

**CONTENTS**

Vaccination in Pregnancy

**EDITORIAL BOARD**

*Editor: Delane Shingadia*

**Board Members**

*David Burgner (Melbourne, Australia)*  
*Kow-Tong Chen (Tainan, Taiwan)*  
*Luisa Galli (Florence, Italy)*  
*Steve Graham (Melbourne, Australia)*

*Cristiana Nascimento-Carvalho (Bahia, Brazil)*  
*Ville Peltola (Turku, Finland)*  
*Emmanuel Roilides (Thessaloniki, Greece)*  
*Ira Shah (Mumbai, India)*

*George Syrogiannopoulos (Larissa, Greece)*  
*Tobias Tenenbaum (Mannheim, Germany)*  
*Marc Tebruegge (Southampton, UK)*  
*Marceline Tutu van Furth (Amsterdam, The Netherlands)*



# Vaccination in Pregnancy—Recent Developments

*Christine E. Jones, PhD,\*†‡ Anna Calvert, MRCPCH,§ and Kirsty Le Doare, PhD§¶||\*\**

**Key Words:** vaccine, pregnancy, immunization

As early as the 19th century vaccination in pregnancy has been observed to protect both mothers and infants against smallpox,

Accepted for publication November 1, 2017.  
 From the \*Faculty of Medicine and †Institute for Life Sciences, University of Southampton, Southampton, United Kingdom; ‡Clinical and Experimental Sciences, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; §Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's, University of London, London, United Kingdom; ¶Centre for International Child Health and ||Department of Academic Paediatrics, Imperial College, London, United Kingdom; and \*\*West Africa Global Health Alliance, Institut en Recherche en Santé, Dakar, Senegal.  
 C.E.J. has received funding from the Immunising PRenant women and INFants neTwork (IMPRINT), funded by the GCRF Networks in Vaccines Research and Development, which was co-funded by the MRC and BBSRC, the National Vaccine Program Office (NVPO) and Bill & Melinda Gates Foundation, Grant OPP1119788, Global Alignment of Immunization Safety Assessment in pregnancy (GAIA). K.L.D. has received funding from Immunising PRenant women and INFants neTwork (IMPRINT), funded by the GCRF Networks in Vaccines Research and Development, which was co-funded by the MRC and BBSRC. K.L.D. has also been supported by Thrasher Foundation 12250 and Bill and Melinda Gates Foundation OP1153630 for the assessment of antibody against Group B Streptococcus. A.C. has no funding or conflicts of interest to disclose.  
 Address for correspondence: Christine Jones, PhD, Clinical and Experimental Sciences, Mail point 810, F Level, South Academic Block, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, United Kingdom. E-mail: c.e.jones@soton.ac.uk.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.  
 ISSN: 0891-3668/18/3702-0191  
 DOI: 10.1097/INF.0000000000001822

pertussis and tetanus. More recently the pace and focus of maternal vaccination has accelerated, most significantly since the influenza pandemic of 2009. Vaccination in pregnancy boosts the concentration of vaccine-specific antibody in the mother to increase antibody concentration in the infant at birth, providing protection until the period of maximum susceptibility or risk has passed or until the infant has completed the routine infant immunizations.

There are now 3 vaccines, which have specific recommendations for routine use in pregnancy in an increasing number of countries, and other vaccines are progressing through clinical trials. Here we review the mechanisms of protection, the current recommendations and future prospects, and evaluation of safety of vaccines in pregnancy.

## MECHANISMS OF PROTECTION BY VACCINATION IN PREGNANCY

Immunoglobulin G (IgG) is the only antibody isotype actively transferred across the placenta from around 13 weeks of gestation and increases exponentially during the third trimester such that the concentration of IgG in the newborn infant is similar to, or exceeds, that in the mother. IgG provides passive immunity to the infant in the first months of life.

The neonatal Fc receptor facilitates transcytosis of maternal IgG. IgG is transferred from maternal blood across the syncytiotrophoblast layer of the placenta, initially by endocytosis of IgG. Within the acidic endosome, IgG binds to membrane-bound neonatal Fc receptor, which is then released

on the fetal side of the syncytiotrophoblast as the pH returns to physiologic pH. Neonatal Fc receptor is then recycled back to the maternal side of the syncytiotrophoblast to bind further IgG.

There are a number of factors that may affect the efficiency of IgG transcytosis, including gestation, IgG subclass and maternal infection.<sup>1</sup>

The concentration of fetal IgG in late second and early third trimester is 25%–50% lower than that found in term infants, which has significant relevance for the timing of vaccination in pregnancy to provide protection to preterm infants. There remains debate in the literature about the optimal timing of vaccination in pregnancy.<sup>2</sup> Vaccination in the second trimester would provide longer cumulative exposure to maternal IgG, and potentially result in higher functional IgG in the infant. Later vaccination, around 28–32 weeks, would more closely match the peak of the vaccine response with the timing of maximal transplacental transfer of IgG and therefore potentially provide greater protection to the infant. The ideal timing for vaccination is of scientific importance; however a more pragmatic approach might be to provide a wide window of opportunity for vaccination in pregnancy, to allow a greater number of women the opportunity to be vaccinated.

The 4 subclasses of IgG are transferred across the placenta with differing efficiency—with IgG1 being found in highest concentration in cord blood, followed by IgG4, IgG3 and IgG2. Therefore, maternal immunization with a polysaccharide vaccine, inducing predominately IgG2, might offer less protection to the infant against infection

The ESPID Reports and Reviews of *Pediatric Infectious Disease Journal* series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.

compared with a protein or protein-conjugated vaccine, which elicits predominately IgG1 and IgG3.

Maternal infections such as malaria and HIV can also affect transplacental transfer of antibody and therefore the concentration of specific antibody in the infant. This underlines the importance of optimizing maternal health for the benefit of both mother and infant.

While the predominant mechanism of protection afforded by maternal vaccination is transplacental transfer of IgG, there is potential for additional protection conferred by antibody in breast milk. Secretory IgA (sIgA) is thought to protect against diarrheal and respiratory pathogens through a variety of mechanisms, including immobilization, prevention of adhesion or by neutralization of toxins or virulence factors.<sup>3</sup> Several clinical trials have identified significantly higher vaccine-specific sIgA in the breast milk of women vaccinated in the third trimester of pregnancy compared with unvaccinated women. These antibodies appear long-lived with elevated sIgA in breast milk measured up to 7 months postpartum. As maternal vaccination strategies develop, it will be important to monitor the potential effects of vaccination on the composition of breast milk; concerns have been raised about the potential blunting of infant immune responses to live oral vaccines from high breast milk sIgA; however further research is required to confirm these findings and understand the clinical implications.

## VACCINES WITH SPECIFIC RECOMMENDATIONS FOR USE IN PREGNANCY

### Tetanus

Maternal vaccination with inactivated tetanus toxoid vaccine has played a major role in reducing the global burden of neonatal tetanus and has been part of the Expanded Programme of Immunization since it began in 1974. The World Health Organization estimates that there has been a more than 95% reduction in deaths from neonatal tetanus since the 1980s, from an estimated 787,000 deaths in 1988 to 34,019 deaths in 2015 (the latest year for which data are available), an achievement in which vaccines have played a significant role. The vaccine schedule required in pregnancy depends on the number of doses previously received; a lifetime total of at least 5 doses are required for maximal protection.<sup>4</sup> The tremendous success of maternal tetanus vaccination has set the precedent for further development of vaccination in pregnancy.

### Influenza

It has been known since the global influenza pandemic of 1918 that pregnant

women are disproportionately affected by the complications of influenza. Influenza vaccination has been introduced for pregnant women in many countries, and the World Health Organization recommends that pregnant women are the highest priority for countries considering the initiation or expansion of seasonal influenza immunization programs. Vaccination is offered primarily for the protection of the pregnant women, but studies have also shown that vaccination in pregnancy can protect infants from influenza.<sup>5</sup> In countries where recommendations for maternal influenza vaccination exist, a single dose is recommended at any gestation during the influenza season. This should be repeated during each pregnancy.

### Pertussis

Whole-cell pertussis vaccination in pregnancy was first explored in the 1930s, but it was not until 2012 that acellular pertussis vaccination first became part of national programs for all pregnant women. This was introduced first in the United States and United Kingdom in response to significantly increased rates of pertussis observed across all age groups, but particularly in infants less than 3 months old, who are at highest risk of serious morbidity and mortality. Vaccination in pregnancy with a pertussis containing vaccine has been shown to be highly effective in preventing disease in young infants, with vaccine effectiveness of up to 93%.<sup>6</sup> Most countries recommending its use administer a single dose of vaccine in the third trimester; however, the United Kingdom has recently extended the recommendation to include any women from 16 weeks gestation onward. As there is currently no monovalent pertussis vaccine available, the pertussis vaccine is given in combination with tetanus and diphtheria, and in some countries also with polio. Pertussis vaccination should be repeated in each pregnancy.

## FUTURE PROSPECTS FOR VACCINATION IN PREGNANCY

### Group B Streptococcus

Human trials of the group B streptococcus (GBS) vaccines were carried out in the 1980s, and were based on capsular polysaccharide (CPS). The initial vaccine was developed as a plain CPS-based vaccine, but with variable immunogenicity in healthy adults, subsequent formulations have been developed as CPS–protein–conjugate vaccines. Monovalent, tetanus toxoid–conjugated vaccines incorporating each of the 5 major CPSs of GBS (Ia, Ib, II, III, V) have been evaluated in nonpregnant women in phase 1 and 2 trials. Trivalent vaccines conjugated to CRM<sub>197</sub> (nontoxic mutant of diphtheria toxin) have

entered clinical trials and over 500 pregnant women have received the experimental vaccine.<sup>7</sup> The vaccine appears well tolerated and highly immunogenic. A phase 1 clinical trial with a GBS protein vaccine (NCT02459262), made from the N-terminal domains of the Rib and AlphaC surface proteins of GBS, has recently been completed.

### Respiratory Syncytial Virus

Early clinical trials of a formalin-inactivated respiratory syncytial virus (RSV) infant vaccine resulted in enhanced RSV disease in infants, halting further development of this vaccine. A number of new formulation RSV vaccine candidates are in development. These include gene-based adenovirus vector vaccines, particle-based vaccines and live attenuated vaccines.<sup>7</sup> Good safety and immunogenicity of an RSV subunit vaccine containing purified RSV fusion protein has been demonstrated in pregnant women who received the vaccine in the third trimester.<sup>8</sup> In this study, the largest of its kind, both mothers and their infants showed a 4-fold rise in serum RSV IgG concentration with similar rises in breast milk sIgA and IgG. A large, international, phase 3 efficacy trial of an RSV F nanoprotein vaccine in pregnant women is currently in progress (NCT02624947).

### Cytomegalovirus

Developing a vaccine to prevent congenital cytomegalovirus (CMV) infection is complex and our understanding of the immunologic factors that prevent congenital CMV transmission is incomplete.<sup>9</sup> However, as for GBS and RSV there is proof of concept that maternal antibody may be protective against fetal transmission and severe sequelae from disease.

Initial vaccine candidates were live attenuated CMV vaccines. Though safe and immunogenic in seronegative adults, they failed to boost CMV-specific immunity in seropositive adults and have failed to prevent seronegative women acquiring CMV when exposed to young children who were actively shedding virus.<sup>9</sup> These live attenuated vaccines have now been further developed to include recombination with less-attenuated CMV strains and co-administration with interleukin 12. Other vaccines include subunit vaccination incorporating the CMV surface glycoprotein B (gB) that mediates CMV cell entry or subunit vaccines using viral vectors. A recombinant protein gB adjuvanted with the squalene-based adjuvant MF59 has proven safe and immunogenic in phase 1 and phase 2 studies in healthy seronegative and seropositive adults, transplant recipients and adolescents. There have been no trials of any CMV vaccine in pregnant women to date.

## SAFETY OF VACCINES IN PREGNANCY

The most important consideration for pregnant women, health-care providers, manufacturers and regulators is safety. The assessment of this is complicated by the frequency of adverse events associated with pregnancy itself and, when these occur within the context of a clinical trial, it is vital to fully assess safety endpoints to make a judgment on causality of such events. Knowledge of background rates of key adverse events in pregnancy and infants is important to assess whether events are occurring at a higher frequency than in an unvaccinated population of women and their infants.

There is an increasing body of evidence to support the safety of tetanus, influenza and pertussis vaccination in pregnancy for the pregnant women, fetus and infant. Comparing studies or pooling data is hampered by failure to collect or report essential data and by inconsistent use of case definitions. Recently, the Global Alignment of Immunization Safety Assessment in Pregnancy Project (<http://gaia-consortium.net>) has developed guidelines for the collection of essential safety data in clinical trials of vaccines in pregnancy and defined key adverse obstetric and neonatal events to facilitate data harmonization.<sup>10</sup> Comparison of studies and pooling of data are essential to detect

rare events, which require very large sample sizes, and thorough safety assessment is essential to maintaining confidence in a particular vaccine and immunization programs.

## CONCLUSIONS

The field of maternal vaccination is rapidly advancing. There is increasing evidence to support the safety, immunogenicity and effectiveness of vaccination in pregnancy. A number of challenges and key knowledge gaps remain including acceptance of an increasing number of vaccines with an indication for use in pregnancy, optimal timing of vaccination, the effect of antigen type on transplacental transfer of antibody, correlates of protection against key pathogens, and the effect on subsequent infant immune responses to vaccination.<sup>11</sup> Despite these challenges, vaccination in pregnancy has and continues to play an important role in protecting pregnant women and developing fetuses and infants from infection.

## REFERENCES

1. Wilcox CR, Holder B and Jones CE (2017) Factors Affecting the FcRn-Mediated Transplacental Transfer of Antibodies and Implications for Vaccination in Pregnancy. *Front. Immunol.* 8:1294. doi: 10.3389/fimmu.2017.01294.
2. Calvert A, Jones CE. Placental transfer of antibody and its relationship to vaccination in

pregnancy. *Curr Opin Infect Dis.* 2017;30:268–273.

3. Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: a review on its composition and bioactivity. *Early Hum Dev.* 2015;91:629–635.
4. Khan R, Vandelaer J, Yakubu A, et al. Maternal and neonatal tetanus elimination: from protecting women and newborns to protecting all. *Int J Womens Health.* 2015;7:171–180.
5. Madhi SA, Cutland CL, Kuwanda L, et al.; Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med.* 2014;371:918–931.
6. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet.* 2014;384:1521–1528.
7. Heath PT, Culley FJ, Jones CE, et al. Group B streptococcus and respiratory syncytial virus immunisation during pregnancy: a landscape analysis. *Lancet Infect Dis.* 2017;17:e223–e234.
8. Munoz FM, Piedra PA, Glezen WP. Safety and immunogenicity of respiratory syncytial virus purified fusion protein-2 vaccine in pregnant women. *Vaccine.* 2003;21:3465–3467.
9. Krause PR, Bialek SR, Boppana SB, et al. Priorities for CMV vaccine development. *Vaccine.* 2013;32:4–10.
10. Bonhoeffer J, Kochhar S, Hirschfeld S, et al.; GAIA project participants. Global alignment of immunization safety assessment in pregnancy - The GAIA project. *Vaccine.* 2016;34:5993–5997.
11. Marchant A, Sadarangani M, Garand M, et al. Maternal immunisation: collaborating with mother nature. *Lancet Infect Dis.* 2017;17:e197–e208.