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REVIEW

# Vaccination during pregnancy: current and possible future recommendations

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## Abstract

Immunizing pregnant women to protect the mother, fetus and infant from infection has increasingly been used over the last decade. Protection against infectious diseases in neonates is mainly provided by maternal antibodies transferred from mother to infant during pregnancy through transplacental transport or after delivery via breastfeeding. Both the transplacental- and breast milk–derived maternal antibodies function as the primary source of protection against infectious diseases in neonates during the first vulnerable weeks of life. During recent infectious disease outbreaks (influenza, pertussis, Zika…) and for other infectious diseases (CMV, GBS…), pregnant women are increasingly identified as an important target for vaccination. For some of these diseases, vaccines are already on the market, and recommended during pregnancy. For others, vaccines are currently under development; furthermore, some are even specifically designed to be administered during pregnancy.

*Conclusion*: This review article provides an overview on the rationale and main mechanism of the maternal vaccination strategy and gives a summary about the current and possible future recommendations for maternal vaccination.

**What is Known:**
- *Maternal vaccination has a far-reaching potential in the protection of both women and offspring.*
- *Currently, tetanus, pertussis and influenza vaccination during pregnancy is recommended in some countries. Several new vaccines specifically designed for use in pregnancy are currently under development.*

**What is New:**
- *Review providing a timely overview of the rationale and main mechanisms of the maternal vaccination strategy*
- *Up-to-date summary of the current and possible future recommendations for maternal vaccination*

**Keywords** Immunization · Influenza · Maternal · Pregnancy · Pertussis

## Abbreviations

| | |
|---|---|
| aP | Acellular pertussis |
| CDC | Center for Disease Control and Prevention |
| CFR | Case fatality ratio |
| CMV | Cytomegalovirus |
| CRM | Cross-reacting material |
| DT | Diphtheria toxoid |
| FHA | Filamentous hemagglutinin |
| GBS | Group B *Streptococcus* |
| HIV | Human immunodeficiency virus |
| IFN-γ | Interferon-γ |
| Ig | Immunoglobulin |
| MNT | Maternal and neonatal tetanus |
| MNTE | Maternal and neonatal tetanus elimination |
| Prn | Pertactin |
| PT | Pertussis toxin |
| RSV | Respiratory syncytial virus |
| Tdap | Tetanus diphtheria acellular pertussis |
| TT | Tetanus toxoid |
| WHO | World Health Organization |
| wP | Whole cell pertussis |

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## Introduction

Immunizing pregnant women to protect the mother, fetus and infant from infection has increasingly been used over the last decade [1]. Maternal antibodies are transferred from mother to infant during pregnancy through transplacental transport [2] or after delivery via breastfeeding [3] and provide protection against infections in early life.

The transplacental transport is regulated by the neonatal Fc receptor with a gradual increase in the amount of transported maternal antibodies from mother to infant as the pregnancy proceeds [4]. The placental transport system is highly selective for IgG antibodies and essentially excludes the transport of other major immunoglobulin classes including IgE, IgM and IgA. Within the IgG antibodies, preferential transport of IgG isotype 1 is noted, leading to a more efficient transport of antibodies elicited by vaccines containing protein antigens compared with vaccines containing polysaccharide antigens (eliciting IgG2 isotype antibodies) [5]. Some chronic maternal infections like malaria and HIV can cause an impaired transplacental transport [6, 7].

Secretory IgA antibodies are secreted into the colostrum and breast milk and are ingested by the neonate during breastfeeding providing mucosal immunity to the newborn. After maternal vaccination, an increased amount of disease-specific maternal antibodies is observed in the breast milk up to several weeks postpartum [3, 8, 9]. These maternal antibodies provide mucosal immunity through neutralization and prevention of adherence of toxins and virulence factors in the respiratory and gastrointestinal tract [10]. However, whether these antibodies can be transported across the upper respiratory mucosa and the intestinal epithelial barrier into the circulation is unknown.

The amount of maternal antibodies transferred to the neonate through both the placenta and breast milk depends on the timing of vaccination during pregnancy [11], the placental function and on the concentration of maternal antibodies in the pregnant women [12]. The latter depends on the vaccination status of the women or the time since last vaccination or disease [13]. In order to transfer the maximum amount of maternal antibodies to the fetus, the concentration of antibodies in the maternal blood should be high during pregnancy. Therefore, for some infectious diseases, increasing the maternal antibody level induced by vaccination during pregnancy is currently the only option to offer passive protection to the newborn immediately after birth [2, 14].

Maternal antibodies wane exponentially during the first weeks or months of life and the rate of decay is consistent regardless of the amount of antibodies received at birth [15]. Therefore, infants starting with a higher level of maternal antibodies at birth will still have a longer persistence of these antibodies until the start of the infant's own primary immunization schedule [13, 16].

High concentrations of vaccine-induced maternal antibodies are known to interfere with the infant's humoral immune response with an inhibition of the antibody generation after their own vaccination and lower antibody titers as a consequence [17]. However, this interference effect is mostly a temporary effect which mainly affects humoral immune responses after primary vaccination and to a lesser extent after booster vaccination [5]. Whether high concentrations of maternal antibodies also affect cellular immune responses in infants is not completely clear yet and needs further investigation [18]. Also, the clinical consequences, if any, of this blunting can vary depending on the vaccine and the disease [19].

During recent infectious disease outbreaks (influenza, pertussis, Zika…) and for some other infectious diseases (CMV, GBS…), pregnant women are increasingly identified as an important target for vaccination. For some of these diseases, vaccines are already on the market, and recommended during pregnancy. For others, vaccines are currently under development; furthermore, some are even specifically designed to be administered during pregnancy. Therefore, in this review, we focused on three vaccines that are currently recommended during pregnancy and also on some other vaccines that are currently under development and that can be used during pregnancy in the future.

## Existing maternal vaccination recommendations

### Tetanus

Maternal and neonatal tetanus (MNT) is an important cause of maternal and neonatal morbidity and mortality. MNT is often fatal and characterized by muscular rigidity and spasms and without medical care; case fatality ratio (CFR) is close to 100%. Maternal tetanus, defined as tetanus during pregnancy or within 6 weeks after delivery, is linked to miscarriages, abortion and unhygienic delivery conditions, whereas neonatal tetanus is secondary and a consequence of poor postpartum cord care practices [20, 21].

Neonatal tetanus was estimated to be responsible for over half a million of deaths globally in the early 1980s. In 1988, the WHO estimated that 787,000 newborns died due to neonatal tetanus corresponding with a global incidence of approximately 6.7 deaths per 1000 live births. In low- and middle-income countries, the overall incidence was even higher with 50 to 110 deaths per 1000 live births due to neonatal tetanus [20, 22].

Therefore, the World Health Assembly launched the Maternal and Neonatal Tetanus Elimination Program (MNTE) in 1989. The goal of this program is to eliminate MNT through the promotion of birth hygiene, surveillance and maternal immunization with tetanus toxoid. WHO

recommends that unimmunized pregnant women or pregnant women without documentation of previous tetanus vaccination should receive two doses of tetanus toxoid (TT) at least 4 weeks apart. The first dose should be given as early as possible during pregnancy and the last dose should be given at least 2 weeks prior to delivery. A total of 5 doses are considered sufficient for life-long immunity so further doses should be given during subsequent pregnancies or at intervals of at least 1 year [23].

Following the launch of this program and with an increasing coverage of minimum two doses of TT in pregnant women, the incidence of MNT declined substantially. According to the WHO, 34,019 newborns died from tetanus in 2015 which corresponds with a 96% reduction in burden of tetanus-related mortality compared with the early 1980s. In 2014, 34 of the 59 countries targeted by the program achieved elimination. In March 2018, elimination was even achieved by 41 countries [20].

Extensive and longtime research showed that TT has an extensive safety profile in pregnant women [24]. It has also been shown that TT administered to pregnant women is efficient and effective for protection against maternal and neonatal tetanus. A recent systematic review shows a decrease in mortality from neonatal tetanus by 94% in infants from women that have been vaccinated in pregnancy with at least 2 doses of TT [25].

## Pertussis

Despite the availability of successful universal pertussis vaccination programs (85% global DTP3 coverage in 2017) [26], the disease remains an important public health problem with an estimated 89,000 deaths yearly [27]. During recent years, some countries with high vaccination coverage experienced a rise in the incidence of pertussis with the highest incidence, disease burden and case fatality rate in infants below 1 year of age. These infants are too young to be protected by the currently available vaccines and vaccination schedules since infant pertussis vaccination does not start before the age of 6 weeks, resulting in a susceptibility gap for pertussis infection in infants [28]. As a result of the resurgence of pertussis disease and to better protect these vulnerable infants, national advisory bodies from both industrialized and developing countries have recommended immunization with a tetanus, diphtheria, acellular pertussis (aP) (Tdap) vaccine for all pregnant women in the second or third trimester of pregnancy [29, 30]. Many studies have reported the safety of maternal Tdap vaccination concluding that the current strategy of maternal pertussis vaccination is a safe strategy for mother, fetus and infant [31, 32].

Protection against pertussis disease is dependent on both the humoral and cellular immune response. Vaccinating pregnant women with an aP-containing vaccine induces similar humoral immune responses compared with non-pregnant women [33, 34]. Overall, pertussis-specific antibodies wane quite rapidly with already a significant decline in antibody titers 1 year after maternal Tdap vaccination [34, 35]. This observation supports the recommendation for repeated booster vaccinations in successive pregnancies. In the case of cellular immune responses, maternal Tdap vaccination stimulates significantly weaker proliferative and IFN-γ responses in pregnant compared with non-pregnant women [34], but the vaccination is still immunogenic and induces a sufficient amount of maternal antibodies in women. These antibodies can be transported actively across the placenta to the fetus to protect the offspring in the first weeks of life. Recent studies show that maternal Tdap vaccination, administered in the second or third trimester of pregnancy, prevents pertussis in at least 9 out of 10 infants below 6 months of age [36–38].

Regarding the optimal timing of pertussis vaccination in pregnancy, different considerations should be carefully taken into account including safety, vaccine effectiveness, uptake and timing of antenatal care visits [39]. However, recent data show that vaccination earlier in pregnancy, even second rather than third trimester vaccination, is the best option since this timing offers the necessary time to develop and transport maternal antibodies towards the unborn child. An Australian study reported higher pertussis-specific antibody titers in cord blood of infants born to women immunized at 28–32 weeks of gestation compared with women immunized between 33 and 36 weeks of gestation suggesting that vaccination earlier in the third trimester is more effective than later in pregnancy [40]. More recently, a Swiss study found that second trimester immunization was associated with significantly higher titers in cord blood of term born infants compared with third trimester immunization [41]. The same effect was seen in the cord of preterm born infants, even when they were born before 33 weeks of gestation [11], a time point where transplacental transport is considered to be suboptimal.

Blunting or interference of the infant immune response is currently one of the areas of investigation of the maternal pertussis vaccination strategy. In the 1990s, blunting of naturally acquired maternal pertussis antibodies with the infant's humoral immune response to whole cell pertussis (wP), yet not to aP vaccines, was already described [42]. On the other hand, it has been shown that the presence of vaccine-induced passive maternal antibodies may blunt the infant immune response to childhood aP vaccination. However, this interference effect is highly variable for different aP-containing vaccines and even in different studies on the same aP-containing vaccine [2, 14, 33, 43–47]. More recently, also blunting of the infant immune response to childhood wP-containing vaccines in the presence of vaccine-induced maternal antibodies has been shown [48]. Besides blunting of the infant humoral immune responses to the same vaccine antigens as the ones included in the Tdap vaccine, also blunting of vaccine antigens

conjugated to the diphtheria toxoid variant (CRM) or TT has also been demonstrated, for example, blunting of the pneumococcal immune response, mainly after primary immunization [47, 49]. Up until now, no clinical evidence of blunting has been shown [50]. But, ongoing surveillance in older, vaccinated infants and toddlers is still essential to understand the longer-term impact and possible significance of these immunological findings.

## Influenza

Influenza infection affects all age groups and causes mild to severe illness. The World Health Organization (WHO) estimates that during normal seasonal epidemics, 5–15% of the population is infected, with 3 to 5 million cases of severe illness and up to 650,000 influenza-associated deaths annually. Pregnant women are at increased risk of influenza-associated complications and are recognized as a priority group for seasonal and pandemic influenza vaccination. During recent seasonal influenza episodes, pregnant women had a significantly higher risk of hospitalization [51] compared with non-pregnant women. The disease severity increased with each trimester and was the highest for pregnant women with medical co-morbidities, e.g. metabolic disorders and chronic lung diseases [52]. Besides, influenza infection during pregnancy is associated with an increased risk of preterm delivery and small for gestational age for infants [53, 54]. Additionally, infants under 6 months of age are at high risk of severe influenza and associated complications with high rates of influenza-associated hospitalizations and even mortality [55]. However, currently, there is no influenza vaccine approved in any country for use in infants below 6 months of age. So, protection of infants during the first months of life can only be achieved by influenza vaccination during pregnancy [56]. Several national and international institutions, e.g. the WHO and the Center for Disease Control and Prevention (CDC), recommend that every pregnant women should be vaccinated with one dose of an inactivated influenza vaccine during any trimester of pregnancy before the start of the flu season [57, 58]. In 2012, the WHO stated that pregnant women should be prioritized above other groups for influenza vaccination in countries considering the initiation or expansion of their programs for seasonal influenza vaccination [59].

Several studies on the safety of maternal influenza vaccination showed that the inactivated influenza vaccine is well tolerated in pregnant women without unexpected side effects in the fetus and infant [53, 60]. Regarding the immunogenicity of the strategy, some studies report a slightly lower immune response to vaccination and significant differences in seroconversion rates in pregnant versus non-pregnant women while other studies report comparable immunogenicity [61, 62]. Yet, in general, pregnant women mount a good immune response to influenza vaccination with a significant increase in antibody titers to all vaccine strains and a significantly higher seroconversion rate in influenza-vaccinated compared with placebo-vaccinated pregnant women [63, 64]. After influenza vaccination during pregnancy, effective transplacental antibody transfer is seen with a correlation between maternal and cord blood antibody titers at delivery [65].

For the moment, no consensus has been reached on the timing of influenza vaccination during pregnancy. A recently published systematic review and meta-analysis found that vaccinating women later in pregnancy, at least 15 days before delivery, results in higher influenza-specific maternal antibody concentrations at birth and thus transfer of more antibodies to the unborn child. On the other hand, vaccinating earlier in pregnancy will provide protection against influenza during a longer proportion of the pregnancy, which is beneficial for the pregnant women, but may increase the probability that protection does not last until delivery and that consequently protection is not transferred to the offspring [66]. Additionally, safety data on influenza vaccination during the first trimester of pregnancy are lacking.

Maternal influenza vaccination protects both pregnant women and newborns against the disease. Up until now, it is hard to estimate the exact effectiveness of the strategy since studies are conducted in places with different epidemiological background, use influenza vaccines with different composition and are inconsistent in measuring end points as there are laboratory-confirmed influenza, influenza like illness or respiratory infection symptoms… However, several observational studies and clinical trials already demonstrated that maternal influenza vaccination is effective in preventing laboratory-confirmed influenza in pregnant women [67]. The duration of passive protection against influenza in the infants depends on the maternal level of antibodies, the amount of antibodies transferred from mother to infant and on how quickly these passively acquired antibodies wane during the first months of life. Studies in South Africa and Bangladesh describe a half-life of vaccine-induced maternal influenza antibodies in the infant of 42–50 days corresponding with a protection of approximately 2–3 months [64, 65].

## Maternal vaccination recommendations for future vaccines

Given the far-reaching potential of maternal immunization for both women and offspring, several new vaccines specifically designed for use in pregnancy are currently under development. These maternal vaccines have the potential to change the epidemiology of several infectious diseases in pregnant women and their infants and may improve global maternal and neonatal health [68].

Up until now, the strategy of maternal immunization is not used to its full potential in many places. Accelerating access to maternal immunization and the development of new maternal vaccines is key. Therefore, several international bodies are bringing together stakeholders from around the world to create a pathway to enable informed decision-making and rapid launch of maternal vaccines. Here, we highlight a few vaccines that are currently in the pipeline.

A first focus for a new vaccine is on respiratory syncytial virus (RSV). RSV causes a significant global respiratory disease burden, especially in young infants. Of the more than 30 million RSV childhood cases worldwide, the disease causes 1.4 million hospitalizations in the first year of life and 120,000 deaths before 5 years of age each year [69]. Currently, vaccination of pregnant women is considered as the most plausible strategy to protect these infants against RSV. Several maternal vaccines are currently under various stages of development and could be available within a few years [70]. One of these vaccines, the RSV F nanoparticle vaccine (Novavax®), was already tested in 4636 pregnant women in an international phase 3 clinical trial. Despite the fact that the primary outcomes of the study were not met, the candidate vaccine showed no significant safety issues in pregnant women and their offspring, a good immunogenicity and seroresponse rate in pregnant women, an efficient transplacental antibody transfer with high concentrations of RSV antibodies in the infants at birth and a progressively greater efficacy against severe outcomes of RSV infection in young infants [71].

Another target for maternal immunization is Group B *Streptococcus* (GBS). GBS can be found in the vagina or lower gastrointestinal tract of about 10–40% of women of reproductive age and is a leading cause of neonatal and infant invasive bacterial disease, often leading to death or neurological sequelae. GBS infections during pregnancy can lead to stillbirth and premature delivery, puerperal sepsis and other maternal morbidities [72]. Recently, the WHO drafted a "Group B Streptococcus Vaccine Development Technology Roadmap" with priorities for development, testing, licensure and global availability of GBS vaccines [73]. For the moment, several companies have vaccine candidates against GBS in their pipelines. But these vaccines are only in phase 1 or phase 2 clinical trials yet and additional research is needed to get these vaccines on the market [74–76].

Finally, vaccine development against cytomegalovirus (CMV) is also proceeding with potential use of the vaccine both before and during pregnancy to benefit both mother and neonate. CMV infection is a major public health priority which causes substantial long-term morbidity, particularly sensorineural hearing loss in newborns [77]. Up until now, progress towards the development of a CMV vaccine has been limited due to an incomplete understanding of the correlates of protective immunity for the fetus. Additional research within this field in the near future is crucial [78].

Additional vaccines that can offer protection against other infectious agents including Zika, Ebola, and herpes simplex are only in the developmental phase but certainly have the potential to be successful when being developed and on the market [79].

## Conclusion

Immunizing pregnant women to protect the mother, fetus and infant from infection has increasingly been used over the last decade. Currently, vaccines against three diseases, tetanus, pertussis and influenza, are broadly recommended to be safely used during pregnancy. Other vaccines specifically designed for use during pregnancy, e.g. RSV, GBS, and CMV, are in various stages of development.

Some other vaccines can be considered to reduce a personal risk of a woman and her offspring in case of travelling during pregnancy or potential close contact to a source of infection. In that case, as a general rule, all inactivated and toxoid-based vaccines are considered to be safe to use during pregnancy. Due to a theoretical teratogenic risk, live-attenuated vaccines should be avoided in pregnancy. However, if accidental vaccination occurs, termination of the pregnancy is not advised [80].

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### Compliance with ethical statements

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

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