**Vaccination in pregnancy to protect the newborn**

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**Abstract**

Infectious diseases pose a particular risk to newborns and there is a global need to protect this vulnerable group. Because of the challenges of developing vaccines that are effective in newborns, only the hepatitis B and tuberculosis (BCG) vaccines are given in the first 28 days of life, and even those vaccines are mainly only offered to high-risk groups. Maternal antibodies cross the placenta and can afford some protection to the newborn, so an alternative strategy is vaccination in pregnancy. This approach has been successfully used to protect newborns against tetanus and pertussis, and vaccines that are primarily offered to protect the mother during pregnancy, such as influenza and COVID-19 vaccines, also provide some protection to newborns. A respiratory syncytial virus (RSV) vaccine has recently been approved for use in pregnancy to protect newborns, and a new vaccine that will be offered during pregnancy to prevent Group B Streptococcus (GBS) infection in infants is on the horizon. Here, we discuss the current vaccines that are offered during pregnancy and to newborns, the vaccines in development for future use in these groups and the challenges that remain concerning the delivery and uptake of such vaccines.

**[H1] Introduction**

Newborns are particularly vulnerable to infectious diseases due to their developing immune systems. In particular, they lack protective immune memory due to limited previous exposure to pathogens. In 2015, approximately 610,000 newborns died from infectious disease worldwide, a rate of 4.4 deaths per 100,000 livebirths.1 The vast majority of deaths take place in low- and middle-income countries; in higher income countries, infectious diseases are more likely to result in hospitalisation than death, but this still imposes a significant burden on families and healthcare systems and can have long-term consequences for the infant. Therefore, there is a global need to protect newborns from infectious diseases.

In this Review, we will discuss how vaccination in pregnancy and at birth can protect the newborn from infectious disease, by preventing infection or attenuating disease when infection is not prevented. Our focus here is on vaccines developed to protect newborns (infants under 28 days old); for a discussion of the vaccination schedule in older infants, we refer the reader to a recent review [Ref. 2]. However, it is also important to note that many of the approaches geared towards newborns will continue to provide some protection during the first 3-6 months of life.3–9

**[H1] Immunology of vaccination in pregnancy**

Part of the newborn’s vulnerability to infection stems from the fact that the neonatal immune system is functionally ‘immature’. There has been a growing consensus that the term ‘immature’ may not be accurate and that this might better be considered a mechanism that protects the newborn from excessive immune responses against harmless environmental antigens and commensal organisms encountered for the first time after birth.10 Nonetheless, this poses a challenge for the vaccination of newborns, who raise less effective immune responses to a number of vaccines, compared to older children and adults.11

Maternal antibody crosses the placenta and is secreted into breast milk, affording newborns some protection against antigenic challenges encountered by their mothers. One strategy is therefore to vaccinate during pregnancy and rely on maternal antibody to protect the newborn. Live vaccines are contraindicated in pregnancy, due to the theoretical possibility of attenuated pathogens being able to infect the placenta and fetus, so vaccination of the newborn is preferred where the only available vaccines contain live-attenuated pathogens (such as the Bacillus Calmette-Guérin (BCG) vaccine for tuberculosis). Vaccination of the newborn is also preferred where maternally derived antibody does not provide protection to the newborn (for example, as is the case with Hepatitis B virus (HBV) vaccine).

*[H2] Responses to vaccination in pregnancy*

Although pregnancy is not an immunosuppressed state, it is characterised by subtle changes to systemic immune responses.12 Therefore, when the aim of a vaccination programme is to protect newborns via transplacental transfer of antibody, it is important to confirm that the vaccine to be used raises an appropriate antibody response.

The tetanus, diphtheria, acellular pertussis (Tdap) vaccine is commonly given in pregnancy to protect babies against tetanus and pertussis, but the evidence on pregnancy-specific responses to this vaccine is mixed. Some studies find no differences in antibody titres between pregnant and non-pregnant individuals following Tdap vaccination.13,14 However, others report that although vaccination with Tdap in pregnancy elicits protective antibody titres, the response is nonetheless lower than that seen outside of pregnancy.15,16 For both influenza and COVID-19 vaccines, antibody titres elicited by vaccination in pregnancy are similar to those produced outside of pregnancy.17–20 However, systems serology approaches reveal some subtle differences in COVID-19 vaccination in pregnant and non-pregnant groups: the first dose of a COVID-19 mRNA vaccine induced antibodies with Fc receptor (FcR) binding and effector functions with slightly delayed kinetics in pregnant compared to in non-pregnant vaccinees.21 A study examining three different COVID-19 vaccines delivered during pregnancy also found a subtle reduction in antibody-mediated effector functions following COVID-19 vaccination in the second trimester, compared to in the first or third trimesters.22

Vaccination in pregnancy, then, may elicit a qualitatively different antibody response in some circumstances. However, the antibody response induced is sufficient to be protective and since antibody titres wane over time, it is still preferable to vaccinate in pregnancy to maximise protection of the newborn, rather than relying on vaccination prior to conception.

*[H2] Transplacental transfer of antibody*

Underpinning vaccination in pregnancy as a strategy to protect the newborn is the effective transfer of maternal antibody across the placenta. Of the five antibody classes, IgG is the only one to traverse the placenta, a process mediated specifically by the neonatal Fc receptor (FcRn; **Figure 1**).23–25 To cross from the maternal blood into the fetal blood circulation, the antibody must first traverse the trophoblast cells that cover the placental villi, then the villous connective tissue and finally through endothelial cells into the fetal capillaries. FcRn is unambiguously expressed by villous trophoblast cells26–28 and the mechanism by which FcRn mediates IgG transport across villous trophoblast has been defined using trophoblast-derived cells or cell lines engineered to express FcRn.29,30 Villous trophoblasts take up IgG from the maternal blood by pinocytosis. In the endosome, FcRn binds to IgG at low pH, protecting it from proteolytic degradation during transcytosis to the fetal side of the cell. As the endosome fuses with the fetal side of the trophoblast, the increasing pH causes FcRn to release its IgG cargo into the villous connective tissue. It is less clear how IgG is transported through the connective tissue and into the fetal blood vessels. Placental macrophages (Hofbauer cells) express FcRn and other FcγRs, which could allow them to support this process.31,32 Meanwhile, there is no consensus on whether villous endothelial cells express FcRn and it is possible that other IgG receptors may mediate the transfer of IgG into the fetal capillaries.26,28,33 IgG1 is transferred with the highest efficiency, followed by IgG4 and then IgG2 and IgG3.34 The extent to which vaccines raise each of these subclasses may therefore influence their effectiveness at protecting the newborn.

There is little placental transfer of IgG in the first trimester35, with transport gradually established over the second trimester: at weeks 12-22 of pregnancy, cord blood IgG titres are ~10% of maternal titres and by the end of the second trimester they are ~50% of those in maternal blood.36 In the third trimester, the rate of transfer increases significantly and by term fetal IgG concentrations usually exceed maternal ones.37 As a result, vaccination between 26 and 34 weeks of pregnancy maximises antigen-specific IgG in the umbilical cord blood of babies born at term, although the proportion of infants who are seropositive to any degree is similar for vaccination at any time between 13 and 34 weeks.38,39 In a randomised trial, vaccination at any time between 23 and 32 weeks resulted in equivalent concentrations of IgG antibodies in infants against two of the three pertussis antigens assessed.40 Vaccination after 32-34 weeks results in lower levels of antigen-specific IgG in newborns because there is insufficient time for the mother to raise a response and antibody to cross the placenta before birth. Studies examining the effectiveness of vaccination in pregnancy against disease in infants have largely found that vaccination later in pregnancy is more protective,41–44 but where protection against severe disease in pregnancy is the primary goal, vaccination may be offered earlier in pregnancy, at the expense of subsequent infant protection. Factors affecting the timing of vaccination in pregnancy are summarised in **Box 1**.

Estimates of the half-life of transferred IgG in the infant range from 28.745 to 48.4 days,46 depending on antigen specificity. For IgG1 against tetanus toxoid, titres drop to 10% of those at birth titres by four months and 3% at six months.46 For this reason, maternally derived protection against disease gradually declines over the first six months of life.9,43,44,47 This also affects the infant vaccination schedule, since transferred IgG modulates infant response to vaccination. In a meta-analysis of 7,630 infants, 2-fold higher maternal antibody concentrations were associated with a lower infant post-vaccination antibody concentration of 20-28% for inactivated polio vaccine, 11% for pertussis toxin and 13% for tetanus toxin.48 This effect is less pronounced in babies who are immunized when they are older, once maternal antibody has waned. Thus, in infant vaccination schedules, the goal is administration as soon as possible after maternally derived antibody drops below the threshold at which it interferes with the response.

*Antibody in breast milk*

Another way in which maternal immunity can protect the newborn is by the transfer of antibody into breast milk, allowing it to neutralise pathogens in the infant gut. This consists largely of IgA, although low concentrations of IgG and IgM are also detectable in breast milk.49 Plasma cells in the breast produce IgA and IgM, which are then transported into the milk across the mammary epithelial cells.50–52 Circulating IgG is transported into milk by FcRn but with lower efficiency than transport across the placenta.53

IgA-secreting cells in the breast largely originate in the gut: correspondingly, the breast plasma cell repertoire mirrors that of the gut.50–52 This allows breast milk to supply the most relevant antibodies to the infant’s gut but does suggest that vaccines optimised to raise a circulating IgG response in the mother may have limited ability to transfer protection to the infant via breast milk. Nonetheless, there is still some evidence that breastfeeding can confer limited protection: in a randomised controlled trial of influenza vaccination in pregnancy, exclusive breastfeeding after birth was associated with significantly fewer respiratory illnesses specifically in the influenza vaccinated group.54

*[H2] Interruption of pathogen transmission by vaccination*

In addition to the direct antimicrobial protection that is mediated by the transfer of maternally derived antibody to the newborn, maternal immunisation can also indirectly protect newborns from infection by interrupting pathogen transmission. This strategy is sometimes extended to include vaccination of other close contacts of the newborn (referred to as ‘cocooning’) and has been shown to be effective for protecting infants from influenza.55,56 The cocoon vaccine strategy has also been attempted to protect infants from pertussis, but the number of individuals that needed to be vaccinated in order to observe any benefit was too high to be cost-efficient in settings where there is a low incidence of pertussis.57 Therefore, the effectiveness of cocooning vaccination strategies in protecting infants will depend on the overall disease incidence in an area.

The mechanisms by which vaccination during pregnancy protects the newborn are summarised in **Figure 2.**

**[H1] Established vaccine programmes**

Vaccination in pregnancy to protect the newborn has a long pedigree: as early as 1877, it was reported that infants born to mothers who had received the smallpox vaccine during pregnancy were themselves protected from smallpox.58 From the mid-20th century onwards, vaccination in pregnancy increasingly became an important tool for protecting newborns. Below, we discuss the vaccines that are currently widely offered during pregnancy (see also **Figure 3** and **Table 1** for current vaccine schedules in pregnancy in the UK, USA and India).

*[H2] Tetanus vaccination in pregnancy*

Tetanus is caused by spores of the bacterium *Clostridium tetani* entering open wounds and newborns are particularly at risk of tetanus in low-resource settings, where non-sterile instruments may be used to cut the umbilical cord. Neonatal tetanus presents between the third and the 28th day of life, with infected infants losing the ability to suck and suffering from muscle spasms. Without medical treatment, neonatal tetanus is universally fatal and even with hospital care, between 10 and 60% of infected newborns die.59

The first approved tetanus vaccine consisted of tetanus toxoid adsorbed onto aluminium salts and was widely used during the Second World War. In 1959, an observational study of maternal tetanus vaccination demonstrated almost 95% protection against neonatal tetanus.60 The first randomised controlled trial reported no deaths from neonatal tetanus among infants born to mothers who received two or three doses of the tetanus vaccine in pregnancy, compared to a tetanus mortality rate of 7.8% in the control group.61 Subsequent trials have found 2-3 doses of tetanus vaccine in pregnancy is 98% effective at reducing neonatal tetanus deaths (95% CI: 70 – 100%) with no increased risk of serious adverse events in mothers or babies.3

In 1988, an estimated 787,000 newborns died of tetanus every year. Consequently, in 1989, the World Health Assembly resolved to reduce neonatal tetanus to less than one case per 1,000 live births in every district. In 2018, around 25,000 newborns died of neonatal tetanus, a 97% reduction from the death rate in 1988 largely attributable to scaled-up immunisation.62

*[H2] Pertussis vaccination in pregnancy*

Pertussis (whooping cough) is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis* and characterised by a paroxysmal cough with an inspiratory whoop. In the USA between 1940 and 1948, pertussis killed almost three times as many infants as measles, mumps, rubella, scarlet fever, diphtheria, polio and meningitis combined.63 Pertussis continues to kill 85,900 infants per year worldwide,64 making it a leading cause of vaccine-preventable deaths.65

Whole-cell pertussis vaccines were developed in 1914, and in 1943 the first observational study demonstrated transplacental transfer of antibody and some protection of newborns following administration of these vaccines in pregnancy.66 A campaign of pertussis vaccination in pregnancy was not immediately pursued, partly because of concerns about whole cell vaccine reactogenicity but also because the success of the infant vaccination campaign meant there was little clinical need. The development of an acellular pertussis vaccine in the 1970s and 1980s, together with a dramatic resurgence of the disease in the early 21st century, prompted the USA and UK to begin recommending pertussis vaccination in pregnancy in 201067 and 20125, respectively. Following the introduction of a pertussis vaccine in pregnancy, the UK saw a 78% reduction in cases in babies under 3 months old.5 Estimates of effectiveness against hospitalisation of infants under 3 months old range from 66-94% , with no increase in adverse perinatal outcomes.4

Recommendations about the timing and type of vaccine to be used in pregnancy have changed since the programme was introduced. In the UK, pertussis vaccination was initially offered between 28 and 38 weeks of pregnancy5 but from 2016 the offer was extended to between 16 and 32 weeks. This was primarily to broaden the window of opportunity for vaccination, with the earlier offer meaning that babies who were born preterm were more likely to be protected. A 2016 study reporting that immunisation earlier in pregnancy maximises infant seropositivity to pertussis antigens38 was also a consideration, and the subsequent publication of a randomised trial showing that vaccination at any time between 23 and 32 weeks resulted in equivalent infant antibody titres also supports the policy of vaccination earlier in pregnancy.40

In response to findings that the use of dTap/IPV (a multivalent tetanus, diphtheria and pertussis vaccine containing an inactivated polio vaccine (IPV) component) in pregnancy reduces subsequent seroconversion in response to infant polio immunisation,48,68 from July 2024, pregnant individuals in the UK have been offered a Tdap vaccine that does not contain an IPV component. Pertussis immunisation during pregnancy can blunt the subsequent infant response to primary pertussis vaccination and this effect is particularly observed in infants who receive whole-cell rather than acellular vaccine as part of the primary series.48,69 However, current epidemiological evidence does not suggest that blunting has a clinical impact on protection and the benefit of maternal immunisation to newborns outweighs the potential for an increase in disease in the toddlers and young children.70

*[H2] Influenza and COVID-19 vaccination in pregnancy*

Pregnancy increases the risk of severe disease from viral pneumonia.71 As a result, influenza and COVID-19 vaccines are offered to protect both the mother and fetus during pregnancy. Vaccination during pregnancy is 49% effective at preventing influenza virus infection (95% CI: 14-71%)6 and 94% effective at preventing hospitalisation with COVID-19 (95% CI: 29-99%).8 Neither of these vaccines is associated with any increased risk of adverse perinatal outcomes,6,8 with some studies even reporting reduced rates of preterm birth and stillbirth in vaccinated pregnancies8,72, potentially because of protection against these as complications of infection. Although these vaccines are primarily offered with the goal of protecting against severe disease during pregnancy, it is increasingly being recognised that protection of the newborn is a significant additional benefit.

Randomised controlled trials conducted in low-income countries consistently report that seasonal influenza vaccination during pregnancy is 56% effective at preventing laboratory-confirmed influenza virus infection in babies under two months old (95% CI: 28-73%) and 35% effective in those under six months old (95% CI: 19-47%).7 In high-income countries, observational studies find seasonal influenza vaccination in pregnancy between 41 and 71% effective at preventing laboratory-confirmed influenza virus infection in infants73,74 and 39 – 92% effective against hospitalisation.73–76 COVID-19 vaccination in pregnancy ranges from being 21 – 84% effective at preventing SARS-CoV-2 infection in infants43,44,77 and from being 32 – 95% effective against hospitalisation42,43,47,78–80 of infants with COVID-19, with vaccines that are matched to the current viral variant and given after 20 weeks of pregnancy showing the highest effectiveness.

This clear protective effect, along with the evidence that infants are particularly vulnerable to influenza and COVID-19, has prompted calls to modify the schedule to maximise protection for newborns, rather than for the mother and fetus during pregnancy.81,82 Influenza vaccination in pregnancy is widely offered as a seasonal campaign, ahead of predicted winter waves of viral infection. COVID-19 vaccination was also offered in the UK as a seasonal campaign (prior to Spring 2025) or in the USA when a vaccine targeting a new variant was available. To maximise infant protection, boosters would be offered in a similar window to that of pertussis vaccination. To our knowledge, there are no plans to implement these changes, but there is updated advice in the USA that summer vaccination can be considered in the third trimester, to maximise protection to the newborn,83 and the recent move by Australia's regulatory authority for medicines to license an influenza vaccination in pregnancy specifically to protect the newborn84 suggests that some countries may consider this in the near future.

*[H2] Hepatitis B vaccination at birth*

Hepatitis B virus (HBV) can cause either acute or chronic infection and 85-90% of babies born to mothers testing positive for HBV viral antigens develop chronic infection, putting them at risk of developing cirrhosis, liver failure or liver cancer.85,86 Since perinatal transmission is one of the primary routes of HBV spread worldwide, prevention of this is essential if the WHO is to meet its goal to eradicate HBV by 2030.87

There is little evidence that transplacental transfer of anti-HBV antibodies protects newborns from infection.88 On the other hand, the administration of an HBV vaccine to babies at birth reduces the risk of infant infection by 73% (95% CI: 60-82%) and combining HBV vaccination and passive immunisation with anti-HBV immunoglobulin reduces infant infection by 92% (95% CI: 83-97%).89 No safety concerns with HBV vaccination at birth have arisen, either in trials89 or from pharmacovigilance data.90,91

As a result of this, the WHO recommends vaccination of all babies against HBV at birth. Almost all countries in the Americas and Asia have taken up this recommendation, but many European countries, including the UK, instead screen for HBV in pregnancy and offer vaccination at birth only to at risk babies, with the majority receiving an HBV-containing multivalent vaccine as part of the infant schedule.92 However, the success of this approach relies on the ability to identify a high proportion of HBV-infected pregnant patients – something that has not always been possible, even in high-income countries.93,94

*[H2] Tuberculosis and oral polio vaccination in endemic regions*

Tuberculosis and polio are major causes of infant and childhood mortality in countries where these diseases are endemic**.** As a result, the WHO recommends vaccination against polio as soon as possible after birth in Afghanistan and Pakistan,95 and against tuberculosis in most of sub-Saharan Africa, South and South-East Asia.96

The only currently available tuberculosis vaccine is BCG. As a live-attenuated vaccine, BCG is contraindicated in pregnancy so a vaccination in pregnancy strategy is not current possible for tuberculosis. However, an infant dose of BCG is 80% effective at protecting against death from tuberculosis in children under five (95% CI: 31-94%).97 An additional birth dose of oral polio vaccine is recommended because it enhances seroconversion following subsequent completion of the three-dose infant schedule, which alone is inadequate at protecting against polio in regions where the virus is endemic.98–100

Because the BCG and oral polio vaccines are both live attenuated vaccines, they have the potential to cause disease, particularly in immunodeficient infants. In the UK, BCG is only recommended to at-risk infants and, in regions where severe combined immunodeficiency (SCID) screening is offered, the administration of the BCG is delayed until the results are available.101 The potential for harm from BCG administration, together with the relatively low effectiveness of this vaccine, means that the development of a new tuberculosis vaccine is a priority. For the oral polio vaccine, administration at birth is thought to reduce the risk of vaccine-associated disease, since babies are still somewhat protected by maternal antibodies. As global eradication of the disease approaches, the oral vaccine will be phased out entirely.95

**[H1] Emerging programmes to protect against respiratory syncytial virus**

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory tract infection (LRTI) in children. Globally in 2019, an estimated 33 million cases of RSV-associated LRTI (RSV-LRTI) occurred in children under 5 years old, of which 95% of cases and 97% of the 100,000 deaths occurred in low- and middle-income countries.102,103 In high-income countries, RSV is the leading cause of hospitalisation and an important healthcare resource issue. Young infants are disproportionately affected by severe disease,104,105 with the highest rates of hospitalisation among those between 28 days and 3 months of age.102 Preterm infants account for 25% of hospital admissions due to RSV-LRTI.106 Safe, effective, affordable strategies to prevent RSV-associated morbidity and mortality, including in premature babies, are therefore a global priority107. Recently, vaccination during pregnancy and universal infant immunisation with anti-RSV fusion (F) protein monoclonal antibody have become available. Both strategies aim to protect newborns and infants entering their first RSV season by delaying the first RSV infection until the child is older, when there is a lower risk of severe disease.

*[H2] RSV vaccination in pregnancy*

An RSV pre-F protein vaccine has recently been developed for use in pregnancy and is licensed in several countries as Abrysvo. In a phase III trial, this vaccine demonstrated efficacy of 81.8% against medically attended severe RSV-LRTI in infants younger than 90 days (99.5% CI: 40.6-96.3%) and 69.4% in those younger than 180 days (97.58% CI: 44.3-84.1%).9 Vaccination with Abrysvo during pregnancy has been implemented as a seasonal programme in Argentina and the USA from 2023 and as a year-round programme in the UK from 2024.

Of note, the phase III trial of Abrysvo reported a non-statistically significant imbalance of preterm births – but not associated mortality —in South Africa and Brazil, but not in high-income countries. This signal has been carefully considered during the licensure process, particularly in the light of the phase III trial of another RSV pre-fusion protein vaccine, which was halted in February 2022 due to significant difference in preterm deliveries between the vaccine and placebo groups (237/3496 [6.8%] versus 86/1739 [4.9%]; relative risk 1.37, 95% CI 1.08-1.74), driven by an imbalance observed during a specific period in low- and middle-income countries.108 This signal might reflect epidemiological features specific to lower income settings but the challenge of performing robust trials across multiple sites, where standards of antenatal care may vary, could also be a contributing factor. The interval between vaccination and delivery were similar between groups and no imbalance was seen in phase III trial specifically in high-risk pregnancies.108

That no signals emerged in high-income countries indicates that the benefits of RSV vaccination in pregnancy exceed the risks in these countries, but to ensure confidence in the programme, rates of prematurity are being closely monitored. Emerging data from the USA shows that the rate of preterm birth following RSV vaccination is in line with historical rates.109 To mitigate against any potential increased risk of preterm birth, the USA has chosen to offer the RSV vaccine after 32 weeks of gestation.110 Argentina also offers RSV vaccination from 32 weeks and the UK from 28 weeks. This means that the most premature infants — that is, those preterm infants born before vaccination could be offered — will not benefit from maternally derived RSV-specific IgG transferred across the placenta but may still benefit from interruption of transmission of RSV and from RSV-specific antibody transferred in breastmilk. The seasonal nature of the offer in the USA and Argentina further limits the potential for benefit, as those with pregnancies outside the gestational age limits during the season will not be offered an RSV vaccine.

An mRNA vaccine (mRNA-1345, Moderna) encoding a stabilized pre-fusion F glycoprotein is currently progressing through a global phase III clinical trial in pregnancy (NCT06143046) and has recently been licensed for other indications.

*[H2] Passive immunisation against RSV at birth*

Since the 1990s, monthly administration of palivizumab, a humanised anti-RSV fusion (F) protein monoclonal antibody, during the RSV season has been recommended for infants at highest risk of severe RSV disease in high-income countries. The recent development of nirsevimab, a long-acting anti-RSV monoclonal antibody with a half-life of up to 79 days given as a single intramuscular dose,111 has been groundbreaking, allowing wider implementation of passive immunisation to protect newborns across Europe and North America.

In phase III studies, nirsevimab (now licensed as Beyfortus) showed efficacy against medically attended RSV-LRTI up to 150 days in healthy term and preterm infants (>35 weeks of gestation) of 74.5% (95% CI: 49.6-87.1%)112 and in preterm infants (29 to <35 weeks of gestation) of 70.1% (95% CI: 52.3-81.2%).112 The high efficacy of nirsevimab has since been confirmed in a multi-country clinical trial aiming to approximate real-world conditions, with efficacy of 83.2% against RSV-associated hospitalisations (95% CI: 67.8-92.0%) and 75.7% against RSV-associated very severe LRTI (95% CI: 32.8-92.9%) in infants less than 12 months of age entering their first RSV season and born at a gestational age at least 29 weeks.113

Since licensure and subsequent implementation of nirsevimab, multiple countries have shown excellent coverage with high efficacy. Following the introduction of an infant universal programme in Spain in September 2023, coverage of 78.7% - 98.6% across three regions with an efficacy of 70.2% (95% CI: 38.3-88.5%) against RSV-LRTI hospitalisations has been observed.114 These rates have been borne out in subsequent studies in the Galicia region of Spain and in France, which showed that the number of infants that needed to be passively immunised to prevent one RSV-associated hospitalisation was between 25 [Ref115] and 39 [Ref.116]. For those children less than 5 years of age hospitalised for RSV-LRTI in 2023 in Luxembourg, where the infant coverage was 84%, the mean age at admission increased (14.4 months versus 7.8 months in 2022) and the length of stay decreased amongst infants less than 6 months (3.4 days versus 5.6 days).117 The reduction in severe RSV disease requiring admission to paediatric intensive care units observed in the pivotal phase III studies in nirsevimab recipients has been confirmed in real-world data from France, with effectiveness of 75.9% (95% CI: 48.5–88.7%) 118 Coverage observed in the New Vaccine Surveillance Network in the USA has been significantly lower (4-12%) than studies from Europe; however, among those infants that received nirsevimab, effectiveness against RSV-associated hospitalisation was 90% (95% CI: 75–96%).119

Administration of anti-RSV monoclonal antibodies to newborns is a very attractive strategy to protect infants up to six months of age, particularly in populations hesitant to receive vaccines during pregnancy. However, in most countries, a choice is not available to families, with the strategy decided at national level (**Table 2**). Moreover, the cost of this strategy limits global availability currently. The licensure of additional long-acting RSV monoclonal antibodies will improve global supply and resilience, and may reduce costs. To this end, clesrovimab, which binds an alternative site on RSV F protein,120 is nearing completion of a phase 3 study (MK-1654, NCT04767373).

RSV vaccination in pregnancy and monoclonal antibody administration to newborns protects the youngest and most vulnerable infants, and RSV vaccines administered to older infants and young children have recently entered clinical trials. However, the US Food and Drug Administration (FDA) has put all trials of RSV vaccines in children less than two years of age on hold.121 It is not anticipated that an RSV vaccine will be available for infants under six months of age. Therefore, it is unlikely that interference between the current maternal and newborn passive immunisation programmes and infant vaccination will be a consideration in the near future.

**[H1] Future programmes to protect against Group B Streptococcus**

Group B Streptococcus (GBS) is a leading cause of sepsis and meningitis amongst newborns and young infants worldwide.122 Between 8.9% (lower bound, East and South-east Asia) and 24.2% (upper bound, North Africa and West Asia) of pregnant individuals are colonised with GBS,123 a prerequisite for maternal and infant infection. Worldwide, GBS is estimated to cause 46,200 stillbirths, 518,100 preterm births and 91,900 infant deaths annually.123 Currently, intrapartum antibiotic prophylaxis is the only strategy to reduce early onset disease (occurring within the first 7 days of life) but it has no impact on late-onset disease (7 to 90 days of life), stillbirths or preterm deliveries. Vaccination in pregnancy has the potential to impact all these aspects of GBS disease as well as reducing the need for intrapartum antibiotics, which may have long-term consequences for the newborn’s microbiome.124

The mothers of newborns who developed invasive GBS disease have lower titres of GBS serotype-specific capsular antibodies,125 so vaccine development initially focussed on capsular polysaccharide vaccines. A hexavalent polysaccharide CRM197 conjugated vaccine covering the major serotypes associated with disease has shown an acceptable safety profile in a phase I/II study (C1091002) with robust immune responses in pregnancy and transplacental antibody transfer at concentrations associated with a reduced risk of invasive GBS disease in infants.126–128 A phase III pivotal global study (C1091009) is being planned.

Protein vaccines containing structurally conserved proteins across all GBS strains is an alternative approach. Minervax have developed a vaccine based on fusions of GBS surface proteins called the Alpha-like Proteins which are predicted to cover >99% of clinical isolates. A phase II global study has been completed (NCT05154578) and a further study including pregnant individuals living with and without HIV has also completed in South Africa and Uganda (NCT04596878). A phase III study is planned, likely based on immunological endpoints.

The major obstacle in moving these vaccines through phase III clinical trials and towards licensure is the vast number of mothers and infants who would need to be included in a clinical efficacy study, making such studies commercially unviable. Immunological endpoints based on serological correlates of protection are a more attractive option; however, these must be defined for each GBS serotype and standardised assay methodology using standardised reference sera is essential. The greatest benefit of GBS vaccination is likely to be realised in low-income countries, but variable standards of antenatal care in these settings also pose a challenge to the delivery of robust clinical trials. Despite these hurdles, the last few years have seen significant progress and investment, which provides hope for the emergence of an effective vaccine to tackle GBS globally.

**Outlook**

The development of new vaccines for use in pregnancy and newborns is complicated by the additional logistical and ethical challenges of performing trials in these groups, as well as the fact that they have been historically neglected. New approaches are on the horizon, but greater engagement with vaccine development and testing in pregnancy and newborns is still needed at all levels.

Even well-established programmes continue to face barriers to their success. Access and logistics can pose a particular challenge in low-income settings, where financial, structural and organisational support are vital to ensure equity of access. Overcoming these hindrances is essential given the higher burden of neonatal mortality, and the correspondingly higher value of maternal immunisation in these settings. Even in high-income settings, ensuring supply is not without its difficulties. In France, supply issues resulted in available doses of nirsevimab being diverted to newborns on maternity wards129 and temporary shortages were also seen in some healthcare settings in the USA between October 2023 and January 2024.130 Even where a vaccine against an infectious agent has been licensed, it is crucial that trials of other vaccines continue to ensure global supply and resilience. The limited timeframe during which vaccination is most effective during pregnancy also poses programmatic challenges: as more vaccines are added to the schedule, considerations around co-administration will become increasingly important.

Another challenge is acceptance. The low rates of uptake for vaccines recommended in pregnancy is a concern: coverage of prenatal pertussis and influenza vaccination declined over the course of the COVID-19 pandemic, from 71% to 61% and from 44% to 35%, respectively,131,132 and have not yet recovered. Effective strategies to increase uptake require co-ordination of health authorities, scientific societies and healthcare professionals to ensure that vaccination is fully covered in antenatal medical guidance and that the concerns of specific groups are adequately addressed (**Box 2**). Delivering this is demanding but is essential to ensure that we realise the maximum benefit from the much greater resources we have already committed to developing new strategies to protect newborns from infectious disease (**Box 3**).

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The authors contributed equally to all aspects of the article.

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**Table 1: Vaccines recommended during pregnancy in the UK**

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| --- | --- | --- | --- | --- | --- |
| Pathogen targeted | Vaccine name | Formulation | Timing | Considerations | Ref. |
| *Bordetella pertussis* | ADACEL (Sanofi Pasteur) Tdap vaccine | Inactivated protein (diptheria, tetanus and pertussis toxoids, and three further acellular pertussis antigens). Aluminium phosphate adjuvant. | 16 – 32 weeks | ADACEL is preferred since it does not contain an IPV component, which may blunt infant responses to polio vaccination. If ADACEL is not available, IPV-containing formulations may be offered. | 133 |
| Influenza virus | Cell-based quadrivalent influenza vaccine Seqirus (CSL Seqirus UK) | Inactivated virus (four strains of influenza virus). Unadjuvanted. | Autumn | Cell-based influenza vaccines are preferred since they are safe for individuals with egg allergy. If cell-based vaccines are unavailable, formulations grown in chicken eggs may be offered to those without allergies. | 132 |
| Respiratory syncytial virus (RSV) | Abrysvo (Pfizer) | Recombinant protein (pre-fusion from two strains). Unadjuvanted. | From 28 weeks | Abrysvo is currently a ‘black triangle’ product, indicating that it has been recently introduced and that all suspected adverse reactions should be reported to the MHRA using the Yellow Card scheme. | 134 |

Abbreviations: IPV, inactivated polio virus; MHRA, medicines and healthcare products regulatory agency; Tdap, tetanus, diphtheria and pertussis.

### **Table 2: Considerations for respiratory syncytial virus (RSV) immunisation programmes**

|  |  |  |
| --- | --- | --- |
|  | **RSV vaccination in pregnancy** | **Infant monoclonal antibody** |
| **Effectiveness** | **Immediate protection for newborn through transplacental antibody transfer, lasting until at least six months of age** | **Provides protection to infant from time of administration, lasting until at least six months of age. May have longer duration of protection than vaccination in pregnancy, mediated through Fc modification of antibody** |
| **Provides protection for mother** | **No protection for mother** |
| Potential for additional protection through RSV-specific antibody in breastmilk | **No potential for additional protection through breastmilk** |
| **Highly effective at preventing severe RSV disease and hospitalisation** | **Highly effective at preventing severe RSV disease and hospitalisation** |
| **Protection of preterm infants** | **No protection for extremely preterm infants and limited protection for moderate- or late-preterm infants, depending on timing of administration of maternal vaccine** | **Can provide protection to preterm infants from time of administration** |
| **Immunity generated** | **Elicits a polyclonal antibody response, expected to be robust to vaccine escape** | **Monoclonal antibody with theoretical potential for vaccine escape**  |
| **Safety and side effects** | **Common side effects for pregnant vaccine recipients include arm pain, headache, muscle pain, and nausea.** | **Common side effects in infants include pain, redness, or swelling at the injection site.**  |
| **Potential for increased late preterm deliveries to be closely monitored. No other safety concerns identified in clinical trials, but post-implementation monitoring is essential.** | **Rare hypersensitivity reactions have been reported.** |
| **Timing and administration** | **Administered between 28 and 36 weeks of pregnancy, depending on country-specific recommendations, as either a year-round or seasonal programme** | **Administered shortly before or during the RSV season, ideally within the first week of life if born during the season** |
| **Programmatic considerations** | **Challenges of timing with routine antenatal care visits and co-administration with other vaccines** | **Challenges of delivery of immunisation to newborns in countries where this is not routine; challenges of co-administration where other neonatal vaccine programmes exist.**  |
| **Challenges of delivering a seasonal programme, in countries where this is relevant** | **Challenges of delivering a seasonal programme** |
| **Financial, structural and organisational support is vital to ensure equity of access and programmatic success** | **Financial, structural and organisational support is vital to ensure equity of access and programmatic success**  |
| **Cost and availability** | Lower cost product  | **Higher cost product** |
| Not currently available for most of the global population  | Not currently available for most of the global population; temporary supply issues in some high-income countries |
| **Uptake and acceptability** | Uptake of other vaccines during pregnancy has been lower than that observed for infant RSV monoclonal administration in the first countries implementing this strategy, but this may vary with country or population |

 **Figure 1. Transplacental transport of IgG.**

(a) The maternal and fetal circulations are separated by villous trophoblast cells, fetal connective tissue and fetal endothelial cells. IgG is transported through the villous syncytiotrophoblast by FcRN-mediated transcytosis (detail shown in B). It is less clear how IgG moves through the connective tissue and fetal endothelium, but FcRN and other FcγRs expressed by placental macrophages (Hofbauer cells) and fetal endothelial cells may play a role. (b) Syncytiotrophoblast cells take up maternal IgG by pinocytosis. The IgG-containing vesicles fuse with endosomes containing FcRn, which protect IgG from proteolytic degradation at low pH. As the endosome fuses with the fetal side of the syncytiotrophoblast, the increasing pH causes FcRn to release its IgG cargo into the villous connective tissue.

**Figure 2. Mechanisms by which vaccination during pregnancy protects the newborn**

Vaccination in pregnancy protects the newborn from infectious disease in four ways. (a) Protection against severe disease during pregnancy reduces complications that may be harmful to the fetus. Influenza and COVID vaccination are offered for this reason. (b) Maternal IgG raised by vaccination crosses the placenta and protects the baby after birth. Pertussis and RSV vaccination are offered for this reason. (c) Maternal IgA raised by vaccination is transferred into breast milk, and then into the infant’s gut. There is some evidence that influenza vaccination in pregnancy provides additional protection to the newborn via this route. (d) Vaccinated parents and other carers are less likely to become infected and are therefore less likely to infect the infant (cocooning).

**Figure 3. A timeline of vaccinations offered during pregnancy in the UK, USA and India.**Vaccines offered seasonally are indicated by (S), those offered when a formulation targeting a new variant is available by (NV) and those offered only to those infants at high risk by (HR). In the UK, COVID-19 vaccination was offered as a seasonal campaign until Spring 2025, but cost-benefit analysis does not currently favour continuing the offer.135 In the USA, influenza vaccination is usually offered in the autumn, but where the third trimester occurs in the summer, summer vaccination to protect the newborn can be considered.83 In India, the second tetanus vaccination may be combined with the pertussis booster as a Tdap. RSV, respiratory syncytial virus; HBV, hepatitis B virus; BCG, Bacillus Calmette-Guérin; SCID, severe combined immunodeficiency.

**Box 1: Factors affecting the timing of vaccination in pregnancy**

Where the primary goal is to protect the baby after birth:

* Vaccines are most effective when they are given between 23 and 34 weeks.38–40 Before 2016, the UK pertussis vaccine offer largely covered this time window (28 – 38 weeks).
* However, restricting the offer of vaccination to later in pregnancy may prevent babies born preterm from benefiting. This was one reason that, in 2016, the UK moved to offering pertussis vaccination between 16 and 32 weeks. Countries that restrict the offer of RSV vaccines to after 32 weeks or pregnancy may limit protection afforded to infants born preterm.
* Restricting the offer of vaccination to earlier in pregnancy may mean that some pregnant individuals miss the opportunity to be vaccinated. For this reason, in the UK, individuals who do not receive the pertussis vaccination during the recommended offer window can still receive it later.

Where the primary goal is to protect mother and fetus during pregnancy:

* Vaccinations targeting seasonal viruses may be offered as seasonal programmes. In the UK, an ‘autumn booster’ influenza vaccination is offered, before the time of highest predicted viral circulation.
* For viruses that rapidly mutate, a booster may be offered as soon as a vaccine against a new variant is available. This approach is currently used in the USA for COVID-19 vaccination.

General considerations:

* When shortages occur, it may be necessary to offer vaccines when they become available.
* As more vaccines are developed for use in pregnancy, it will become increasingly necessary to consider their safety and effectiveness when co-administered.

The schedule of vaccinations in pregnancy in the UK, USA and India are shown in **Figure 3**, with additional detail for the UK in **Table 1.**

**Box 2: Factors affecting the uptake of vaccinations in pregnancy**

**[bH1] Access.** People who are willing to be vaccinated during pregnancy may delay or fail to attend for vaccination because of financial or logistical barriers. Programmes should ensure that vaccination is free at the point of delivery and available in multiple healthcare settings, including at antenatal appointments.136

**[bH1] Information.** Some people who would accept a recommendation to be vaccinated outside pregnancy are hesitant during pregnancy, because of concerns about safety for the fetus. The perception that the risk of disease is low also reduces the willingness of individuals to be vaccinated. Provision of evidence that addresses risks and benefits to the fetus/newborn increases uptake in these individuals.137

**[bH1] Trust.** Some people decline vaccination during pregnancy as part of a wider distrust of vaccines, healthcare authorities and healthcare professionals.137 Motivational interviewing can be a useful tool to build rapport, increasing receptiveness to new information,138 but this requires structural support for training and additional time in antenatal appointments.

**Box 3: Future targets of vaccination in pregnancy or prior to conception**

**[bH1] Infections associated with significant congenital abnormalities**

*[bH2] Cytomegalovirus.*

Congenital cytomegalovirus infection is a leading cause of hearing loss, visual impairment and neurodevelopmental delay. Vaccine development has been hampered by extensive immune evasion strategies employed by the virus, but one candidate mRNA vaccine is now undergoing phase III trials in adults (NCT04232280) and adolescent girls (NCT05085366).139

*[bH2] Zika virus.*

Zikavirus is a mosquito-borne virus that is endemic to equatorial Africa and Asia. Its spread to the Americas led to an epidemic in 2015-16, with over 3,500 cases of microcephaly and brain abnormalities occurring in infants as a result of congenital infection. Currently, there are four vaccine candidates in or entering phase 2 clinical trials.140

**[bH1] Infections that are more severe in pregnancy**

*[bH2] Lassavirus.*

Lassavirus is a zoonotic disease endemic to West Africa, which causes haemorrhagic fever. Pregnancy is associated with a 2.86-fold increased risk of death from lassavirus infection.141 A vesicular stomatitis virus (VSV)-vectored vaccine candidate entered phase 2 trials in 2024 (NCT05868733).

*[bH2] Hepatitis E virus.*

Hepatitis E virus is transmitted by the fecal–oral route and causes acute hepatitis.Infection in pregnancy is associated with a 6-fold increased risk of death.142 A virus-like-particle vaccine against Hepatitis E has been licensed for use in China. The WHO has not recommended its widespread adoption, due to insufficient information on safety and effectiveness143 but the publication, in 2024, of results from a ten-year phase 3 trial may change this.144

**[bH1] Infections that are more severe in newborns**

*[bH2] Tuberculosis*

Infants are at greater risk of tuberculosis but the potential for harm from BCG administration, together with the relatively low effectiveness of this vaccine, means that the development of a new vaccine is a priority. Trials of a new adjuvanted subunit vaccine (M72/AS01E) in non-pregnant adults began in South Africa in 2024, and vaccination prior to conception may provide some protection for newborns.

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