Vaccination during pregnancy: current and possible future recommendations

Kirsten Maertens1 · Marjolein Rozemarie Paulien Orije1 · Pierre Van Damme1 · Elke Leuridan1

Received: 13 September 2019 / Revised: 15 November 2019 / Accepted: 23 December 2019 / Published online: 7 January 2020
© Springer-Verlag GmbH Germany, part of Springer Nature 2020

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

Communicated by Nicole Ritz

Kirsten Maertens
kirsten.maertens@uantwerp.be

Marjolein Rozemarie Paulien Orije
marjolein.orije@uantwerp.be

Pierre Van Damme
pierre.vandamme@uantwerp.be

Elke Leuridan
elke.leuridan@uantwerp.be

1 Centre for the Evaluation of Vaccination, Vaccine & Infectious Diseases Institute, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

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
Prt Pertactin
PT Pertussis toxin
RSV Respiratory syncytial virus
Tdap Tetanus diphtheria acellular pertussis
TT Tetanus toxoid
WHO World Health Organization
wP Whole cell pertussis
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 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 pre-term 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 woman 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 endpoints 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 designated 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].

Acknowledgements Kirsten Maertens is beneficiary of a postdoctoral mandate fellowship from the FWO (FWO12R5719N).

Author contribution KM drafted the manuscript. MRPO, PVD and EL performed a critical revision of the manuscript.

Compliance with ethical statements

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Kachikis A, Englund JA (2016) Maternal immunization: optimizing protection for the mother and infant. J Inf Secur 72(Suppl):S83–S90
2. Maertens K, Cabore RN, Huygen K, Hens N, Van Damme P, Leuridan E (2016) Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study. Vaccine 34:142–150
3. Maertens K, De Schutter S, Braeckman T, Baerts L, Van Damme P, De Meester I, Leuridan E (2014) Breastfeeding after maternal immunisation during pregnancy: providing immunological protection to the newborn: a review. Vaccine 32:1786–1792
4. Calvert A, Jones CE (2017) Placental transfer of antibody and its relationship to vaccination in pregnancy. Curr Opin Infect Dis 30:268–273
5. Faucette AN, Unger BL, Gonik B, Chen K (2015) Maternal vaccination: moving the science forward. Hum Reprod Update 21:119–135
6. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Cameiro-Sampaio M (2012) IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol 2012:985646
7. Abu-Rayba B, Smolen KK, Willems F, Kollmann TR, Marchant A (2016) Transfer of maternal antimicrobial immunity to HIV-exposed newborns. Front Immunol 7:338
8. De Schutter S, Maertens K, Baerts L, De Meester I, Van Damme P, Leuridan E (2015) Quantification of vaccine-induced antipertussis toxin secretory IgA antibodies in breast milk: comparison of different vaccination strategies in women. Pediatr Infect Dis J 34:e149–e152
9. Abu Rayba B, Snugo I, Kessel A, Peterman M, Bader D, Peri R, Ashmar N, Gonda R, Bamberger E (2014) The induction of breast milk pertussis specific antibodies following gestational tetanus-diphtheria-acellular pertussis vaccination. Vaccine 32:5632–5637
10. Demers-Mathieu V, Underwood MA, Beverly RL, Nielsen SD, Dallas DC (2018) Comparison of human milk immunoglobulin survival during gastric digestion between preterm and term infants. Nutrients 10
11. Eberhardt CS, Blanchard-Rohner G, Lemaître B, Combescure C, Othenin-Girard V, Chilin A, Petre J, Martinez de Tejada B, Siegrist JM (2016) Pertussis antibody transfer to preterm neonates after second- versus third-trimester maternal immunization. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 64:1129–1132
12. Malek A, Sager R, Schneider H (1994) Maternal-fetal transport of immunoglobulin G and its subclasses during the third trimester of human pregnancy. Am J Reprod Immunol 32:8–14
13. Leuridan E, Hens N, Hutse V, leven M, Aerts M, Van Damme P (2010) Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ 340:c1626
14. Hoang HT, Leuridan E, Maertens K, Nguyen TD, Hens N, Vu NH, Cabore RN, Duong HT, Huygen K, Van Damme P, Dang AD (2016) Pertussis vaccination during pregnancy in Vietnam: results of a randomized controlled trial. Vaccine 34:151–159
15. Voysey M, Pollard AJ, Sadarangani M, Fanshawe TR (2017) Prevalence and decay of maternal pneumococcal and meningococcal antibodies: a meta-analysis of type-specific decay rates. Vaccine 35:5850–5857
16. Vilajeliu A, Ferrer L, Munros J, Gorina A, Lopez M, Costa J, Bayas JM (2016) Pertussis vaccination during pregnancy: antibody persistence in infants. Vaccine 34:3719–3722
17. Marchant A, Sadarangani M, Garand M, Daubny N, Verhasselt V, Pereira L, Bjornson G, Jones CE, Halperin SA, Edwards KM, Heath P, Openshaw PJ, Scheifele DW, Kollmann TR (2017) Maternal immunisation: collaborating with mother nature. Lancet Infect Dis 17:e197–e208
18. Orije MRP, Maertens K, Corbieri V, Wanlapakorn N, Van Damme P, Leuridan E, Mascart F (2020) The effect of maternal antibodies on the cellular immune response after infant vaccination: a review. Vaccine 38:20–28
19. Niewiarski S (2014) Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol 5:446
20. WHO (2019) Protecting all against tetanus. Guide to sustaining maternal and neonatal tetanus elimination (MNTE) and broadening tetanus protection for all populations.
21. Thwaites CL, Beeching NJ, Newton CR (2015) Maternal and neonatal tetanus. Lancet 385:362–370
22. Stanfield JP, Galazka A (1984) Neonatal tetanus in the world today. Bull World Health Organ 62:647–669
23. United Nations Children’s Fund / World Health Organization / United Nations Population Fund (2002) Maternal and neonatal tetanus elimination by 2005: strategies for achieving and maintaining elimination.
24. Liang JL, Tiwari T, Moro P, Messonnier NE, Reingold A, Sawyer M, Clark TA (2018) Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 67:1–44
25. Blencowe H, Lawn J, Vandelaa J, Roper M, Cousens S (2010) Tetanus toxoid immunization to reduce mortality from neonatal tetanus. Int J Epidemiol 39(Suppl 1):i102–i109
26. WHO (2018) Global Health Observatory (GHO) data. Diphtheria-tetanus-pertussis (DTP3) immunization coverage
27. Sealey KL, Belcher T, Preston A (2016) Bordetella pertussis epidemiology and evolution in the light of pertussis resurgence. Infect Genet Evol 40:136–143
28. Hasenoot C, Martin CK, Krishnarajah G, Becker LK, Buikema A, Tan TQ (2017) Incidence and burden of pertussis among infants less than 1 year of age. Pediatr Infect Dis J 36:e54–e61
29. Public Health England (2016) Vaccination against pertussis (Whooping cough) for pregnant women - 2016: information for healthcare professionals
30. Centers for Disease Control and Prevention (2013) Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women-Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Mortal Mortal Wkly Rep 62:131–135
31. McHugh L, Marshall HS, Perrett KP, Nolan T, Wood N, Lambert SB, Richardson P, Ware RS, Binks P, Binks MJ, Andrews RM (2019) The safety of influenza and pertussis vaccination in pregnancy in a cohort of Australian mother-infant pairs, 2012-2015: the FluMum Study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 68:402–408
32. McMillan M, Clarke M, Parrela A, Fell DB, Amirthalingam G, Marshall HS (2017) Safety of tetanus, diphtheria, and pertussis vaccination during pregnancy: a systematic review. Obstet Gynecol 129:560–573
33. Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, Walter EB, Jackson LA, England JA, Edwards MS, Healy CM, Petrie CR, Ferreira J, Goll JB, Baker CJ (2014) Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. Jama 311:1760–1769
34. Huygen K, Cabore RN, Maertens K, Van Damme P, Leuridan E (2015) Humoral and cell mediated immune responses to a pertussis vaccine containing vaccine in pregnant and nonpregnant women. Vaccine 33:4117–4123
35. Abu Rayba B, Snugo I, Kessel A, Peterman M, Vaknin A, Bamberger E (2015) The decline of pertussis-specific antibodies after tetanus, diphtheria, and acellular pertussis immunization in late pregnancy. J Infect Dis 212:1869–1873
36. Dahreba G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Fry NK, Ramsay M (2015) A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 60:333–337
37. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, Fry NK, Miller E, Ramsay M (2014) Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 384:1521–1528
38. Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, Andrews N (2016) Sustained effectiveness of the maternal pertussis immunization program in England 3 years following
introduction. Clinical infectious diseases: official publication of the Infectious Diseases Society of America 63:S236–S243

39. Abu-Rayba B, Edwards KM (2019) Optimizing the timing of vaccine administration during pregnancy. Jama 321:935–936

40. Naidu MA, Muljadi R, Davies-Tuck ML, Wallace EM, Giles ML (2016) The optimal gestation for pertussis vaccination during pregnancy: a prospective cohort study. American journal of obstetrics and gynecology 215:237.e231–236

41. Eberhardt CS, Blanchard-Rohner G, Lemaitre B, Boukrid M, Combescure C, Othenin-Girard V, Chilin A, Petre J, de Teijada BM, Siegrist CA (2016) Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. Clinical infectious diseases: official publication of the Infectious Diseases Society of America 62:829–836

42. Englund JA, Anderson EL, Reed GF, Decker MD, Edwards KM, Eberhardt CS, Blanchard-Rohner G, Lemaitre B, Boukrid M, Gansert J, Kampmann B, van der Klis F, Vamvakas G, Donaldson B, Bouqueau M, Holder B, Kampmann B (2019) Antibody responses to Bordetella pertussis during pregnancy in Belgium: follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age. Vaccine 34:3613–3619

43. Maertens K, Cabore RN, Huygen K, Vermeiren S, Hens N, Van Damme P, Leuridan E (2016) Pertussis vaccination during pregnancy in Belgium: follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age. Vaccine 34:3613–3619

44. Maertens K, Hoang TT, Nguyen TD, Cabore RN, Duong TH, Huygen K, Hens N, Van Damme P, Dang DA, Leuridan E (2016) The effect of maternal pertussis immunization on infant vaccine response to a booster pertussis-containing vaccine in Vietnam. Clinical infectious diseases: official publication of the Infectious Diseases Society of America 63:S197–S204

45. Halperin SA, Langley JM, Ye L, MacKinnon-Cameron D, Elsherif M, Allen VM, Smith B, Halperin BA, McNeil SA, Vanderkooi OG, Dwinnell S, Wilson RD, Tapiero B, Boucher M, Le Saux N, Gruslin A, Vaubry W, Chandra S, Dobson S, Money D (2018) A randomized controlled trial of the safety and immunogenicity of tetanus, diphtheria, and acellular pertussis vaccine immunization during pregnancy and subsequent infant immune response. Clinical infectious diseases: official publication of the Infectious Diseases Society of America 67:1063–1071

46. Rice TF, Diavatopoulos DA, Smits GP, van Gageldonk P, Berbers G, van der Klis F, Vanvaks G, Donaldson B, Bouqueau M, Holder B, Kampmann B (2019) Antibody responses to Bordetella pertussis and other childhood vaccines in infants born to mothers who received pertussis vaccine in pregnancy- a prospective, observational cohort study from the UK. Clin Exp Immunol

47. Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waith PA, England A, Matheos M, Bai X, Findlow H, Burbidge P, Thalassellis V, Hallis B, Goldblatt D, Borrow R, Heath PT, Miller E (2015) Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. Clinical infectious diseases: official publication of the Infectious Diseases Society of America 61:1637–1644

48. Wanlapakorn N, Maertens K, Vongpunsawad S, Peumpa J, Tran TMP, Hens N, Van Damme P, Thiiriaed A, Raze D, Locht C, Poovorawan Y, Leuridan E (2019) Quantity and quality of antibodies after acellular versus whole cell pertussis vaccines in infants born to mothers who received Tdap during pregnancy: a randomised trial. Clinical infectious diseases: official publication of the Infectious Diseases Society of America

49. Maertens K, Burbidge P, Van Damme P, Goldblatt D, Leuridan E (2017) Pneumococcal immune response in infants whose mothers received tetanus, diphtheria and acellular pertussis vaccination during pregnancy. Pediatr Infect Dis J 36:1186–1192

50. Campbell H (2019) An update of the maternal pertussis immunization programme in England. Paper presented at Bordetella2019 Brussels.

51. Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M (2017) Pregnancy as a risk factor for severe outcomes from influenza virus infection: a systematic review and meta-analysis of observational studies. Vaccine 35:521–528

52. Louie JK, Acosta M, Jamieson DJ, Honein MA (2010) Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 362:27–35

53. Giles ML, Krishnaswamy S, Macartney K, Cheng A (2018) The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother:1–13

54. Fell DB, Savitz DA, Kramer MS, Gessner BD, Katz MA, Knight M, Luteijn JM, Marshall H, Bhat N, Gravett MG, Skidmore B, Ortiz JR (2017) Maternal influenza and birth outcomes: systematic review of comparative studies. Bjog 124:48–59

55. Nair H, Brooks WA, Katz M, Rocca A, Berkley JA, Madhi SA, Zimmerman JM, Gordon A, Sato M, Howe S, Krishnan A, Ope M, Lindblade KA, Carosone-Link P, Lucero M, Ochigew N, Kamimoto L, Duerger E, Bhat N, Yong S, Thedotatou E, Chittaganpitch M, Chima O, Balmaseda A, Buchy P, Harris E, Evans V, Katayose M, Gaur B, O’Callaghan-Gordo C, Goswami D, Arvelo W, Venter M, Briese T, Tokarz R, Widdowson MA, Mounts AW, Breiman RF, Feikin DR, Klugman KP, Olsen SJ, Gessner BD, Wright PF, Rudan I, Broor S, Simoes EA, Campbell H (2011) Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet 378:1917–1930

56. Madhi SA, Nunes MC, Cutland CL (2014) Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 371: 2340

57. Centers for Disease Control and Prevention (2019) Pregnant Women & Influenza (Flu)

58. World Health Organization Europe (2014) European Vaccine Action Plan 2015–2020

59. World Health Organization (2012) Vaccines against influenza WHO position paper - November 2012. Wkly Epidemiol Rev 87: 461–476

60. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, Hvid A (2012) Risk of adverse fetal outcomes following administration of a pandemic influenza A (H1N1) vaccine during pregnancy. Jama 308:165–174

61. Schlautelder EP, Ambroggio L, McNeil MM, Finkelma BF, Way SS (2018) Declining responsiveness to influenza vaccination with progression of human pregnancy. Vaccine 36:4734–4741

62. Kay AW, Bayless NL, Fukuyama J, Aziz N, Dekker CL, Mackey S, Swan GE, Davis MM, Blash CA (2015) Pregnancy does not attenuate the antibody or plasmablast response to inactivated influenza vaccine. J Infect Dis 212:861–870

63. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, Adrian PV, van Niikker N, Truemicht F, Ortiz JR, Venter M, Violari A, Neuzil K, Simoes EA, Klugman KP, Nunes MC (2014) Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 371:918–931

64. Steinhoff MC, Omer SB, Roy E, Arifeen SE, Raqib R, Altaye M, Breiman RF, M BBSK (2010) Influenza immunization in pregnancy-antibody responses in mothers and infants. N Engl J Med 362:1644–1646

65. Nunes MC, Cutland CL, Digheo B, Bate J, Jones S, Hugo A, van Niekker N, Kuwanda L, Izu A, Weinberg A, Madhi SA (2015) Kinetics of hemagglutination-inhibiting antibodies following maternal influenza vaccination among mothers with and those without HIV infection and their infants. J Infect Dis 212:1976–1987

66. Cuningham W, Geard N, Fielding JE, Brant S, Madhi SA, Nunes MC, Christian LM, Lin SY, Lee CN, Yamaguchi K, Bisgaard H,
Chawes B, Chao AS, Blanchard-Rohner G, Schlaudecker EP, Fisher BM, McVernon J, Moss R (2019) Optimal timing of influenza vaccine during pregnancy: a systematic review and meta-analysis. *Influenza Other Respir Viruses*

67. Sullivan SG, Price OH, Regan AK (2019) Burden, effectiveness and safety of influenza vaccines in elderly, paediatric and pregnant populations. *Ther Adv Vaccines Immunother* 7: 2515135519826481

68. Kachikis A, Eckert LO, Englund J (2018) Who’s the target: mother or baby? *Viral Immunol* 31:184–194

69. PATH (2017) The advancing maternal immunization collaboration. Forging a way forward to save infant lives from infectious diseases by vaccinating mothers

70. PATH (2018) Advancing RSV maternal immunization: a gap analysis brief. An analysis to identify needs for vaccine decision-making and introduction

71. Munoz FM (2019) Phase 3 PREPARE study: efficacy and safety of an RSV vaccine administered to pregnant women. Paper presented at 37th annual meeting of the European Society for Pediatrihc Infectious Diseases. Malmö, Sweden.

72. Vornhagen J, Adams Waldorf KM, Rajagopal L (2017) Perinatal group B streptococcal infections: virulence factors, immunity, and prevention strategies. *Trends Microbiol* 25:919–931

73. WHO (2017) Group B Streptococcus vaccine development technology roadmap. Priority activities for development, testing, licensure and global availability of Group B streptococcus vaccines

74. Hillier SL, Ferrieri P, Edwards MS, Ewell M, Ferris D, Fine P, Carey V, Meyn L, Hoagland D, Kasper DL, Paoletti LC, Hill H, Baker CJ (2019) A phase 2, randomized, control trial of Group B Streptococcus (GBS) type III capsular polysaccharide-tetanus toxoid (GBS III-TT) vaccine to prevent vaginal colonization with GBS III. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 68:2079–2086

75. Leroux-Roels G, Maes C, Willekens J, De Boever F, de Rooij R, Martell L, Bedell L, Witte F, Slobod K, Dull P (2016) A randomized, observer-blind phase Ib study to identify formulations and vaccine schedules of a trivalent Group B Streptococcus vaccine for use in non-pregnant and pregnant women. *Vaccine* 34:1786–1791

76. Madhi SA, Cutland CL, Jose L, Koen A, Govender N, Witte F, Olugbosi M, Meulen AS, Baker S, Dull PM, Narasimhan V, Slobod K (2016) Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial. *Lancet Infect Dis* 16:923–934

77. Bergin N, Murtagh J, Philip RK (2018) Maternal vaccination as an essential component of life-course immunization and its contribution to preventive neonatology. *Int J Environ Res Public Health* 15

78. Schleiss MR, Pernar SR, Plotkin SA (2017) Progress toward development of a vaccine against congenital cytomegalovirus infection. *Clin Vaccine Immunol* 24

79. Omer SB (2017) Maternal immunization. *N Engl J Med* 376:1256–1267

80. Psarris A, Sindos M, Daskalakis G, Chondrogianni ME, Panayiotou S, Antsaklis P, Loutradis D (2019) Immunizations during pregnancy: how, when and why. *Eur J Obstet Gynecol Reprod Biol* 240:29–35

**Publisher’s note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.