



Closer and closer? Maternal immunization: current promise, future horizons

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Abstract

This state-of-the art manuscript highlights our current understanding of maternal immunization—the practice of vaccinating pregnant women to confer protection on them as well as on their young infants, and thereby reduce vaccine-preventable morbidity and mortality. Advances in our understanding of the immunologic processes that undergird a normal pregnancy, studies from vaccines currently available and recommended for pregnant women, and vaccines for administration in special situations are beginning to build the case for safe scale-up of maternal immunization. In addition to well-known diseases, new diseases are emerging which pose threats. Several new vaccines are currently under development and increasingly include pregnant women. In this manuscript, targeted at clinicians, vaccinologists, scientists, public health practitioners, and policymakers, we also outline key considerations around maternal immunization introduction and delivery, discuss noninfectious horizons for maternal immunization, and provide a framework for the clinician faced with immunizing a pregnant woman.

Introduction

Of all the contributions made to global health, immunization has had one of the most profound impacts on morbidity and mortality worldwide [1, 2]. Current estimates show that immunization against diphtheria, tetanus, pertussis, and

measles prevents ~2–3 million deaths annually [3]. Yet, there remains much to be done. Infectious diseases are still a leading cause of death in children under 5 years of age, and more than four million infants die before their first birthday each year worldwide; 63% of these deaths occur within the first month of life [4]. Maternal immunization—the practice of vaccinating women during pregnancy—has the potential to significantly reduce neonatal mortality when infants are dependent on maternally transferred antibodies for protection. Recent advances in the field could change the way we protect mothers and their infants and potentially save thousands of lives every year.

Maternal Immunization

Every pregnant woman deserves an optimal pregnancy, a safe delivery, and a healthy baby. Every child deserves the opportunity to survive and thrive [5]. Maternal immunization is this principle turned into action.

Pregnant women and young infants have increased susceptibility to certain infectious diseases and/or are at heightened risk of experiencing severe disease. In women, some of this increased vulnerability is due to pregnancy-associated hormones interacting with immune responses [6];

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by contrast, in infants, immature immune systems require time and often multiple vaccine doses to mount adequate responses to many infectious diseases [7]. Maternal immunization can address this vulnerability by offering protection to a woman and her young infant by passive infant immunity conferred through the active transfer of antibodies, specifically immunoglobulin G (IgG), from the mother across the placenta [8]. IgG persists through the first few, most vulnerable months of life before degrading to unprotective levels. While some definitions of maternal immunization include protection conferred through breast milk, this discussion will be restricted to vaccines and the subsequent protection through placental transfer of maternal antibodies.

Since its inception in 1977, the World Health Organization's (WHO) Expanded Programme on Immunization (EPI) has worked to prevent childhood illnesses through vaccination during infancy and childhood [9]. And while childhood vaccinations remain a critical priority, global interest recently has grown to promote health throughout the full life course by expanding vaccination to other age groups. Such "life-course" vaccination includes women before, during, and after pregnancy, as well as newborns, children, adolescents, and older people [10]. These populations, many of which are not covered by current immunization strategies, face greater vulnerability to infectious diseases. The 1918 influenza pandemic and the 2009–2010 influenza A/H1N1 outbreak, for instance, disproportionately affected mothers, fetuses, young children, and the elderly—providing compelling evidence for an expanded life-course approach [10, 11].

Immunological principles underlying maternal immunization

During pregnancy, there is a complex and dynamic immunological interaction between the mother and her fetus. Key principles that underly maternal immunization are outlined below.

Maternal aspects

Half of the total fetal antigen load is inherited paternally, which the maternal immune system perceives as "foreign" [12]. In pregnant immunocompetent women, many immunologically adaptive processes occur in a synchronized fashion to ensure the mother can tolerate the presence of these paternally derived antigens. Key among these processes is an increased concentration of sex hormones such as estrogen and progesterone, which induce a shift in maternal pro- and anti-inflammatory responses [12]. Typically, pro-inflammatory responses are a prominent feature of the first trimester, and anti-inflammatory responses are more prominent in the

second and third trimesters [13]. During pregnancy, there is a rise in sex hormone levels, which, in addition to the shift in maternal pro- and anti-inflammatory responses, modulates the balance between type 1 helper (Th1) cells necessary for cell-mediated immunity and type 2 helper (Th2) cells necessary for humoral immunity. Increases in estradiol result in increases in Th2 cells, which then suppress cytotoxic T lymphocytes and stimulate B lymphocytes to increase production of antibodies that are then transferred across the placenta to the fetus [14].

Placenta

Emerging evidence suggests the placenta plays an active role in immunologic reactions and can interact and respond to pathogens [15]. For example, local immunologic mechanisms mediated at the fetomaternal junction help protect the fetus from rejection, while cytokines provide the required growth factors necessary for fetal implantation in the placenta. Several factors can influence the placenta's role in immunity [15]. Maternal infection with malaria or HIV, for instance, decreases the placenta's ability to transport IgG by impairing antibody Fc (crystallizable fragment) receptor function, whereas higher levels of total maternal IgG reduce transfer of antigen-specific IgG by competitively binding to placental Fc receptors [16]. IgG transfer across the placenta also appears to differ by subtype. For example, IgG1, which is induced by protein antigens such as tetanus toxoid, is more efficiently transferred than IgG2, which is induced by lipopolysaccharide antigens such as those in encapsulated bacteria [16].

The fetus and young infant

The immature immune system of the developing fetus and young infant cannot mount a full-blown protective response to pathogens. Fetal and neonatal T cells display Th2 responses that are ineffective against intracellular pathogens, and antibody responses to bacterial polysaccharides are ineffective [16]. This results in the fetus and young infant relying on supplemental maternal protection provided by the active transport of IgG across the placenta. IgG efficiently crosses the human placenta via syncytiotrophoblast cells that are in contact with maternal blood [16]. Circulating maternally derived IgG is internalized in endosomes and binds to neonatal Fc receptors, which are expressed on the internal endosomal surface. These endosomes fuse with the membrane on the fetal aspect of the syncytiotrophoblast and release IgG, which then passes through villous stroma and fetal capillary endothelium to enter the fetal circulation [16]. There is active transport of IgG during the second and third trimesters, with IgG flux enhanced significantly after 32 weeks of gestation. Some

studies report the concentration of fetal IgG in the late second trimester and early third trimester is 25–50% lower when compared to term infants [17]. When a fetus reaches full term, its IgG concentrations are sometimes even greater than those in the maternal circulation, because of the active transport mechanism [18]. Multiple factors can affect the transfer, including placental integrity, maternal non-infectious diseases, total maternal IgG concentration, IgG subtype, presence of neonatal Fc receptors, nature of the antigen, and timing of vaccination or infection [8].

Vaccines currently available and recommended for use in pregnant women

The safety and effectiveness of immunization during pregnancy against diphtheria, pertussis, tetanus, and influenza is well documented, and these vaccines are regularly included in national routine immunization schedules. Yet, uptake is inconsistent even among these recommended vaccines. For example, uptake of tetanus toxoid vaccine has been successful, while high coverage of pertussis and influenza vaccines is still limited by cost concerns, a paucity of disease data, lack of clear guidelines for health care providers, vaccine hesitancy on the part of some pregnant women, and decreased global drive and commitment. Issues related to immunization against these different pathogens are outlined below.

Tetanus

The vast majority of the 30,848 cases of neonatal tetanus reported in 2017 occurred in low-income settings, where poor hygienic or cultural practices following birth may be prevalent (e.g., cutting the umbilical cord with a non-sterilized blade or applying a local poultice or remedy to the exposed umbilical stump) [19]. Tetanus is characterized by painful muscle spasms and rigidity caused by blockade of inhibitory neurons by tetanus toxin, thus resulting in excitatory motor neurons lacking any counterbalance or modulation [20]. The average incubation period is 3–21 days. Untreated, neonatal tetanus usually results in death from respiratory failure; however mortality can be significantly attenuated through supportive care and treatment [21].

Maternal immunization with tetanus toxoid-containing vaccine (TTCV) represents a global health triumph. WHO estimates that from 2000 to the end of 2017, there was an 85% decrease in neonatal tetanus deaths. This was due, in large part, to a globally sustained initiative called the Maternal and Neonatal Tetanus Elimination initiative, which targeted pregnant women and women of reproductive age with TTCV [22]. Pregnant women and their newborn infants are protected from birth-associated tetanus if the

mother received either six TTCV doses during childhood or five doses if first vaccinated during adolescence (documented by card, immunization registry, and/or history), before the time of reproductive age. While complete eradication remains unlikely because of the ubiquitous and highly resistant nature of the causative pathogen, *Clostridium tetani*, efforts are underway to reduce the global burden of this devastating disease through a four-pronged strategy [23]:

1. Routine vaccination of pregnant women with TTCV.
2. Supplementary immunization activities, such as immunization of all women of childbearing age in areas at highest risk of maternal and neonatal tetanus and school- or community-based immunization.
3. Safe deliveries attended by a skilled birth attendant who uses sterilized equipment/materials and clean cord care practices.
4. Improved neonatal tetanus surveillance and enhanced preventive strategies with vaccination, and improvement of perinatal care and post-exposure prophylaxis in high-risk areas—especially among the most vulnerable populations.

As a result, as of March 2018 maternal and neonatal tetanus has been eliminated from all but 13 countries (where elimination is defined as a neonatal tetanus rate of <1 case per 1000 live births in each district of the country) [22].

Because regular booster doses with TTCV provide long-term immunity, and neonates born to women who lack sufficiently high levels of circulating tetanus IgG antibodies are at heightened risk of neonatal infection, WHO recommends that all women of childbearing age in high-risk areas for maternal and neonatal tetanus receive three doses over a 12-month period. Additional guidance states that pregnant women with an inadequate or unknown vaccination history should receive two doses of TTCV, at least 1 month apart, with the first dose as early in pregnancy as possible [22].

Pertussis

Pertussis is an endemic disease globally, and highly contagious. Pre-vaccination, it often affects children in their first years of life and clinically is characterized by paroxysmal coughing spells, inspiratory whoop, and post-tussive vomiting [24]. Modeled estimates indicate that ~24 million cases occurred in 2014, accompanied by 160,700 deaths in children under the age of five [25]. The highest burden was in Africa, where an estimated 7.8 million (33% of total) cases and 92,500 (58% of total) deaths occurred that year. Approximately 5.1 million (21%) estimated pertussis cases and 85,900 (53%) estimated deaths were in infants younger

than 1 year, many of whom had not started or completed their primary immunization schedules [25].

WHO recommends maternal pertussis immunization take the form of a combined tetanus-diphtheria-acellular pertussis (Tdap) vaccine, and function as a complementary intervention to timely infant immunization in countries or settings with high or increasing infant morbidity or mortality from pertussis. Maternal immunization should occur in the second or third trimester, or at least 15 days before the end of the pregnancy, though there are national variations to this recommendation [25, 26]. For example, the United States recommends Tdap vaccination during each pregnancy regardless of previous vaccination status, and while 27–36 weeks is promoted as the ideal time frame, vaccination can be administered at any time. Argentina, Ireland, and Australia also recommend Tdap vaccination during each pregnancy; however, the time frames vary: Argentina starting at 20 weeks of pregnancy, Ireland at 16–36 weeks, and Australia recommending Tdap in the third trimester. In the United Kingdom, reduced diphtheria-tetanus-pertussis-inactivated poliomyelitis vaccination is recommended during each pregnancy, ideally between 16 and 32 weeks [13].

Numerous authors have systematically assessed the safety profile, immunogenicity, and effectiveness of maternal immunization with Tdap and shown that it results in clinically and statistically significant reductions in mortality and morbidity of young children before they receive or complete their immunization schedules. One systematic review cited 90–93% effectiveness against pertussis infection in children from birth to 59 days old [27]. Another study compared pertussis cases in young Argentinian infants whose mothers were immunized during pregnancy and who lived in states with high Tdap coverage—defined as >50%—versus those who lived in states with low maternal pertussis immunization coverage. There was a 51% relative reduction in the cohort whose mothers were immunized during pregnancy against pertussis [28]. In the United States, a network of managed care organizations examined the association of maternal pertussis vaccination with obstetric events and birth outcomes and found that of 123,000 singleton pregnancies occurring between 2010 and 2012, there were no adverse events or birth outcomes [29]. A recent study of 68,500 women in New Zealand did not find any association of vaccination in pregnancy with birth outcomes [30].

Influenza

Pregnant women and young children are more vulnerable to severe complications from influenza relative to the general population. Influenza is characterized by the sudden onset of constitutional and upper respiratory symptoms such as fever, myalgia, headache, malaise, non-productive cough, sore

throat, and rhinitis. In young children, nausea, vomiting, and diarrhea may accompany influenza infection. Complications can include dehydration, pneumonia, sinusitis, otitis, encephalitis, or worsening of pre-existing medical issues [31]. Reports have documented an increase in influenza-related hospitalizations and deaths in pregnant women and their newborn infants during seasonal influenza outbreaks or pandemics [13, 32]. Fetuses are not exempt and are more likely to be stillborn, born prematurely, and/or have low birth weight if their mothers were infected with the influenza virus during pregnancy. The 1918 and 2009–2010 influenza A/H1N1 pandemics, which were associated with an increase in mortality and morbidity in these two groups, underscore these observations. A growing number of studies have examined the safety, immunogenicity, and effectiveness of pandemic influenza vaccines in pregnancy. One study from Norway reported that influenza diagnoses decreased by 70% when 117,000 pregnant women were given adjuvanted pandemic influenza vaccine [32]. In a Swiss cohort, maternal vaccination given at least 2 weeks before delivery during the 2010–2011 influenza season increased antibody titers in cord blood between 6- and 17-fold and provided seroprotection rates between 6- and 34-fold, depending on the strain and interval between vaccination and delivery [33]. In a matched case–control study in an urban hospital in the northeastern United States, influenza vaccine given to pregnant women was 91.5% effective in preventing hospitalizations (95% confidence interval [CI]: 61.7–98.1, $P = 0.001$) for infants aged < 6 months [34]. Another study in three geographically diverse US counties reported the vaccine was 45% to 48% effective in preventing seasonal laboratory-confirmed influenza-related hospitalizations in infants aged < 6 months between 2002 and 2009 (adjusted odds ratio = 0.52; 95% CI: 0.30–0.91) [35]. Four randomized controlled trials, conducted in Mali, South Africa, Nepal, and Bangladesh, evaluated the efficacy of inactivated influenza vaccine administered during pregnancy [36–39]. Efficacy against laboratory-confirmed influenza in infants born to vaccinated mothers ranged from 30% in Nepal to 63% in Bangladesh. Vaccine efficacy in mothers in Mali was 70.3% (95% CI: 42.2–85.8) and 50.4% (95% CI: 14.5–71.2) in non-HIV infected mothers in South Africa. Reductions in febrile respiratory illness were also reported in mothers in Bangladesh and Nepal (19% [95% CI: 1–34] and 36% [95% CI: 4–57], respectively).

Nevertheless, some authors are beginning to question the effects of maternal influenza vaccine on adverse birth outcomes [40]. For reasons that remain unclear, there is a well-documented association between influenza infection and subsequent bacterial infections, especially pneumococcal infection and disease. For example, a US-based study conducted in a managed care organization reported higher efficacy of the pneumococcal conjugate vaccination against

infant otitis media when mothers had received inactivated influenza vaccine [41].

Considering these data, WHO recommends that countries considering initiating or expanding seasonal influenza vaccination programs should identify pregnant women as the highest priority [42]. An increasing number of countries now recommend that all women who are pregnant or plan to get pregnant should receive seasonal inactivated influenza vaccine at any stage of pregnancy [43, 44]. And while use of live attenuated influenza vaccine for pregnant women is cautioned against, inadvertent administration does occur; one study examined a cohort of 834,999 pregnancies and identified 138 cases in which a woman had received a live attenuated influenza vaccine. There were no adverse fetal events and all other maternal outcomes occurred at similar rates to unvaccinated pregnant women [45].

Additional vaccines may be recommended for pregnant women in certain special situations (Table 1) [46–55].

Clinicians should be well versed in how to manage immunization appointments for their pregnant patients (Table 2) [56–58].

New vaccines under development

Many new vaccines are on the horizon and clinical trials are underway to assess their effectiveness in reducing and preventing maternal and newborn infections when administered to women prior to or during pregnancy. Some of these (e.g., vaccines to prevent Group B *Streptococcus* and respiratory syncytial virus) are intended primarily for administration to pregnant women. Others, including vaccines for hepatitis E, herpes simplex, Zika [59], and cytomegalovirus, would optimally be provided prior to pregnancy, given the associated morbidity and mortality in early pregnancy. There is also a growing need to include

Table 1 Vaccines for administration to pregnant women in special situations [46–55].

Vaccine	Indication and recommendation
Pneumococcal vaccines	The 23-valent pneumococcal polysaccharide vaccine is recommended for women with certain chronic health conditions. The 13-valent pneumococcal vaccine (PCV13) is recommended for women of immunocompromised status. PCV13 vaccine should only be provided to women when benefits outweigh risks.
Yellow fever	Yellow fever vaccine is generally not recommended for pregnant women, but physicians should balance risks and benefits and provide the vaccine where travel, epidemics, or other exposure cause benefits to outweigh risks.
Hepatitis A	Recommended for women with increased risk of hepatitis A acquisition or complications, if not previously vaccinated.
Hepatitis B	Recommended for at-risk pregnant women based on behavioral or travel history or certain health conditions.
Anthrax	Recommended only where risk of exposure is high. At-risk pregnant women should receive anthrax vaccine adsorbed and 60 days of antimicrobial treatment.
Japanese encephalitis	Limited data on the safety, immunogenicity, and efficacy of the inactivated vaccine. The vaccine should be considered when outbreak, travel, or another exposure situation may pose a threat to the health of the mother and fetus and the potential benefit outweighs risk.
Rabies	May be used where otherwise recommended. Given the risks associated with inadequate management, the vaccine is not contraindicated in pregnancy for post-exposure prophylaxis.
Polio	Inactivated poliovirus vaccine is indicated in outbreak situations, for travel to polio-endemic areas, or where exposure cannot be avoided, and when the benefits outweigh the risks. Oral poliovirus vaccine is contraindicated in pregnancy.
Cholera	Targeted vaccination of high-risk groups in cholera outbreaks and endemic areas, including groups vulnerable to severe disease (such as pregnant women), where vaccination is not otherwise contraindicated.
Tick-borne encephalitis	Indicated for use in pregnant women where incidence of disease is high (>5 cases/100,000 population per year). Risks and benefits should be weighed in areas where incidence is low.
Meningococcal conjugate (MenACWY and MenB recombinant)	Indicated for travelers to endemic regions and in outbreak situations. The serogroup B vaccine should be deferred and provided to pregnant women only when the benefits outweigh the risks.
Smallpox	Small but serious potential risk to fetus associated with vaccination. The vaccine should not be provided to pregnant or periconceptual women except when they are at high risk of contracting the disease, given the severity of disease means that benefits outweigh risks.
Typhoid	Inactivated vaccine (Vi polysaccharide) recommended for pregnant women only when clearly indicated (outbreak or where risk of exposure is high). Live vaccines (Ty21a) are contraindicated in pregnancy.

Table 2 For the clinician: immunizing pregnant women – managing the antenatal care visit [56–58].

Situation	Action
Background	<ul style="list-style-type: none"> • Vaccine coverage rates continue to be less than optimal for pregnant women. • Provider recommendation is one of the strongest predictors of vaccine uptake in pregnant women.
Assessment	<ul style="list-style-type: none"> • Evaluate the vaccination status of pregnant patients, including missing or incomplete childhood vaccinations and other special conditions that may warrant additional vaccinations. • Only written records should be accepted as evidence of previous vaccination.
Counsel and administer	<ul style="list-style-type: none"> • Provide information on why the vaccine is needed, highlighting safety, efficacy, and benefits to mom and infant. • Acknowledge and address questions and concerns. • Remind patient of the risks of nonvaccination. • Make a strong recommendation for vaccination. • Administer required vaccines.
Adverse event reporting	<ul style="list-style-type: none"> • Vaccine Adverse Event Reporting System and Vaccine Safety Datalink: for broad populations. • Vaccines and Medications in Pregnancy Surveillance System: for pregnant populations. • Vaccine-specific registries (e.g., for varicella, human papillomavirus, and herpes zoster vaccines) focused on inadvertent immunization with live vaccines during pregnancy.

pregnant women in the clinical development of epidemic vaccines; as such, WHO recently approved the inclusion of pregnant women in the deployment of an investigational Ebola vaccine [60].

Respiratory syncytial virus vaccines

Lower respiratory tract illness caused by respiratory syncytial virus (RSV) is the most common cause of serious and life-threatening pulmonary disease in infants, with the highest disease incidence within the first 3 months of life [61]. Protection of infants at risk of severe RSV disease has been shown through passive prophylaxis, including use of a monoclonal antibody, palivizumab (Synagis®), but the high cost and need for multiple injections limits its use in low-income countries, where disease burden is greatest [62–66]. Infant vaccines against RSV have been in development for decades but have faced challenges, including the ability to elicit sufficient immunogenicity and safety concerns regarding an early whole virus vaccine candidate [67–70]. These concerns, along with the need to protect infants in early life and maternal immunization's track record of reducing influenza and pertussis in young infants, has prompted evaluation of maternal RSV vaccine candidates [48].

The most advanced vaccine candidate is a RSV pre-fusion F protein nanoparticle vaccine (NCT02624947) developed by Novavax, Inc. [71]. While the company announced in February 2019 that the candidate's phase 3 trial did not meet the primary objective of prevention of medically significant RSV lower respiratory tract illness, the vaccine was found safe in mothers and their infants through

180 days post-delivery [72]. Infants born to mothers vaccinated from 28 weeks to <33 weeks of pregnancy showed 53 percent vaccine efficacy rates against hospitalization with RSV lower respiratory tract infection (LRTI) and 70 percent against severe RSV hypoxemia through their first 90 days. The trial also demonstrated a 25% reduction in all-cause LRTI hospitalizations and a 39% reduction in all-cause LRTI severe hypoxemia in infants observed through the first 180 days of life. A peer-reviewed manuscript is forthcoming. Although additional studies will be needed to meet regulatory and licensure requirements for this vaccine, these results begin to provide data to support proof of concept for maternal RSV vaccines. Three other early clinical-stage RSV F protein maternal vaccine candidates are currently in development, all of which are stabilized pre-fusion F protein vaccine candidates. Developers include Pfizer, New York, NY, USA (NCT03529773); GlaxoSmithKline, Brentford, UK (NCT02753413); and the US National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA (NCT03049488) [73–75].

Hepatitis E vaccines

Hepatitis E virus (HEV) is the most common cause of acute viral hepatitis in adults in South Asia and Africa [76]. HEV occurrence during pregnancy, especially during the second and third trimesters, increases the risk of intrauterine fetal death, preterm delivery, and maternal death [77]. An *Escherichia coli*-expressed hepatitis E capsid protein vaccine adsorbed to aluminum salts (Hecolin®, Xiamen Inovax Biotech Co., Ltd., China) is approved for use in adults in China, but not yet approved elsewhere [78]. Vaccinating

an at-risk pregnant woman against HEV could protect her and her unborn child. Furthermore, as anti-HEV IgG protects nonhuman primates from high-dose intravenous virus challenge [79], maternal immunization should transfer similarly protective maternal IgG to the fetus, potentially offering additional months of protection postpartum. In a large prospective cohort study of 2404 pregnant women in Nepal, where HEV is hyper-endemic, >60% of subjects were susceptible, as they lacked detectable anti-HEV antibodies (Innis BL, unpublished data). A follow-up study is underway (NCT02759991) [80].

Group B *Streptococcus* vaccines

Group B *Streptococcus* (GBS) is a Gram-positive, opportunistic pathogen that colonizes the gastrointestinal and genitourinary tracts of up to 50% of healthy adults [81, 82]. GBS exacts a significant mortality toll in neonates, young infants, and immunocompromised adults, and is a major cause of morbidity in pregnant women and the elderly [82]. Neonates are especially susceptible and develop septicemia, meningitis, and pneumonia [83].

Worldwide, vaginal colonization of GBS has been reported in between 12% and 27% of women [82]. During pregnancy, vaginal GBS colonization is believed to increase the incidence of premature delivery and perinatal transmission of the organism. GBS is also a leading cause of chorioamnionitis and is one of several bacteria thought to enhance the risk of preterm rupture of membranes [84, 85]. Further, GBS is responsible for cases of endometriosis and urinary tract infections. It is now the most important cause of bacterial meningitis in infants under 3 months of age in countries reporting late-onset disease incidence [86, 87].

GBS infections in neonates are divided into early onset (<7 days) and late onset disease. Maternal administration of intrapartum antibiotics prevents early-onset GBS disease but does not prevent late-onset disease [83]. Intrapartum antibiotic prophylaxis poses implementation challenges in lower-resourced settings and the potential impact of increased perinatal antibiotic use on neonatal gut microbiome as well as on antimicrobial resistance has raised concerns [88]. WHO has developed preferred product characteristics for GBS vaccines and called for the acceleration of vaccine development and licensure; [88, 89] phase 1 and 2 trials of GBS vaccine candidates intended for maternal administration are underway. One trivalent GBS vaccine candidate demonstrated acceptable safety and immunogenicity in nonpregnant and pregnant women [90]. Due to the large sample size required for phase 3 efficacy studies, efforts are underway to identify a serological correlate of protection as a basis for licensure [91, 92]. To date, no vaccine candidates have entered phase 3 trials.

Cytomegalovirus, herpes simplex virus, Zika virus, and Ebola virus vaccines

Cytomegalovirus (CMV) is a double-stranded herpes DNA virus. Congenital infection with CMV can be asymptomatic at birth in 85–90% of cases [93], although in 10–15% of neonates, infection is associated with microcephaly, periventricular calcifications, chorioretinitis, dermal hematopoiesis, thrombocytopenia, and progressive bilateral sensorineural hearing loss and impaired neurodevelopmental outcomes [94].

Several cytomegalovirus candidate vaccines are currently being evaluated in phase 1 and 2 clinical trials, however there are no phase 3 trials to date [95, 96].

Herpes simplex virus (HSV) is a double-stranded herpes DNA virus. The majority (95 percent) of neonatal infections result from virus presence in the vagina while ~5% are transplacental. Transmission occasionally occurs via breast milk or contact with infected skin lesions. Primary maternal genital infection during pregnancy confers a 10–20 times higher risk compared with recurrent, secondary lesions because of higher viral replication, longer excretion rates from primary lesion and lack of maternal antibodies which can be passed to the infant. Three types of clinical presentations occur: in 20% of patients, a disseminated, systemic infection presents earliest (days 4–10 of life); in the most common type of perinatally acquired HSV, a skin, eye, and mucus membrane symptom complex predominate; and in up to 30 percent of cases, infection is localized to the central nervous system as encephalitis [93]. Prompt recognition, antiviral administration, and supportive treatment form the mainstay of therapeutic management [97]. Mortality is worst for disseminated disease, and long-term, neurodevelopmental morbidities worst with CNS disease. Herpes simplex candidate vaccines are being evaluated in clinical trials [98], however, conclusive protective benefit has not been established nor has licensure been granted [99].

Zika virus is a flavivirus transmitted by the *Aedes aegypti* mosquito. Increasing evidence suggests that in pregnant women, symptomatic, PCR-confirmed Zika infection results in neonates with microcephaly, neurological sequelae such as visual and hearing deficits, seizure activity, hypertonicity, spasticity, hyperreflexia, contractures, dysphagia, and feeding difficulties [100]. Zika infection in the first trimester results in worse sequelae than infections later in pregnancy [100]. Multiple Zika virus vaccine candidates are currently under investigation, including whole virus inactivated vaccines, nucleic acid vaccines, vectored vaccines, and protein-based and peptide-based candidates [101]. Some of these are currently in phase 1 and 2 trials [102]. An additional area of interest in Zika prophylaxis is the development of “therapeutic vaccines,” which aim to prevent infection of the fetus in women infected with the Zika virus periconceptually or during pregnancy [103].

Table 3 Key considerations before introducing a new maternal vaccine [112, 113].

Issue	Key considerations
Disease	<ul style="list-style-type: none"> • Public health and political priorities. • Alignment with global and regional recommendations. • Disease burden. • Status of other disease prevention and control measures.
Vaccine	<ul style="list-style-type: none"> • Performance and characteristics of available vaccines. • Economic and financial issues. • Availability of vaccine supply.
Strength of health system	<ul style="list-style-type: none"> • Capability and capacity of immunization and maternal health programs, including infrastructure. • Collaboration between immunization and maternal health programs. • Continuous implementation of lessons learned.
Optimal timing	<ul style="list-style-type: none"> • Plans for introducing other new vaccines or maternal health services. • Opportunities for integration with current disease prevention or health initiatives.

Ebola virus are filoviridae that cause fever and non-specific symptoms such as fatigue, dyspepsia and headache, which then progress to vomiting, diarrhea, bleeding, and abdominal pain. Due to the loss of gastrointestinal fluids and increased vascular permeability, patients may go on to develop shock, ultimately resulting in multiple organ failure and death. Ebola virus disease (EVD) is transmitted through contact with the bodily fluids (blood, urine, semen, saliva, sweat, and breast milk) of infected people or animals. Among pregnant women, case fatality rates in earlier outbreaks have ranged from 89 to 93% with universally (100%) poor perinatal outcomes; the vast majority of pregnancies resulting in spontaneous abortion or stillbirth (78%) and none of the live births (22%) surviving beyond the third week of life [104]. Pregnant women despite having an enhanced risk of morbidity, mortality, and adverse birth outcomes associated with Ebola have been systematically excluded from Ebola vaccine trials and until recently were excluded from immunization, such as during the 2018 outbreak in the Kivu region of the Democratic Republic of the Congo (DRC), which deployed a replicating live virus vaccine, rVSV-ZEBOV-GP [105, 106]. In December 2018, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization called for special consideration of pregnant and lactating women in EVD vaccine research. Three new non-replicating or replication deficient vaccines are currently in advanced stages of clinical evaluation or have been licensed [107]. SAGE provided updated interim recommendations in February 2019, announcing support for inclusion of pregnant women in vaccine trial protocols with the new vaccines [105, 106]. As of October 2019, more than 840 pregnant women have received the vaccine with birth outcomes and safety data under consideration [108]. The rVSV-ZEBOV-GP vaccine was approved by the US Food and Drug Administration on 19 December 2019, with guidance that the “decision to vaccinate a woman who is pregnant should consider the woman’s risk of exposure to

Zaire ebolavirus” [109, 110]. In February 2020 as part of “WHO Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease” a recommendation was made for these women to be offered vaccination with the prequalified rVSV-ZEBOV-GP vaccine “during an active Zaire EBOV outbreak in affected areas, in the context of rigorous research or in accordance with a compassionate use protocol” [111].

Key considerations around maternal immunization introduction and use

The WHO’s general guidance to countries considering the introduction of new vaccines can be applied to maternal vaccines, with added health system strengthening and timing considerations (Table 3) [112, 113]. These considerations are especially important for maternal vaccines provided seasonally, such as influenza vaccines, and potentially future RSV vaccines, as they require a short-term surge in the number of vaccines delivered and health system workload support.

The introduction and delivery of maternal vaccines often falls outside the reach of traditional immunization programs targeting young children and may require novel approaches to attain high coverage. Strategies for delivering maternal vaccines include routine delivery incorporated into existing services (antenatal, primary, and HIV care, and well and sick child visits), vaccination campaigns, and outreach [114]. Effective integration of maternal immunization into routine health care services, such as antenatal care, can provide an opportunity to strengthen and improve the maternal health platform through access to new resources; potentially increase uptake by improving the perception of the quality of care; and increase overall antenatal care attendance while also expanding vaccine delivery systems [115, 116]. A coordinated, integrated delivery effort can

ensure a “one-stop shop” where vaccines are available and offered to pregnant women where, when, and by the same provider they attend for pregnancy care. This approach will minimize missed opportunities for vaccination and provide continuity of care [117]. However, it necessitates close policy, fiscal, and programmatic coordination between EPI and maternal, newborn, and child health programs.

Low-resource settings that suffer disproportionate maternal and neonatal mortality, like sub-Saharan Africa and South Asia, may benefit the most from maternal immunization—but they may also face additional challenges due to inadequate infrastructure for safety monitoring [118, 119]. Strengthening the safety evidence base could address issues around risk perception and vaccine hesitancy and inform communication strategies. Reliable, robust tracking systems with the capacity to monitor implementation and outcomes will also provide information to assess vaccine effectiveness and delivery feasibility [120, 121].

Available maternal immunization guidance

Multiple guidance documents are available around development, decision-making, and introduction of maternal vaccines, with a focus on low-income settings [114, 122, 123]. WHO’s vaccine research and development roadmaps for maternal vaccines against RSV and GBS outline priority activities for development, testing, licensure, and global availability of maternal RSV and GBS vaccines, respectively [122, 123]. The Global Alliance to Prevent Prematurity and Stillbirth developed a set of references for maternal immunization safety monitoring in low- and middle-income countries and published a roadmap for improving reporting systems for adverse events following immunization, which evaluates the strengths and weaknesses of current systems and offers suggestions for addressing current gaps that include system strengthening [121]. The Advancing Maternal Immunization collaboration published a maternal immunization gap analysis and roadmap in 2018 to provide tools to help stakeholders navigate decision-making and successful introduction and uptake of maternal vaccines, with a focus on RSV [113, 124]; although those documents focus on a single vaccine, they offer a useful introduction framework for other maternal candidates currently in development.

Noninfectious horizons for maternal immunization

The effects of maternal immunization may go beyond infectious disease prevention. During pregnancy, maternal

hypercholesterolemia is associated with markedly increased formation of fatty streaks in fetal arteries and accelerated development of atherosclerosis during normocholesterolemic childhood [125]. Oxidized low-density lipoproteins (OxLDL) accumulate in atherosclerotic lesions and are highly immunogenic. Immunizing rabbits and mice with various models of OxLDL is thought to induce antibodies that form complexes with circulating LDL. Immunization may also induce a switch from Th1 cells, which secrete proatherogenic interferon gamma, to Th2 cells that secrete antiatherogenic interleukins [126, 127]. Studies into whether immunizing rabbits and mice with OxLDL before pregnancy protected the fetus from atherogenic in-utero programming showed up to 56% reduced atherosclerosis in adult offspring. These studies also noted that maternal immunization with OxLDL caused a persistent change in specific postnatal B cell and antibody responses—in some cases, independent of transplacental passage of immunoglobulins. They concluded that maternal immunization with selected antigens may open a new preventive approach not solely for atherosclerosis, but for other immunomodulated diseases [128]. Similar conclusions can be made about the positive effects of maternal immunization on in-utero programming and subsequent reduction in offspring of insulin resistance, type 2 diabetes, and adult allergy-related responses [129, 130].

Another promising area is the use of maternal immunization to treat or prevent cancers. In a mouse model (BAL-neuT mice), mammary cancer progression in offspring prone to develop this cancer is inhibited when anti-neu DNA vaccination is given to mothers during pregnancy [131]. Childhood cancers, particularly neuroblastoma and lymphoma, may be most susceptible to maternal immunization [132, 133].

Conclusion

Mounting evidence suggests that maternal immunization is a safe and effective strategy to combat vaccine-preventable diseases. Numerous clinical trials are underway to investigate new maternal vaccine candidates. Successfully operationalizing a maternal immunization program will require integrated EPI and antenatal care systems to ensure standardized, efficient, and equitable operations and logistics, such that effective delivery occurs, pregnancy outcomes are improved, and many more lives are saved.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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