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Review

Vaccine protection of the mother, the fetus, neonates and infants

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Abstract: Pregnant women, the fetus, neonates, and young infants are at an increased risk for serious diseases from many infections due to their immunocompromised or immunonäive statuses. Vaccines are available for many diseases, but not all of the serious infectious diseases for which these individuals are at risk. Some of these vaccines can be administered to the mother either prior to or during pregnancy. The antibodies that are generated can benefit the mother, the fetus, and the neonate. Other vaccines can be administered to the neonate soon after birth to elicit important protections. This review outlines the available vaccines and the need and potential for new vaccines for pathogens that challenge pregnant women, the fetus, neonates, and the infant.

Keywords: vaccine; neonate; fetus; infant; pregnant; virus; infection

1. Introduction

Vaccines are possibly the most beneficial treatment that can be provided to a patient since they allow the individual to elicit their own protections against serious and potentially life-threatening infections. Pregnant women, the fetus, and neonates are at an increased risk for serious diseases from many infections, some of which are less of a problem for older children or another adult [1–8]. Vaccines are available and proven safe for many diseases (Table 1), but not all of the serious infectious diseases for which these individuals are at risk (Table 2) [5]. Some of these vaccines can be administered to the mother either prior to or during pregnancy. The antibodies that are generated can benefit the mother, the fetus, and the neonate. Other vaccines can be administered to the neonate, or within 2 months of birth, to elicit protections.

Unfortunately, not all vaccines can be safely administered during pregnancy or early in life and must be deferred until they are safe or can elicit an effective immune response to establish protective immunity. During this period, the infant is susceptible to diseases (e.g., measles).

Table 1. Available vaccines for routine maternal or infant immunization [9–14].

Microbe	Fetal, neonatal, and maternal[1] disease manifestations	Vaccine type	When to administer
Bordetella pertussis	Pertussis (whooping cough), coryza, fever	Subunit/toxoid (TdaP)	Prior to or during pregnancy At 2, 4, 6 months
Clostridium tetani	Painful muscle spasms, respiratory failure, convulsions	Toxoid (TdaP)	Prior to or during pregnancy At 2, 4, 6 months
Corynebacterium diphtheriae	Diphtheria, sore throat, airway blockage, myocarditis, polyneuropathy, kidney failure	Toxoid (TdaP)	Prior to or during pregnancy At 2, 4, 6 months
Haemophilus influenzae B	Meningitis, epiglottitis, cellutis, otitis, sinusitis, pneumonia	Conjugated polysaccharide	At 2, 4, 6 months
Mycobacteria tuberculosis	Tuberculosis, pneumonia, disseminated disease in immunocompromised	BCG vaccine[2]	At, or soon after birth
Neisseria meningitidis	Meningitis, sepsis, fever, stiff neck, headache, nausea, vomiting, rash	MenACYW: Conjugated MenB: protein subunit	Prior to or during pregnancy Older than 2 months
Streptococcus pneumoniae	Pneumonia, sepsis, meningitis	Conjugated polysaccharide Polysaccharide	Prior to or during pregnancy At 2, 4, 6 months At 2,4, 6, 12–15 months
Hepatitis A virus	Hepatitis, miscarriage, preterm birth, stillbirth	Inactivated	Prior to or during pregnancy
Hepatitis B virus	Hepatitis, miscarriage, chronic HBV in neonate or child, preterm birth, and stillbirth	Virus like particle	Prior to or during pregnancy At or soon after birth, 2, and 6 months
Influenza A and B	Cough, fever, chills, sore throat, coryza, headache, myalgia	Inactivated	Prior to or during pregnancy At 6 months
Polio virus	Minor disease or major meningitis or paralytic disease	Inactivated (U.S.A. and other countries) Live attenuated[3]	At 2, 4, 6 months Birth, 6, 10, 14 weeks
Respiratory Syncytial Virus	Pneumonia in neonate, young child; sepsis, pneumonia during pregnancy	Subunit +/– adjuvant, Monoclonal antibody	At 32–36 weeks of pregnancy[4]
Rotavirus	Life threatening infantile diarrhea	Live oral attenuated	At 2, 4 months (Rotarix) or 2, 4, 6 months (Rota Teq)
Rubella virus	Cataracts, congenital heart disease (patent ductus arteriosus), "blueberry muffin" rash, miscarriage	Live attenuated	Prior to pregnancy After 12 months
SARS-CoV-2	COVID-19, pneumonia	mRNA or nanoparticle	Prior to or during pregnancy mRNA: at 6 months; nanoparticle: at 12 years
Varicella zoster virus	Varicella rash, growth restriction, scarring on limbs, ocular defects, microcephaly, encephalitis	Live attenuated	Prior to pregnancy After 12 months
Yellow Fever virus	Fever, chills, fatigue, myalgia, nausea, vomiting, jaundice, hemorrhagic disease	Live attenuated	Prior to pregnancy After 12 months
Ebola virus[3]	Spontaneous abortion, fever, myalgia, headache, sore throat, GI symptoms, unexplained hemorrhage or bruising	ERVEBRO: VSV expressing ebola glycoprotein [15–17]	Only during epidemic
Hepatitis E virus[3]	Pregnant women: acute liver failure, fetal loss and mortality.	Hecolin-Virus like capsid [18–20]	Prior to pregnancy in endemic regions
Plasmodium falciparum	Malaria	Adjuvanted fusion protein in particle [21–23]	Children older than 5 months

[1] Included if different from the fetus or neonate.

[2] Not utilized in the United States and immunization of neonates is poorly or not protective for adults.

[3] WHO approved for use in endemic areas.

[4] Only during RSV season, from September through January in the USA.

Table 2. Vaccines to be developed for pregnant women, neonates and infants.

Microbe	Fetal, neonatal and maternal[1] disease manifestations	Examples of vaccines in development
Chlamydia trachomatis	Conjunctivitis, pneumonia	OMVs of *E. coli* housing HtrA (surface serine protease), Recombinant multivalent MOMP [24–26]
Escherichia coli	Sepsis, neonatal meningitis, pneumonia	Multivalent O antigen, Conjugated polysaccharide [27,28]
Listeria monocytogenes	Sepsis, meningitis, diarrhea	Live attenuated, mRNA [29]
Neisseria gonorrhoeae	Ophthalmia neonatorum, sepsis	Outer membrane vesicles (OMV), recombinant proteins [24,30–33]
Staphylococcus aureus	Sepsis, pneumonia, skin and disseminated disease	Multiple protein with conjugated polysaccharide [34]
Streptococcus agalactiae (Group B Strep)	Early and Late disease, stillbirth, blindness, hearing loss, and meningitis	Conjugated polysaccharide [35]
Streptococcus pyogenes	Sepsis, meningitis, pneumonia, skin and disseminated disease	M protein-based and non-M protein-based vaccines [36–38]
Treponema pallidum	Syphilis	Outer membrane protein [24,39,40]
Cytomegalovirus	Fetus, Neonate: Chorioretinitis, microcephaly, intracranial calcifications, "blueberry muffin" rash, cataracts, sensorineural hearing loss, bone marrow suppression, deafness, etc.	Adjuvanted subunit, multiple glycoprotein, RNA, etc. [41–44]
Herpes simplex virus	Miscarriage (fetal death), Neonate: vesicular skin lesions, seizures, blindness, encephalitis, severe sepsis	Adjuvanted subunit, multiple glycoprotein, RNA, etc. [24,45–48]
HIV	Low birth weight, hepatosplenomegaly at birth, chronic infection, immunosuppression	Multiple formats [49–54]
Parvovirus B19	Hydrops fetalis and fetal anemia	Virus like particle [55]
Toxoplasma gondii	Fetal infection: intracranial calcifications, abortion, low birth weight, hydrocephaly, and retinochoroiditis	Multiple formats [56]
Zika	Microcephaly, seizures, issues with feeding, issues with limb movement, issues with vision and hearing	Multiple formats [24,57,58]
Plasmodium falciparum	In utero malaria	Adjuvanted placental promoting malarial VAR2CSA protein [59,60]

[1] Included symptoms if different from those of the fetus or neonate.

The protections afforded by vaccines require their implementation. Until recently, pregnant women and neonates were excluded from vaccine trials. However, guidelines and studies have been implemented [61–63] that allowed newer vaccines, including the coronavirus disease 2019 (COVID-19) and respiratory syncytial virus (RSV) vaccines, to be utilized during pregnancy [64–67]. Other limits to vaccine implementation include barriers to access and vaccine hesitancy, the latter of which is due to misinformation, cultural or religious beliefs, and other influences [68]. This was especially evident for the COVID-19 vaccination programs [69]. However, the use of motivational interviewing, sharing facts, and other approaches can help some individuals overcome their hesitancy [68].

There are still many infectious diseases that do not have associated vaccines (Table 2). New technologies, new understandings of infections and immunology, and an increased interest and funding for human trials may provide vaccines for these diseases. This review will present a brief background to the immunology, need, and technology behind the vaccines that are currently available and for the development of future vaccines.

2. Antibody mediated protections

Vaccines elicit the release of antibodies, which are the primary protection against infection. It takes at least 8 days following an initial challenge by infection or vaccination to elicit antibody protections and a memory response to the immunogen. Due to the immune memory, the response (an anamnestic response) to an infectious rechallenge or a vaccine booster occurs within approximately 3 days and is much stronger than the primary response. Eliciting an immune memory for more rapid and stronger protective anamnestic responses is the purpose of vaccinations.

Antibodies prevent disease by limiting the spread of the microbe from the site of infection to the target tissues that cause disease and by facilitating the clearance of the microbe. They also act by neutralizing the binding and activity of microbes and toxins, by facilitating phagocytic uptake as an opsonin, and by activating the complement cascade. Activation of the complement cascade initiates antimicrobial inflammation, the direct killing of the microbe, and also promotes opsonization. Secretory antibodies can protect mucosal surfaces. Antibodies are most effective at limiting microbes that are spread extracellularly.

Immunoglobulin (Ig)M is the earliest antibody to be produced and does not require T-cell help for its production. IgM is pentameric, very large (900 kDa compared to 154 kDa for IgG), is restricted to a large extent to the bloodstream, and is associated with shorter memory responses. Polysaccharide immunogens primarily elicit the IgM responses. IgM is especially important to protect against encapsulated organisms, such as *Streptococcus pneumoniae*.

Protein containing antigens can elicit CD4 helper T-cell responses, that can then promote IgG, IgE, and IgA production. The protein component of an antigen is processed into peptides and presented by antigen presenting cells (dendritic cells, macrophages, and B lymphocytes) to the antigen specific CD4 T-cells. Then, cell-cell interactions and specific cytokine conversations from different CD4 T-cells will promote the genetic switch from IgM production to IgG, IgE, or IgA within B-cells and their maturation into plasma or memory cells. The different antibody types are distinguished by a region of the antibody that remains constant and does not bind to the antigen, which is called the fragment crystallizable (Fc) portion.

The different CD4 T helper (Th) cells are categorized as Th1, Th2, Th17, etc., based on the expression of transcription factors and their cytokine conversations [70–72]. Th1 responses are delivered by interferon gamma, granulocyte macrophage colony stimulating factor (GM-CSF), IL2, and tumor necrosis factor (TNF) β. This response promotes IgG production and activates B- and T-cells (including CD8 T cells), innate lymphocytes, macrophages, and dendritic cells. Th2 responses are characterized by interleukin (IL) 4, IL5, IL10, GM-CSF, and IL13. This response promotes an antibody class switch, mucus production, eosinophil activation, and other responses. Most inactivated vaccines elicit Th2 responses and antibody production. A combination of Th1 and Th2 responses promote longer term immune memory and protections. Combined Th1 and Th2 responses are elicited

by live attenuated vaccines, messenger RNA (mRNA), DNA vaccines, and inactivated vaccines that are enhanced by certain adjuvants [70–72].

IgG responses are elicited towards molecules other than proteins, including polysaccharide antigens, if those molecules are conjugated to protein. Capsular polysaccharide-protein conjugate vaccines for *Streptococcus pneumococcus, Hemophilus influenzae B,* and *Neisseria meningitidis* have been developed to engage T-cell help to generate anti-capsular IgG antibodies [73].

Antimicrobial IgM and IgG are important protections to prevent the systemic spread of microbes. In an unimmunized individual, the microbe has 3–4 days before IgM is produced, and at least 8 days before a competent IgG response is mounted to spread, establish the infection and cause disease. A previously infected or vaccinated individual is likely to have protective antibodies and will elicit a faster and more robust memory response following an infectious rechallenge due to the presence of memory lymphocytes [74–76].

IgG can transfer across placental endothelial cells and mucoepithelial cells to protect the fetus and the cervico-vaginal region of the woman. The transfer of the IgG is mediated by the neonatal Fc receptor (FcRn) [77–79]. The FcRn binds to the constant region of the IgG. The FcRn transfers the IgG into and then through the syncytiotrophoblast cells of the placenta to provide the fetus with the maternal IgG. Additionally, the FcRn transfers IgG across other body membranes and helps to recycle IgG after its use for opsonization. Moreover, the FcRn transfers the IgG generated in response to the human papilloma virus (HPV) vaccine and other vaccines across the mucosal membranes to elicit protections from infection [77].

Secretory IgA (sIgA) is produced by plasma cells associated with mucosal membranes. Serum IgA can be produced elsewhere in the body. Large amounts of sIgA are secreted across the mucosal membranes to protect the openings of the body and the respiratory, urinary, and gastrointestinal (GI) tracts [80]. Oral and respiratory administered vaccines, such as the live oral rotavirus and poliovirus vaccines and the nasal live attenuated influenza vaccine (LAIV), elicit sIgA production [80]. The sIgA can prevent entry of the microbe into the body; then, the IgG can block any subsequent dissemination within the body to prevent replication and disease to provide a sterilizing immunity [80,81].

Antibody protections have their limitations, especially when it comes to resolving intracellular infections. Cytokines produced by Th1 responses activate macrophage, CD4 T-cell, and cytotoxic CD8 T-cell responses that are important for these antimicrobial protections. Cytotoxic CD8 T-cells kill the infected cells and reinforce protections with cytokines. Th1 responses are necessary to control intracellular pathogens, such as *Mycobacteria tuberculosis* (MTB), *Listeria monocytogenes,* and latent and enveloped viruses [70]. Chronic activation of macrophages and CD4 T-cells, which occur during an intracellular MTB infection, can lead to granuloma formation, which walls off the infected cells to protect the rest of the body.

3. Why do the pregnant mother, fetus and neonate need immunizations

The pregnant mother, fetus, and neonate are either immunodeficient or immunonäive and susceptible to certain microbial infections. The immune system of a pregnant woman undergoes a shift that favors the humoral Th2 responses and suppresses Th1 responses and cell mediated immunity to protect, but not reject, the fetus. Without this shift, the mother's CD8 T-cell responses would see the fetus as a tissue graft and terminate the pregnancy [82]. Maintenance of the Th2 humoral response and antibody provides protections against most pathogens of the mother and fetus. However, suppression

of the Th1 responses increases the mother's susceptibility to infections that would require cell mediated immune responses for protection or resolution, which include certain viruses, fungi, and intracellular bacteria.

The fetus, neonate, and infant are especially susceptible and at risk for more serious outcomes to certain infectious diseases because their immune systems are uneducated and are focused on regulating immune responses to prevent inflammation and autoimmunity during their rapid growth and development [83–87]. They depend upon their innate immune protections and the protections of the maternal IgG and IgA antibodies, for as long as they last [87,88].

The fetus is susceptible to infections that can ascend to the womb or cross the placenta from blood-borne infections of the mother, including bacteremia. These infections were previously designated as sTORCH (syphilis, toxoplasmosis, other, rubella, cytomegalovirus (CMV), and human immunodeficiency virus (HIV) and herpes simplex virus (HSV)). The 'other' category includes B19 parvovirus, VZV, HTLV 1, and Zika virus [88]. Immunization prior to, or during, pregnancy can boost the maternal and fetal IgG levels to protect the mother and block transmission and infection of the fetus (e.g., rubella and zika virus) [89].

Upon birth, the neonate is exposed to the microbial world that we live within. The neonate is susceptible to infections acquired while passing through the birth canal, as well as to exposures early in life. Some of these microbes can evade or overpower the neonatal protections, either with their virulence mechanisms or due to their numbers, and cause serious disease. These include the previously mentioned microbes as well as diphtheria, tetanus, pertussis, *Group B Streptococcus,* other *Streptococci, Escherichia coli* (sepsis and meningitis), *Listeria monocytogenes, Enterococci, Staphylococcus aureus, and Candida species* [90]. Innate immune protections are sufficient for protection against most microbes supplemented by the maternal IgG acquired in utero, and a smaller amount through breast milk. The IgG and IgA secreted into the milk also protect the gastrointestinal tract from infection and help to select a proper microbiome [91]. The presence of these antibodies supplements the babies' innate protections while the infant develops its own immune protections.

Within the first year of life, the newborn is especially susceptible to enveloped viral infections (e.g., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza, RSV, measles, other paramyxoviruses, herpesviruses, poxviruses, and Zika virus), non-cytolytic viral infections (e.g., hepatitis A, B, C, and E viruses, and HIV), infections that can spread directly from cell to cell (e.g., *Listeria monocytogenes* and HSV), intracellular microbes (e.g., *MTB* and *Histoplasma spp*.), and some other infections (toxoplasma, malaria) [92–93]. In addition, neonates are especially susceptible to sepsis [2]. Vaccines are available for some of these microbes (see Table 1), but not others (see Table 2).

4. Protecting the mother, fetus and neonate

Protection for the pregnant mother, fetus, and neonate from infectious diseases can occur by restricting their exposure or by eliciting a protective immunity. During the COVID pandemic, a combination of masking and social distancing, to limit aerosol exposure, and immunization reduced infections and serious outcomes within the population [94]. Building herd immunity by vaccination against measles, mumps, and rubella has limited the presence of these microbes in the population and has provided protections for the mother, fetus, and neonate [95]. Since rubella is generally a benign disease for children, the vaccination programs are essentially a means for protecting the fetus from the serious consequences of congenital infection.

Immunity generated by prior infection or vaccination of a mother provides her with protections, which also protects the fetus and, subsequently, the neonate [96]. The IgG transported across the placenta into the fetal blood supply continues to protect the neonate after birth. For example, the antibodies elicited within the mother by a prior infection with B19 parvovirus can protect the fetus from both an infection and the consequences of B19 infection (e.g., serious anemia and hydrops fetalis) [97]. Similarly, the risk and severity of congenital cytomegalovirus (CMV) is much less for the fetus within a mother who developed an immunity due to a prior CMV infection. As such, the CMV infection of a seronegative woman during pregnancy increases the risk for serious congenital outcomes [98–100]. Prior to pregnancy, women should be immunized to elicit and boost their protections, which they will provide to the fetus. This is especially important for live virus vaccines that cannot be administered during pregnancy due to the immunosuppression within pregnant women and the potential risk to the mother and fetus. These vaccines include those for yellow fever, measles, mumps, rubella, or varicella zoster viruses [3,4]. During pregnancy, antibody production can either be provided or boosted by non-living, non-replicative vaccines composed of proteins, polysaccharides, or mRNA (see Table 1).

5. Maternal Immunization

Vaccination during pregnancy has the potential to protect the mother and provide the fetus and neonate with IgG antibody protections (Table 1) [1,61,101,102]. Immunization of the mother provides approximately 6 months of protection to the newborn, which is primarily based on the half-life of IgG [103]. Recommendations for the vaccines that are appropriate prior to or during pregnancy, and for neonates, newborns, and children, are provided by the USA Centers for Disease Control (CDC) [9] and the World Health Organization (WHO) [104]; however, implementation differs by country and even within the individual states of the U.S. The recommended maternal vaccines include the following: the diphtheria, tetanus, and acellular pertussis (DTaP) vaccines, which provide antibody protections against toxin mediated diphtheria, tetanus, and pertussis diseases, respectively; the inactivated influenza A and B vaccines; pneumococcal vaccines, either the pneumococcal conjugate vaccine (PCV)20 or pneumococcal polysaccharide vaccine (PPSV)23; meningococcal vaccines; and vaccines for *Hemophilus influenzae B* (Hib) and hepatitis B and A (HBV, HAV, respectively) (See Table 1). Most recently, the mRNA and protein subunit-nanoparticle vaccines for COVID-19 and the unadjuvanted RSV vaccines, have been added to the list. The RSV vaccine is administered during weeks 32–36 of pregnancy, and more specifically during the contagion season of September to January [64].

Passive immunization is another means for protecting the mother, fetus, and neonate. Treatment with immunoglobulin is a safe approach to elicit an immediate but temporary protection after exposure to a microbe. Some of the licensed antibody products that are available are for RSV, CMV, measles, HBV, HAV, rabies virus, varicella virus, tetanus, and botulism [105]. For RSV, a monoclonal antibody (e.g., nirsevimab) may be given to the mothers, newborns, neonates, or children who are aged 8–19 months who are at risk to severe RSV disease during RSV season, which is from October to March [106].

6. Current neonatal and newborn immunizations

The current vaccines available for neonatal and newborn administration are listed in Table 1. Neonatal vaccines are administered within the first 28 days of life. The hepatitis B vaccine is administered soon after birth and elicits antibody protections that are important to prevent chronic HBV, for which neonates

and infants are especially prone [107]. Where appropriate, the oral poliovirus and Bacillus Calmette-Guérin (BCG) vaccines would also be administered at this time [108,109]. Infants receive most of their first well-baby immunizations at 2 months of age. These vaccines are directed against pathogens that cause serious diseases in individuals of this age group and incorporate identified immunogens that are safe and elicit sufficient protective immunity [85].

The BCG vaccine is a live vaccine administered in countries other than the U.S. and protects against MTB infection and establishment of chronic disease. It is administered at birth [107,108]. The live vaccine elicits innate, antibody, and cell mediated immune responses important to protect against this intracellular bacterial pathogen. Although safe, the protection does not extend to adolescents and adults and the presence of immunity interferes with the routine purified protein derivative (PPD) skin test screening procedures. The PPD test is used in the U.S.A. and other regions that have a low risk for infection. Newer, genetically modified BCG vaccines, and subunit vaccines that utilize MTB protein antigens enhanced with adjuvants, are being developed to improve and extend protections [108–111].

The oral polio virus vaccine (OPV) is easy to administer, elicits long term and mucosal immunity, and is still administered in many countries. The inactivated polio virus vaccine (IPV) is preferable, despite the requirement for injection and a more limited immune response, due to its safety. The OPV is administered at birth and the IPV is administered at 2, 4, and 6 months of age [112].

The live rotavirus vaccines are administered at 2 and 4 months of age to elicit gastrointestinal IgA production to protect against potentially lethal dehydration due to diarrhea. The rotavirus vaccines have made a great difference worldwide by protecting babies from this potentially lethal disease [63]. At 2 months of age, infants also receive their first DTaP, capsular polysaccharide conjugate vaccines for *Haemophilus influenzae type b* and *Streptococcal pneumonia*, the inactivated poliovirus (IPV), and the mRNA COVID-19 vaccines [113].

Of the major bacterial causes of sepsis in the neonate (*S. aureus, S. pneumoniae, S. pyogenes, Group B streptococci, Salmonella spp., Pseudomonas, Klebsiella,* and *E. coli*), only *S. pneumoniae* is preventable by a vaccine [90]. The conjugated capsular polysaccharide vaccine (Prevnar 15 or Prevnar 20) is preferable because it elicits IgG production in addition to IgM. Although *Neisseria meningitidis* can also cause serious disease in neonates and newborns, the CDC recommends vaccination with the MenACWY capsular conjugate and protein Men B vaccines at 2 months and 10 years for only those individuals at a greatest risk (e.g., those with a complement deficiency, damaged spleen, sickle cell disease, have HIV, or are traveling or living in regions where the disease is common) [9].

7. Microbe specific challenges to vaccine development

Despite new developments in vaccinology, vaccines for the diseases listed in Table 2 continue to elude development and implementation. Several hurdles must be overcome for each of them.

Once the need and economic feasibility for a new vaccine have been determined, the first step in vaccine development is to identify appropriate immunogens and the means for delivery that will elicit safe and dependable immune protections against all exposures to infection. To complicate the process, protection may either require immunization with a group of immunogens or require a specific protein conformation or antigenic structure to elicit protection. For example, CMV, HSV, [114] and *S. aureus* [34] use multiple proteins to infect different cells, establish their infection, establish latency, or colonize an individual to cause disease. As for the RSV F glycoprotein [115] and SARS-CoV-2 spike protein [116], the protein structures that confer efficient neutralization are either unstable or hidden and require

genetic engineering to develop and deliver conformers that are stable and expose the immunogenic structures necessary to elicit protection.

Vaccine development is especially problematic for those microbes that exist as multiple serotypes, clades, or that readily mutate to generate new serotypes. These include rhinoviruses, influenza, hepatitis C virus, HIV, and SARS-CoV-2. For influenza A, the composition of the annual vaccines is predicted a year ahead to accommodate the prevalent strains [117–119]. Similarly, boosters for the COVID-19 vaccines have incorporated modifications to accommodate the predominant disease-producing strains [116]. For *Streptococcus pneumoniae*, the current vaccine mixture covers the most prevalent disease-causing strains but does not provide universal protection. Newer approaches are targeted towards identifying vaccines that elicit broad spectrum immunity towards multiple strains of these microbes [120,121].

Protective immunity may require cell mediated and/or secretory IgA responses not provided by most killed and subunit vaccines. These vaccines only elicit IgM and/or IgG (and possibly serum IgA) that can block the spread of microbes in the bloodstream but are less effective or ineffective for intracellular pathogens (e.g., MTB), and those that can be spread by cell-cell transfer (e.g., Listeria, RSV, HSV, or HIV). As such, mRNA and DNA vaccines or vaccines that utilize certain adjuvants that promote the necessary protective IgG and cell mediated responses may be appropriate during pregnancy in lieu of more risky live attenuated vaccines [3–5].

Vaccines that produce sIgA may be necessary to block the infection of mucosal surfaces, such as the respiratory and GI tracts, and to promote secretion into milk [91,96]. The oral rotavirus, poliovirus, and nasal influenza vaccines elicit secretory immunity that can block infection before viral entry into the body. Nasal COVID-19 vaccines are being developed for this reason [122]. However, safe and effective secretory IgA vaccines, other than those listed, have proven difficult to design.

The ability to establish a lifelong microbial presence (chronicity or latency) very soon after the initial infection, as for HIV and the herpesviruses, make it difficult to elicit immune protection of an individual. Success in most vaccine trials requires that the vaccine prevents the replication and spread of the microbe from the initial site of infection (sterile immunity). So far, the only vaccines that elicit sterile immunity are the sIgA producing oral or nasal administered vaccines (e.g., rotavirus vaccines), which can stop the virus before systemic infection.

Another hurdle to vaccine development is the acquisition of funds, the design, and the implementation of appropriate clinical trials to prove the safety and efficacy of a new vaccine for the at-risk populations. This is especially difficult for pregnant women and neonates, who are generally excluded [3–6,123].

8. New technologies

Modern genetic engineering approaches have been utilized to identify, create, and produce many of the newer vaccines (e.g., HBV, SARS-CoV-2, RSV, herpes zoster). Newer vaccine formats include particulates, DNA, RNA, hybrid viral vaccines, and the use of appropriate adjuvants. [124–126].

Most vaccines elicit protective antibodies directed against external structures of the pathogen that either mediate attachment or entry into human cells to neutralize the potential for infection. The relevant structure may be hard to identify, is unstable, is hidden by carbohydrates, or is variable due to the presence of multiple serotypes of the pathogen. For example, the HIV gp120 glycoprotein is a viral attachment protein, is highly glycosylated, and is very variable, differing between the different

strains and clades and even changes during infection of an individual [49]. These and other characteristics of the virus have impeded development of an effective vaccine.

For SARS-CoV-2 and RSV, genetically engineered variants of the viral attachment or fusion proteins, the S and F glycoproteins, respectively, had to be developed to retain the immunogenic shape of the protein to elicit neutralizing antibodies [114]. For influenza A, a pan-influenza vaccine is being developed, which utilizes a highly conserved protein sequence within the hemagglutinin (HA) glycoprotein that is frozen into a configuration that elicits broad spectrum neutralizing antibodies [71,127].

To replace the need for multiple capsular polysaccharide vaccine components for *S. pneumoniae*, a bacterial surface protein immunogen is being sought using 'reverse vaccinology' [120]. This approach was pioneered for the *Neisseria meningitidis* B vaccine. After a scan of the bacteria's mRNA (transcriptome) for surface protein encoding sequences, the proteins were generated, then tested for their immunogenicity in mouse models and for recognition by protective human antibodies [128]. These immunogens would provide broader immunogenic protection regardless of the different capsular serotypes.

RNA vaccines [54,124,126] can be readily designed, synthesized, and manufactured, and have been shown to elicit strong, protective immune responses with the COVID-19 vaccines. The coding sequence within the mRNA can be optimized for stability, for minimal adverse reactions, and to encode the most appropriate immunogen. The RNA itself can be an adjuvant, though the current mRNA vaccines are delivered within an adjuvanting liposome. DNA vaccines offer similar advantages; however, no DNA vaccine has been approved for human use [129].

Particles are more efficient immunogens than individual proteins because they are phagocytosed more readily and the particles provide protection from premature degradation [76,130]. The successes of the HBV and HPV vaccines are largely due to the self-assembly of the capsid protein immunogens into virus-like particles. The Novavax SARS-CoV-2 vaccine is a nanoparticle, and some other new vaccines are also being developed which incorporate antigens into particles with or without adjuvant molecules.

Adjuvants can enhance the immunogenicity of a vaccine, reduce the amount of vaccine protein required for immunization, and elicit cell mediated and humoral responses to provide better and longer protections [81,125,131]. The adjuvants are especially useful to enhance immunogenicity in adults. Aluminum phosphate or hydroxide (Alum) adjuvants aggregate the immunogen to promote Th2 antibody responses and have been proven safe for most individuals. Most of the newer adjuvants resemble microbial structures, such as endotoxin or microbial DNA, to activate innate responses, especially in dendritic cells. Effective adjuvanted vaccines currently used in the U.S. are against influenza, hepatitis B, varicella zoster virus (VZV), and RSV. The Fluad influenza vaccine contains MF59, which is an oil-in-water emulsion of squalene oil. The Heplisav B vaccine contains cytosine phosphoguanine (CpG) to mimic microbial genetic sequences. The Shingrix vaccine for zoster (shingles) incorporates the glycoprotein E of the virus with the AS01B adjuvant system to elicit both antibody and interferon gamma producing T-cell responses (Th1). AS01B contains monophosphoryl lipid A (MPL), which is a safe mimic of endotoxin, and QS-21, which is a compound from the Chilean soapbark tree, in a liposomal particle. Use of the adjuvant in Shingrix makes it more economical to produce and more effective than the high-titer, live, attenuated varicella zoster Zostavax vaccine that it replaced. The AREXVY RSV fusion protein vaccine utilizes an adjuvant similar to AS01B. None of these adjuvants are utilized in vaccines administered to neonates or infants [131].

The success of the different COVID-19 vaccines illustrates the different approaches to deliver an effective immunogen [116]. The Novavax vaccine delivers the S protein within an immunogenic and adjuvanting particle. The Johnson and Johnson vaccine incorporates the genetically engineered S protein gene (described earlier) into an adenovirus so that the infected cells will make the stabilized S protein. The Moderna and Pfizer vaccines deliver mRNA that encodes the modified S protein encased within an adjuvanting liposome into cells, which then make the protein as if infected by the virus [116]. These RNA vaccines utilize Nobel Prize winning mRNA technology that incorporates an altered uridine into the RNA sequence to promote the stability of the RNA, reduce adverse side effects, and enhance the immunogenicity. Additionally, these COVID-19 vaccines utilize an RNA sequence that generates the stabilized structure of the protein. All of these vaccines can be administered either during pregnancy or during breast feeding as initial or booster immunizations [65,66,123].

The successes of the aforementioned newer vaccine technologies open the door for other vaccine technologies that can enhance the immunogenicity, protections, and the nature of the immune response to the vaccine. These and other technologies may help to develop safe vaccines for protection of the mother, fetus, and neonate.

9. Future vaccines

Table 2 lists targets for vaccine development and for vaccines that are still not available to protect the pregnant mother, fetus, or neonate. The availability is either impeded by the properties of the pathogen or by difficulties in eliciting the immune response necessary for protection. However, newer vaccine technologies, a greater willingness to approve their use, and appropriate testing in vaccine trials may provide vaccine protections against some of these pathogens.

Screening and antibiotic treatment are currently used to prevent Group B streptococcus (GBS) infection at and after birth. Early GBS disease, which is acquired from the mother at birth, causes a more serious disease than at a later exposure. Vaccines for GBS are in development but not yet available. Ideally, a GBS vaccine would be administered to the mother to provide protective antibodies to the neonate. Vaccines in development include a conjugated polysaccharide vaccine that would elicit IgG that could transfer to and protect the fetus and the neonate [35].

Streptococcus pyogenes is a common and very contagious pathogen that causes skin, mucosal, and systemic infections. Untreated infections may also result in autoimmune and other sequelae. Fortunately, antibiotic treatments are still effective against most infections. *S. pyogenes* vaccines in development include protein subunit vaccines that contain portions of the M protein and other proteins [36].

S. aureus is ubiquitous and part of the normal flora for many individuals but is a very successful pathogen with multiple mechanisms to produce disease and for immune escape. A tetravalent vaccine was developed that elicited protection by blocking adhesion and virulence proteins of the bacteria; however, the timing of vaccine administration proves challenging. In order to be effective, the vaccine must be administered and elicit antibodies before the bacteria initiates colonization. Development of this vaccine ended during Phase III trials [34].

E. coli is a common normal flora bacterium and a source of vitamin K; however, it can cause sepsis and meningitis in a neonate. Conjugated polysaccharide vaccines targeting the outer membrane are being developed for adult Extraintestinal Pathogenic Escherichia coli (ExPEC) disease; however, vaccines for pregnant women or neonates are not in development [27,28].

The Ebola virus causes a life-threatening hemorrhagic disease [15–17]. A hybrid vaccine (ERVEBO) incorporates the Ebola glycoprotein gene into vesicular stomatitis virus (VSV), which is a safe vector. Although the Federal Drug Administration (FDA) approved the vaccine, it is primarily reserved for healthcare personnel at risk to infection and only individuals over 18 years of age. However, during the 2018–2020 outbreak in the Democratic Republic of Congo, the WHO made the vaccine available to children over 6 months of age and to pregnant or lactating women. In an outbreak in Guinea, the vaccination of close contacts of Ebola-infected individuals protected them from the disease [16].

Hepatitis E virus (HEV) causes acute hepatitis and exists as 4 types, with HEV 1 as the most problematic [18–20]. Although disease is similar to vaccine preventable HAV, pregnant women are at a great risk for lethal disease by HEV. Hecolin (HEV239), which was developed in China, consists of self-assembling capsid proteins from HEV 1 that form a virus-like particle vaccine. The WHO recommends the use of the vaccine to either mitigate or prevent outbreaks. In 2022, the WHO approved the use of the vaccine for administration in South Sudan in response to an outbreak at a displaced persons camp [20,132].

Parvovirus B19 compromises the developing erythropoietic system of the fetus and neonate by infecting and killing erythroid precursor cells [55,133,134]. Parvovirus can pass to the fetus to cause fetal anemia and cardiomyopathy and results in the loss of the fetus due to hydrops fetalis. Additionally, infection of the pregnant mother can cause anemia, especially in individuals with HIV infection, another immunodeficiency, or a chronic anemia, such as thalassemia or sickle cell disease. Parvovirus vaccines exist for dogs and cats, but not humans. A virus-like particle vaccine consisting of the virus protein (VP)1 and VP2 capsid proteins, has been developed but is not yet licensed for human use [55].

For CMV and HSV, vaccine development is difficult for several reasons [41,45]. The vaccine should elicit both antibody and cell-mediated immune responses. The generated antibody must be able to block the different viral attachment proteins and the rapid establishment of latent infection in neurons (HSV) or myeloid stem cells (CMV). Several different approaches have been taken towards developing vaccines, including adjuvanted protein subunit and mRNA vaccines. Some of the CMV vaccines in development contain multiple proteins or RNA sequences for the different attachment proteins to elicit antibody to block all the different cellular interactions that would initiate infection [41–44]. HSV vaccines are being developed that utilize one or more adjuvanted glycoprotein subunits, attenuated mutant viruses, RNA, or DNA formats [45–48]. For CMV, a four-protein vaccine, an adjuvanted glycoprotein B (gB) protein vaccine, and a gB expressing mRNA vaccine are being developed [41,135]. Glycoprotein B is an envelope protein and one of the attachment proteins of CMV.

Zika virus is transmitted by mosquitos and by sexual transmission. Although relatively benign for adults, infection of the mother can lead to a congenital syndrome, including microcephaly, craniofacial disproportion, spasticity, ocular abnormalities, and miscarriage. Ideally, a vaccine would be administered prior to or during pregnancy to protect the mother and the fetus [57].

Vaccines have been developed for *Plasmodium falciparum,* one of the causes of malaria, approved by the WHO for children older than 5 months, and implemented in endemic regions of Africa. These vaccines reduce the incidence and symptomatology, but do not provide universal protection. The RTS, S/AS01 (RTS, S) consists of a part of a circumsporozoite protein fused to the hepatitis B surface antigen protein to promote the formation of a particle (similar to the virus-like particle of the hepatitis B vaccine) and is administered with the AS01 adjuvant [22]. The R21/Matrix-M vaccine consists of a different fusion protein between the circumsporozoite protein and the hepatitis B surface antigen administered with the Matrix-M adjuvant [23]. Neither vaccine is currently approved for

pregnant women. Human trials have progressed with vaccines against the VAR2CSA protein to block the transmission of the parasite to the fetus. The parasite uses VAR2CSA to bind and traverse the placenta [59,60].

10. Vaccines of the distant future

Despite being one of the most common sexually transmitted infections, there are still no vaccines for *Neisseria gonorrhoeae* [30–33]. A vaccine would be important because pregnant women, the fetus, and the neonate are at risk, and gonorrhea infections are increasingly difficult to treat due to antibiotic resistance. A candidate vaccine under development combines outer membrane vesicles (OMVs) shed from the bacteria that contain antigenic proteins and polysaccharides with adjuvants [33].

Chlamydia trachomatis is the most common sexually transmitted bacterial pathogen, can compromise pregnancy, and can cause conjunctivitis upon neonatal infection. As an obligate intracellular pathogen, the bacteria rapidly infect macrophages and other cells and hides from antibodies. Ideally, a vaccine should either elicit IgA production and generate sterilizing immunity or elicit T-cell protections; however, no vaccine candidates have succeeded in these feats [24–27]. Vaccines under investigation have incorporated different forms of the major outer membrane protein (MOMP), or other surface proteins, with different adjuvants in order to elicit T-cell responses. Other vaccines have been developed to be either intranasally or orally administered to elicit IgA responses.

Pregnant women and newborns are especially at risk for serious infection by *Listeria monocytogenes.* There are no vaccines available for humans. Bacteria lacking virulent factors have been genetically engineered and tested in animals [29].

Hepatitis C virus exists as many different serotypes and rapidly mutates to generate new serotypes to challenge vaccine development. Proteins that contain multiple antigenic variations of the relevant immunogen, nanoparticles, mRNA, T-cell generating vaccines, and other approaches are being investigated, but have not reached human trials [44,136–138].

As mentioned earlier, HIV poses many problems for vaccine development [49]. The vaccine must elicit protections against the initial viral infection of macrophages and the early transfer of infection to CD4 T-cells to block the establishment of chronic disease and to elicit protection against the many clades and strains of HIV in the population. One approach that is being investigated is the development of immunogens that elicit broadly neutralizing antibodies that would act on the multiple strains of HIV [50–54]. Many other vaccine formats have been tested; however, none have succeeded in several large-scale trials [50].

Despite the need, there is no vaccine to prevent syphilis caused by *Treponema pallidum.* In addition to having a unique bacterial structure that hides potential targets for a vaccine immunogen, the spirochete cannot be grown in the laboratory, which complicates vaccine development [24,39]. Reverse vaccinology (as done for the *N. meningitis* B vaccine) is being used to identify potential immunogens against outer membrane proteins. Genetic sequences that encode flagellar proteins or other surface proteins have been utilized to generate DNA vaccines; these sequences have either been incorporated into non-infectious strains of *Borrelia burgdorferi* (the cause of Lyme disease) or used to generate the proteins as immunogens. These vaccines have been tested in rabbit models of the disease with limited success.

11. Summary

Vaccines are available for many, but not all, of the serious infectious diseases for which pregnant women, the fetus, neonates, and young infants are at greater risk. Currently recommended vaccines can be administered prior to or during pregnancy to generate antibodies that would benefit the mother, fetus, and neonate, while others can be directly administered to the neonate soon after birth or within the first 2–4 months of life. Despite new technologies, there remain numerous obstacles for vaccine development towards some pathogens. These include difficulties in identifying appropriate immunogens that provide broad-spectrum, safe, and effective immune coverage and the lack of funding for basic studies and clinical trials, especially those that include pregnant women and neonates. For those microbes that have eluded the standard means of vaccine development, new technologies are being utilized to identify, produce, and enhance the immunogenicity of the appropriate microbial components.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

KSR and MLW both contributed to the conceptualization, researching, writing, reviewing and editing of this manuscript.

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