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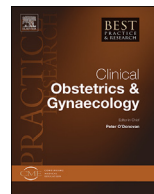
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Vaccines - safety in pregnancy

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A B S T R A C T

Vaccination during pregnancy is important for active immunity of the mother against serious infectious diseases, and also for passive immunity of the neonate to infectious diseases with high morbidity and mortality. As a rule, live vaccines are contra-indicated during pregnancy as they may cause fetal viremia/bacteremia. Inactivated vaccines are generally safe.

Vaccines safe to be administered to all pregnant ladies are tetanus toxoid (TT; tetanus, diphtheria, acellular pertussis (Tdap) and Flu vaccines. During pre-pregnancy counselling, vaccination for MMR (measles, mumps, and rubella) should be offered, with an advice to avoid pregnancy for a month. All pregnant mothers should receive TT and Tdap vaccination during the third trimester. Flu vaccine can be given to all mothers at any gestation, and if not offered during pregnancy, it can be given postpartum.

Vaccinations that should be offered to women if at high risk of exposure are for hepatitis A and B, pneumococcal, meningococcal, yellow fever, Japanese encephalitis (JE), polio, typhoid, and cholera infections. Vaccines to be given only for post-exposure prophylaxis (PEP) are smallpox, rabies, and anthrax. Postpartum women should be offered human papillomavirus (HPV) vaccination. If not immunized earlier, they should be offered MMR, Tdap, and Flu vaccines. Future vaccines being developed are for malaria, Zika virus, respiratory syncytial virus (RSV), group B streptococcus, CMV, and COVID-19 (SARS-Cov-2).

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Introduction

The first vaccine ever developed was the small pox vaccine in 1796. Since then, a number of vaccines have been developed to protect against both viral and bacterial infections. Vaccines are administered to neonates, toddlers, adolescents, and adults to ward off infections. Pregnant women, when vaccinated have benefit for themselves as well as in the prevention of vertical transfer of infection to the fetus. However, not all vaccines are safe to be administered during pregnancy.

Rationale for immunization in pregnancy

Immunization of a pregnant woman protects her, the fetus, and the newborn, against infections that have greater morbidity and mortality in this population, compared with the general population. It also contributes to reducing under-five morbidity and mortality. It is the most cost-effective way of reducing under-five mortality. The GAIA project (Global Alignment of Immunization Safety Assessment in Pregnancy), formed by the WHO, focuses on monitoring the safety of various vaccines during pregnancy [1].

Pregnancy is an immunologically dynamic state with high estrogen levels modifying the immune responses and altering the T-helper cells 1 and 2 (Th1/Th2) ratio. This may be the reason for altered cell-mediated immunity and suboptimal responses to certain viral infections. Pregnant women often have increased severity of influenza, hepatitis E, herpes simplex, and other viral infections.

Immunological changes in pregnancy

The maternal immune system is altered in pregnancy to tolerate the allogeneic fetus. Local decidual immune cells, such as uterine natural killer (uNK) cells and macrophages, by producing local cytokines and angiogenetic factors, regulate implantation of blastocyst, placentation, and play an important role in the acceptance of semi-allogenic fetus.

Maternal immunizations for special medical indications include

Functional or anatomic asplenia due to

- Sickle cell disease/other hemoglobinopathy
- Congenital (primary immunodeficiency) or acquired asplenia

Immunocompromised persons

- Congenital or acquired immunodeficiency, e.g. HIV infection
- Chronic renal failure and nephrotic syndrome
- Organ transplant patients
- Lymphoma, Hodgkin's disease, and malignant hematological disorders

Immunocompetent persons with medical disorders

- Chronic lung disease, chronic obstructive airway disease, and chronic smoking
- Diabetes mellitus
- Chronic liver disease and cirrhosis
- Chronic heart disease

Specific vaccinations for pregnant women at high risk of infection

- Occupational exposure to infection (laboratories handling bacteria/viruses)
- Has travel plans to endemic areas

Classification of vaccines

Live attenuated vaccines

• **Live viral and bacterial vaccines:**

These are made using viruses or bacteria that are attenuated before being used in a vaccine. The weakened vaccines do not usually cause any disease, but may cause severe disease in people with impaired immune system like leukemia, HIV, and persons on immunosuppressive medications. They are generally avoided in pregnancy as well. Examples of live attenuated vaccines (LAIV) include Rota virus, chickenpox, measles, mumps, rubella (MMR), and bacillus Calmette–Guérin (BCG).

• **Vector Vaccines**

These are liquid or freeze-dried preparations of one or more types of live micro-organisms (bacteria or viruses) that are non-pathogenic or have low pathogenicity for the target species and into which have been inserted one or more genes that encode antigens, usually surface proteins, of pathogens. Large DNA viruses, such as adenoviruses, vaccinia, and poxviruses are often used as vectors (Fig. 1).

Inactivated vaccines

These are made using bacteria or viruses that have been inactivated before being included in a vaccine.

There are several **subunit vaccines**, depending on whether toxins or polysaccharide fragment from bacteria or virus have been used to make the vaccine. Dane particle, a surface antigen of hepatitis B virus is used for hepatitis B vaccine.

Subunit vaccines are

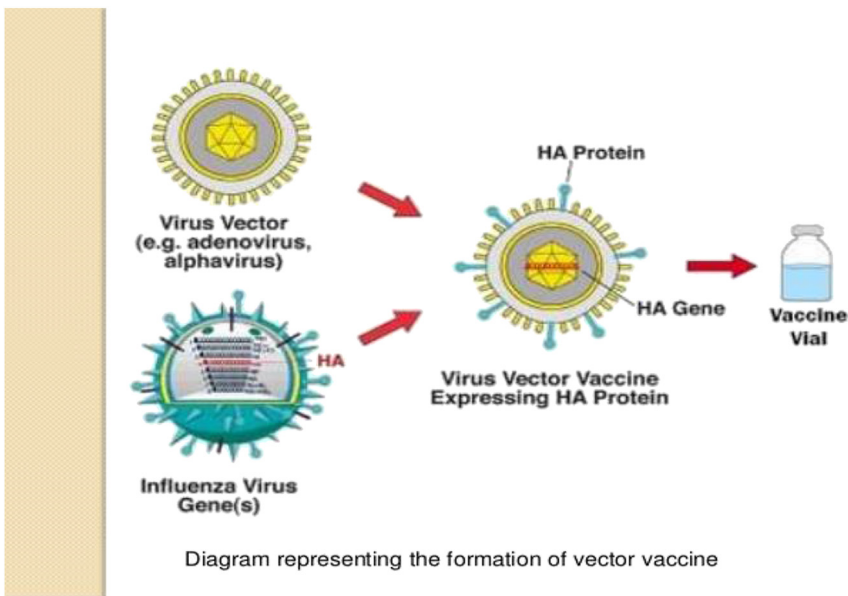


Diagram representing the formation of vector vaccine

Fig. 1. Formation of a vector vaccine.

- **Toxoid Vaccines:** Used for diphtheria, tetanus, and pertussis Vaccines
- **Polysaccharide Vaccines:** For example, 23-valent pneumococcal Polysaccharide vaccine (**PPSV23**)
- **Conjugate Vaccines:** Polysaccharide molecules are taken from outside layer of the bacteria and joined to a carrier protein. For example, PCV13 inactivated (13-valent pneumococcal conjugate vaccine), hemophilus influenza type B (Hib).
- **DNA Vaccines:** It uses a gene from virus or a bacterium to stimulate an immune response. When administered, the cells incorporating the administered gene are directed to make a viral or bacterial protein that is recognized by the immune system. These vaccines are effective in eliciting cell-mediated responses that can target cells infected by bacteria or viruses as well as cancer cells. Hence, a DNA vaccine is being studied for the treatment of infections like HIV, HBV, HCV, Ebola, COVID, malaria, tuberculosis (TB), and also as immune therapy against cancers, autoimmune diseases, degenerative diseases like Alzheimer's disease, multiple sclerosis, and various allergies.

DNA vaccines, which are safe and well-tolerated, can be made in a short time, offering huge advantage in a quickly mutating virus or bacteria, and are easy to transport or store, but are poorly immunogenic.

Vaccine safety by type

Generally, all vaccines except live vaccines can be safely administered to pregnant women. Live vaccines, on the other hand, are administered very selectively when there is imminent and substantial risk of increased morbidity and mortality. Good examples are vaccines for attenuated oral polio and yellow fever.

Mechanisms of maternal vaccination induced fetal and neonatal immune protection

Maternal vaccination generates both humoral and cell-mediated immune responses in the mother, protecting against infections, thereby reducing the risk of vertical transmission to the fetus.

Immunoglobulin G (IgG) antibodies formed by the mother and transferred to the fetus via placental circulation (Fig. 2A) as well as the mucosal IgG, IgA, and IgM antibodies, secreted into the colostrum and milk, protect the newborn in the postpartum period before it develops active immunity following neonatal vaccination (Fig. 2B). [2].

Indications for maternal vaccination

Pre-exposure vaccinations for tetanus, diphtheria, acellular pertussis, and influenza vaccine for maternal and neonatal protection

Vaccination during pregnancy for specific infections boosts the level of antibodies against the vaccine-specific infection and also protects the neonate by passive transmission of antibodies before the infant acquires its own immunity by routine active vaccinations.

The different subclasses of IgG; IgG1, IgG4, IgG3, and IgG2 are transferred across the placenta to the fetus in diminishing concentrations. Hence, maternal immunizations with polysaccharide vaccine eliciting predominately IgG2 response are less effective than protein or protein-conjugated vaccines eliciting IgG1 and IgG3 responses [3].

The predominant mechanism of protection of newborns from infections is by transplacental transfer of maternal antibodies and later through breastfeeding after birth. There are concerns that these maternal antibodies may blunt the infant's immune responses to neonatal vaccinations.

Influenza virus vaccination

Pregnant woman suffers greater morbidity due to seasonal Flu which is more severe in the last 3 months of her pregnancy.

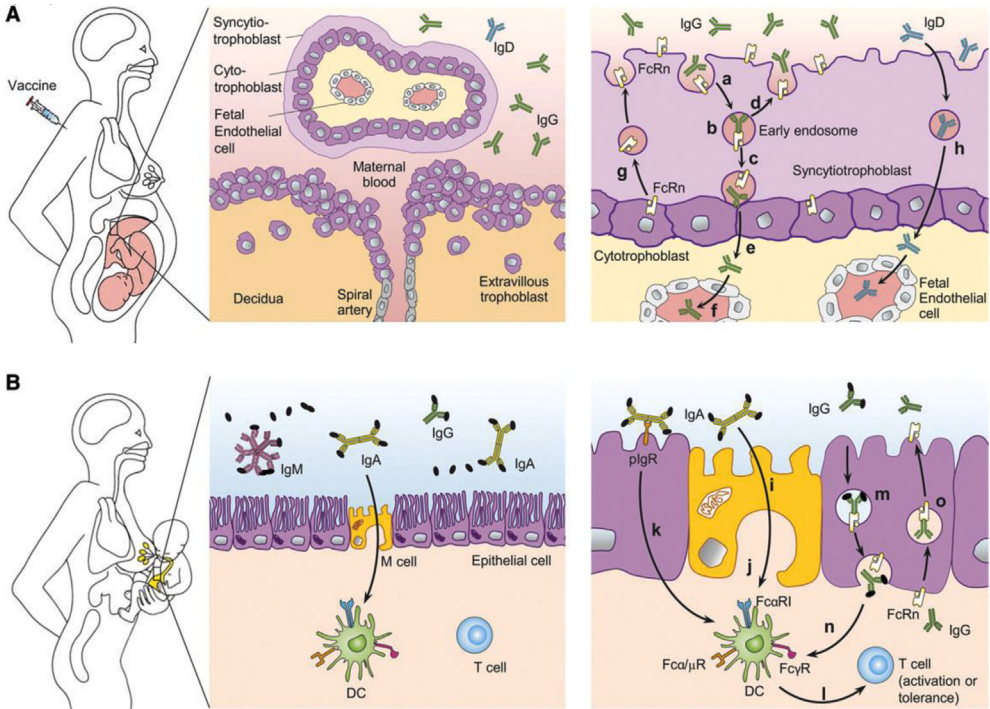


Fig. 2. Maternal immune response during pregnancy (A) and breast feeding (B) [18].

Influenza is an RNA virus of the *ortho*-myxo virus family, with three sub-types A, B, and C, determined by different antigens in the nucleus [5]. The surface antigens are hemagglutinin H (subtypes H1, H2, and H3) and neuraminidase N (subtypes N1 and N2). Influenza A viruses may infect both humans and animals, but influenza types B and C are found in human hosts only.

Influenza vaccines. Flu vaccination protects the mother and her newborn, with the benefits outweighing any risks due to the vaccine. Attenuated live influenza vaccine is contraindicated in pregnancy, but the inactivated vaccine can be given. The available vaccines are:

- ♣ Inactivated influenza vaccine (IIV) given intramuscular or intradermal.
- ♣ Inactivated monovalent non-adjuvanted pandemic influenza vaccine
- ♣ Inactivated monovalent adjuvanted H1N1 pandemic influenza vaccine (MF59, AS03, and aluminum phosphate adjuvanted). Single dose of AS03-adjuvanted H1N1 2009 vaccine when given to pregnant women produces a protective antibody response in 93% of pregnant women.
- ♣ Trivalent vaccine contains three inactivated viruses: type A(H1N1), type A(H3N2), and type B.
- ♣ Recombinant influenza vaccine (RIV), a trivalent inactivated vaccine, administered by intramuscular injection
- ♣ LAIV given intranasal

Adverse effects of IIV and LAIV. Local reactions like soreness and redness are the most common adverse events following vaccination with IIV (15–20%). Allergic reactions like (hives, angioedema, and anaphylaxis) are very rare. Although the incidence of Guillain–Barré syndrome (GBS) in the general

population is very low, persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS [5]. GBS has not been associated with LAIV in post-licensure safety monitoring.

Tetanus toxoid vaccination

Maternal vaccination with inactivated tetanus toxoid (TT) has a major role in reducing the global burden of death from neonatal tetanus by more than 95% since 1980 [4]. Besides is safe during pregnancy and are also suitable for use in HIV-infected and immune-compromised persons. Mild local reactions, such as pain and erythema, are common after the vaccination, but more serious reactions are rare.

A primary series of three TT conjugate vaccine (TTCV) doses in infancy plus a booster during the second year of life provides 3–5 years of protection. A booster dose in early childhood provides protection into adolescence, and another booster during adolescence provides immunity that lasts through much of the women's childbearing years. Protective immunity persisting for 20–30 years after the sixth dose of TTCV has been suggested in several studies.

TT inactivated vaccine can be given alone or in combination with diphtheria toxoid, and Tdap. The vaccine can be given at any gestation, but if given in third trimester between 27 and 36 weeks, allows for significant placental travel of antibodies to protect the newborn.

Pertussis vaccination

Pertussis (whooping cough) is an acute respiratory infection caused by the bacteria *Bordetella pertussis*. Pertussis vaccine given in later half of pregnancy has been shown to be 93% effective in preventing the disease in mother and her newborn.

Three doses of whole-cell pertussis-containing vaccine introduced initially in 1930 are suboptimal in protection and waning of immunity occurs within 5–10 years of vaccination. Acellular pertussis vaccine incorporated with tetanus and diphtheria vaccines have now become a part of National Vaccine programs across the world. Vaccination is ideally initiated in the second trimester to cover immunity for the newborn. Unfortunately, the waning of immunity is even faster, at 1–3 years after vaccination [3,6].

Also, there is a theoretical concern that these vaccine-induced maternal antibodies resulting in increased concentrations of pertussis antibodies in infants might reduce the immunogenicity of infant tetanus–diphtheria–pertussis (Tdap) vaccine.

The vaccine did not produce any significant pregnancy adverse effects except for a non-significant increase in chorioamnionitis (6.1% vs 5.5% among those who did not receive Tdap vaccine), and no significant increased risk of fever, preterm labor, or small for gestational age (SGA) was noted. There were no incidences of Arthus reaction or GBS.

Maternal vaccinations for vaccine-preventable infections in women with medical co-morbidities and risk of high mortality during pregnancy, especially if she has risk of exposures and likely has no prior immunity

Flu vaccine during pregnancy: Refer to section above

Hemophilus influenza b

(Hi type b vaccine) is recommended for pregnant women with congenital (primary) immunodeficiency, malignant hematologic disorders, HIV, anatomic or functional asplenia, including sickle cell disease, all transplant recipients, and cochlear implant recipients.

Hib is one of the most common cause of bacterial meningitis in children and this risk has been eliminated by more than 95% with the use of conjugate vaccines, which are given as two to three doses in infancy, followed by a booster dose at 12–18 months, to achieve sustained protective levels of antibodies. Since a large proportion of infection occurs before 18 months of age, maternal immunization to protect the newborn is an attractive option [7].

Maternal vaccination with conjugate vaccine produced greater antibody response compared with polysaccharide vaccine, in infant antibody titers levels, at birth and at 2 months and the infant response was not blunted by the maternal vaccination.

Japanese encephalitis virus

(JEV) is a flavivirus, similar to dengue and yellow fever viruses. It is transmitted by the bite of *Culex* mosquitoes. The infection is mostly asymptomatic, manifesting clinical symptoms in less than 1% of cases. But cases presenting with encephalitis, case fatality may be as high as 30%, and another 30–50% may have permanent neurologic or psychiatric sequelae. So far, there are no antiviral treatments available for JEV infections [8].

JE vaccines currently in use are

- Inactivated mouse brain-derived vaccines
- Inactivated vero cell-derived vaccines
- LAIVs
- Live recombinant (chimeric) vaccines.

Live attenuated SA14-14-2 JE vaccine manufactured in China has become the most widely used vaccine in endemic countries.

There are no adequate studies of the safety of JE vaccination in pregnancy but considering the severity of the sequelae with an acquired infection, CDC recommends vaccinating the women traveling to endemic areas for a longer stay, as the risk of vaccination appears to be lesser than the risk of infection [9].

Meningococcal vaccine

Neisseria meningitidis is a gram-negative diplococcus, which is classified into different groups on the basis of the polysaccharide capsule, of which six groups (A, B, C, W, X, and Y) are responsible for causing the majority of the invasive disease.

The first vaccines were polysaccharide vaccines, targeting groups A, C, W, and Y, and primarily boosted IgG2 response in pregnant women, which is poorly transferred across the placenta. These were then replaced by protein–polysaccharide conjugate vaccines, which produced predominant IgG1 antibodies, that are very well transmitted across the placenta in the third trimester of pregnancy.

The bivalent meningococcal polysaccharide vaccine (Men AC-PS) against capsular groups A and C, and quadrivalent polysaccharide vaccine (Men ACWY-PS) against capsular groups A, C, W, and Y, are the two vaccines that have been studied so far in pregnancy and their use did not show unusual adverse events in the mother or her fetus. The colostrum of women contained 2.6-fold higher levels of IgA than that of the unvaccinated mothers [10].

Streptococcus pneumoniae infection

In pregnancy, manifests with complications like meningitis, otitis media, bacteremia, and pneumonia. The preventive pneumococcal vaccination in pregnancy has been successful in controlling this infection, which is responsible for significant morbidity and mortality in the pregnant woman.

Women with medical risk factors are recommended the inactivated PPSV23 vaccine. Those with the highest risk, both **PCV13 inactivated** (13-valent pneumococcal conjugate vaccine) and **PPSV23 (23-valent pneumococcal polysaccharide vaccine)** are recommended. When administering both vaccines, PCV13 should be given first when possible. Spontaneous miscarriages or preterm labor in the mother nor teratogenicity in the newborn has not been noted so far. Thus, pneumococcal vaccination in pregnancy is safe [7,9].

Inactivated poliovirus vaccine

Polio vaccine is not routinely administered during pregnancy. But if the woman is at increased risk due to travel to endemic areas or has risks of exposure in a laboratory setting, she may be vaccinated. The inactivated (Salk) vaccine is preferred by the intramuscular route. Though oral poliovirus vaccines

(OPV) is a live vaccine with the theoretical possibility of infecting the fetus, the use of OPV in pregnancy in large studies has not found any association with fetal anomalies or Polio sequelae to the fetus [7].

Rabies virus, inactivated

The benefits of administering rabies vaccine in pregnancy post-exposure outweigh the risks of the vaccination. Also, a few studies done so far have not shown any increase in the risk of miscarriage, preterm birth or fetal abnormalities with vaccine exposure, hence an inadvertent exposure during pregnancy is not an indication to terminate a pregnancy.

If the risk of rabies exposure is high during pregnancy, a pre-exposure vaccination can be considered [9].

Typhoid inactivated vaccine

Two vaccines, the oral live attenuated Ty21a vaccine and the parenteral Vi polysaccharide vaccine against typhoid, are available, but live vaccines are contraindicated for pregnant women. There are no specific data on the safety or adverse effects of the use of typhoid vaccines in pregnancy, but in clearly indicated situations, an inactivated Vi polysaccharide vaccine should be administered [12].

Cholera vaccination

Cholera results in severe diarrheal illness and is caused by bacterium *Vibrio cholerae*. It can result in severe dehydration, marked hypotension, fetal loss, and even maternal death. The spread of infection is mainly through contaminated water and food. In 2010, the WHO recommended that oral cholera vaccine (OCV) should be given in cholera outbreaks. Whole-cell killed OCV is available and it requires two doses for full protection. Oral vaccines are safe in pregnancy and no untoward adverse effects have been seen in pregnant mother and her fetus [12].

Yellow fever

Is a live vaccine. Vaccination has not been associated with risk of major congenital anomalies, and is not contraindicated in pregnancy, but the risks of yellow fever vaccination itself can be serious, and even be fatal, hence the vaccine is given only if the woman is traveling to endemic areas with significant risk of acquiring the infection.

Adverse effects of vaccination include: **Yellow fever vaccine-associated neurotropic disease (YEL-AND)** is estimated to occur in 0.8 cases per 100,000 doses. The clinical symptoms may start immediately, or even up to 2 months later, with complaints of fever, headache, occasionally progressing to encephalitis. But most patients recover completely.

Rarely, in 0.3 cases per 100,000 cases, they may present as **YEL AVD (yellow fever vaccine-associated viscerotropic disease)**, which is a rare, but serious event with clinical presentation beginning within 1–18 days (median 4 days) following vaccination, with fever, malaise, headache, and myalgia, hepatitis, hypotension, or even multi-organ failure and death (case fatality rate is approximately 48%) [12,13].

Smallpox, live

Though Smallpox infection has been eradicated, there are concerns regarding intentional reintroduction through bioterrorism and accidental exposure (e.g., in a laboratory). Transfer of the vaccine virus to the fetus is rare, but can have severe clinical consequences, including fetal or neonatal death. Therefore, pre-exposure vaccination is contraindicated for women who are pregnant or are trying to become pregnant. However, post-exposure vaccination is recommended because the risk of smallpox to the pregnant women and her fetus outweighs any risk associated with the vaccine [14].

Anthrax vaccine

Anthrax is caused by *Bacillus anthracis* and may be the likely agent in potential bio-terrorism attacks anywhere in the world. It is unsure if anthrax causes more severe disease in pregnant woman, but can cause both fetal and maternal death. Hence, she should be given same post-exposure prophylaxis (PEP), such as antimicrobial treatment, and vaccination with anthrax vaccine adsorbed (AVA), given at

any gestational period, if she has high risk of exposure to the spores [12]. So far, no risks of birth defects have been noted.

BCG Vaccine

BCG for tuberculosis: It is a live bacterium, hence there are concerns regarding its use in pregnancy. It is best avoided unless there is a close contact with active tuberculosis (TB). So far, studies have not shown any harmful effects on the mother or the fetus following BCG vaccination [15].

Maternal vaccinations to prevent risks of vertical transmission of infection from mother to her fetus

Vaccination during pregnancy is warranted, if the vaccination can prevent maternal infections and the risks of vertical transmission of infection to the unborn fetus, provided the vaccine is unlikely to cause maternal or fetal harm.

For bacterial infections that are transmitted vertically from mother to fetus, the transmission can be prevented by adequate and timely treatment of mother with antibiotics, before permanent harm ensues to the fetus or the neonate. These include infections like syphilis, group B streptococcus (GBS), chlamydia, and gonorrhoea.

However many viral infections acquired by mother can be transmitted to the fetus and to the newborn, during pregnancy, peripartum, and subsequently during breast feeding. These viral infections include hepatitis virus subtypes A, B, C, and E, human papilloma virus, and HIV infections.

Hepatitis A vaccine (HAV), inactivated

It is indicated in woman with high risk of acquiring hepatitis A infection. This includes intravenous drug users, having poor hygiene, staying near sewage or endemic areas, having chronic liver conditions or regularly requiring clotting factor concentrates.

The HAV, available both in a monovalent form and in combination with the hepatitis B virus, is safe during pregnancy, as it is prepared from an inactivated virus. Since the protective levels of antibodies develop within 2 weeks after the first dose of the vaccine, the HAV administered immediately before travel, ensures adequate protection, and this effect lasts 10–30 years or even for a lifetime [16].

Hepatitis B vaccine (HBV)

Hepatitis B infection in pregnancy is high risk, as it may not only cause severe and permanent hepatic damage for the mother, but may also cause chronic infection for the baby. Hence she should be vaccinated against hepatitis B, if she has high likelihood of exposure, as in a pregnant woman with hepatitis B surface antigen (HBsAg)-positive sex partner, sex workers, woman with more than one sex partner in the previous 6 months, has been treated for a sexually transmitted disease (STD), and recent or current injection drug users. Also, women who receive regular blood products, have chronic liver disease or kidney disease and women traveling to endemic areas, belong to this vulnerable group.

HBV vaccination first became available in 1980. A combination of HBV vaccine and hepatitis B immune globulin (HBIG) given within the first 12 h after birth to the neonate, gives the greatest long-term immunity in 85–95% of cases [15,17].

Routine postpartum immunizations and vaccinations contraindicated in pregnancy

Both inactivated and live vaccines (except smallpox and yellow fever vaccines) may be administered to nursing mothers, and breastfeeding does not adversely affect the success or safety of vaccination. Smallpox and yellow fever vaccines are avoided in non-emergency situations because breastfed infants of vaccinated women are at risk of developing vaccinia and meningoencephalitis, respectively. Vaccines that are contraindicated during pregnancy, e.g. MMR, should be given before her discharge to protect a non-immune mother and her new born.

MMR Vaccine

It is a LAIV, and hence, it is Contraindicated in pregnancy.

Measles and mumps are paramyxoviruses, while rubella, a togavirus, which are all transmitted by contact with infected person. Though the infections are mild, it can lead to an increased risk of spontaneous miscarriage, preterm birth, and low birth weight, but rubella if contracted in early pregnancy can result in severe malformations in the fetus, categorized as congenital rubella syndrome (CRS).

So far, no safety concerns have been identified after inadvertent rubella or MMR immunization in pregnancy and this should not be considered an indication for pregnancy termination.

Pregnant women are screened for rubella immunity during antenatal care, so that non-immune women can receive MMR immunization postpartum, prior to discharge from the hospital [8,19].

Varicella-zoster virus (VZV)

VZV is a herpes virus that causes chickenpox and shingles. A live attenuated varicella vaccine was introduced in 1995, reduced the incidence by 90%, but it is contraindicated in pregnancy, though no complications of the vaccine or congenital varicella syndrome (CVS) were detected in women vaccinated inadvertently in pregnancy.

Maternal varicella infection can cause VZV pneumonia, besides a 0.5–1.5% incidence of CVS, if she acquires the infection in the first or the second trimester. Affected fetuses manifest with skin scarring, limb hypoplasia, low birth weight, microcephaly, cortical atrophy, chorioretinitis, cataracts, and other anomalies. Maternal varicella infection near the time of delivery poses a risk for neonatal varicella disease.

Screening of all women planning a pregnancy, for evidence of varicella immunity is recommended and vaccination, if non-immune, is advised. Pregnant women if identified as varicella non-immune should be immunized in the postpartum period prior to her discharge from health care facility [19].

Live attenuated influenza vaccine

This is contraindicated during pregnancy, but can be given to her during the postpartum period, if indicated. The postpartum mother is eligible to receive either the IIV or the LAIV. There is a risk of transmitting the infection to her neonate, due to the close physical contact between them [19]. Breastfeeding is not a contraindication to LAIV, although specific information regarding excretion in breast milk is not available.

Tdap vaccine

If this has not given as recommended during pregnancy, **Tdap** should be given postpartum to women. This reduces the risk of maternal pertussis, which can be transmitted to the infant causing significant morbidity and mortality, before the infant can be protected by own immunity following neonatal immunization programs that cover pertussis.

However, the maternal response may not be effective in providing immediate protection to the infant until at least two weeks post-immunization. Hence, it is recommended that pertussis vaccine can be given in the second trimester of pregnancy, so that the fetus can get sufficient passive immunity in the immediate neonatal period, prior to acquiring its own active immunity through neonatal vaccination programs.

Human Papilloma virus vaccination

These viruses are often associated with premalignant lesions like CIN, VIN, VAIN, and AIN, cervical cancers, and genital warts. The subtypes 6 and 11 are often associated with genital warts, while 16 other high-risk HPV types, such as 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70, have been associated with the development of premalignant and malignant genital lesions. Subtypes 16 and 18 are responsible for nearly 70% of the cervical cancers.

The recombinant quadrivalent HPV vaccine Gardasil protects against subtypes 6, 11, 16, and 18, while Gardasil 9 protects against subtypes 16, 18, 31, 33, 45, 52, and 58 causing genital cancer, and the types 6 and 11 causing genital warts (condyloma acuminata).

The HPV vaccinations are not recommended for use during pregnancy as their safety has not been evaluated in pregnant women. If a woman is found to be pregnant during the administration of an HPV

series, the remainder of the three-dose regimen should be delayed until the completion of the pregnancy.

In their large nationwide study in Denmark, the risks of spontaneous miscarriage, major birth defect, stillbirth, preterm birth, and SGA fetus were not significantly higher with quadrivalent HPV vaccination during pregnancy [20].

Dengue vaccination

Dengue is a mosquito-borne viral infection which may be present clinically with mild viral fever symptoms in some cases, and severe and fatal hemorrhagic disease in some patients.

Smaller studies have suggested higher risk of miscarriage, pre-eclampsia, preterm labor, SGA, stillbirths, postpartum hemorrhage (PPH), and vertical transmission to the fetus.

There is no recommendation for vaccination concerning pregnant and lactating women due to lack of sufficient data.

A live, attenuated, tetravalent vaccine against dengue (CYD-TDV) was first approved in 2015, but it is contraindicated in pregnancy, though no adverse effects have been noted in patients who received the vaccine inadvertently. In high endemic areas, dengue vaccination may be considered for mothers prior to pregnancy [21].

New perspectives on maternal DNA vaccination to protect children against non-infectious diseases and cancers

Studies have shown the benefits of maternal immunization in protecting infants even from non-infectious diseases like allergy, asthma, and metabolic disorders [22]. Maternal immunization with DNA vaccines may help the offspring against tumor progression or prevent onset of tumor in cancer-prone offspring.

Use of live or attenuated pathogens can be problematic in people whose immune system is compromised, as in cancer and AIDS patients, those undergoing chemotherapy, with a risk that these attenuated viruses may become virulent in these patients. DNA vaccines produce strong humoral and cell-mediated immune responses, without the risk of activating the disease [23]. They are effective in producing a cellular response to intracellular pathogens like TB, malaria, and AIDS.

DNA vaccines can be delivered through many different routes, including the intramuscular, intradermal, subcutaneous, oral, intranasal, mucosal, intraperitoneal, intravenous, and vaginal routes.

Prospective future vaccines

Respiratory Syncytial virus vaccine

Respiratory syncytial virus causes severe bronchiolitis and pneumonia more often affecting infants less than 6 months of age with the highest morbidity in preterm infants.

No vaccine is yet available to prevent RSV infection and many are in preclinical and clinical stages of development. Two surface glycoproteins, respiratory syncytial virus (RSV) F and G proteins are thought to induce neutralizing antibodies. An F protein nanoparticle vaccine is being investigated in phase 3 clinical trials involving pregnant women.

Group B Streptococcal vaccine

GBS is associated with adverse fetal and neonatal outcomes. Hence, there have been multiple attempts at developing group B streptococcal vaccines. An early onset group B streptococcal infection occurs in neonates less than 7 days of age, while the late onset group B streptococcal infection occurs in infants 7–89 days of age, but is associated with greater risk of meningitis.

Human trials of the GBS vaccines were carried out in the 1980s based on capsular polysaccharide (CPS). Subsequently, CPS–protein conjugate vaccines, such as monovalent, TT–conjugated vaccines incorporating each of the five major CPSs of GBS (Ia, Ib, II, III, and V) have undergone phase 1 and phase 2 trials.

Cytomegalovirus vaccine

Cytomegalovirus (CMV) is a DNA virus of the herpes family and the primary infection may be asymptomatic for years, but vertical transmission associated with severe fetal sequelae may occur in 21–50% of fetuses following primary maternal infection, with a fetal mortality of 20–30%. Of the symptomatic neonates, 90% may have severe sequelae.

Developing a vaccine to prevent CMV infection is of paramount importance.

Initial vaccine candidates were live attenuated CMV vaccines. These attenuated live vaccines are now co-administered with interleukin (IL)-12, to boost CMV-specific immunity, with advice to avoid pregnancy for at least 28 days following the immunization.

Other vaccines include subunit vaccine incorporating the CMV surface glycoprotein B (gB) that mediates CMV cell entry. A recombinant gB adjuvanted with MF59 has proven safe and immunogenic in phase 1 and phase 2 trials in healthy seronegative adults as well as in adolescents, seropositive adults, and transplant recipients. So far, there have been no trials on pregnant women.

Zika virus vaccination

ZIKA is an arbovirus of Flaviviridae family, transmitted by bites of Aedes mosquito being the primary mode of transmission. Other potential routes of transmission have also been demonstrated, as it is also present in body fluids, such as semen, saliva, vaginal fluids, breast milk, tears, and urine following infection with potential vertical, sexual, breast milk, and transfusion-acquired transmissions [11].

The ZIKA Virus 2015–2016 pandemic showed the severe teratogenic effects of the infection in pregnancy with an incidence of congenital Zika syndrome (CZS) of 49.9 cases per 10,000 live births, in highly affected Brazil. The fetal abnormalities, described as CZS, include features like severe microcephaly, brain abnormalities like ventriculomegaly, hypoplasia of cerebellum, anomalies of the corpus callosum, neurological, and ocular abnormalities. About 5–15% of fetuses are affected when maternal infection was acquired in the first trimester.

ZIKA vaccine development. Currently, several vaccine candidates are under development from multiple laboratories [24]. These include.

- ♣ DNA vaccines
- ♣ Purified inactivated viruses (PIVs)
- ♣ Live attenuated viruses (LAVs)
- ♣ mRNA vaccines
- ♣ Viral vectored vaccines
 - Modified vaccinia virus Ankara (MVA)
 - Measles virus (MV)
 - Adenovirus vectors (Ad).

Malaria vaccine

Malarial parasite goes through several stages of development, both in the human host and in the vector female anopheles mosquito. It presents different antigens at each of the stages making it complicated to develop a single vaccine, hence vaccines targeting the different stages have been attempted.

Development of the malaria vaccine. Some vaccines are directed against the sporozoite and/or liver stages of the life cycle (pre-erythrocytic stages), some against the asexual erythrocytic stages, and some against the sexual erythrocytic and mosquito stages (Fig. 3).

Pre-erythrocytic vaccine candidates aim to prevent all disease, while erythrocytic stage vaccines try to limit parasite growth in the bloodstream by blocking red blood cell invasion by the parasite.

The various vaccines developed include

- (a) **RTS, S/AS01 (RTS, S):** A recombinant protein together with adjuvant for pre-erythrocytic stages of the parasite's life cycle is the world's first malarial vaccine that was found to provide a partial

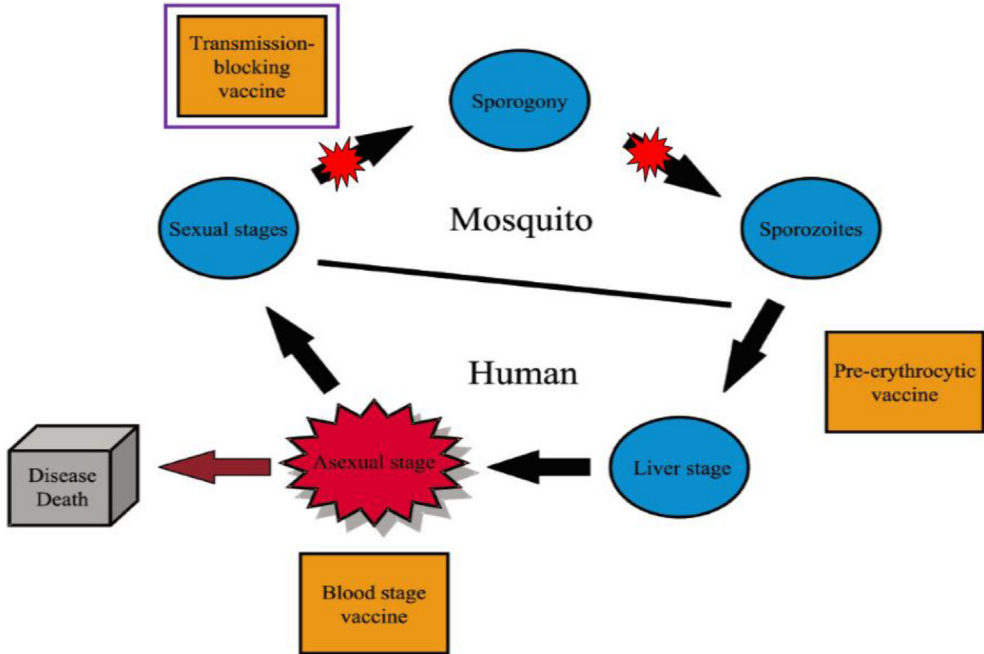


Fig. 3. Life Cycle of Malaria Parasite. Schematic life cycle of *Plasmodium falciparum* showing where vaccination may be expected to intervene. A transmission-blocking vaccine targets the parasite during its sexual development within the Anopheles mosquito host.

protection when given to children. It prevents the parasite from infecting the liver, where it can mature, multiply, and then be released into the blood stream, infecting the red blood cells, leading to symptomatic disease.

- (b) **The PfSPZ Vaccine:** Whole sporozoite preparations for pre-erythrocytic stages contain aseptically, metabolically active, purified, non-replicating, cryopreserved *P. falciparum* sporozoites, and when injected parenterally, induces immune responses to the sporozoite and liver stages of parasite development in the human host and prevents progression to blood-stage parasitemia. Studies have shown that the vaccine is well-tolerated and safe [25,26].
- (c) **VAR2CSA Vaccines: Erythrocytic-stage vaccine** is one that targets the IE surface antigens of placenta-sequestering parasites, such as the surface antigen VAR2CSA that binds the placental chondroitin sulfate A (CSA) receptor, to specifically control placental parasitemia. This vaccine targeting placenta-sequestering parasites aims to protect pregnant women exclusively and prevent poor pregnancy outcomes. Two vaccines, namely, PRIMVAC and PAMVAC, directed against subregions of VAR2CSA are being tested.

The erythrocytes infected with malaria adhere to the lining of the syncytiotrophoblast and the parasites express a protein called VAR2CSA which binds to the chondroitin sulfate A. Women who develop antibodies to this protein are protected against complications of malaria in pregnancy, including low birth weight and maternal anemia. The vaccine is safe, well-tolerated, and induces functionally active antibodies [26,27].

- (d) **Transmission blocking vaccines (TBV) like Pfs25 or Pfs230:** Sexual-stage vaccines aim to induce antibodies that prevent parasite transmission to mosquitoes. These vaccines are used in malaria elimination programs. The vaccine combines a recombinant protein with an adjuvant for use against sexual erythrocytic and mosquito stages.

These vaccines do not prevent a person from becoming infected by the bite of an infected anopheles mosquito, but if sufficient people in the community are vaccinated, the prevalence of infected

vectors will diminish. Most current targets for TBVs are either parasite surface antigens, ookinete-secreted proteins, mosquito components, or recombinant proteins.

Both transmission-blocking and **anti-infection vaccines** are expected to be components of vaccines that target multiple life cycle stages of the parasite to interrupt malaria transmission, which could be useful for malaria elimination and eradication programs.

COVID-19 Vaccine

Several countries are independently involved in the development of a vaccine against corona virus disease 2019 (COVID-19), since the pandemic struck the world in December 2019.

Various types of vaccines are being developed [28].

- Nucleic acid-based (mRNA and DNA) vaccines. The mRNA 1273 codes for the SARS-CoV-2 spike protein. This vaccine has been tested in phase 1 studies, which show that there was an immune response in all participants (mRNA-1273 [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04283461) number, NCT04283461) [29].
- Recombinant protein-based adjuvant vaccine is being developed in China.
- Viral vector vaccines [30,31] phase 2 trial of an adenovirus-vectored vaccine of SARS-CoV-2 spike protein has been conducted. The results showed that it induced both humoral and cellular immune responses and had an acceptable safety profile.

The following updates on these vaccines are available.

The US National Institute of health has partnered with multiple pharmaceutical companies to accelerate the development of a vaccine (ACTIV). Three of them have entered the phase 3 trial:

- Moderna mRNA 1273 in July 2020.
- Astra Zeneca and the University of Oxford (UK) AZD1222 in August 2020.
- Pfizer and BioNTech's BNT 162 in September 2020.

For a complete documentation of the vaccines under development, the reader is referred to the WHO draft guidelines on COVID vaccine released on July 24, 2020 [32] A recent review of vaccine development was published in July 2020 [32].

BCG vaccination induces a cellular immunity that may be effective against viral infections. However, WHO advises against BCG vaccination for COVID protection, pending further trials [33].

Summary of recommended vaccines for pregnant and postpartum women

Table 1
Vaccination during pregnancy.

Target Population	Vaccine	Type	Recommendation	Safety
Pre-pregnancy	MMR	Live Attenuated	Avoid Pregnancy for 1 month post vaccination	Mild local reaction Fever
All pregnant women	Influenza	Inactivated IIV	1 dose at any gestational age	Local redness soreness Anaphylaxis (rare)
Pregnant women with risk factors	Tetanus/Tdap	Toxoid/Inactivated bacteria	1 dose between 27 and 36 weeks	Mild local pain
	Hepatitis A	Inactivated viral	2 doses in some circumstances	No side effects
	Hepatitis B	Inactivated Viral recombinant subunit	3 doses if high likelihood of exposure HBsAg-positive sex partner	Local site redness soreness Headache fatigue
	Pneumococcal	Inactivated bacteria polysaccharide	1 dose if there is risk	No risk of teratogenicity
	Meningococcal	Inactivated bacteria polysaccharide (Men AC-PS & MenACWY)	1 dose if there is risk	No unusual Side effects

Table 1 (continued)

Target Population	Vaccine	Type	Recommendation	Safety
	Yellow fever	Live attenuated viral	1 dose if there is risk (avoided in breast feeding)	Serious side effects Neurotropic & viscerotropic Avoid during breast feeding
	Polio	Inactivated polio vaccine (IPV)	1 dose if there is risk of exposure	Mild local pain
	Japanese encephalitis	Live attenuated viral	1 dose if traveling to endemic area	No adequate safety studies in pregnancy
	Typhoid	Inactivated Vi polysaccharide vaccine	If risk of exposure	Insufficient data during pregnancy
	Cholera	Whole-cell killed oral cholera vaccine (OCV)	If risk of exposure	No adverse effects in pregnancy
	Anthrax	Inactivated subunit	Only PEP	No teratogenicity
	Rabies	Inactivated viral	Only PEP	No risk of miscarriage or teratogenicity
	Small pox	Live attenuated viral	Only PEP	Transfer of vaccine virus to fetus Avoid during breast feeding Insufficient data during pregnancy
	BCG	Live bacterium	Only if close contact with case	No harmful effects noted
Postpartum	MMR	Live attenuated viral	1 dose	
	Varicella	Live attenuated viral	1 dose	
	HPV	Live attenuated	3 doses	
	Influenza	Live attenuated influenza vaccine	If not given during pregnancy	
	TDaP	Inactivated bacteria	If not given during pregnancy	

Safety of new adjuvanted vaccines in pregnancy

The use of adjuvants in vaccines

Pregnant women are usually excluded from the majority of clinical trials on vaccines, hence the safety of adjuvanted vaccines in pregnant women has not been tested in clinical trials.

The human data analysis thus far suggests safety of use of vaccines during pregnancy, but since these are mostly based on experience with unadjuvanted seasonal influenza vaccines and alum-adjuvanted tetanus vaccines, their effects cannot simply be extrapolated to all vaccines. Human data on the safety of the more recently introduced adjuvants during pregnancy, that is, the oil-in-water emulsions MF59 and AS03 and the MPL/Alum combination of AS04, are limited [34].

Initially, vaccines consisted of live attenuated or inactivated bacteria or viruses.

Later, highly purified proteins, which are weak antigens with reduced immunogenicity, were used to improve safety of the vaccine. To enhance the immunogenicity, adjuvants were added to the vaccine formulation. Adjuvants may cause local and systemic effects, trigger cytokines effect like IL-1, IL-6, tumor necrosis factor alpha (TNF- α), and may qualitatively change the Th1/Th2 balance.

Adjuvants were first described in the 1920s and have been used for decades to improve the immune response to vaccine antigens. Aluminium salts are the most widely accepted and used adjuvants. Many pregnant women have received an alum-adsorbed TT vaccine and, thus far, no association with fetal malformations has been demonstrated.

Other adjuvants used are AS03, AF03, and MF59 for influenza vaccines, AS04 used for HPV and hepatitis B, and aluminium used for hepatitis A, hepatitis B, HPV, Tdap, polio, Hib, influenza, and pneumococcal vaccines.

In theory, the strong activation of the maternal immune system during this period could have an impact on the implantation of the embryo and acceptance of the fetus by breaking immune tolerance

against the fetus. This could result in pregnancy loss, restricted growth of the fetus and/or the placenta or in the development of pre-eclampsia.

Mode of delivery of vaccines

- **Mucosal Vaccines:** Efficient mucosal vaccine would make immunization procedures easier and be better suited for mass administration.
- **Oral Vaccines:**
 - ❖ Poliomyelitis: Live attenuated polio vaccine
 - ❖ Cholera: Cholera toxin B subunit
 - > Inactivated *V. cholerae* 01 whole cells.
 - > Live attenuated *V. cholerae* 01 strain.
 - ❖ Typhoid: Ty21a LAIV
 - ❖ Rota Virus: Live attenuated monovalent human rotavirus strain
Pentavalent live vaccine.
- **Nasal Vaccines:** For influenza, pertussis, diphtheria
- **Vaginal Vaccines:** Many pathogens are transmitted sexually through the genital tract, e.g. HIV, HPV, chlamydia, Neisseria gonorrhoeae, and herpes simplex virus (HSV).

Protective mucosal immune response against sexually transmitted infections should be triggered in vaginal mucosa. Despite several advantages, as compared to systemic injections, the delivery of vaccines by genital routes has not been shown to be very practical in human trials.

- **Ocular Vaccination:** Ocular immunization has been attempted in rabbits against infection with HSV.

Thiomersal and vaccine safety in pregnancy

Although some vaccines given to adults contain thiomersal (a mercury preservative used in vaccines), there is no evidence that thiomersal-containing vaccines cause adverse effects in offspring of women who received these vaccines during pregnancy. The Advisory Committee on Immunization Practices (ACIP) does not recommend avoidance of thiomersal-containing vaccines for any group, including pregnant women.

Conclusion

Maternal vaccination serves the dual purpose of protecting the mother, her fetus as well as her newborn. Live vaccines are contraindicated in pregnancy. Most other vaccines are safe during pregnancy. The vaccines given routinely to pregnant women are tetanus, diphtheria, pertussis, and influenza vaccines. Many other vaccines are indicated if there is risk of exposure or post prophylaxis. Postpartum vaccination with MMR, varicella, and HPV is recommended in non-immune mothers.

Declaration of competing interest

Authors Dr mala arora has no conflict of interest to declare
Dr rama lakshmi has no conflict of interest to declare

Practice Points

- ♣ Women contemplating pregnancy should be offered the MMR vaccine
- ♣ All pregnant mothers should receive the TDAP and flu vaccines during pregnancy
- ♣ Mothers at risk of exposure should be vaccinated against the infectious diseases mentioned in Table 1
- ♣ Post exposure prophylaxis should be offered in rabies, herpes zoster, hepatitis B, Small pox and Polio
- ♣ Post Partum Immunisation should include MMR, TDAP, and Flu vaccine if not administered during pregnancy. Besides HPV vaccination should be offered.
- ♣ Newer Vaccines are being developed for Malaria, Zika virus, and Covid. Their safety in pregnancy needs to be assessed

Research Agenda

- ♣ Safety of Adjuvanted vaccines during pregnancy
- ♣ Safety of Thimerosal in vaccines during pregnancy
- ♣ Safety of newer vaccines like Covid malaria during pregnancy
- ♣ Long term follow up of neonates over 10–15 years in vaccinated mothers to study any delayed side effects and effect on reproduction

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