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Future vaccines in pregnancy

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A B S T R A C T

Vaccination in pregnancy provides an important opportunity to target illnesses that are known to impact pregnant women, fetal development, and newborns in particular. The ability to create antibodies through safe vaccination that cross the placenta can provide protection against maternal, congenital, and newborn infections.

At present, multiple vaccines are being developed which have direct benefits for pregnant women and their newborns. Group B streptococcus, Respiratory Syncytial Virus, Cytomegalovirus, Zika, Ebola, Malaria, and Coronavirus SARS-CoV-2 are all being researched with the view to develop a safe vaccine available for pregnant women.

There is also an increased movement towards the inclusion of pregnant women in vaccine development and trials – challenging the historical, ethical, and medicolegal arguments against their involvement in such research.

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Introduction

Vaccination in pregnancy provides an important opportunity to target illnesses that are known to impact pregnant women, fetal development, and newborns in particular. At present, multiple vaccines are being developed which have direct benefits for pregnant women and their newborns. There is also an increased movement towards including pregnant women in vaccine development and trials – challenging the historical, ethical, and medicolegal arguments against their involvement in such research.

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Present vaccinations in pregnancy

As of now, maternal vaccination for diphtheria, tetanus, and pertussis (DTPa), and influenza provide increased maternal antibodies that protect both the mother and the baby. These vaccinations provide passive immunity to the fetus and newborn by boosting maternal antibody levels and facilitating the transmission of antibodies across the placenta and through breast milk.

At present, vaccination in pregnancy relies upon the following principles:

1. Evidence of safety of the vaccination for the mother and foetus.
2. Evidence of maternal vaccination providing protection to the fetus and newborn, as it is performed in influenza and tetanus/pertussis vaccination.
3. Transplacental passage of IgG antibodies that are triggered or boosted by immunisation and cause seropositivity in newborns and infants.
4. Evidence that newborns and infants do not produce a rapid antibody titre following active immunisation [1].

Expanding vaccinations in pregnancy

Vaccinations targeting illness that cause increased morbidity and mortality in both pregnancy and the newborn period are perfectly placed to be targeted for future vaccinations in pregnancy.

The use of such vaccines may change the landscape of child and maternal health. Infection is a significant contributor to maternal, fetal, and newborn mortality and morbidity. Examples of long-standing and important infections include Human Immunodeficiency Virus (HIV), malaria and Respiratory Syncytial Virus (RSV). At present, there are hundreds of vaccines in various states of trials, many of which aim to address maternal, fetal, and neonatal infection.

Potential future vaccinations in pregnancy

Group B Streptococcus

Group B Streptococcus (GBS) is a gram-positive commensal organism in the lower urogenital and gastrointestinal tract, present in 20–40% of women [2,3]. GBS is known to cause neonatal GBS pneumonia, sepsis, and meningitis when neonates are exposed to GBS through the genital tract. The presence of GBS in the urogenital tract is also associated with maternal sepsis, preterm births, and stillbirths through ascending infection.

Currently, the most widely used approach to manage GBS colonisation in pregnancy is intrapartum antibiotic prophylaxis in either screened or risk factor-based populations. In Australia, the present recommendation is universal screening at 36 weeks with a rectovaginal swab followed by intrapartum antimicrobial prophylaxis in those women who screen positive [4]. The use of intrapartum antibiotics has made a significant impact on early onset GBS infection (within the first 7 days of life), yet this approach has not completely removed early onset GBS with the rate of this significant infection has plateaued – from 1.7 per 1000 live births in 1993 to 0.4 per 1000 live births [2,5]. Furthermore, the use of screening and antibiotics has not been beneficial to the neonates affected with late onset of infection – which is likely acquired through breast milk or from within the community. Challenges to screening and intrapartum antibiotics include antibiotic resistance to clindamycin and erythromycin, and other clinical challenges such as appropriate coverage in preterm births or in precipitate labours.

Vaccination against GBS is an attractive strategy for GBS disease prevention with benefits to the mother and transplacental antibody passage providing protection against fetal and neonatal infection – both during early and late onset [6]. Neonatal vaccination is unlikely to be beneficial given the rapidity of illness in those affected by early onset GBS sepsis.

Antibody-mediated protection against GBS has been investigated since the 1970s. Baker demonstrated that women with lower levels of maternal antibodies to serotype III GBS had higher rates of neonates affected by GBS, conferring that transplacental transfer of maternal antibodies are protective

against invasive group B streptococcal infection with type III capsular strains [7]. More recent studies on HIV affected women have further demonstrated that they have increased rates of both early and late GBS sepsis. The same phenomena are observed even in neonates that are not HIV positive, which is thought to be caused by low circulating concentrations of serotype-specific capsular antibodies to GBS with reduced transplacental transfer [8].

The development of a vaccine against GBS has been slow—the first work that commenced in the 1980s has yet to achieve appropriate immunogenicity or has yet to be taken into phase 3 trials to show efficacy in pregnancy [9]. Other bacterial vaccinations have been successful and became part of routine schedules – pneumococcal, meningococcal, and Haemophilus influenzae type b conjugate vaccines.

GBS contains several virulence factors that have been targeted in vaccine development. The most widely studied virulence factor is the capsular polysaccharide (CPS) which aids evasion of the host's immune system and consist of various arrangements of monosaccharides, of which nine distinct structures have been identified [2].

Phase 1 and 2 trials occurred by using a capsular polysaccharide conjugated vaccination directed against six capsular polysaccharide serotypes (Ia, Ib, II, III, IV, and V) of GBS. The first of these trials were held in the 1980s with purified native type Ia, II, or III polysaccharides injected into healthy adult volunteers [6]. These trials showed overall safety; however, the vaccines did not produce high levels of immunogenicity. It was found in trials for vaccines against *Haemophilus influenzae type B* and *Neisseria meningitidis* that by conjugating polysaccharides to protein carriers, the immunogenicity of polysaccharide vaccinations increased. This approach was then employed in animal models with specific GBS CPS types conjugated to tetanus toxoid [6]. This resulted in increased immunogenicity and clinical trials in humans.

There has been one clinical trial of GBS vaccination in pregnant women using a group B streptococcal type III CPS-tetanus toxoid (GBS III-TT) vaccination. This vaccination was found to be well-tolerated, safe, and produced antibodies that were functionally active; however, the vaccines were type-specific and each vaccine was only immunogenic to that particular GBS serotype [5]. Multivalent vaccines against multiple CPS serotypes have been developed and trialled in animal models and healthy, nonpregnant participants [6].

Another protein carrier, a nontoxic variant of the diphtheria toxin isolated from *Corynebacterium diphtheriae* C7 (β197) cultures, has been shown to be effective in conjugation with GBS capsular polysaccharides. This conjugate was used in a phase 2 trial in African pregnant women with and without HIV infection, who were between 24 and 25 weeks of pregnancy, by using a trivalent non-adjuvanted CRM197-conjugated GBS vaccine against CPS serotypes Ia, Ib, and III. It was found that the vaccine was safe in pregnancy with no serious adverse events and immunogenicity was achieved; however, it was less in the HIV-affected group [8].

There is an ongoing interest in the use of a vaccine against GBS in pregnancy; however, the progress is slow. The relatively low incidence of neonatal disease means that clinical trials to test vaccine efficacy are difficult.

Respiratory Syncytial Virus

Respiratory Syncytial Virus (RSV) is a ubiquitous respiratory virus that causes a significant disease burden, with millions of hospitalisations and thousands of deaths in children each year before age 5. In 2015, there were 3.2 million hospitalisations for RSV of which half were of children less than 6 months of age, and there were 118,000 deaths [10]. Infants are particularly susceptible to RSV given their small airways and immature immune systems. RSV infection can also affect pregnant women causing upper and lower respiratory tract infection symptoms. There is limited data on the rates of infection on pregnant patients; however, based on influenza studies, RSV may affect 10–13% of pregnancies [11].

Given the young age of patients affected by RSV, targeting vaccination in the newborn period or using passive immunity by maternal immunisation is desirable. Furthermore, given that pregnant women may still suffer from infective symptoms of RSV, vaccination in pregnancy will confer benefits to the mother too. There is currently no vaccination against RSV in any age group.

RSV is an orthopneumovirus that is composed of a nonsegmented, single-stranded genome that encodes 11 proteins. Of the eight structural proteins produced, three are surface proteins (small hydrophobic (SH), attachment (G), and fusion (F) glycoproteins). The F and G proteins are responsible for

the pathogenicity of the virus, with the G protein targeting the ciliated cells of the airway and the F protein allowing viral penetrance causing cell fusion. Protein F is the ideal target for vaccination as it carries several antigenic sites for antibodies to neutralise its function [12].

The history of vaccination development against RSV is rocky. The first vaccine was produced in the 1960s as a formalin-inactivated RSV vaccination and was initially found to be well-tolerated; however, it ultimately resulted in more serious infections in naïve infants with an 80% hospitalisation rate and 2 deaths [13]. Since then, multiple vaccines have been developed including live-attenuated, chimeric, particle-based, vector-based, and subunit vaccines [14].

There are now several vaccines in clinical development for maternal vaccination and the most advanced vaccine is the particle-based vaccination against protein F. Live and live-attenuated vaccinations are also being developed for paediatric and elderly populations, but are not suitable for maternal vaccination given their live status and risk of maternal infection.

A recombinant, adjuvant RSV nanoparticle vaccine (RSV F vaccine) has been studied in pregnant women in the PREPARE trial. The phase 2 trial in 50 women was promising, showing significantly increased antibody production against RSV epitopes in the vaccinated group with evidence of transplacental antibody transfer, particularly in those women who delivered after more than 30 days of vaccination, resulting in no severe RSV disease in the infants of vaccinated mothers [15]. The phase three trial evaluated the use of RSV F vaccine among 4636 pregnant women in the third trimester in a randomised, observer-blind, placebo-controlled trial across 87 sites in 11 different countries. The percentage of infants who had RSV-associated significant lower respiratory tract infection through 90 days was 1.5% in the vaccine group and 2.4% in the placebo group, giving an estimated vaccine efficacy of 39.4% [10]. Overall, the vaccination was found to be safe with no major side effects; however, the study did not meet the success criterion to define an effective vaccination against RSV-associated illness.

The search for a successful RSV vaccination is still ongoing. RSV F protein vaccination in pregnant women has not met the prespecified success criterion for efficacy against RSV-associated, medically significant lower respiratory tract infection in infants up to 90 days of life; however, sub-analyses and further studies may show other benefits without harm.

Cytomegalovirus. Cytomegalovirus (CMV) is the most common congenitally transmitted pathogen worldwide. It is commonly transmitted through close contacts in households with relatively high rates of reinfection or reactivation. CMV congenital infection impacts 1 in 150 live-born infants globally, making it a major cause of congenital abnormality and a suitable target for vaccination [16].

Congenital CMV infection is a well-recognised and important cause of sensorineural hearing loss, growth restriction, cognitive, and motor impairment in newborns [17]. Vertical transmission occurs during primary or reinfection with CMV during pregnancy, causing viral infection in the cytotrophoblasts in the placenta [16]. It has been found that there are lower congenital infections in women reinfected with CMV compared with primary infections and that the severity of congenital infection reduced in seropositive mothers [18].

A maternal vaccination to prevent CMV, particularly primary infection, would have benefits for both the mother and the child. Attempts to produce such a vaccine has been occurring for over 40 years with the target population of childbearing females prioritised [16].

In the 1970s, two attenuated viral vaccines were developed against CMV. The AD169 CE attenuated strain was quickly abandoned in the laboratory, whereas the 'Towne' vaccination went on to be tested in male and female volunteers. This vaccine exhibited a nonstatistically significant immunogenic response, and no protection to women who were exposed to CMV by children in daycare [18].

In the 1990s, a vaccine against the CMV surface protein glycoprotein B with the adjuvant MF59 (a squalene-in-water emulsion) was developed and entered into clinical trials [18]. This was found to be both safe and immunogenic over three injections in a 6-month period. Pass et al. [17] conducted a phase 2 trial with 230 postpartum females who were CMV antibody negative and matched to a placebo arm. Analysis at two years showed that the vaccinated group had lower rates of infection; however, the vaccine only produced a vaccination efficacy rate of 50% and there was still one episode of congenital CMV infection in the vaccine group. This trial was important as it was the first CMV vaccine trial that

progressed towards maternal vaccination and proffered the potential role of vaccine boosted immunity against recurrent infection [19]. Bernstein et al. [20] also used the glycoprotein B vaccination to immunise adolescent females, again showing it to be a well-tolerated vaccine with immunogenic response and with an overall vaccination rate of 43%.

Multiple other vaccines have been attempted with ongoing research. Enveloped virus-like particle vaccines use protein structures that mimic viruses; however, do not contain any live viral or viral genomic material, to create an immune response. This technology has been used to create vaccines that express CMV glycoprotein B and pp65 antigens and has only recently undergone phase 1 testing [19]. These forms of vaccines may provide a safe approach to vaccination in pregnancy if shown to be effective. Other vaccines include vectored CMV vaccines using attenuated canarypox or Venezuelan equine encephalitis vaccine [19]. Canarypox vectored vaccines have failed to produce an increased neutralising antigen titre on their own, and also did not have any advantage over natural CMV infection when combined with live attenuated vaccines such as the Towne vaccine [21]. Preclinical work has begun on DNA- and RNA-based vaccines with positive results in animal studies; however, their potential use in pregnant women is unclear [19].

The unique immunology and consequences of CMV infection and reinfection is challenging the development of CMV vaccines. With seropositivity not fully protective against maternal reinfection with or without congenital transmission, the question of whether a vaccine will truly ever be efficacious continues. However, there is evidence that preconception immunity does confer lower chances of reinfection, or severity of sequelae if infection occurs. The potential reduction of harm with the combination of the sheer magnitude of infection drives the ongoing search for a CMV vaccine.

Zika

The Zika virus, a member of the *Flaviviridae* family, was first isolated in 1947 from a febrile rhesus monkey in the Zika Forest and has since been identified as an endemic infection in Sub-Saharan Africa and tropical areas of South eastern Asia [22]. However, it came to be more widely recognised from mid-2015, when epidemic status was achieved after rapidly spreading through South America, Central America, and the Caribbean Islands (Maslow, 2020).

Zika virus is spread through mosquito-borne transmission and through sexual contact, with reports of it being carried in the male urogenital tract for up to 9 months [23]. Infection with the virus ranges from asymptomatic to rash, fever, myalgia, arthralgia, headache, and retroorbital pain. In the non-pregnant adult population, the complication of a Guillain-Barre like illness has a prevalence of 0.24 per 1000 infections.

Zika virus became clinically important and recognised by the WHO as a significant threat when the epidemic outbreak of 2015 showed that in the obstetric population, Zika infection may result in fetal microcephaly and other congenital impacts such as deafness, visual deficits, neural calcifications, learning difficulties, and arthrogryposis. Zika viral syndrome is higher when infection occurs in early pregnancy, with rates of abnormal clinical or brain findings up to 42% [22]. Thus, Zika virus infection in the general population generally results in mild self-limiting symptoms, whereas vaccination against Zika in the reproductive population may prevent congenital abnormalities.

Vaccine development against Zika accelerated in 2015 following the reports of congenital effects. Almost 40 different Zika virus vaccines have been designed, ranging from live attenuated and inactivated whole virus vaccines, peptide, and protein subunit vaccines, viral vectored vaccines, and RNA and mRNA vaccines. As of 2017, only 7 vaccines had progressed to phase 1 testing and only two vaccines entered into clinical trials.

The GLS-5700, a DNA vaccine encoding for the Zika virus prME gene, was the first Zika vaccination to enter clinical trials. Mice and nonhuman primate studies showed B- and T-cell immune responses against the Zika virus envelope and protection provided by these cells against neurological damage, testicular damage, and atrophy [24]. Phase 1 studies using intradermal injection followed by electroporation showed seroconversion between 83–100% with vaccine response up to one year in individuals. The GLS-5700 vaccine is currently being evaluated as a phase II trial in Puerto Rico. Two other DNA vaccines, based on the French Polynesian strain of Zika, have been developed. These two vaccinations are chimeric DNA vaccines with Japanese Encephalitis Vaccine prM signal sequence, resulting in the expression of the Zika enveloped (E) gene. These two vaccines have been used in nonhuman

primates through intradermal and needle-free devices and have shown high levels of seroconversion. One of the vaccines, VRC5283, has been advanced into phase II studies in the Americas [22].

Three inactivated vaccines have entered clinical studies. The only vaccination with clinical data is the ZIPV vaccine, a whole inactivated vaccine from the Puerto Rican strain PRVABC59 [23]. Studies in mice and nonhuman primates have shown high levels of protection against viraemia following challenges with multiple Zika strains. In clinical trials, there were no adverse side effects and high levels of seroconversion (92%).

Challenges faced by the progression of Zika virus vaccine include the regression from epidemic status with a lower rate of viral infection. The role of controlled human infection models has created significant interest with its associated medical and ethical considerations. Furthermore, it has been recognised that the major benefit in vaccination against Zika is the reduction in Zika congenital syndrome, yet there have been no studies directly evaluating maternal vaccination. Shan et al. [25] have used a pregnant mouse model to show there were no adverse effects on pregnancy, fetal development, or pup behaviour. Their studies, however, exhibited that higher levels of neutralising antibodies were required to prevent infection in the pregnant mice population compared with the nonpregnant group, potentiating the role of boosting immunity with antenatal vaccination.

Malaria

Malaria is a severe illness caused by the spread of parasites from the genus *Plasmodium* by female anopheles mosquitos [26]. Malaria is the leading cause of morbidity and mortality around the world and accounts for over 200 million infections and nearly 500,000 deaths in 2017. The most common parasite, *Plasmodium falciparum*, accounts for 10–20% of maternal mortality in malaria-endemic countries, resulting in approximately 30,000 deaths per year [27].

Malaria in pregnancy is associated with fetal growth restriction, pre-eclampsia, preterm delivery, miscarriage, stillbirth, neonatal death, maternal anaemia, and maternal death [27]. In pregnancy, *Plasmodium* parasites sequester in the placenta and bind to glycosaminoglycan chondroitin sulphate A (CSA) on the syncytiotrophoblast lining of the maternal blood space, causing placental malaria and poor placentation, impaired vascularisation, and subsequent placental dysfunction [1]. Furthermore, maternal effects of malaria such as significant anaemia and organ damage results in adverse pregnancy outcomes. Congenital malaria is defined as the presence of parasites in the cord blood or blood smear of the newborn at delivery and may occur in up to 6% of cases.

Present management options to prevent malaria include medication use for prophylaxis, and treatment and vector control such as in insecticide and repellent use. However, mass vaccination or vaccination of at-risk populations would cause a significant reduction in the mortality and morbidity experienced by malaria affected regions with a significant flow in its effect on pregnant women and their newborns.

The process of developing a malaria vaccine has been ongoing for 50 years. The development of a vaccine for Malaria is complicated; secondary to the complex life cycle of the *Plasmodium* parasites – with different vaccines designed to affect the pre erythrocytic, blood, and sexual stages of the life cycle. Furthermore, there is a need to develop vaccines against separate parasites with *P. falciparum* being responsible for the majority of infections in Sub-Sahara and *P. vivax* in Southeast Asia. The complexity of the genetic makeup of the parasites also contributes to the delay in vaccination production, with the *P. falciparum* genome alone made of 5300 genes with demonstrable geographic diversity [28].

At present, there is one vaccine that is being implemented in Africa against malaria causing *Plasmodium falciparum*. The vaccine, RTS,S/AS01 (known as Mosquirix), is the first vaccine to show partial immunity in young children. It was first developed in 1987, resulting in a recombinant protein-based malaria vaccine that provides an immune response against the circumsporozoite protein, targeting the sporozoite phase of the lifecycle, preventing the parasite from entering the liver [29]. The phase 3 trial ended in 2014 and the present implementation program will also form the basis for phase 4 studies. The vaccination is not for pregnant women and it does not offer any protection against *P. Vivax* [30].

Research is underway specifically targeting malaria in pregnancy. The placental-binding parasites express a protein that binds to CSA called VAR2CSA, with areas of this complex protein acting as targets for the PRIMVAC and PAMVAC vaccines. PRIMVAC is a vaccine targeting the CSA-binding VAR2CSA

protein from *P. falciparum*, expressed by *E. coli*, then purified and adjuvanted with Alhydrogel or Glucopyranosyl Lipid A (GLA) adjuvant stable emulsion [31]. PRIMVAC was initially revealed to be potent, stable, and well-tolerated with antibodies induced in vaccinated rats. Sirima et al. [32] then demonstrated that PRIMVAC was safe and immunogenic in a human (all female) randomised, double-blind, placebo-controlled trial. Three successive injections were given to both naïve and exposed women with seroconversion and no serious adverse events. The PAMVAC vaccine is similar to PRIMVAC, also targeting a recombinant fragment of VAR2CSA from *P. falciparum* and adjuvanted with Alhydrogel or GLA or in a liposomal formulation. An initial trial testing all combinations in healthy adult volunteers exhibited all PAMVAC formulations to be safe, well-tolerated and immunogenic, with the highest antibody production to the PAMVAC-GLA vaccine [33]. Future trials of both PRIMVAC and PAMVAC in pregnant women are planned.

The pursuit of a malaria vaccine is ongoing. There has yet to be any testing in pregnant women. However, the PAMVAC and PRIMVAC vaccinations should be pursued and will make a significant impact on the morbidity and mortality of women and their children in endemic areas.

Ebola

Ebola viruses, part of the *Filoviridae* family, are highly contagious with high mortality. They are spread and transmitted from animals to human with bats and nonhuman primates being the carriers of the virus, and also transmitted from human to human through bodily fluids. The virus causes an illness with fever, myalgia and arthralgia, diarrhoea, vascular permeability and coagulopathy, and multiorgan failure. The mortality for Ebola virus disease ranges from 25% to 90% with only supportive care available for its management. The virus was first discovered in 1976 and took until the 2013–2016 Ebola virus outbreak in West Africa to really spur the advancement in the clinical development of a vaccination against Ebola [34].

Ebola virus can affect pregnant women with increased poor outcomes in neonates. Foeller et al. [35] have shown that infection in pregnant women has the same morbidity and mortality as in nonpregnant women. However, obstetric outcomes may be worse as obstetric care is compromised in the place of supportive care of Ebola symptoms. Ebola virus can be detected in blood, amniotic fluid, placental tissue, and breast milk; and last up to 32 days after maternal clearance of the virus from blood with ongoing risk of neonatal transmission [35].

Ebola viruses are enveloped filamentous particles with a single-stranded RNA genome. There are now five strains known, with Ebola Zaire the cause for the majority of outbreaks and therefore, the main target for immunisation. In 1980, Lupton et al. [36] published in the Lancet about their inactivated vaccine being efficacious in a guinea pig model. Now, there are two vaccinations in phase 2, 3, and 4 trials – a DNA-based vaccine and a recombinant adenovirus serotype 5-based vaccine [34].

The most promising vaccine in clinical trials is the Merck/NewLink Genetics live-attenuated recombinant vesicular stomatitis virus (VSV)-based vaccine which has been approved for emergency use during outbreaks in the Democratic Republic of Congo. The vaccine expresses the Ebola glycoprotein G in place of the VSV glycoprotein G and has been trialled in 17,000 participants as part of phase two and three trials during Ebola outbreaks [37]. Immunogenicity data showed up to 100% seroconversion for antiglycoprotein antibodies at 28 days post vaccination. Furthermore, vaccine efficacy was shown through 'ring vaccination' where high-risk subjects such as contacts and contacts of contacts from proven Ebola cases were the recipients of the vaccination, and efficacy was shown at 10 days after a single dose of the vaccine. The vaccine was shown to be well tolerated when administered to healthy, nonpregnant adults [34].

A recombinant human adenovirus serotype 5-based vaccination has been developed to express the Ebola virus glycoprotein P [38]. This vaccine was tested in 500 participants in a double blind, placebo-controlled study to test for optimal dosing, safety, and immunogenicity. This vaccination was found to be safe with only mild injection-site reactions; however, the vaccine appeared to only elicit short-lived antibodies which peaked at day 28 and declined quickly over the following months. This vaccination has been approved for use by the Chinese Ministry of Science and Technology; however, it is likely to be best used in acute outbreak scenarios [39].

Pregnancy has been an exclusion in the testing of Ebola vaccinations as the majority are live-attenuated vaccines. The VSV-Ebola vaccination clinical (STRIVE) trial performed during the 2015 Sierra Leone outbreak excluded pregnant women; however, of the 3103 women of reproductive age, 84 women had a pregnancy with an estimated date of conception within 60 days of vaccination resulting in 51 live births and 30 pregnancy losses including miscarriage and stillbirth. This study was not designed to specifically look for pregnancy outcomes and the small sample size and missing data such as gestation of pregnancy loss meant that the data gathered was difficult to interpret [40]. The WHO Strategic Advisory Group of Experts (SAGE) interim recommendations on vaccination against Ebola Virus in 2019 recommended the use of the recombinant VSV-Ebola vaccination in pregnant and lactating women with the provision of ongoing safety monitoring and follow-up of these women [41].

Coronavirus (SARS-CoV-2)

The late 2019 outbreak of the novel coronavirus, SARS-CoV-2 (COVID19), has seen a widespread impact on health and the economy. The magnitude of infection from SARS-CoV-2 was declared a global pandemic in March 2020, with the ongoing effects still felt in January 2021, with nearly 100 million people having been infected and with over 2 million deaths [42].

The SARS-CoV-2 virus is a coronavirus, transmitted through respiratory droplets, secretions, faeces, and fomites, and produces a spectrum of illness from asymptomatic infection to acute respiratory distress syndrome, pneumonia, and death [43]. Severe symptoms such as marked hypoxia requiring intensive care unit admission is seen more in older patients with other comorbidities. There is also a range of long-term effects from survivors of the illness which are still being studied. Pregnant women infected with SARS-CoV-2 have higher rates of iatrogenic preterm birth and caesarean delivery with low rates of vertical transmission [44].

Vaccination against SARS-CoV-2 is thought to be the key to increased population immunity, prevention of disease, and improvement in the ongoing health care and economic crisis. This has driven the unparalleled movement to find an effective vaccination, with 58 vaccines developed in 2020 and 11 tested in phase 3 trials [45,46]. As of January 2021, three main vaccines were approved for emergency use – one adenovirus-vectored and two mRNA vaccines.

The AstraZeneca vaccine (ChAdOx1 mCoV-19 AZD1222) was developed at Oxford University using a replication-deficient Chimpanzee adenovirus vector containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein) [46]. Phase 1 clinical trials began in April 2020 on healthy subjects and then to randomised controlled trials (Phase 2/3) that commenced in the UK, Brazil, and South Africa, and included older adults over 56 years with a wider range of comorbidities. Efficacy of 70.4% after two doses was shown across different sites, with no safety concerns. Furthermore, this vaccine is relatively cheap, expected to cost only US 2–3 dollars per vaccination and does not require freezing; therefore, more attainable for lower income settings [45].

Both Moderna and Pfizer have produced mRNA vaccines which have been rapidly developed and tested. The Moderna mRNA-1273 vaccine is a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes for the SARS-CoV-2 spike protein. Over 30,000 participants who were considered high-risk for contracting COVID-19 were enrolled in the COVE trial— a phase 3, randomised, observer-blinded, placebo-controlled trial in the United States. The efficacy from this trial was found to be 94.1%, with high levels of efficacy noted in all demographic groups with low rates of local mild reactions and no serious adverse events [46,47]. The Pfizer BNT162b2 vaccine also employs mRNA vaccine technology, with the lipid nanoparticle–formulated, nucleoside-modified RNA (modRNA) encoding a prefusion conformation SARS-CoV-2 spike protein [48]. The phase 3 placebo-controlled, observer-blinded trial that occurred worldwide across multiple continents and included over 44,000 people, showed an overall vaccine efficacy of 95%. Both vaccines had higher rates of minor vaccine reactions such as fever, fatigue, and local site erythema compared with that of placebo, but overall had extremely low serious adverse reactions in both arms.

Pregnant women were not included in any of the trials. There are wide calls to include pregnant and breastfeeding women in the ongoing trials [49]. At present, SARS-CoV-2 vaccines are being rolled out and offered to pregnant women in higher risk occupations such as healthcare. Advice from leading bodies such as the Royal College of Obstetricians and Gynaecologists for pregnant women is to choose

between having the vaccine or awaiting further information, with guidance stating that it is biologically implausible to cause harm to pregnancy or fertility [50].

Challenges in the creation of future vaccination in pregnancy

There are significant challenges in ascertaining the safety and efficacy of vaccinations in pregnancy that includes historical, ethical, medicolegal, and pathophysiological issues. Yet, the potential benefit for both mother and child are increasingly being recognised as a missed opportunity to test and develop vaccines for pregnant women.

In 2015, the American College of Obstetricians and Gynecologists stated "Although there is concern that including pregnant women in the study of new drugs potentially could cause fetal harm, it is critical to recognize that excluding pregnant women from research also can lead to harm" [51].

Pregnant and breastfeeding women were historically and automatically excluded from any clinical trials, including vaccination trials [52]. This was a runoff effect following adverse reactions to the medication thalidomide, which resulted in significant birth defects. The result of the exclusion of these women has led to a massive gap in knowledge around safety, efficacy, and dosing in pregnancy and lactation. Information on the safety of vaccination in pregnancy is often obtained from following women who are inadvertently vaccinated in pregnancy, as demonstrated above with the Ebola vaccine.

Ethically, pregnant women and their unborn fetuses have a right to evidence-based, scientifically sound health care. The development of guiding principles to allow testing of pregnant women in clinical trials is imperative. All vaccine trials that include pregnant women should complete appropriate preclinical testing and reproductive testing in animal models, and at first complete safety and immunogenic testing in nonpregnant adults [52]. Patients, medical scientists, healthcare providers, health authorities, and those involved in clinical research must all be reminded and educated of the importance of including pregnant women in their studies. Important clinical end points must be defined when researching new vaccines in pregnancy, keeping in mind that they may be different to the nonpregnant population.

Pregnancy needs to be respected as a condition that can cause altered physiology and changes in immunological factors for both the foetus and mother. Research into the effects of these changes on how vaccines work in pregnancy is also imperative to further our understanding on efficacy, dosing, and side effects [51]. The inclusion of pregnant women in vaccine trials need to be viewed as a unit that has two outcomes – maternal and fetal. The interests of both mother and baby usually align, often with the aim to improve outcomes for the mother or the baby. The design of these trials must reflect the dual outcomes and post marketing research having access to linked health records of mothers and their infants for longitudinal studies.

Challenges that face testing in the pregnant population include enrolment of large numbers to test for rare outcomes such as congenital malformations, still birth, or maternal deaths. Also, recruitment of enough candidates to ensure an appropriate level of exposure to an antigen may also be difficult in the face of public health advice on how to avoid exposures and changes in the epidemiology of particular viruses such as Zika and Ebola.

Practice points

- Pregnancy offers a unique opportunity for vaccines that can benefit the mother, foetus, and newborn.
- Hundreds of vaccines are in various states of research aimed at targeting illnesses that are clinically important to pregnant women and their newborns. Current vaccines under development include those against Cytomegalovirus, Respiratory Syncytial Virus, Ebola virus, Zika virus, Group B streptococcus, Malaria, and SARS-CoV-2.
- The inclusion of pregnant women in future vaccine trials is imperative, with those involved in health care and clinical research being asked to consider the historical, ethical, medicolegal, and pathophysiological issues of pregnancy and future vaccinations.

Research agenda

- Ongoing research is required to increase the armamentarium of vaccines available to pregnant women including those against CMV, RSV, GBS, Malaria, Zika, Ebola, and coronavirus.
- The inclusion of pregnant women in vaccine trials will address the massive gap in knowledge around safety, efficacy, and dosing in pregnancy and lactation.

Declaration of competing interest

There are no conflicts of interest to declare.

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