Review
The Evolving Maternal Vaccine Platform

Rebecca M. Adams and Bernard Gonik *

Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI 48201, USA; rebecca.adams3@med.wayne.edu
* Correspondence: bgonik@wayne.edu

Abstract: Maternal vaccination is a safe and effective means of preventing infection in pregnant women, their fetuses, and infants after birth. Several vaccines are routinely administered in pregnancy as a valuable part of prenatal care with supporting recommendations from national and international health organizations. Fears concerning vaccine safety in pregnancy are pervasive despite sufficient available safety data to support their use, leading to underutilization of maternal immunization. Despite this hesitancy, the field of maternal vaccination is evolving to include more vaccines in the routine prenatal vaccination schedule, including the new RSV vaccine. This review discusses the currently recommended vaccines in pregnancy, evidence for their use, and an overview of ongoing clinical trials investigating prospective vaccines for pregnant women.

Keywords: maternal vaccination; immunogenicity; prenatal care; pregnancy; influenza vaccine; Tdap vaccine; COVID-19 vaccine; RSV vaccine

1. Introduction

Vaccination is an essential component of prenatal care. Pregnancy and early infancy are periods of relative immunosuppression and heightened vulnerability to infection, with resultant high morbidity and mortality [1]. Immunosuppression in pregnant women is due in part to the pregnancy-induced shift from cell-mediated immunity, a Th1 mediated response, to humoral immunity, a Th2 mediated response [2]. This is a physiologic adaptation to protect the semi-allogenic fetus against immunologic rejection. However, it renders pregnant women more susceptible to infection [2]. Physiologic cardio-respiratory adaptations further increase a pregnant woman’s predilection for infection by respiratory viruses, putting this population at a higher risk of morbidity and mortality from pneumonia [2]. Vaccination against these types of pathogens during pregnancy is imperative to preserve a woman’s health during this physiologically demanding period of life.

Immunization during pregnancy facilitates the passive transfer of neutralizing immunoglobulin G (IgG) antibodies across the placenta, providing both fetal and neonatal protection against infection in addition to boosting maternal immunity. Secretory immunoglobulin A (IgA) antibodies can additionally be transferred through the mother’s breast milk [3]. This immune support is essential for neonates who have a higher rate of invasive disease than any other period of life, specifically 100 per 100,000 infants [4]. This is primarily due to their inability to mount an effective immune response through production of neutralizing antibodies during the first few weeks after birth [5].

Except for the hepatitis B vaccine, many immunizations are not routinely administered until at least six weeks of age and typically require more than two doses to achieve sufficient immunity. Neonates are therefore extremely vulnerable to infectious pathogens before they can acquire their own vaccinations. Maternal vaccination can provide appropriate immune coverage during this period so that infants have a consistent level of protection after birth [1].

Maternally derived neonatal immunity was first observed for measles during an 1846 outbreak on the Faroe Islands. Infants born to mothers who survived the disease did
not develop symptoms, prompting curiosity about neonatal benefits of infection during pregnancy [1]. In 1879, maternal vaccination with vaccinia demonstrated protection against smallpox in infants during early life, and decades later in 1938 the whole cell pertussis vaccine was first administered during pregnancy [1]. In 1961, the first known vaccine trial including pregnant women was performed in Papua New Guinea. Two or more doses of tetanus toxoid vaccine administered prenatally protected infants from neonatal tetanus [6].

The 1960s also introduced inactivated influenza vaccination in pregnancy. At the time, influenza was known to result in more severe health consequences for both mother and fetus, and therefore United States public health authorities recommended prioritization of maternal influenza vaccination in 1960 [7]. However, the Centers for Disease Control and Prevention (CDC) in the US did not endorse this recommendation until 1997 [8]. Australia and the United Kingdom (UK) included influenza in the recommended vaccine schedule for pregnant women after the H1N1 pandemic in 2009 [9,10].

In the 1970s and 1980s, additional advances in acellular vaccination led to the production of the DTaP vaccine against diphtheria, tetanus, and pertussis that is still routinely administered today. Removing the exotoxin from preparation limited its reactogenicity, improving the safety profile compared to the whole cell preparation (DTwP) [11–13]. In 2012, the Advisory Committee on Immunization Practices (ACIP) recommended universal tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (Tdap) vaccination during pregnancy between 27 and 36 weeks of gestation, regardless of prior vaccine status, to confer passive immunity to infants [14].

Two vaccinations have been approved and recommended for administration in pregnancy during the past few years. The rise of COVID-19 in 2020 initiated prompt development of multiple vaccines, which were determined to be safe for use in pregnancy to protect both mothers and infants in April 2021 [15]. Most recently in August 2023, the U.S. Food and Drug Administration (FDA) authorized the first vaccine against respiratory syncytial virus (RSV) for pregnant individuals who are 32–36 weeks pregnant to prevent lower respiratory tract illness in infants from birth through six months of age [16].

This review will discuss the current recommendations for vaccination in pregnancy and evidence for each vaccine’s use, including the new RSV vaccine. We will additionally cover vaccinations that are approved during pregnancy under special circumstances and the current scope of trials developing prospective maternal vaccines. The presented research was compiled through PubMed searches of only randomized controlled trials, reviews, and systematic reviews using the search phrase “maternal vaccination” along with the terms “immunogenicity”, “prenatal”, “Tdap”, “COVID-19”, “influenza”, “RSV”, “GBS”, “CMV”, and “malaria”. No specified time period or language restrictions were implemented for the searches. We additionally consulted the CDC website and searched for current vaccine guidelines for pregnant women by using the phrase “guidelines for vaccines in pregnancy” in their search bar.

2. Vaccine Safety in Pregnancy

Until 1993, the FDA excluded pregnant women from trials involving drugs or vaccines. Safety concerns accompanying vaccination in pregnancy included local or systemic reactions leading to preterm birth, fetal loss, congenital abnormalities, or alteration of responses to neonatal vaccination [1]. The thalidomide tragedy in the late 1950s and early 1960s prompted the expansion of this exclusion category to include all “women of childbearing potential”, not just pregnant women [17]. The FDA reversed this policy in 1993 stating that prohibiting this group from participating in clinical trials had severely limited scientific data on the risks and benefits of drugs for young women. Since the 1993 revision of this guideline, the FDA Office of Women’s Health has actively encouraged female participation in clinical trials [17]. However, the FDA still approaches inclusion of pregnant women in clinical research with caution, and pregnant and lactating women remain underrepresented in vaccine trials [17].
Vaccine safety in pregnancy has been studied since the initiation of maternal vaccination with vaccinia in 1879. Vaccines that are deemed safe to administer in pregnant women include inactivated vaccines, toxoid vaccines, protein subunit vaccines, and conjugate vaccines consisting of protein–toxoid, peptide–protein, and protein–protein conjugates [18]. Presently, there is no evidence of adverse fetal outcomes from vaccination with inactivated virus, bacterial, or toxoid vaccines during pregnancy, and growing data continue to support their safe use [19,20]. However, pregnant women continue to be excluded from clinical trials of live virus vaccines due to the possible risk of viral transmission to the fetus. As a result, live vaccines are contraindicated during pregnancy. It is also routinely recommended to prevent pregnancy in the immediate period after vaccination with live vaccines to minimize the potential for fetal exposure [21,22].

Currently, vaccines go through Phase 1 and Phase 2 studies in reproductive-age non-pregnant women before they are approved for Phase 1 assessment in pregnant individuals [18]. In cases such as disease outbreak or pandemics, this strict process may substantially delay production of adequate data supporting the safe vaccination of pregnant and lactating women [18].

With the emergence of the COVID-19 pandemic, development of SARS-CoV-2 messenger RNA (mRNA) vaccines began without involving pregnant and lactating women in clinical trials [23]. Initial vaccine safety data on pregnant women who elected to receive the COVID-19 vaccine or were inadvertently immunized were collected to determine infection rate, maternal antibody response, antibody transfer, local adverse events, and systemic adverse events [24]. These early data suggested that the Pfizer-BioNTech (Shibuya City, Tokyo) and Moderna mRNA vaccines can prevent SARS-CoV-2 infection in this population without evident harm to the fetus [25]. The SARS-CoV-2 mRNA vaccines are therefore encouraged for pregnant women, but long-term effects on pregnancy have yet to be determined [25].

A similar situation occurred with the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) after the 2014 Ebola outbreak in West Africa. The study accelerated introduction of a monovalent recombinant vesicular stomatitis virus Ebola vaccine (rVSVΔG-ZEBOV-GP) with exclusion of pregnant participants [26]. However, 84 women inadvertently received a vaccine in early pregnancy or became pregnant less than 60 days after immunization. Their pregnancy outcomes were assessed, but no definitive conclusions could be made on risk of pregnancy loss or congenital anomalies due to the very small sample size [26]. The World Health Organization’s Strategic Advisory Group of Experts on Immunization endorsed meticulous evaluation of the risks and benefits of rVSVΔG-ZEBOV-GP vaccination in pregnancy during local Ebola outbreaks [27]. There is a high risk of maternal and fetal death from Ebola virus infection, and therefore the choice to administer the rVSVΔG-ZEBOV-GP vaccine in pregnancy will need to balance this risk with the potential for vaccine-induced adverse fetal outcomes [27].

The absence of pregnant women in early clinical trials and the subsequent concern over vaccine safety in pregnancy during significant disease outbreaks emphasizes the need for earlier inclusion of this population in vaccine trials. Remedies to this issue may include incorporation of pregnancy-safe vaccine platforms and implementing developmental toxicology studies early in vaccine production [28].

3. Current Vaccine Recommendations in Pregnancy

The following vaccines are currently recommended in pregnancy on a routine basis by US and international health organizations. Table 1 summarizes these vaccines, their vaccine platform, and their coverage among pregnant women both in the US and globally.
Table 1. Summary of recommended vaccines in pregnancy and estimated percentage of pregnant women covered.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccine Platform</th>
<th>US Coverage</th>
<th>Global Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Inactivated virus</td>
<td>47.2%</td>
<td>1.7–95%</td>
</tr>
<tr>
<td>Tdap</td>
<td>Toxoid + acellular</td>
<td>55.4%</td>
<td>TT2+/Td2+ * 72%</td>
</tr>
<tr>
<td>COVID-19</td>
<td>mRNA, inactivated whole virus, protein subunit, viral vector</td>
<td>27.3%</td>
<td>27.5%</td>
</tr>
<tr>
<td>RSV</td>
<td>Protein subunit</td>
<td>17.8%</td>
<td>Data unavailable</td>
</tr>
</tbody>
</table>

* Either two doses of tetanus toxoid (TT2+) or two doses of tetanus–diphtheria toxoid (Td2+). Tdap, Tetanus, diphtheria, acellular pertussis; COVID-19, Coronavirus disease of 2019; RSV, Respiratory syncytial virus. Data obtained from the Centers for Disease Control and Prevention (CDC) guidelines for vaccinating pregnant women [29], April 2023 Morbidity and Mortality Weekly Report [30], the Weekly RSV Vaccination Dashboard [31], Galiza et al., 2024 [32], Buchy et al., 2020 [33], Njuguna et al., 2020 [34], and Galanis et al., 2022 [35].

3.1. Influenza

Since the 2009–2010 influenza season, the CDC has recommended a single influenza vaccine dose during the first, second, or third trimester of pregnancy [29]. If feasible, pregnant women are encouraged to get vaccinated in anticipation of the influenza season. The World Health Organization (WHO) emphasizes prioritizing influenza vaccination in pregnant women, also recommending one dose at any time of year [36]. The inactivated vaccine contains either three (trivalent) or four (quadrivalent) strains of the influenza virus. The intranasally administered live attenuated vaccine is withheld during pregnancy due to the possibility of transmitting the live influenza virus to the growing fetus [18].

Studies have consistently demonstrated that pregnant women are at a higher risk of morbidity and mortality from influenza illness in comparison to their non-pregnant counterparts [37–39]. The 2009 H1N1 pandemic was a noteworthy example of influenza’s ability to cause severe disease during pregnancy. The likelihood of hospitalization and death from H1N1 infection was greater in pregnant women than those who were not pregnant [40]. Severe influenza infection in these women can also have detrimental consequences on their fetuses. A recent prospective cohort study discovered that influenza infection during pregnancy was associated with a greater likelihood of adverse pregnancy outcomes, including late pregnancy loss and lower infant birthweight, compared to uninfected women [37].

The inactivated influenza vaccine is successful in reducing hospitalizations in pregnancy due to severe disease by approximately 40% [41]. Not only are pregnant women protected by this vaccine, but their infants also experience substantial benefit. Newborns receive transplacental influenza antibodies from their mothers and are protected from influenza until they receive their own inactivated influenza vaccination at six months of age. Infants may also be additionally protected by secretory IgA antibodies against influenza in the mother’s breast milk [42]. A meta-analysis demonstrated that maternal influenza vaccination was correlated with a 34% reduction in influenza incidence in infants [43]. Influenza vaccination in pregnancy is also correlated with a decreased risk of preterm birth and low-birth-weight neonates [44].

Optimal timing of influenza vaccination in pregnancy has been up for debate. A systematic review and meta-analysis identified no difference in the rate of seroconversion among women who received the injection during varying trimesters of pregnancy [45]. Despite this finding, the mean titer of anti-influenza neutralizing antibodies present in the cord blood was found to be 1.44 (95% CI, 0.95–2.44) times higher among third-trimester-vaccinated women compared to women immunized during the first trimester [45]. Overall, evidence suggests that the threat of fetal demise and other poor birth outcomes is higher for women with influenza infection during the first trimester compared to later trimesters [46]. This supports prompt inactivated influenza vaccination in pregnant women.
3.2. Tdap

The current recommendation from the CDC is to administer one dose of the Tdap vaccine between 27 and 36 weeks of gestation [29]. The WHO recommends one dose of Tdap in the second or third trimester, optimally 15 or more days before the pregnancy ends [47]. Tdap may be given at any point during pregnancy, especially if an earlier indication is present such as possible tetanus infection or a pertussis outbreak. Interestingly, the guidelines for Tdap vaccination in the UK advise administration between 16 and 32 weeks of pregnancy. A recent study conducted in 2023 reported comparable concentrations of IgG antibodies in newborns of Tdap-vaccinated mothers at three different time intervals during pregnancy (≤23 weeks + 6 days, 24–27 weeks + 6 days, and 28–31 weeks + 6 days) [48]. This study supports a broader interval of Tdap vaccination.

A systematic review of 1.4 million pregnant women vaccinated with Tdap was conducted in 2020 to assess vaccine safety. The vaccinated women had no increased risk of preterm birth or other adverse birth outcomes [49]. One notable finding was that those who were vaccinated had a slightly greater incidence of chorioamnionitis compared to the unvaccinated pregnant women. However, no studies in this systematic review reported an increased risk of clinical consequences of chorioamnionitis after Tdap vaccination, including preterm birth and admission to the neonatal intensive care unit (NICU) [49].

A retrospective review performed in Ontario, Canada in 2021 analyzed birth data over five years and did not find any association between Tdap vaccination and chorioamnionitis or other poor birth outcomes [50].

Maternal and neonatal tetanus are rarely observed in wealthy countries, but significant mortality from this disease persists in several poorer nations [51]. To combat tetanus disease in these areas, the WHO created the 1999 Maternal and Neonatal Tetanus Elimination Program. This project aimed to augment vaccine coverage in mothers and neonates and improve delivery hygiene [52]. The ultimate goal of the initiative was to reduce the risk of tetanus infection in these populations. The WHO’s initiative has been incredibly successful, eradicating maternal and neonatal tetanus in approximately 80% of “at-risk” nations [52].

Young infants are especially susceptible to severe respiratory illness from pertussis. According to the CDC, approximately 24.1 million cases of whooping cough in children younger than age five occur annually worldwide, including 160,700 deaths [53]. Cases are resurging in many countries despite sufficient vaccine coverage. In the US, pertussis cases increased from 7857 in 2000 to over 48,000 cases in 2012 [54]. The ACIP spearheaded the “cocooning” initiative in 2005 in response to rapidly climbing cases, encouraging an infant’s close contacts to get the pertussis vaccine. This recommendation was discontinued after studies demonstrated cocooning’s lack of efficacy [55]. Today, maternal vaccination with Tdap remains the preferred method of neonatal protection against pertussis.

Infants do not receive their first dose of DTaP until two months of age, and therefore maternal vaccination with Tdap is imperative to mitigate infection risk during this vulnerable period. Vaccination also permits the significant passage of IgA antibodies against pertussis in breast milk, which may persist for up to eight weeks postpartum [56]. This provides an additional mechanism of immune support against pertussis for breastfeeding infants. A large retrospective cohort study in 2017 determined that Tdap administration in pregnancy was highly protective against infant pertussis infection, especially within the first two months of life [57]. There was a 91.4% effectiveness among infants during those first two months and a 69% effectiveness during the first year after birth. Protection against severe illness leading to hospitalization was 94% and 95% against pertussis-associated death, reinforcing the importance of maternal vaccination against this bacterium [57].

3.3. COVID-19

After the first COVID-19 vaccines were rolled out in December 2020, several obstetric and reproductive healthcare organizations across the globe drafted a joint statement encouraging emergency use of COVID-19 vaccines in pregnant women [58]. The CDC released new data depicting the safety of this vaccine in pregnancy in July 2021. The American
College of Obstetricians and Gynecologists (ACOG) strongly recommended COVID-19 vaccination in pregnancy at this time [58]. Since 2021, COVID-19 vaccination has been recommended by the CDC for women who are pregnant, breastfeeding, attempting to become pregnant, or may become pregnant soon. This recommendation additionally encourages healthcare providers to offer the COVID-19 vaccine at the same time as other routine immunizations to increase vaccine adherence in this population [59]. The WHO echoes this statement, recommending a single dose of the COVID-19 vaccine during pregnancy regardless of prior vaccination [60].

More than 50% of COVID-19 infections during pregnancy present with no symptoms. However, infection in pregnant women is correlated with greater risks of preterm birth, stillbirth, maternal mortality, and intensive care unit (ICU) stay compared to uninfected pregnant individuals [32]. An English population-based cohort study discovered the presence of a heightened risk of preeclampsia/eclampsia, preterm delivery, and fetal death in pregnant women who were infected with COVID-19 [61]. Neonates born to infected women also have an increased risk of prematurity necessitating NICU admission [32].

A 2022 systematic review of mRNA COVID-19 vaccines administered in 48,000 pregnant women found that both the Pfizer-BioNTech and Moderna vaccines can prevent SARS-CoV-2 infection in pregnancy [25]. Another systematic review discovered that pregnant women who received the vaccine did not have a greater risk of adverse maternal or neonatal outcomes compared to their unvaccinated counterparts. These adverse outcomes included placental abruption, postpartum hemorrhage, miscarriage, pulmonary embolism, maternal death, preterm delivery, low birthweight, or ICU or NICU stays [62]. Not only is the COVID-19 vaccine effective in pregnancy without poor maternal or fetal outcomes but it has also been associated with a decrease in stillbirth [62]. Studies have additionally exhibited SARS-CoV-2 IgG antibody placental transfer as well as the presence of SARS-CoV-2 IgA and IgG antibodies in the breast milk of vaccinated pregnant women. Compounding evidence has supported that infants of vaccinated mothers are protected against COVID-19 for four to six months after birth [63,64]. This length of coverage is beneficial given that infants are eligible for COVID-19 vaccination at six months of age [65].

No current data exist to support recommendations for COVID-19 vaccination during a specific period of gestation. However, common practice involves immunization during the second or third trimester to avoid any theoretical disruption of first trimester organogenesis [66]. In February 2021, Pfizer and BioNTech initiated worldwide recruitment for their Phase 2 and 3 clinical trials assessing the safety, immunogenicity, and tolerability of their COVID-19 vaccine in pregnant individuals between 27 and 34 weeks of gestation (ClinicalTrials.gov (accessed on 15 May 2024) Identifier: NCT04754594). The trial was completed in July 2022 with results pending. A Phase 2 trial is ongoing in the UK investigating the optimal timing of COVID-19 vaccination in pregnant women ([https://doi.org/10.1186/ISRCTN15279830](https://doi.org/10.1186/ISRCTN15279830) (accessed on 15 May 2024)). Further long-term safety data are required to establish potential consequences of these vaccines in infants of vaccinated mothers.

3.4. RSV

The RSV vaccine is the most recent addition to the list of routine immunizations in pregnancy. In August 2023, the FDA approved Pfizer’s bivalent RSVpreF (Abrysvo) vaccine, the first and currently only RSV vaccine authorized for use in pregnant women to prevent RSV lower respiratory tract disease in newborns during their first six months of life [16]. Abrysvo is approved for administration as a single intramuscular dose from 32 through 36 weeks’ gestation during RSV season (September–January). The CDC echoes this recommendation by the FDA [67]. Abrysvo was approved in the UK for use in pregnant women in November 2023, with the hope of initiating vaccination in late 2024 [68,69].

Pregnant individuals at less than 32 weeks should not receive the vaccine due to the potential for preterm birth [67]. More preterm births were observed among women vaccinated with Abrysvo than among placebo recipients in clinical trials, but this difference
was not statistically significant. There is currently insufficient evidence to establish or deny
the presence of a causal relationship between Abrysvo and preterm birth, and therefore
administration only after 32 weeks is recommended out of an abundance of caution [67].
Additionally, clinical trials reported that preeclampsia and other hypertensive disorders
of pregnancy were more frequently observed in Abrysvo recipients compared to placebo.
Preeclampsia occurred in 1.8% of vaccinated women versus 1.4% in the placebo group. This
finding also lacked statistical significance, but vaccinated mothers should still be monitored
appropriately for hypertensive conditions in pregnancy [67].

RSV is a significant cause of acute lower respiratory tract infections in infants and
children around the world [70]. Infants are especially vulnerable during the first few
months of life. A population-based study discovered that newborns less than two months
old represented 44% of hospitalizations due to RSV. Significantly preterm infants born
at less than 30 weeks' gestation were three times as likely to be hospitalized from severe
RSV disease than term infants [71]. Treatment of RSV is primarily supportive, although
monoclonal antibodies have demonstrated effectiveness in reducing the risk of hospitaliza-
tion in infants and children. Palivizumab (Synagis), a humanized monoclonal antibody
targeting the RSV fusion (F) glycoprotein antigenic site, has exhibited effectiveness in
reducing hospitalizations among high-risk children less than 24 months of age [72,73].
Nirsevimab (Beyfortus) is also an available monoclonal antibody against the prefusion
conformation of the RSV fusion protein and has demonstrated efficacy in RSV infection
prevention [74]. It is recommended for all infants younger than eight months of age who
are born during or are about to enter their first RSV season. Infants younger than eight
months do not require nirsevimab injection if they were born at least 14 days after their
mother received Abrysvo [75].

The RSV vaccine is new, but its clinical trials demonstrated great success. In a world-
wide, Phase 3 clinical trial, maternal vaccination with RSVpreF effectively prevented lower
respiratory tract disease due to RSV necessitating medical treatment in infants, with vaccine
efficacy of 81.8% (99.5% CI, 40.6 to 96.3) within 90 days after delivery. Prevention was
69.4% (97.58% CI, 44.3 to 84.1) within 180 days after birth [76]. The addition of Abrysvo
to the routine vaccination schedule for pregnant women is promising for reducing infant
morbidity and mortality from RSV, and healthcare providers serve an indispensable role in
educating future mothers about the benefits of vaccination for their infant.

4. Vaccines Recommended in Pregnancy with Special Considerations

Some vaccines are currently recommended in pregnancy based on maternal risk
factors or other unique circumstances, including travel or a disease outbreak. The following
vaccines may be administered during pregnancy with these special considerations in mind.
Table 2 summarizes these vaccines, their vaccine platform, and the situations in which they
are considered.

Table 2. Summary of recommended vaccines in pregnancy with special considerations.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccine Platform</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Recombinant antigen</td>
<td>Postexposure prophylaxis</td>
</tr>
<tr>
<td>Cholera</td>
<td>Inactivated bacterium</td>
<td>High disease risk</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated virus</td>
<td>High exposure risk</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Recombinant subunit</td>
<td>High risk of Hep B infection</td>
</tr>
<tr>
<td>Hib</td>
<td>Polysaccharide–protein conjugate</td>
<td>Determined that protection is necessary</td>
</tr>
<tr>
<td>Japanese encephalitis virus</td>
<td>Inactivated virus</td>
<td>High exposure risk</td>
</tr>
</tbody>
</table>
Table 2. Cont.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccine Platform</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Polysaccharide–protein conjugate, protein-based</td>
<td>High disease risk/outbreak</td>
</tr>
<tr>
<td>Polio</td>
<td>Inactivated virus</td>
<td>Offered routinely in the UK and New Zealand in combination with Tdap</td>
</tr>
<tr>
<td>Rabies</td>
<td>Inactivated virus</td>
<td>Pre/Postexposure prophylaxis</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Polysaccharide–protein conjugate</td>
<td>Determined that protection is necessary</td>
</tr>
<tr>
<td>Tick-borne encephalitis virus</td>
<td>Inactivated virus</td>
<td>Benefits &gt; risks</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Polysaccharide</td>
<td>Benefits &gt; risks</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Live attenuated virus</td>
<td>Infection risks &gt; risks of vaccination</td>
</tr>
</tbody>
</table>

Hib, Haemophilus influenza type b. Data obtained from the Centers for Disease Control and Prevention (CDC) guidelines for vaccinating pregnant women [29] and Galiza et al., 2024 [32].

4.1. Hepatitis B

No evidence exists supporting hepatitis B infection prevention in infants due to maternal hepatitis B vaccination [77]. However, there are no increased adverse outcomes for pregnant women who receive the hepatitis B vaccination [78]. The CDC advises that pregnant women who are at a high infection risk or who desire vaccination can be administered the hepatitis B vaccine [29].

4.2. Neisseria Meningitidis

Several studies have demonstrated the immunogenicity of meningococcal polysaccharide vaccines and their ability to produce sufficient antibodies in infants born to vaccinated mothers [79–83]. On the contrary, meningococcal conjugate vaccines have no evidence of immunogenicity or efficacy when administered during pregnancy. However, there are no safety concerns with this vaccine in pregnant women [84–86]. Vaccination against *Neisseria meningitidis* with the polysaccharide vaccine can be offered if a woman is at an elevated risk of meningococcal disease or during an outbreak.

4.3. Polio

The inactivated polio virus vaccine (IPV) is routinely offered during pregnancy in the UK and New Zealand in conjunction with the Tdap vaccine [87,88]. The CDC advises against routine administration in pregnant women who are not at an increased risk of polio exposure [89]. A live attenuated polio vaccine is also available and contraindicated in pregnancy. However, there are no reports of adverse birth outcomes in women who received the live attenuated version while pregnant [90].

4.4. Anthrax

The severity of anthrax infection warrants protection during pregnancy. Pregnant women who have potentially inhaled anthrax should receive the anthrax vaccination, regardless of gestational age [91]. No relationship has been demonstrated between anthrax vaccine use during pregnancy and the potential for birth defects [92,93].

4.5. Cholera

The WHO encourages vaccination of pregnant and lactating women against cholera due to its favorable benefit–risk ratio in pregnancy [94]. No adverse outcomes were noted in pregnant women inadvertently vaccinated against cholera in three retrospective studies including 3000 women across three different countries [95–97]. A 2017 observational study also demonstrated no increase in miscarriage or neonatal demise [98]. Therefore, the
inactivated cholera vaccine should be considered in pregnancy on an individual basis, such as during an outbreak. The live attenuated version is contraindicated in pregnancy [95–97].

4.6. *Haemophilus Influenza Type b*

The *Haemophilus influenza* type b (Hib) conjugate vaccine is safe and effective in pregnant women, and increased antibody concentrations are present in infants born to vaccinated mothers [99,100]. However, there is no present evidence that the vaccine reduces Hib disease incidence in these infants [101]. Hib vaccination in pregnancy may be considered depending on the situation, but the likelihood of necessary vaccination is low since severe Hib disease is generally under control in many countries [18].

4.7. *Hepatitis A*

The inactivated hepatitis A vaccine may be administered in pregnancy if exposure is likely since there is no evidence of vaccination-related adverse pregnancy outcomes [102,103]. Live attenuated versions are contraindicated in pregnancy.

4.8. *Japanese Encephalitis Virus*

No data are available about Japanese encephalitis virus vaccination during pregnancy. The inactivated vaccine may be administered if a pregnant individual intends on traveling to an endemic area and the risk of disease outweighs the possible risks of vaccination. The live vaccine is contraindicated in pregnancy. Vaccination should be considered on an individual basis [29].

4.9. *Rabies*

Studies have not indicated a heightened risk of poor pregnancy outcomes following postexposure vaccination with the rabies vaccines [104–111]. Although these studies focused on postexposure prophylaxis, their conclusion that the rabies vaccine is safe in pregnancy supports its use as preexposure prophylaxis for pregnant women at increased risk.

4.10. *Streptococcus Pneumoniae*

There is minimal evidence in the literature supporting use of the pneumococcal conjugate vaccine in pregnancy. A single published study demonstrated that infants born to mothers who received the conjugate vaccine were more likely to develop early acute otitis media [112]. The pneumococcal polysaccharide vaccine is safe to use in pregnant women, with increased antipolysaccharide antibodies evident in their infants [113,114]. However, there is limited evidence that these antibodies affect disease incidence in these newborns [115,116]. Despite this minimal demonstration of effectiveness, the pneumococcal polysaccharide vaccine may be administered in pregnancy if protecting the pregnant woman is deemed essential [18].

4.11. *Tick-Borne Encephalitis Virus*

No current studies have investigated the use of tick-borne encephalitis virus vaccines in pregnancy. At this time, there are no official recommendations for vaccination against this virus in particular circumstances. However, the vaccine platform is an inactivated virus; therefore, there are no theoretical contraindications for use in pregnant women [18].

4.12. *Typhoid*

The typhoid polysaccharide vaccine has no evidence supporting its safety in pregnancy. The theoretical risk is minimal, and therefore vaccination may be advised when the benefits are greater than the potential risks [18]. The live attenuated typhoid vaccine is contraindicated in pregnancy.
4.13. Yellow Fever

Only a live attenuated vaccine platform is available for the prevention of yellow fever. As discussed, live vaccines are typically contraindicated in pregnancy due to the theoretical transfer of a live virus to the fetus. However, there is some support in the literature that vaccination against yellow fever in pregnancy is not associated with a greater risk of unfavorable pregnancy outcomes [117–119]. Congenital infection is still a possibility with yellow fever vaccination [119]. Administration of this vaccine in pregnancy may be considered if the risks of infection are far greater than the possible risks associated with vaccination [120].

5. Contraindicated Vaccines in Pregnancy

Table 3 summarizes vaccines that are currently contraindicated or not recommended in pregnancy, their vaccine platform, and reasons for their contraindication. Inadvertently administering these vaccines to pregnant women is not an indication to end the pregnancy. However, counseling should be performed by the healthcare professional on the potential consequences for the fetus [29].

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccine Platform</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Live attenuated mycobacterium</td>
<td>Live BCG strain culture of <em>Mycobacterium bovis</em></td>
</tr>
<tr>
<td>HPV</td>
<td>Recombinant virus-like particle</td>
<td>Unavailable safety data for pregnant women</td>
</tr>
<tr>
<td>MMR</td>
<td>Live attenuated virus</td>
<td>Live attenuated measles, mumps, and rubella viruses</td>
</tr>
<tr>
<td>Varicella</td>
<td>Live attenuated virus</td>
<td>Live attenuated varicella-zoster virus</td>
</tr>
<tr>
<td>Zoster</td>
<td>Recombinant glycoprotein</td>
<td>Unavailable safety data for pregnant women</td>
</tr>
</tbody>
</table>

BCG, Bacillus Calmette–Guerin; HPV, Human papilloma virus; MMR, Measles, mumps, and rubella. Data obtained from the Centers for Disease Control and Prevention (CDC) guidelines for vaccinating pregnant women [29], Etti et al., 2022 [18], and Galiza et al., 2024 [32].

6. Vaccines under Investigation for Future Use in Pregnancy

6.1. Group B Streptococcus

Group B Streptococcus (GBS) is a prominent cause of neonatal sepsis and meningitis across the globe [121]. Maternal rectovaginal colonization is additionally linked to a greater risk of stillbirth and preterm delivery [18]. The routine implementation of an effective GBS vaccine in prenatal care would play a substantial role in protecting neonates from severe GBS disease after birth.

There are six capsular polysaccharide GBS serotypes that are responsible for approximately 98% of severe GBS disease in newborn infants: Ia, Ib, II, III, IV, and V [18]. Serotype III is the main offender contributing to invasive disease in neonates [122,123]. GBS vaccination was first trialed in 1988, and this study reported the achievability of maternal GBS vaccination. However, their monovalent polysaccharide-based GBS vaccine targeting serotype III displayed poor immunogenicity [124]. A trivalent CRM197-conjugated capsular polysaccharide GBS vaccination was formulated by Novartis targeting serotypes Ia, Ib, and III, but the vaccine did not move forward from Phase 1/2 trials in 2016 (ClinicalTrials.gov Identifier: NCT02046148) [18]. A different Phase 1/2 trial performed by Absalon et al. from 2017–2018 (ClinicalTrials.gov Identifier: NCT03170609) tested Pfizer’s new hexavalent conjugate vaccine (GBS6) in non-pregnant adults. It was deemed safe and immunogenic in this population. Each GBS serotype antibody concentration remained significantly augmented in the vaccinated groups six months postimmunization [125]. Because of this trial’s substantial findings, Pfizer initiated a similar Phase 1/2 trial in pregnant women in 2019, which was completed in March 2024 (ClinicalTrials.gov Identifier: NCT03765073). Initial
data demonstrated that GBS6 elicited anticapsular polysaccharide (CPS) antibodies against GBS in pregnant women that were passed to their infants sufficiently to lower risk of severe GBS disease [126].

June 2020 brought about MinervaX’s Phase 2 trials assessing their novel vaccine, GBS-NN/NN2. This vaccination consists of the immunogenic N-terminals of the Rib and AlphaC surface proteins of GBS (ClinicalTrials.gov Identifier: NCT04596878) [127]. In this trial, MinervaX aims to assess the safety and effectiveness of the vaccine in both healthy pregnant women and those infected with HIV. This would be especially important in sub-Saharan Africa, where both HIV infection in young women and severe neonatal GBS disease are pervasive [18,128]. MinervaX has a second clinical trial currently in Phase 2 (ClinicalTrials.gov Identifier: NCT05154578) assessing the safety and immunogenicity of GBS-NN/NN2 in only healthy pregnant women. Phase 3 clinical trials for both studies are forthcoming.

6.2. Cytomegalovirus

Cytomegalovirus (CMV) is a significant viral source of congenital infection. Although it is common and typically causes a mild and self-resolving illness in healthy adults, it is the leading cause of congenital deafness worldwide [18]. Development of a CMV vaccine is therefore of the utmost priority.

Congenital infection may occur with primary or secondary infection with CMV. Primary infection occurs when a woman becomes infected with CMV for the first time during pregnancy [18]. Secondary infection occurs when a woman with a previous history of CMV infection experiences a reactivation of the virus or becomes infected with a new strain of CMV during her pregnancy [18]. Congenital CMV infection risk is highest during a primary infection of the virus [129]. These various mechanisms of infection have complicated the development of a CMV vaccine.

The 1970s initiated CMV vaccine advancement. Live attenuated strains were primarily the focus, especially the Towne strain [18]. Studies demonstrated that adult populations tolerated this strain well, but it only offered an imperfect defense from the virus [130]. Glycoprotein B (gB), a CMV surface protein, was soon identified. Vaccines containing gB showed a promising neutralizing antibody response, and efficacy of these vaccinations was estimated to approach 50% [18]. Unfortunately, antibody response did not persist [131,132]. The discovery of a pentameric complex promised a higher yield of neutralizing antibody titers compared to gB vaccines. It also demonstrated protection against placental transmission of CMV [131].

Recent developments of a CMV vaccine have been underway. Contenders include replication-defective pentameric vaccines, viral vector vaccines, adjuvanted glycoprotein B vaccines, a DNA plasmid vaccine, and RNA vaccines [133]. In January 2023, Moderna completed their Phase 2 study assessing the immunogenicity and safety of three doses of their mRNA-1647 CMV vaccine in CMV-seronegative and CMV-seropositive healthy adults aged 18–40 years (ClinicalTrials.gov Identifier: NCT04232280). Phase 3 of the trial is underway with expected completion in 2026 (ClinicalTrials.gov identifier: NCT05085366). These trials are promising and represent significant progress towards producing a CMV vaccine, but further investigation is required before we see their routine administration in obstetrical care.

7. Role of Maternal Vaccination in Global Health

This review primarily focuses on US vaccine guidelines instead of providing a comprehensive discussion of those across the globe, which is a limitation of the paper. However, the role of maternal vaccination in low- and middle-income countries is significant and should be briefly addressed. Malaria is a prominent cause of maternal, perinatal, and infant morbidity and mortality in endemic areas around the world, especially in sub-Saharan Africa. Pregnant women are particularly susceptible to malaria infection due to the tendency of parasites to congregate in the placenta, especially the species Plasmodium falciparum [134].
Malaria’s primary detrimental effect on maternal health is anemia, and *P. falciparum* causes approximately 10,000 maternal anemia-related deaths every year in sub-Saharan Africa. Prematurity and low birth weight are commonly seen in infants born to malaria-infected mothers [134]. Therefore, vaccinating pregnant women against malaria has the potential to profoundly impact maternal and fetal health in endemic regions.

As of 2024, no malaria vaccine has ever been tested in pregnant women. The WHO currently recommends two malaria vaccines, both for use in children: RTS,S/AS01 (Mosquirix), a preerythrocytic recombinant protein vaccine against the RTS,S antigen, and R21/Matrix-M, which targets the PfCSP protein [134]. In October 2021, the WHO endorsed vaccination with RTS,S/AS01 for children five months and older living in moderate- to high-malaria-transmission regions [134]. The WHO then authorized immunization with R21/Matrix-M in October 2023, and rollout of this vaccine began in July 2024 for children two years and under in Ivory Coast of West Africa [135]. Malaria vaccine trials are also ongoing in adults. The placental malaria vaccine candidates, PAMVAC and PRIMVAC, were evaluated in Phase 1 trials in 2019 and 2020, respectively, and deemed safe and effective in non-pregnant adults [136–138]. Although malaria vaccines have yet to be studied in pregnancy, their current administration in young children and ongoing evaluation in adults suggest that trials in pregnant women are imminent.

8. Conclusions

Maternal vaccination is an essential tool to prevent serious infection in pregnant women, fetuses, and neonates. Approved vaccines for use in pregnancy should be promptly offered during prenatal visits to ensure timely administration at the recommended gestational age. Pregnant women should have a thorough discussion with their healthcare provider on the risks and benefits of vaccination for them, their fetuses before delivery, and their infants after birth. Vaccine safety during pregnancy should be comprehensively addressed during these visits. In order for healthcare providers to conduct these educated discussions, they should be provided sufficient training to support their pregnant patients through these important decisions. At this time, recommended vaccines for routine administration during pregnancy include influenza, Tdap, COVID-19, and RSV. Active clinical trials developing vaccines for GBS and CMV are promising, and we may see them in obstetrical clinics in the near future. Co-administration of routine vaccines, timely vaccine education, inclusion of pregnant women in clinical trials, and promoting vaccine acceptance may facilitate increased adherence to guidelines and protection of women and their infants against severe infection.

**Author Contributions:** R.M.A. and B.G. contributed equally to deciding on a topic for review. R.M.A. conducted the literature search and wrote the original draft of the manuscript. B.G. also reviewed the literature, provided editorial changes to the manuscript, and supervised all other aspects of the submission process. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Acknowledgments:** The authors would like to thank the journal’s manuscript reviewers for their valuable input and expert review. We would also like to thank both past and present researchers for their contributions to the development of maternal vaccines, without whom significant protection of mothers, fetuses, and infants against vaccine-preventable infection would not be possible.

**Conflicts of Interest:** The authors declare no conflicts of interest.
References

11. Donegan, K.; King, B.; Bryan, P. Safety of pertussis vaccination in pregnant women in UK: Observational study. *BMJ* 2014, 349, g4219. [CrossRef]


Reprod. Med. 2024, 5


119. Suzano, C.E.; Amaral, E.; Sato, H.K.; Papaioannou, P.M.; Campinas Group on Yellow Fever Immunization during Pregnancy. The effects of yellow fever immunization (17DD) inadvertently used in early pregnancy during a mass campaign in Brazil. *Vaccine* 2006, 24, 1421–1426. [CrossRef]


Fowler, K.B.; Stagno, S.; Pass, R.F. Maternal immunity and prevention of congenital cytomegalovirus infection. *JAMA* 2003, 289, 1008–1011. [CrossRef]


Plotkin, S.A.; Boppana, S.B. Vaccination against the human cytomegalovirus. *Vaccine* 2019, 37, 7437–7442. [CrossRef]


Stanisic, D.J.; Good, M.F. Malaria Vaccines: Progress to Date. *BioDrugs* 2023, 37, 737–756. [CrossRef]


Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.