requires both technical and monetary resources, which may strain country health budgets. Since regional disease burdens are usually similar across countries, results from studies within the region or studies in similar populations elsewhere may be used for evidence data.

5.3. Health system infrastructure

Vaccine adoption ideally should not cause undue strain on the current health system with proper planning. A detailed assessment of the vaccine system pre-adoption can help identify strengths and weaknesses that will ultimately determine the success of the implementation process (211).

5.3.1. Maternal vaccine delivery strategy

Antenatal care service is an attractive strategy to deliver maternal vaccines as it is already well established and will be less disruptive on the maternal and child health program than would a newly-designed vertical program (212). Antenatal care coverage is not adequately high in low income countries (table 2), but it can be strengthened by the plethora of vaccines that provide multiple benefits (212) It is likely that multiple visits will be to be required to receive all vaccines, which creates an opportunity to provide other maternal health services and improve overall health. Furthermore, frequent linkage with health care staff may promote acceptability of delivering with skilled birth assistance (doctor, nurse or midwife), which will help reduce delivery-related maternal and child morbidity and mortality (2).

5.3.2. Vaccine system management

The addition of multiple vaccines will impact immunization system operations (214). Cold chain expansion will be required; supplies for vaccine administration and waste management will be required; logistics may become more complex; the workforce will need to be trained; and recording tools (including mothers immunization card) will need to be updated (211, 215, 216). These activities require resources and need to be taken into consideration by decision-makers.

5.4. Demand & supply

Recognition of the burden of disease is one factor that drives demand (217). In some cases, the disease is not seen as serious or prevalent, thereby reducing demand (218). Pre-adoption surveys to ascertain population knowledge and attitudes about the vaccines considered for adoption can enlighten decision makers. This can also determine what messages and channels to use in demand creation campaigns.

On the supply side, there must be consideration of the challenges that might exist in maintaining timely and sustainable vaccine supply, especially if there are multiple simultaneous adoptions (219). The manufacturing process from some vaccines are complex and with limited producers there may be significant shortages in supply if manufacturing issues arise (220). Logistical issues such as vaccine dose presentation, storage requirements, and wastage rates should also be considered, as they may vary by manufacturer (221, 222).

5.5. Cost

Possibly one of the most important considerations in adopting vaccines is cost. The ability to afford implementation of the program and sustain it long-term should be assessed early. Vaccine prices (and cost to administer) may be considerable depending on the size of the target population. The costs of newer vaccines are mostly supply-driven when limited manufacturers exist. Vaccines can

be even more costly when bargaining one-on-one with manufactures as opposed to pooled procurement where economies of scale dictate price (214).

For childhood vaccines, some low income countries have enjoyed complete vaccine support from external partners in the form of financial assistance to procure vaccines or through donation (210, 223); others have been partially supported and required to co-finance the vaccine (210). Studies have shown that in cases where external support was substantial, there was less concern about cost and sustainability (209, 224). It is plausible that some countries may gain support from external partners to adopt, while others may not. Even with donor support, countries have to ascertain their capacity to continue funding vaccines after support ends. In the absence of external support, there needs to be a clear mechanism outlined that ensures consistency of funding.

Another cost dimension involves assessment of the value of maternal immunization. A cost-effectiveness analysis provides economic evidence that is essential to decision making (discussed below). In some cases, the expertise to conduct such studies is lacking. Technical support from regional health partners, such as the regional WHO office, can be provided upon request (216). Omitting an economic evaluation lessens the rigor of the adoption process and opens up the endeavor to the possibility of an overlooked error.

5.6. Ethical and vaccine acceptability issues

A number of ethical issues should be considered. Equity in gaining access to maternal immunization should be assessed. Since antenatal care coverage rates are lower than optimal, it should be ascertained what barriers impede women from utilizing those services. These may be geographic distance to clinics, distrust of westernized care, vaccine mistrust due to propaganda, or economic challenges, among others (225, 226). Acceptability of the vaccine should also be assessed. With the number of vaccines available in pregnancy, there may be concern of overloading the immune system and harming the fetus. Studies have shown that pregnant or recently-pregnant women refused vaccines over concerns of safety (226, 227). Such insight can help in the design of in-country vaccine trials.

Opportunity costs to other interventions should be considered. It is not farfetched to assume funding for maternal immunization could be spent elsewhere in implementing or improving another health program. Although it may not be part of the economic evaluation, performing such an analysis can further justify vaccine adoption or it can enlighten decision-makers on more pressing health needs. Addressing these ethical issues will add to the rigor of the decision-making process.

5.7. Decision-making process

Any vaccine adoption decision-making process should be evidence-based, taking into consideration all the above factors. It should also be representative and inclusive of relevant actors.

5.7.1. Political leadership

For the reason that vaccine adoption inherently is a political act (as it governmentally-regulated), there needs to be political commitment to the endeavor. Leaders, including ministers of health and finance, influence the decision and can determine if and when adoption takes place (224). In countries like Peru and Brazil, where vaccine laws and a budget line for immunization funding exist, adoption of vaccines is less challenging as it does not rely as much on political will around each specific vaccine (210, 228).

5.7.2. Public health staff

Public health staff of various specialties provide unique insight to the decision-making process as they are front-line workers and will be responsible for implementation. This group collaborates with researchers and internal and external partners to generate evidence to support the decision.

5.7.3. Advocacy groups

Special interest groups, such as academicians, researchers, women's groups, and pediatric and obstetric groups, represent non-governmental interests and can better reflect the concerns of the target populations in the decision-making process. Furthermore, having buy-in from this group can promote adherence to the maternal immunization schedule once implemented.

5.7.4. National advisory bodies

National Immunization Technical Advisory Groups (NITAG) are essential as they assess vaccine evidence and provide guidance on its use, thereby directing national immunization policy. Their leadership in the decision-making process ensures transparency and accountability (223). However, not every low income countries has a NITAG, and not every NITAG is of sufficient expertise to evaluate the evidence (223). Thus, NITAG strengthening in deficient areas is key.

5.7.5. National Regulatory Authority

The responsibility of regulating biological falls on national regulatory bodies. External licensing is often not enough and National Regulatory Authorities assure safety, efficacy and quality before licensing the vaccine for widespread use. It is uncertain the number of low income countries with functioning National Regulatory Authorities, but ideally they factor into the decision-making process (212).

5.7.6. External groups

International agencies, such as the WHO and the Immunization Interagency Coordinating Committee, are stakeholders involved in the process. However, there is variability on their influence in the decision-making process.

5.7.7. The process

Studies have shown that low income countries rarely have a formal structured process by which vaccine adoption decisions are made (209, 210, 223, 224, 229). In fact, in some cases, political clout has pushed vaccines onto the country portfolio instead of a participatory decision-making process (209, 223). Nonetheless, the common process in low income countries either begins with vaccine adoption discussion at the political level, which filters down to core public health staff, or it begins within core public health staff. The evidence (disease burden, vaccine cost estimate, affordability, cost-effectiveness and immunization systems assessments, etc.) is generated and if convincing, is passed on to the NITAG, which expertly evaluates the evidence and makes a recommendation to the ministry of health. If the recommendation is positive, the onus to move forward with implementation rests with the ministry of health.

6. Proposed roadmap for adoption

Current evidence indicates that these 10 vaccines have the potential to substantially impact morbidity and mortality in neonates, infants and mothers in low income countries. The first six—Tdap, IIV, *H. influenzae* type B, Hepatitis B, pneumococcal and meningococcal—are available for adoption by willing countries. Accessibility of Hepatitis E is currently limited, and GBS, RSV and Malaria vaccines

are in the development pipeline with the expectation of licensure in next few years. The pace of adoption of non-childhood vaccines is relatively slower in low income countries compared to high income countries; however, in the case of maternal vaccines, achieving these four objectives can pave the way for accelerated adoption.

i. Strengthen the evidence base

Important public health decisions are rarely made in the absence of a strong evidence base. Consequently, gaps in the evidence base of most of these vaccines will prevent adoption in the very countries that will benefit the most from them. Obtaining definitive evidence on the safety and efficacy of these vaccines from large, adequately-powered trials with pregnant women of heterogeneous populations is crucial. This will ensure that decision makers have a firm basis to implement routine use of these vaccines in pregnant women.

ii. Clear recommendations for routine use of these vaccines in pregnancy by WHO

A major barrier to country adoption of vaccines is the absence of clear guidance from WHO. Studies assessing decision-making processes find that WHO recommendations are highly valued by decision-makers and are the precipitating factor in adopting health interventions (209, 228). WHO-SAGE's recommendations are not static; in fact, policy position can be altered following compelling evidence. This was the case in 2012 when WHO revised its 2005 influenza policy to

recommend that pregnant women become the highest priority risk group and should be routinely immunized in pregnancy. This signified a change in practice that was quickly adopted by many countries. A similar measure with Tdap, *H. influenzae* type b, Hepatitis B, pneumococcal and meningococcal policies will topple this barrier and bring countries closer to adopting these vaccines for use in pregnancy. Additionally, prequalification of the Hepatitis E vaccine by WHO has the potential to facilitate wide spread adoption.

iii. Strengthen the country vaccine adoption decision-making processes

A strength of several HIC that facilitates early vaccine adoption is the structured, rigorous decision-making process that they use (230). In low income countries, the decision making-process can be unstructured, untechnocratic or deficient in its evidence-base. This can lead to poor planning and implementation, unsustainability of immunization, and public resentment, all of which will weaken the immunization and antenatal care systems. There are already initiatives with aim of strengthening NITAGs and the decision-making process (231, 232). Linking low income countries with these resources will further bridge the gap between recommendation and adoption.

iv. Form private-public partnerships to address acceptability issues related to multiple vaccine administration in pregnancy

Overcoming concerns over multiple—perhaps, simultaneous—injections can be achieved through private-public partnerships with vaccine manufactures in an effort to develop multi-component vaccines that will limit the number of dose administrations, but still provide adequate immunity to the panel of infection agents. This is not farfetched, as it was accomplished with the pentavalent vaccine (diphtheria-tetanus-pertussis (DTP), hepatitis B, *Haemophilus influenzae* type b) given in childhood. Such a vaccine will enhance coverage rates in that the majority of pregnant women will be captured, even if they encounter antenatal care services less than the recommended 4 visits.

Conclusion

Maternal immunization has the potential to avert millions of cases of disease, disability and death. The MNTNT initiative is proof that a simple intervention like a vaccine can change the infectious disease landscape. Ensuring protection of newborns that otherwise remain vulnerable to vaccine-preventable infections due their immature immune system is an ideal that global health partners should strive for. There is some evidence of the effectiveness of this approach; however, there also are barriers preventing adoption of this intervention in countries that would most benefit from it. Overcoming these barriers will require global partnership and policy leadership.

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