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REVIEW ARTICLE

Immunization During Pregnancy: Impact on the Infant

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Abstract Maternal immunization has undergone a paradigm shift in recent years, as women and healthcare providers accept and recognize the benefits of this strategy not only for the pregnant woman but also for the developing fetus and young infant. This article reviews the evidence for active immunization during pregnancy, with an emphasis on perinatal and infant outcomes. Current recommendations for immunization during pregnancy are presented, with particular focus on the routinely recommended vaccines during pregnancy: influenza and Tdap (tetanus, diphtheria, and pertussis). We discuss future research directions, maternal vaccines in development, and considerations for optimizing and advancing this underutilized strategy.

Key Points

Maternal immunization is the optimal strategy for protection of vulnerable infants too young to be vaccinated.

There is emerging evidence of robust effectiveness and safety for the routinely recommended vaccines in pregnancy (influenza and Tdap [tetanus, diphtheria, and pertussis]).

Novel vaccines in development against respiratory syncytial virus and group B streptococcus provide major opportunities to add to the rapidly evolving maternal immunization platform.

1 Introduction

Immunization is one of the world's greatest public health achievements. Implementation of routine immunization programs has resulted in a great reduction, and in some cases eradication, of vaccine-preventable disease (VPDs), significantly contributing to the 25-year increase in average lifespan over the last century [1, 2]. However, despite the ongoing remarkable progress made through increasing the uptake of new and underused vaccines, the World Health Organization (WHO) estimates that over 1.5 million children aged <5 years died due to a VPD in 2014 [3]. In particular, young infants remain exquisitely vulnerable to VPDs because of both an inability to be adequately vaccinated and sub-optimal immune responses to pathogens. The WHO estimates that up to two-thirds of newborn

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deaths can be prevented if known effective health measures are provided [4].

This article reviews the effects of VPD during pregnancy and early infancy and discusses active immunization during pregnancy for maternal and infant benefit (known as maternal immunization) as the optimal strategy for prevention of infant disease. Particular emphasis is given to the impact and benefit of the vaccines currently recommended for routine maternal immunization for the developing fetus and infant. Potential future research directions and opportunities are highlighted.

1.1 Effects of Vaccine-Preventable Disease (VPD) During Pregnancy

Pregnant women are at risk for the same infectious diseases as non-pregnant women and in some cases are at higher risk because of the physiologic and immunologic changes that increase a pregnant women's susceptibility to infection. During pregnancy, there is a shift from a T-helper (Th)-1 response toward a more Th2-favoured response, which allows for fetal antigen tolerance but potentially increases vulnerability to infectious diseases [5]. This concept has been repeatedly reported, with disproportionately high rates of influenza-related morbidity and mortality in pregnant women during the Spanish Flu epidemic of 1918 [6], the Asian Flu epidemic of 1959 [7], and the more recent H1N1 pandemic of 2009 [8, 9]. In one study, H1N1-infected pregnant women were four times more likely to be hospitalized with influenza-related complications than the general population [10]. Additionally, pregnant women with co-existent HIV infection (even when managed with antiretroviral agents) were more susceptible to influenza disease than HIV un-infected pregnant women in a South African trial [11]. Other studies have shown pregnant women to have higher rates of intensive care unit (ICU) admission and death than the general population [8] or women of child-bearing age [12], and the risk is higher in the second and particularly the third trimester of pregnancy [8, 13] and immediately post-partum [12]. A meta-analysis of laboratory-confirmed H1N1 infection data from ten countries computed a relative risk (RR) of 6.8 (95% confidence interval [CI] 4.5–12.3) for hospitalization and an increased RR of 1.9 (95% CI 0.0–2.6), although this was not significant for death among pregnant women compared with women of child-bearing age [13]. It was postulated that this was because higher rates of death among pregnant women were not consistently observed in all countries; however, in further pooled analyses, a higher fraction of total deaths was observed in women of child-bearing age during the 2009 pandemic, similar to during the 1918 and 1957 pandemics [14]. Of note, the discovery that all pregnant women, not just those with pre-existing and chronic respiratory conditions, were at increased risk of morbidity and mortality led to an increase in emphasis on pregnant women as a priority group for influenza vaccination.

Although influenza disease in pregnancy, and its related adverse effects, is the most well studied VPD, others, such as measles and *Haemophilus influenzae* during pregnancy, have also been shown to significantly increase maternal morbidity and mortality [15, 16].

1.2 Effects of VPD on the Fetus and Infant

It has been suggested that the fetus is susceptible to infections during pregnancy because of the immaturity of the fetal immune system and its tendency to mount tolerogenic immune responses [17]. Observations of high rates of stillbirth and preterm delivery among pregnant women during the Spanish Flu epidemic of 1918 were the first documented evidence that influenza disease during pregnancy could have adverse effects on the developing fetus [6]. More recently, multiple studies of pregnant women with laboratory-confirmed influenza infection during the 2009 H1N1 pandemic reported an increased risk of adverse fetal outcomes, including preterm birth, low birth weight, small for gestational age (SGA) infants, and need for caesarean delivery [14], compared with pregnant women with non-influenza acute respiratory infections, pregnant women who were disease free during the pandemic or pregnant prior to the pandemic, and a historical non-pregnant cohort of women [18–20].

Young infants are particularly susceptible to more severe or prolonged infections than adults because of their reduced ability to mount optimal immune responses to many viral, bacterial, and fungal pathogens. The reasons for this are multifactorial, including immaturity of the immune system, propensity to mount tolerogenic responses, lack of existing immunological memory, and a less intact mucosal barrier [17, 21, 22]. Infants aged <6 months have been shown consistently across populations and influenza seasons to have the highest rates of influenza-associated hospitalizations, with rates second only to older adults (aged >65 years). Young infants also have more severe influenza disease, evidenced by the need for intensive care or death, compared with older children [23]. Furthermore, pertussis, a highly contagious endemic–epidemic infectious disease, has repeatedly been shown to primarily affect infants before they are fully immunized. During recent epidemics in Norway, Sweden, and Finland from 2003 to 2007 and in California, USA, in 2010, the highest incidence rates were reported in infants (35.5 [24] and 38.5 [25] per 100,000, respectively). Furthermore, young infants have the highest rates of both hospitalization and death [26, 27] and account for around 90% of all

pertussis-associated deaths [24, 28, 29]. In addition, tetanus remains an important cause of neonatal mortality globally—albeit no longer in resource-rich countries—with a case fatality approaching 100% in the absence of medical treatment [30] and up to 60% with hospital care (depending on the availability of intensive care facilities) [31]. Other potentially VPDs such as group B streptococcus (GBS) and respiratory syncytial virus (RSV) cause significant infant morbidity and mortality and are discussed in Sect. 3.

2 The Maternal Immunization Strategy

As newborns do not efficiently develop protective immunity in response to many vaccines, routine infant immunizations to diseases such as pertussis only commence at the age of ≥6 weeks, and influenza is only licensed for infants aged >6 months [32–34]. Furthermore, for most vaccines given in infancy, two or more doses are required to achieve antibody levels that are considered protective, leaving a critical window of vulnerability for the infant between birth and up to around the age of 4 months. Infants therefore depend on passive maternal antibodies for protection.

Immunization during pregnancy as a strategy for minimizing infectious conditions previously responsible for substantial perinatal morbidity and mortality is not new. Indeed, the infant protection afforded from passively acquired maternal humoral immunity (immunoglobulin G [IgG] antibodies produced from either natural infection or active immunization during pregnancy) has been appreciated for over 100 years and was first noticed in the 1870s as a consequence of maternal smallpox vaccination. A small number of early maternal immunization trials led the way with this strategy, against early infant pertussis [35], influenza [36, 37], and *H. influenzae* type b [38]. However, significant gaps in knowledge of the efficacy and safety of these vaccines impeded progress for many years.

An ongoing major concern cited by parents and providers is the potential for vaccines administered during pregnancy to harm the developing fetus [39]. Theoretically, immunizing a pregnant woman with a live, albeit attenuated, vaccine could expose the developing fetus to a live pathogen that could acquire secondary mutations, leading to a reversion to virulence. Furthermore, in immunocompromised pregnant women, live attenuated vaccines could cause potentially severe complications. Live attenuated vaccines are therefore generally contraindicated in pregnant women. However, inadvertent administration of rubella or varicella to women unknowingly in the first trimester of pregnancy has not been shown to cause congenital rubella or varicella syndrome, respectively [40, 41]. Accordingly, the Centers for Disease Control and Prevention (CDC) and the WHO advise that, if a live viral vaccine such as measles, mumps, and rubella (MMR) or varicella is inadvertently administered to a woman who did not realise she was pregnant, she should be counselled about the theoretical risk to the fetus, although this administration should not be considered a medical indication to terminate the pregnancy [42].

2.1 Current Recommendations for Vaccination During Pregnancy

Influenza and Tdap (tetanus, diphtheria, and pertussis) vaccines are routinely recommended in pregnancy and are discussed in detail in the following sections. Tetanus vaccine is used extensively in pregnancy in some resource-poor areas of the world to combat maternal neonatal tetanus. We review this extraordinary program, which has been a trailblazer for maternal immunization. Additionally, while not well studied, other inactivated and very occasionally live attenuated vaccines are sometimes indicated in special circumstances based on the potential for maternal benefit when the risk of infection/exposure or where the potential for severe/complicated infection is high [43] (Table 1).

2.1.1 Tetanus

For almost three decades, the WHO Maternal and Neonatal Tetanus (MNT) Elimination Initiative has been immunizing pregnant women and other women of reproductive age with tetanus toxoid vaccine and promoting more hygienic deliveries and cord care practices in resource-poor countries [46]. Between 1999 and 2016 alone, the MNT Elimination Initiative protected an estimated 148 million women against tetanus [47, 48], assisted 41 additional countries achieve MNT elimination status (one or fewer case of neonatal tetanus per 1000 live births) [46], and produced substantial declines in neonatal tetanus. Indeed, immunization of pregnant women or women of childbearing age (who have never received a tetanus toxoid vaccine or have no documentation of such immunization) with at least two doses of tetanus toxoid more than 4 weeks apart is estimated to reduce mortality from neonatal tetanus by 94% (95% CI 80–98) [30]. Evaluation of this extensive MNT experience has revealed no increased risk of congenital anomalies to the developing fetus [49, 50]. However, the WHO estimates that, in 2013 (the latest year for which estimates are available), 49,000 newborns still succumbed to neonatal tetanus, which continues to persist in 18 countries, indicating continued efforts are needed [46]. At only 60 cents per dose, including full operational costs, it is hoped global elimination from this important and preventable cause of neonatal mortality (aided largely by maternal immunization) will soon be realized [30].

Table 1 Current recommendations for immunizations during pregnancy Adapted from [43–45]

	Vaccine	Recommendation	Notes
Routinely recommended for all pregnant women			
Inactivated	IIV	Recommended. One dose each pregnancy, as early as possible during influenza season	Clinical outcomes and safety data below. May be given with acellular pertussis-containing vaccine. Note: LAIV is contraindicated in pregnancy.
	Acellular pertussis-containing vaccine (Tdap)	Recommended. One dose each pregnancy, optimally at 20–32 weeks' gestation	Clinical outcomes and safety data below. May be given during pregnancy from 16 weeks' gestation. May be given with IIV
Not routinely recommended in pregnancy			
Inactivated bacterial	Td	Routinely recommended during pregnancy in some countries for MNT elimination	May be given for management of tetanus-prone wounds or risk of MNT. Extensive use has not revealed any increase risk to fetus
	Cholera (oral)	Not routinely recommended	Limited data
	Hib	Not routinely recommended	Limited data. May be considered for women at high risk of invasive Hib disease (e.g., asplenia)
	Meningococcal conjugate	Not routinely recommended	Limited data. May be considered for women at high risk of invasive meningococcal disease
	Meningococcal polysaccharide	Not routinely recommended	Limited data. May be given to women at high risk of invasive meningococcal disease
	Meningococcal B	Not routinely recommended	No data. May be considered for women at high risk of invasive meningococcal disease
	13-Valent pneumococcal conjugate	Not routinely recommended	No data. May be considered for women at high risk of invasive pneumococcal disease (e.g., asplenia)
	23-Valent pneumococcal polysaccharide	Not routinely recommended	Limited data. May be given to women at high risk of invasive pneumococcal disease (e.g., asplenia)
	Typhoid Vi	Not routinely recommended	May be given to women at high risk of exposure (e.g., travel to endemic regions)
Inactivated viral	HepA	Not routinely recommended	Limited data. May be used for post-exposure prophylaxis
	HepB	Not routinely recommended	Limited data. May be used for post-exposure prophylaxis
	JE (JEspect)	Not routinely recommended	May be given to women at high risk of exposure (e.g., travel to endemic regions)
	Polio	Not routinely recommended	May be given to women at high risk of exposure (e.g., travel to endemic regions)
	Rabies	Not routinely recommended	Limited data. May be used for post-exposure prophylaxis
	HPV	Not routinely recommended	Insufficient data. Although clinical trial and limited observational data to date indicate no increased risk to fetus, completion of routine course should be deferred until after pregnancy
Live attenuated viral	Yellow fever	Not routinely recommended	Pregnant women should avoid travel to yellow fever-endemic areas; if unavoidable, live attenuated Yellow fever vaccination can be given. Yellow fever vaccine has been given to a large number of pregnant women and no adverse outcomes have been reported
Contraindicated in pregnancy			
Live attenuated bacterial	BCG	Contraindicated	Avoid. Hypothetical risk to fetus
	Oral typhoid	Contraindicated	Avoid. Hypothetical risk to fetus

Table 1 continued

	Vaccine	Recommendation	Notes
Live attenuated viral	JE (Imojev)	Contraindicated	Avoid. If JE vaccine is needed for travel to endemic region, use inactivated JE vaccine (JEspect): see above
	MMR	Contraindicated	Avoid. Hypothetical risk to fetus. Avoid pregnancy for 28 days post-vaccine. If inadvertently given, see above. Pregnant women non-immune to rubella should be vaccinated as soon as possible after delivery
	Rotavirus	Contraindicated	Not registered or recommended for adolescents or adults
	Varicella	Contraindicated	Avoid. Hypothetical risk to fetus. Avoid pregnancy for 28 days post-vaccine. If inadvertently given, see above. Pregnant women non-immune to varicella should be vaccinated as soon as possible after delivery
	Zoster	Contraindicated	Avoid. Hypothetical risk to fetus. Not registered for individuals aged <50 years

Tdap tetanus, diphtheria, and pertussis, *BCG* Bacillus Calmette–Guérin, *HPV* human papillomavirus, *IIV* inactivated influenza vaccine, *JE* japanese encephalitis, *LAIV* live attenuated influenza vaccine, *MMR* measles, mumps, rubella, *MNT* maternal and neonatal tetanus

2.1.2 *Influenza*

Influenza vaccine was first recommended for pregnant women in 1960 [51] and has been widely studied with no demonstrated safety concerns. The current guidelines from the Advisory Committee on Immunization Practices (ACIP) and the WHO recommend inactivated influenza vaccine (IIV) for all women in each pregnancy at the preconception visit or as early in pregnancy as possible during the influenza season. Maternal benefits of this strategy are well documented, with a large randomized controlled trial (RCT) in Bangladesh reporting an influenza vaccine effectiveness of 36% against febrile respiratory illness [52] and one in South Africa reporting an efficacy of 50 and 58% for preventing laboratory-confirmed influenza in HIV-uninfected and HIV-infected pregnant women, respectively [11]. Similar results have been reported in a US case–control study over two inter-pandemic seasons, with a maternal vaccine effectiveness of 44% against laboratory-confirmed influenza A and B [53]. Most recently, in 2016, a large RCT in Mali showed an impressive vaccine efficacy of 77% (95% CI 28–94) in pregnant women; importantly, this trial proved the acceptability and feasibility of administering influenza vaccine in resource-poor settings [54].

Obstetric and perinatal outcomes that have been specifically evaluated to assess the risks of influenza vaccine in pregnancy include spontaneous abortion, stillbirth, fetal death, preterm birth, low birth weight, SGA, and congenital anomalies. Recently, a plethora of epidemiologic studies and a few clinical trials have evaluated these perinatal outcomes. These studies have been comprehensively reviewed, with no evidence found for increased risk of fetal death, spontaneous abortion, or congenital malformations [55–57]. Moreover, a meta-analysis of studies of stillbirth and spontaneous abortion revealed protective effects of influenza vaccination in pregnancy, with a lower likelihood of stillbirth (RR 0.73; 95% CI 0.55–0.96) but no significant protective effect on spontaneous abortion (<20 weeks gestation) [58]. As vaccination would not be expected to affect outcomes early in pregnancy, before immunization, this result is not unexpected. Two outcomes repeatedly found to reduce following maternal influenza vaccination are pre-term birth and low birth weight [59–62]. A recent meta-analysis of these outcomes found maternal influenza vaccination was associated with a decreased risk of preterm birth (odds ratio [OR] 0.87; 95% CI 0.77–0.98) and low birth weight (OR 0.74; 95% CI 0.61–0.88) [63]. Finally, although a reduction in SGA infants has been associated with maternal influenza vaccination in a few studies [61, 64], results have been mixed, and a recent meta-analysis [63] found no statistically significant impact on this outcome.

Earlier studies assessing the effect of maternally derived antibodies to provide passive protection to infants against influenza yielded mixed results, for example, no protective effect was found on hospital admission or outpatient visits for influenza-like illness (ILI) [65] or medically attended acute respiratory infection [66]; however, evidence supporting strong protective effects to the infant of maternal influenza vaccination using more specific outcomes continues to emerge. In 2008, an RCT in Bangladesh found a vaccine effectiveness of 63% against laboratory-confirmed influenza and 29% against febrile respiratory illness in infants aged ≤6 months born to mothers who received a third-trimester influenza vaccine [52]. In 2014, an RCT in HIV-negative pregnant women and their infants in South Africa demonstrated an influenza vaccine efficacy in infants of 49% against laboratory-confirmed influenza [11]. In 2015, an RCT in Nepal reduced laboratory-confirmed

influenza in infants aged ≤6 months by 30% [67], and, in 2016, an RCT of more than 4190 women in Mali reported a vaccine efficacy of 33% [54]. Notably, cumulative vaccine efficacy decreased from 68% at 3 months to 57% at 4 months and was no longer evident by the age of 6 months [54], resembling kinetics from the South African trial showing that, by the age of 6 months, infants no longer have protective titers of maternally derived antibodies [68]. A number of population-based studies reviewing large datasets have also demonstrated that maternal influenza vaccination provides significant protective effects against infant influenza hospitalization and laboratory-confirmed influenza [69–72]. Of note, a recent large cohort of more than 245,000 women and their infants in the USA confirmed protective effects of maternal vaccination, with a risk reduction of 64% for ILI, 70% for laboratory-confirmed influenza, and 81% for influenza hospitalization of infants in the first 6 months of life [73]. In the near future, pooled data from large RCTs in Nepal, Mali, and South Africa supported by the Bill and Melinda Gates Foundation will provide further data on the impact of maternal influenza vaccination on the incidence of complicated or severe influenza disease in infants [74]. Over the next decade, it is likely the full potential impact of maternal influenza immunization on these and other outcomes (such as acute otitis media or febrile illnesses, antibiotic use) in the infants' first 6 months of life will emerge.

2.1.3 Pertussis

A sustained increase in pertussis disease documented in the USA, UK, Australia, and other countries from 2008 to 2012 indicated that innovative strategies to protect young infants and minimize this peak burden of morbidity and mortality in early life were urgently needed. Cocooning, neonatal immunization, and maternal immunization were considered as potential control strategies. Cocooning, a strategy of indirect protection that works via herd immunity from vaccination of groups likely to be the disease transmitters, was implemented as an emergency measure in many countries. In fact, it had been previously recommended, though not publically funded, in several countries, including Australia and France. However, despite vaccination of postpartum women and close contacts, with a pertussis booster being recommended, issues of incomplete coverage [75–77] and only moderate effectiveness [78] and cost effectiveness of the programs [79] limited the utility of this approach to preventing infant disease. Some clinical trials in which the pertussis vaccine was administered as soon as possible after birth, a direct protection strategy, have also shown promise [80, 81]; however, one study was not so reassuring [33]. Furthermore, even with administration at birth, this strategy leaves a window of vulnerability in infancy until sufficient immune response is achieved, and the clinical significance of immune hyporesponsiveness to birth dose antigens and immune interference to concomitant antigens in the infant vaccine schedule remains uncertain [33, 82, 83].

Given the shortcomings of cocooning and birth immunization, maternal immunization became the most attractive option to try to deal with the resurgence of pertussis in young infants seen in some countries. In 2011, the US CDC's ACIP amended their neonatal pertussis-prevention strategy from a cocooning approach to one of maternal immunization with Tdap for all previously Tdap unimmunized pregnant women [84]. However, the recommendation was modified because of evidence of a rapid decline in pertussis antibody levels in adults and postpartum women immunized with Tdap, together with the knowledge that newborns are unlikely to have protective levels of pertussis antibodies at birth if their mothers have not received a recent vaccine [85, 86]. In October 2012, ACIP recommended that all pregnant women be vaccinated with one dose of Tdap during each pregnancy between 27 and 36 weeks' gestation, regardless of the interval since prior Td or Tdap immunization [87]. This strategy was quickly adopted by the American College of Obstetrics and Gynecologists and the American Academy of Pediatrics and remains the current US recommendation. Also in October 2012, after a rapid spike in pertussis disease and infant deaths, the UK Department of Health introduced a temporary emergency program to offer a five-component tetanus, diphtheria, acellular pertussis, and polio (Tdap-IPV) vaccine to all women between 28 and 32 weeks of pregnancy [88]. Other countries have also introduced various maternal pertussis immunization recommendations to combat national pertussis resurgences, including Australia, New Zealand, Argentina, Belgium, and Spain [44, 89, 90].

Of note, although inactivated vaccines are considered safe in pregnancy, these maternal pertussis vaccine recommendations were introduced without any direct evidence of effectiveness or safety. However, post-implementation studies soon emerged from the UK program, confirming that pertussis vaccine is highly effective in the prevention of newborn pertussis [91, 92]. Vaccine effectiveness in the first year of the UK program (over 26,000 live births, with 64% vaccine coverage) was estimated to be >90% for infants aged <2 months whose mothers received Tdap-IPV at least 1 week prior to delivery [91]. The safety of maternal pertussis immunization has been supported by two large observational cohort safety studies also published in 2014 [93, 94]. In the UK cohort, including almost 18,000 pregnant women, there was no evidence of an increased risk in any adverse events related to maternal, fetal, or neonatal outcomes, including

stillbirth, maternal or neonatal death, pre-eclampsia, caesarian delivery, or low birth weight [94]. Safety was further supported by the US cohort, which included over 120,000 women with livebirths. Maternal pertussis vaccination was not associated with adverse pregnancy outcomes. In particular, vaccination was not associated with an increased risk of preterm birth, SGA, or hypertensive disorders of pregnancy (a small but statistically significant increased risk of chorioamnionitis was observed; however, the magnitude of this risk was small [RR 1.19] and not associated with an increased risk of preterm birth) [93]. The first RCT of Tdap administered to 33 pregnant women in the third trimester of pregnancy was also reported in 2014 [95]. It found no increase in adverse events in women or their infants, significantly higher concentrations of pertussis antibodies at delivery and at age 2 months, and no substantive differences to infant responses to Tdap following the fourth dose. Recently, vaccine effectiveness data have been published for 3 years of the UK program; they show sustained levels of protection (>90%) against laboratory-confirmed pertussis and >95% vaccine effectiveness against infant deaths (95% CI 79–100) [96]. Vaccine effectiveness did not differ significantly by vaccine product (dT5aP-IPV and dT3aP-IPV) and, importantly, despite a number of studies demonstrating variable blunting of pertussis responses and other antigens in the routine program in infants born to vaccinated mothers [90, 95, 97, 98], there was no evidence of increased risk of disease after routine primary vaccination in infants of mothers who received maternal immunization (although this warrants ongoing monitoring) [96]. Safety analysis of acute maternal adverse events following Tdap vaccination during pregnancy in a cohort of over 438,000 livebirths has again provided reassuring results: vaccine coverage of 14% revealed no increased risk of medically attended adverse events within 3 days of vaccination or incident events within 42 days of vaccination [99]. Furthermore, a prospective cohort study in New Zealand of 403 infants whose mothers had received Tdap vaccine during pregnancy found no significant differences in birth weight, gestational age at birth, congenital anomalies, or infant growth [100]. In the near future, the results of a large phase IV RCT of Tdap vaccine in over 600 pregnant women (cross-over design, Tdap to women post-natally) will contribute further evidence of the safety and immunogenicity of these strategies (ClinicalTrials.gov identifier: NCT02377349).

In April 2016, the UK Joint Committee on Vaccination and Immunisation (JCVI) changed the recommended timing of the vaccine to 20–32 weeks' gestation (although it may be given from 16 weeks) in light of new evidence that pertussis antibodies (anti-pertussis toxin [PT] and anti-filamentous hemagglutinin [FHA]) were significantly higher in cord blood following immunization in the second versus the third trimester (PT: 57.1 vs. 31.1 EU/ml and FHA: 284.4 vs. 140.2 EU/ml) [101]. A large retrospective cohort study has also recently shown that concomitant administration of Tdap and influenza vaccines during pregnancy is safe, with no increased risk of adverse acute maternal events or birth outcomes compared with sequential vaccination [102]. It is hoped that widening the window of opportunity for vaccination and allowing for concomitant administration of pertussis and influenza vaccines will improve coverage (Table 2).

3 Future Research Directions for Maternal Immunization

A number of novel vaccines are aimed at reducing infant infection through maternal immunization in various stages of development. Two examples, GBS and RSV are discussed in the following sections. In addition, there is potential for maternal immunization (if vaccines are successfully developed) to be used in the prevention of disease caused by other infectious agents that cause significant morbidity and mortality in the fetus (e.g., cytomegalovirus, herpes simplex virus, and zika virus) and young infant (e.g., enteric bacteria and malaria).

3.1 Group B Streptococcus

GBS is a leading cause of sepsis and meningitis in the early infant period. Intrapartum antibiotic strategies have reduced the incidence of early-onset neonatal disease (EOD), occurring before the age of 7 days, but have had no impact on late-onset GBS disease (LOD), occurring between the age of 7 and 90 days [103]. Several studies have shown evidence of transplacental transfer of maternal GBS antibodies, with a correlation between an infant's level of passively acquired antibodies directed against GBS and reduced risk of infant GBS-related infection [104]. Passive immunity afforded to the infant via maternal GBS immunization could offer a better and more cost-effective solution to reliably prevent EOD and LOD and potentially also prevent a proportion of preterm births. Vaccine research and development for GBS vaccines has recently been reviewed [105]. The National Institutes of Health (NIH) and Novartis/GlaxoSmithKline (GSK) have various GBS polysaccharide–protein conjugate vaccines in phase I and II clinical trials, while another manufacturer (MinerVax) has commenced a phase I clinical trial of a novel protein-based GBS vaccine [105]. One of the most promising candidates is the Novartis/GSK CRM197-conjugated trivalent GBS vaccine. A phase Ib trial of two dosages (5 and 20 μg), two schedules, and three

Table 2 Summary of evidence of key fetal/infant outcomes and safety of routinely recommended vaccines in pregnancy

Vaccine during pregnancy	Fetal/infant outcomes	Safety data
IIV	27% lower risk of stillbirth [58]	No increased risk of maternal, fetal, or infant adverse events [55–57]
	13% lower risk of preterm birth [63]	
	26% lower risk of low birth weight [63]	
	30–70% effective against laboratory-confirmed influenza in infants [52, 54, 67, 73]	
	64% reduction of influenza-like illness in infants [73]	
	81% reduction in laboratory-confirmed influenza hospitalizations (infants 0–6 months) [73]	
Tdap	>90% effective against laboratory-confirmed pertussis in infants [91, 92, 96]	No increased risk of maternal, fetal or infant adverse events [93, 94, 100]
	>95% effective in preventing infant death from pertussis [96]	
	No increased risk of pertussis disease after routine infant vaccinations [92, 96]	

Tdap tetanus, diphtheria, and pertussis, *IIV* inactivated influenza vaccine

formulations with various adjuvants of this candidate in healthy non-pregnant women showed no additional potential benefit from higher antigen content, addition of an adjuvant, or a second dose [106]. A phase Ib/II RCT of the same candidate vaccine in 60 non-pregnant, and a dose-ranging study (0.5, 2.5, or 5 μg) in 320 pregnant, Black women in South Africa found it was well tolerated, induced capsular-specific antibody responses, and produced a statistically significant increase in GBS antibody concentrations in infants born to mothers vaccinated between 28 and 35 weeks' gestation [107]. The 5-μg dose of this candidate vaccine was the most immunogenic, with tolerability similar to that of lower doses, and was chosen to proceed to the phase II RCT conducted in Belgium and Canada involving 86 pregnant women. Results of this trial found no maternal or infant safety signals or interference with antibody responses to the routine infant vaccines. Furthermore, antibody concentrations were higher in women who had detectable antibody levels at baseline and persisted in infants until at least 90 days of age [108].

3.2 Respiratory Syncytial Virus

RSV is the most important cause of viral acute lower respiratory illness (ALRI) in infants and children globally. It presents as bronchiolitis and pneumonia and is responsible for high infant morbidity and mortality worldwide. Primary RSV infection occurs in most infants within the first 2 years of life and can recur throughout life; however, as natural immunity increases, the disease becomes less severe. As for other maternal immunization targets, higher concentrations of maternal RSV-specific antibodies correlate with a reduced incidence of early infant RSV disease [109]. RSV vaccine development has a notable history: in the 1960s, seronegative infants received a formalin-inactivated RSV (RSV-FI) vaccine that caused a vaccine-enhanced illness upon subsequent RSV infection due to natural exposure and resulted in an 80% hospitalization rate and two deaths [110]. This experience created a period of hesitancy while vaccine developers sought a balance between safety and immunogenicity; however, RSV development has had a resurgence in recent years. Currently, 60 RSV candidates are in development, 16 of which are advancing through phase I to phase III clinical trials, using multiple vaccine platforms [111]. The success and efficacy of passive immunization with palivizumab and motavizumab, which bind to antigenic site II on the RSV F protein has led many vaccine developers to focus on this as the primary immunogen. The most advanced vaccine candidate, an RSV-F nanoparticle vaccine developed by Novavax is in phase III clinical trials in the elderly and in pregnant women, the latter targeting over 8000 mother–infant pairs globally. Additionally, GSK's RSV-F protein subunit vaccine is in a phase II maternal immunization trial, and MedImmune's RSV-F protein subunit vaccine candidate is in a phase II trial in the elderly [111]. Data are also emerging that, similar to influenza, RSV infection during pregnancy may cause serious maternal complications [112], so the potential benefits of maternal RSV vaccination could be broader than currently appreciated.

3.3 Other Considerations for Optimizing Maternal Immunization

As research continues to add knowledge to the safety and efficacy of recommended vaccines against influenza and

pertussis and novel vaccines in development, research into the most effective strategies to optimize uptake is needed so that the full potential of maternal immunization may be realized. Even in the UK, with a fully resourced maternal immunization platform for influenza and pertussis, uptake for pertussis in only around 60% [96], and sentinel coverage data in Australia estimate uptake to be at 72% (Dr. Helen Quinn, December 2016, personal communication). However, in some states in the USA and in developing countries, coverage rates are far lower [113]. Further research into the determinants of vaccine acceptance [114] and effective evidence-based interventions to improve coverage are urgently needed [115, 116]. Overcoming vaccine hesitancy will likely require a multifaceted approach, with education and interventions aimed not only at pregnant women and their families but also at healthcare workers and government officials [117].

In addition, opportunities for further advancement of a maternal immunization program [118] include the following.

1. Investment in the epidemiology of target pathogens and the true burden of disease in the mother and infant (including the numbers and cases of neonatal deaths), in both resource-poor and resource-rich countries, to enable better estimation of cost effectiveness of maternal immunization [117].
2. Further understanding of the mechanism of breastmilk antibody production and effect on the infant following maternal immunization.
3. Investment in implementation research to understand how the maternal immunization program can be integrated into existing healthcare programs.
4. Ongoing standardization of research methods on vaccines administered in pregnancy and definitions of adverse events following immunization in pregnancy to further strengthen monitoring and analysis of rare outcomes [119].

Recently, great leaps have been made to this end with the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project, coordinated by the Brighton Collaboration Foundation. GAIA was formed in response to a call from the WHO for a globally concerted approach to harmonize safety data collection and serve as a platform for strengthening programs of immunization in pregnancy, particularly in low- and middle-income countries. Guidance documents for the standardized conduct of clinical trials in pregnant women have already been developed [120, 121], and the first ten globally standardized case definitions of key obstetric and neonatal terms have been published [122].

4 Conclusion

Maternal immunization has undergone a paradigm shift in recent years, with mothers accepting not only influenza vaccine to prevent serious disease during pregnancy but also pertussis vaccine, primarily to protect their infant. The importance of maternal immunization as a potential threefold strategy to protect the mother, developing fetus, and young infant from the effects of VPD cannot be understated. However, despite modest gains in recent years, maternal immunization remains an underutilized strategy. It is time to close the susceptibility gap.

Compliance with Ethical Standards

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