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# Review of maternal immunisation during pregnancy: focus on pertussis and influenza

**Blanchard-Rohner Géraldine[ab], Eberhardt Christiane S.[bc]**

[a] Department of Paediatrics, Children's Hospital of Geneva, University Hospitals of Geneva, Switzerland
[b] Centre for Vaccinology and Neonatal Immunology, Department of Pathology-Immunology, Medical Faculty and University Hospitals of Geneva, Switzerland
[c] Department of Neonatology and Paediatric Intensive Care, Children's Hospital of Geneva, University Hospitals of Geneva, Switzerland

## Summary

Seasonal influenza and pertussis infections are known to be significant causes of morbidity and mortality in neonates and infants worldwide. Influenza has also been associated with severe complications in pregnant women and after delivery. The most efficient and safe strategy to protect mothers and their offspring is maternal immunisation during pregnancy. The maternal antibodies thus acquired are transferred to the fetus as of the second trimester and confer passive immunity until the first infant immunisations.

Therefore, it is strongly advised to administer booster doses of seasonal influenza and pertussis vaccines specifically during pregnancy. Influenza vaccines can be given at any time-point during pregnancy and pertussis vaccines after the first trimester. Both need a minimum interval of 14 days between immunisation and delivery and, especially for pertussis, early immunisation has been shown to increase neonatal antibody titres. Healthcare workers play a crucial role in vaccine uptake. This article aims to review the recommendations for maternal influenza and pertussis immunisation, and their physiological rationale, safety and benefit.

***Key words:*** *maternal immunisation*, *influenza*, *pertussis*, *pregnancy*, *vaccination*, *antibody transfer*

**Correspondence:**
*Christiane S. Eberhardt, MD, Center for Vaccinology, University of Geneva and Geneva University Hospitals, 1 Rue Michel-Servet, CH-1211 Geneva 4, christiane.eberhardt[at]unige.ch*

## Introduction

During pregnancy, maternal antibodies are transferred via the placenta to the fetus. This passive immunity helps to protect the infant against several diseases during the first vulnerable months of life when the immune system is still immature and active immunity not yet acquired. This concept is now used to prevent specific diseases by immunising future mothers and thus maximising the amount of antibodies available for transfer. However, there is a certain reluctance to immunise pregnant women.

Since the 1960s, vaccination during pregnancy has been officially promoted by the World Health Organization (WHO) to prevent neonatal tetanus [1]. This recommendation has led to a decrease in maternal and neonatal mortality of 90% [2]. Since then, other vaccines have been specifically implemented for pregnant women, such as seasonal influenza and pertussis vaccine. They are even considered the most efficient and safe strategy to protect neonates and young infants who are at special risk for complications.

In Switzerland, vaccination during pregnancy is now widely recommended, for seasonal influenza since 2010 [3] and pertussis since 2013 [4]. However, health professionals following-up pregnant women often do not comply with these recommendations [5, 6], because of fears about the safety of vaccination during pregnancy and insufficient awareness of the danger the diseases potentially have for the infants and pregnant women.

This article revisits rationales of maternal immunisation and synthesises recommendations, focussing on influenza and pertussis vaccines.

## Literature review methods

We conducted our literature search using PubMed, PubMed Central, and Medline databases. Search terms included "maternal immunization", "pregnancy vaccination", "pregnancy immunization", "maternal antibodies" and were combined with any of the terms "pertussis", "influenza", "blunting", "Tdap,"infant immune response". Original and review articles were used and additional sources were identified within internal references of the initially retrieved documents. All relevant publications were included without any restriction on the date of publication.

## Mechanism of maternal antibody transfer

Maternal antibodies of the IgG isotype cross the placental barrier and then contribute to the newborn's passive immunity. To date, kinetics and detailed physiology of this transfer are only partially understood.

Fully differentiated syncytiotrophoblast cells cover the villous tree of the placenta and are in contact with the maternal blood. They form the epithelial cell line that is responsible for maternal-fetal exchange [7]. Their precursor cells are cytotrophoblast cells, which are located beneath them and act as a barrier for the transfer of IgG [8].

The neonatal Fc receptor (FcRn) is localised on the surface of syncytiotrophoblast cells and binds to the constant (Fc) domain of IgG immunoglobulins. FcRn has the highest



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avidity for IgG subclasses 1, followed by $IgG_4$, $IgG_3$ and finally $IgG_2$ [9]. Antigens in vaccines administered during pregnancy are proteins and mainly induce antibody responses of IgG subclasses 1, 3 and 4 [10].

Once the IgG binds to the FcRn, the complexes enter the cell by endocytosis. In the endolysosomes, IgG molecules are protected from decay only if they are bound to the FcRn. They are then transported to the fetal side and released into the bloodstream.

FcRns are first expressed after 13 gestational weeks, when the transfer of maternal antibodies to the fetus commences [9]. However, this transfer only gradually becomes efficient: between 17 and 22 gestational weeks, the quantity of maternal antibodies in the fetal blood is only 10% of the maternal concentration and rises to 50% between 28 and 32 gestational weeks. At this time, the cytotrophoblast becomes more permeable and thus allows for a better transfer. At the due date, the concentration reaches 120 to 150% of that in the maternal blood [11].

After birth, antibodies are transferred via breastmilk to the newborn. In general, the main antibody isotype is IgA, and around 10% of transferred antibodies are IgG. It has been shown that the colostrum contains ten times more pertussis-specific IgA antibodies than IgG after tetanus-diphtheria-pertussis (Tdap) immunisation during pregnancy. Over the following months and in parallel to a decrease in the amount of protein in the breastmilk, this discrepancy between IgA and IgG grows smaller and less IgA is transferred [12]. For maternal pneumococcal immunisation, transferred antigen-specific IgA antibodies are 3 to 25 times higher than IgG antibodies, depending on the pneumococcus serotype [13].

However, the clinical effect of the transferred antibodies is thought to be restricted to the mucosal immunity and has so far been described for maternal influenza vaccination [14].

## Immunogenicity of vaccination during pregnancy

In order to transfer the maximum amount of maternal antibodies to the fetus, the highest concentration of antibodies in the maternal blood should be prevalent during the second and third trimester. To achieve this for influenza and, especially, pertussis, immunisation during pregnancy is necessary, whereas an additional dose for tetanus is not needed. However, pregnancy-related immune modulations are described for both the innate and adaptive immune systems [15, 16], with increased innate responses, a shift from T-helper 1 cells to T-helper 2 cells [16, 17] and decreased B-cell proliferation [18]. This leads to an increased susceptibility to infections, for example to influenza [19].

The question of whether vaccine immunogenicity is also different during pregnancy has been widely studied. For influenza immunisation, there are somewhat divergent data. A small study reported a decreased antibody response, but the same rate of seroconversion and seroprotection [20]; another showed only a decreased response in the first trimester and in the postpartum phase [21]. However, most studies did not describe any difference [22, 23], which is reassuring as the immunisation is intended to protect the pregnant woman also. For pertussis immunisation, few data are available. There is no alteration in postpartum immune response [24]. However, the sole outcome here is prevention of pertussis in the newborn through a maximised antibody transfer, which can be achieved only if immunisation is performed during pregnancy, owing to the short half-life of the antibody [25, 26].

## Maternal influenza immunisation

Influenza is responsible for many hospitalisations and deaths worldwide each year. The rates of morbidity and mortality vary with the virulence of the circulating strains, which depends mostly on whether the population has already been exposed to the strain in the past. Certain groups of the population are known to be at high risk, such as pregnant women and young infants. Pregnant women are particularly at risk of influenza-related complications (reviewed in [19]) because of physiological alterations occurring during pregnancy (mostly in the third trimester). These include immunological changes (such as the attenuation of the T-helper type 1 cell-mediated cytotoxic T activity), increased cardiac output and oxygen consumption, and decreased lung capacity and tidal volume [27]. Furthermore, maternal influenza infections also increase the risk of poor outcomes of pregnancy such as a higher probability of spontaneous abortion, stillbirth, prematurity or low birth weight [28, 29].

Most importantly, it has been reported that infants and young children younger than 6 months of age have the highest rate of influenza infection and hospitalisation because of the immaturity of their immune system and the absence of previous antibodies against circulating strains of influenza coupled with a more vulnerable cardiorespiratory status. There is also an increased risk of complications, such as pneumonia, laryngotracheobronchitis, encephalopathy and death [30]. A study on paediatric mortality associated with influenza reported that mortality was higher among children of 6 months of age and only one third of the deaths included children with predisposing conditions [31].

However, currently there is no available influenza vaccine licensed for use in infants under the age of 6 months. Thus, the best strategy to protect young children during the first months of life is through a “cocooning” strategy, which aims to reduce the risk of transmission to the newborns inside the family by decreasing the number of susceptible people among the household members. However, a better way to protect newborn infants is through the direct transmission of maternal antibodies during pregnancy. It has been shown that the degree and duration of protection depend on influenza antibody titres in the mother. Puck et al. reported a direct link between the concentration of antibodies specific to influenza in cord blood and the time of culture-documented influenza infection, demonstrating that newborns with the highest level of antibody to influenza had a delay in influenza infection [32]. We have also shown, in a previous study, that vaccination at any time during the second and third trimester of pregnancy, providing it is administered at least 15 days before delivery, conferred significantly higher seroprotection compared with no vaccination during pregnancy [33]. In several trials the influenza vaccine has been shown to be efficacious at preventing influenza in pregnant women and their newborns [34]. Recent randomised controlled trials, performed in



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Africa and Asia, have confirmed that vaccination of pregnant women against influenza reduced the rate of laboratory-confirmed maternal infection between 31 and 70% and of infant infection between 30 and 63% [35, 36] (and reviewed in [37]).

For influenza, it is well known that the immunity does not last, and that the influenza virus evolves and adapts to evade host immune defences. This requires the development of new vaccines against influenza each year and, therefore, it poses a challenge to administer booster doses of influenza vaccine to the susceptible population annually to maintain protection. For all these reasons, it is recommended to vaccinate pregnant women against influenza at each pregnancy. Furthermore, numerous studies assessing the safety of the influenza vaccine during pregnancy have shown the vaccine to be well tolerated, and there has been no report of unusual or severe adverse events for either the mother or the fetus (reviewed in [38] and [39]).

The recommendation to immunise pregnant women against influenza dates from the 1960s in the US [40]. In 2004, the initial recommendation was extended in the US and Canada, and vaccination was recommended at any time during pregnancy for women with underlying conditions and healthy women [41]. The WHO has recommended influenza vaccination during the influenza season for all pregnant women since 2005 [42]. In contrast, most European countries introduced seasonal influenza vaccination for pregnant women only after the H1N1/09 influenza pandemic. In Switzerland, influenza immunisation has been recommended since 2010 [3] and can be administered at any time during pregnancy [43].

Despite the official recommendations, the rate of seasonal influenza vaccination remains low in pregnant women in Switzerland, estimated to be around 20% [5]. Possible factors include a lack of awareness of potential complications associated with influenza infection in pregnant women and in young infants, and safety concerns about vaccination during pregnancy. The most important barrier to influenza immunisation in pregnancy has been shown to be the lack of knowledge of the recommendations by healthcare workers, compounded by the fact that the immunisation was not offered or discussed by obstetricians [5, 6].

Several studies have shown that the most important factor that could increase vaccine acceptability in pregnant women was the communication of clear information by healthcare workers (reviewed in [5] and [6]).

Therefore, every healthcare worker should be aware of the risk associated with influenza in pregnant women and young infants, and should recall the recommendations on influenza vaccine to every pregnant woman, and those in contact with newborn infants.

## Maternal pertussis vaccination

*Bordetella pertussis* is a highly contagious Gram-negative bacterium that is transmitted by airborne droplets. It causes a localised respiratory infection, and is rarely found disseminated in the bloodstream or other organs. The related childhood disease is called pertussis or "whooping cough" and is characterised by severe bouts of coughing. Its complications include apnoea, severe lymphocytosis, multi-organ failure and death, especially in babies under the age of 3 months [44, 45]. Only recently a case of fatal pertussis occurred in a 5-week-old infant in Switzerland [46]. However, this disease is not limited to children, and a history of previous infection does not confer life-long immunity. In adults, whopping cough presents with a large spectrum of symptoms, from prolonged cough to rib fractures and even fatal outcomes in the elderly [47–49].

Two attempts had been made to immunise the population, both with specific weaknesses. The first whole cell vaccine elicited too strong clinical reactions and was replaced by an acellular pertussis vaccine in industrialised countries in the late 1990s. The latter showed decreased efficacy, leading to a resurgence of pertussis (reviewed in [50]). This recently became a major public health issue, and not only because of an increased incidence in adolescents as a sign of vaccine failure. The main concern was a rise in morbidity and thus a higher rate of mortality in neonates and very young infants [51].

Three different strategies to protect this vulnerable population were tested. Immunisation after birth did not confer a sufficient and protective immune response in the first months of life [52–54]. Secondly, with promotion of the so-called "cocooning" strategy, household and family members of neonates were immunised against pertussis to avoid transmission. This is only partially effective [55], as humans and non-human primates who are immunised with the acellular vaccine can still be asymptomatic carriers [51, 56, 57]. In Switzerland, immunisation of household members is recommended if their last pertussis vaccine was more than 10 years ago [43].

To date the only proven strategy is maternal immunisation during pregnancy with a transfer of passive immunity to the fetus. It was first introduced in the United States in 2011 [58, 59] and in the United Kingdom in 2012 [60]. In Switzerland, pregnant women are immunised as of 13 gestational weeks, ensuring an interval of a minimum of 4 weeks after the last tetanus immunisation [4]. Since 2017, maternal vaccination has been recommended during every pregnancy [43].

Several studies have shown Tdap immunisation during pregnancy to be safe [61–64], and in healthy adults no side effects were observed if the last tetanus dose was recent [65]. The Tdap vaccine is, in contrast to influenza vaccination, adjuvanted with aluminium phosphate (0.39 mg/dose for Boostrix® and 1.5 mg/dose for Adacel®). There is no evidence that the aluminium in the vaccine puts the developing fetus at risk, especially because the natural adult dietary ingestion of aluminium is estimated to be 7 to 9 mg per day [66].

Despite its recent introduction, several studies have already proven the efficacy of this measure. Population-based studies from the United Kingdom have estimated a vaccine efficacy of 91 to 95% to prevent infant death [67, 68]. Recently, a retrospective cohort study from California showed that immunisation during pregnancy decreased the likelihood of contracting pertussis up to 2 to 3 months after birth, compared with a postpartum vaccination [69].

Recommendations regarding the timing of maternal immunization were based on assumptions about the kinetics of antibody production after vaccination and the transplacental transfer. Switzerland recommended vaccination as of 13 gestational weeks [4], whereas the US and Great-Britain initially were in favour of a vaccination between 26 and 36 gestational weeks [59, 60]. In a recent observational study,



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we showed that immunisation during the second trimester (13–26 gestational weeks) elicited higher antibody titres in the newborn compared with later vaccination [70], a finding that was also observed after preterm birth [71]. However, the half-life of anti-pertussis toxin antibodies is only about 4 to 5 weeks [26], and maternal antibodies diminish rapidly after birth [72], such that the first childhood active vaccination at 2 months of age should not be postponed.
Currently, maternal pertussis vaccination is the sole strategy to prevent neonatal pertussis and immunisation should be performed early during pregnancy.

## Infant immunisation responses in presence of maternal antibodies

In contrast to influenza immunisation, the first infant pertussis (and diphtheria and tetanus) immunisations take place in the presence of maternal antibodies. Studies examining the influence of those antibodies on the immune response to childhood immunisation at 2 months report contrasting data. In some studies, a slight decrease (blunting) in antibody responses against tetanus or various components of the acellular pertussis vaccine was seen. However, no study showed a persistent blunting after the fourth dose at 15 months [64, 72–75]. Also, there is no evidence that the decreased antibody levels have a clinical effect.
We await the publication of further research on this matter, but current data suggest that the advantageous protection afforded to the newborn by maternal antibodies far supersedes the potential and only temporary negative “blunting” effects in response to active immunisation.

## Conclusion and future directions

During pregnancy, maternal immunisation against seasonal influenza and pertussis are recommended, as they are simple and efficient strategies to protect mothers and their offspring. Immunisation should be performed early during pregnancy to allow for maternal antibody generation and transmission. Healthcare workers have a crucial role in securing high vaccine coverage and they should encourage and advise maternal vaccination when in contact with a pregnant patient.

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