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Review article

Immunizations during pregnancy: How, when and why

Alexandros Psarris*, Michael Sindos, Georgios Daskalakis, Maria Eleni Chondrogianni, Stefani Panayiotou, Panagiotis Antsaklis, Dimitrios Loutradis

1st Department of Obstetrics and Gynecology, "Alexandra" Maternity Hospital, National and Kapodistrian University of Athens, 80 Vas. Sophias Av., 115 28, Athens, Greece

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ABSTRACT

Maternal immunization during pregnancy provide protection for the mother and the fetus against certain pathogens. Immunizations during pregnancy are divided to routine immunizations recommended for all pregnant women, immunizations for certain medical indications and vaccines that are potentially harmful during pregnancy and should be avoided. We conducted a comprehensive review of the literature regarding immunizations during pregnancy. The search terms used were immunization, vaccine, pregnancy, influenza, pertussis, safety and efficacy. We gathered all available guidelines on vaccination during pregnancy. Generally, vaccines are allowed during pregnancy when the benefits outweigh the risks. Tdap and inactivated flu vaccines are routinely recommended during pregnancy. Vaccines containing live attenuated viruses are contraindicated during pregnancy. These are LAIV influenza, MMR, Varicella, Zoster, BCG and smallpox pre-exposure. All other vaccines are given when medically indicated and the possible benefits outweigh the risks. Obstetricians and gynecologists should be familiar with the indications of vaccination during pregnancy. Vaccination coverage of pregnant women with routinely recommended vaccines has increased but further efforts are needed. Our aim is to review vaccination practices during pregnancy, demonstrate the benefits and dangers of different vaccines, evaluate their effectiveness and define the proper timing of vaccination.

Contents

* Corresponding Author.
E-mail address: Psarris.alexandros@gmail.com (A. Psarris).

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Introduction

Pregnancy is a critical period of development and growth for the fetus. Several factors have been shown to interrupt its normal evolution and cause complications. Infections during pregnancy are potentially dangerous for the mother and the fetus and some of them have been linked both with adverse perinatal outcomes and congenital malformations. Timely and appropriate vaccine administration during pregnancy provides protection for the mother, the fetus and in some cases for the newborn as well. However, the administration of a number of vaccines is contradicted during pregnancy if the risks of vaccination outweigh any possible benefits. Finally, immunization with certain vaccines may be acceptable under specific clinical situations.

Routinely recommended vaccines

Tdap (Tetanus, Diphtheria, Pertussis) vaccine

The highest incidence of complications (pulmonary, neurologic and nutritional) of pertussis is reported in infants younger than 6 months old [1]. Increased mortality and severity of pertussis disease has been reported in the first months of life [2]. Pertussis immunization starts at 6–8 weeks, hence before the period of increased incidence.

Current guidelines (CDC, ACOG) suggest that all pregnant women should get vaccinated between 27 and 36 weeks [3]. It has been shown that vaccination in the second trimester is more beneficial due to increased antibody transfer to the fetus [4]. Interestingly, the UK Department of Health recommends vaccination of all previously immunized pregnant women between 16 and 32 weeks of gestation [5]. Antibodies produced by the mother provide protection both for herself and the infant [6]. The immunization timeframe has been established in order to ensure maximum antibody concentration at the time of birth [7]. However, if a pregnant woman is injured with a rusty object, an acute dose of the vaccine is recommended [8]. Also, women with unknown or incomplete vaccination should get the full 3 vaccination series [8]. The recommended schedule for this vaccine series is at 0 weeks, 4 weeks, and 6–12 months. The dose of Td closer to 27 and 36 weeks should be replaced with Tdap [3]. CDC recommends the administration of Tdap in every consecutive pregnancy [9].

A systematic review showed that vaccination during the late second or early third trimester (with at least 2 weeks from the time of vaccination to delivery) can protect the neonate from pertussis [10]. This means less mortality and less frequent need for hospitalization in an intensive care unit. A randomized control trial has shown no difference to the time of delivery and no increase of adverse side effects regarding the use of Tdap in pregnancy [10]. No correlation with autism neither adverse effects on the fetus have been documented so far [11]. Most common side effects include local reactions such as pain and swelling at the injection site [12].

The use of Tdap is contradicted in case of severe allergic reaction after a previous dose and severe allergy to any vaccine component [8]. The vaccine may be given, if the benefits of vaccination outweigh the risks, to people with moderate or severe acute illness (with or without fever), Guillain-Barré syndrome (GBS) within 6 weeks after a previous vaccine dose containing tetanus toxin and history of type III hypersensitivity reactions following a previous vaccine dose [8].

In some countries such as the United Kingdom and Greece the Tdap vaccine includes the inactivated polio vaccine (Tdap-IPV). Tdap-IPV is equally effective and safe in pregnancy as demonstrated by the MHRA study in the United Kingdom of 20,000 pregnant women. There was no increase of stillbirth, neonatal death, maternal death, preeclampsia, eclampsia, hemorrhage or other side effects [13].

Influenza vaccine

Pregnant women undergo some changes concerning heart rate, lung capacity and immunological function [14]. Thus, flu infection during pregnancy has been associated with an increased risk of complications such as secondary pneumonia, acute respiratory failure, endometrial fetal death, preterm delivery and death. The benefit for the newborn occurs due to passive antibody transport [15]. Despite initial concerns about vaccination during the first trimester [16], it has been shown that the vaccine can be given at any term [17,18]. Women planning to become pregnant should be vaccinated beforehand [19]. Vaccination with the inactivated flu vaccine is safe for the fetus since no increased risk of automatic abortions, preeclampsia, prematurity, intrauterine growth retardation or malformations has been reported [20,21].

The most common side effects of the vaccine include pain and swelling at the injection site, fever and physical pain. The absolute contradictions are life threatening allergies to the influenza vaccine or any of its ingredients. The vaccine may be given if the benefits of vaccination are greater than the risks, to women with allergy to eggs or history of Guillain-Barré Syndrome.

Vaccines given for medical indications

Hepatitis B vaccine

Hepatitis B vaccine is a recombinant vaccine containing the surface antigen of Hepatitis B virus (HBsAg) [22]. The Center for Disease Control (CDC) and the American College of Obstetricians and Gynecologists (ACOG) agree that pregnancy is not a contraindication for Hepatitis B vaccination [23,24]. There are two indications for the administration of HepB vaccine during pregnancy: Completion of the vaccination scheme that started before conception, and high risk of infection with Hepatitis B Virus during pregnancy [23]. High risk groups include pregnant women with many sex partners in the last 6 months or with a HBsAg positive sex partner or women who have been evaluated or treated for a sexually transmitted infection or intravenous drug users [23]. The available data regarding vaccine's safety are limited but they

indicate no apparent risk for congenital anomalies to the developing fetus [25].

Pneumococcal vaccine

There are two types of Pneumococcal vaccine: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13) [26].

PPSV23 contains 23 purified capsular polysaccharide antigens of Streptococcus pneumoniae (serotypes 1, 2, 3, 4, 5, 6B, 7 F, 8, 9 N, 9 V, 10A, 11A, 12 F, 14, 15B, 17 F, 18C, 19A, 19 F, 20, 22 F, 23 F, and 33 F) [26]. According to the Advisory Committee on Immunization Practices (ACIP), ideally, the vaccine should be given prior to conception, but the indications for administration in adults are not altered by pregnancy [26]. ACIP recommends administration of PPSV23 for adults who are at substantially increased risk of serious pneumococcal infection, such as those with congestive heart failure, cardiomyopathies, chronic pulmonary disease, diabetes mellitus, cirrhosis, cochlear implement or cerebrospinal fluid leak or immunosuppressive conditions (e.g congenital immunodeficiency, HIV infection, hematologic malignancies, organ or bone marrow transplant, therapy with alkylating agents and antimetabolites, or systemic corticosteroids, chronic renal failure or nephrotic syndrome), since these conditions lead to reduced clearance of encapsulated bacteria from the bloodstream [27]. Its safety is proven only during the second and third semester of pregnancy [28]. However, there are few data for its safe administration during the first trimester of pregnancy [26]. Nevertheless, newborns whose mothers were inadvertently vaccinated during the first trimester of pregnancy didn't have higher incidence of congenital anomalies [26].

PCV13 contains 13 purified capsular polysaccharide antigens of Streptococcus pneumoniae (serotypes 1, 3, 4, 5, 6A, 7 F, 9 V, 14, 18C, 19A, 19 F, 23 F, 6B) bounded to diphtheria CRM_{197} protein [29]. ACIP has not published pregnancy recommendations for PCV13, as its administration during pregnancy has not been extensively studied [30]. According to ACOG this vaccine is suggested to pregnant women in high risk of infection with Streptococcus pneumoniae [30]. Hence, vaccination must be postponed unless there is high risk of pneumococcal infection in which case the gynecologist - obstetrician and the infectious disease specialist must be consulted. There is no information regarding the use of PCV 13 during pregnancy due to the lack of relative human studies [26].

Meningococcal vaccine

There are currently two types of Meningococcal vaccine available: Meningococcal group A, C, W-135 and Y vaccine (MenACWY) and Meningococcal B Vaccine (MenB).

MenACWY is a quadrivalent conjugate vaccine containing purified capsular polysaccharides A, C, Y and W135 of Neisseria meningitidis bacteria bounded to nontoxic mutant of diphtheria toxin [31]. CDC states that pregnancy should not preclude vaccination with MenACWY [32]. However, in case of pregnancy at the time of MenACWY vaccination, the gynecologist - obstetrician must be consulted [32]. Zheteyeva Y et al conducted a study between 2005–2011 regarding the safety of the meningococcal vaccine [33]. The study included 103 cases of pregnant women who had inadvertently received the MenACWY, 37.9% of whom reported pregnancy-specific adverse events while 9.7% reported neonatal adverse events [33]. No maternal or neonatal deaths were reported [33]. The most common pregnancy-specific complication was spontaneous abortion (17 cases; 16.5%) [33]. One case of a congenital anomaly (aqueduct stenosis with severe ventriculomegaly) was reported [33]. However, no concerning patterns of adverse events after MenACWY vaccination in pregnancy were identified [33].

MenB is a recombinant protein vaccine containing proteins of group B Neisseria meningitidis bacteria [34]. ACIP recommends deferring MenB vaccination in pregnancy, unless there is high risk of meningococcal infection, in which case the gynecologist - obstetrician and the infectious disease specialist must be consulted [35]. High risk groups include pregnant women with persistent complement component deficiencies, with anatomic or functional asplenia or travelers in areas with epidemic meningococcal disease (sub-Saharan Africa) [36]. No randomized controlled clinical trials have been conducted to evaluate the use of MenB during pregnancy [35].

Rabies vaccine

Rabies vaccine contains inactivated Rabies Virus (RABV) [37]. CDC states that pregnancy is not a contraindication to postexposure prophylaxis with Rabies vaccine, because of the potential consequences of inadequately managed rabies exposure [38]. For this reason, its administration is recommended after an animal bite. Animals that are most likely to transmit Rabies include stray dogs, bats, coyotes, foxes, raccoons or other wild animals [39]. Certain studies show no increase in the incidence of abortion, premature births and fetal anomalies associated with rabies vaccination during pregnancy [40]. A study conducted at China, demonstrate that Rabies vaccine had a favorable safety profile during all three trimesters [41].

Hepatitis A vaccine

Hepatitis A vaccine contains inactivated Hepatitis A Virus (HAV) [42]. CDC recommends its administration to pregnant women in high risk for exposure to HAV [43]. High risk groups include intravenous drug users, travelers to countries with low standards of hygiene and inadequate water supply facilities (sub-Saharan Africa and parts of South Asia) [44], residents in a household with an infected person or sexual partners of someone with acute Hepatitis A infection. The safety of hepatitis A vaccination during pregnancy has not been determined [43]. However, since Hepatitis A vaccine is produced from inactivated HAV, the theoretical risk to the developing fetus is expected to be low [43]. A review of the Vaccine Adverse Event Reporting System (VAERS) reports did not identify any concerning patterns of adverse events in pregnant women or their infants after receiving Hepatitis A vaccine [45]. In addition, risks of Hepatitis A infection during pregnancy are greater than the risk associated with Hepatitis A vaccination. More specifically Hepatitis A infection is associated with an increased risk of premature birth, fetal ascites and gestational complications such as placental separation, premature contractions, vaginal bleeding and premature rupture of membranes [46,47].

Poliomyelitis vaccine

There are two types of Poliomyelitis vaccine: an inactivated poliovirus given by injection (Salk vaccine or IPV) and a live attenuated poliovirus given by mouth (Sabin vaccine or OPV) [48].

IPV contains inactivated poliovirus types 1, 2, and 3 [48]. CDC indicates administration of IPV for pregnant women in high risk of infection with poliovirus [49]. High risk groups include travelers to polio-endemic countries (e.g Afghanistan, Nigeria, Pakistan, Somalia, Kenya, Cameroon) [50]. Though no adverse events of IPV have been documented among pregnant women or their fetuses, vaccination of pregnant women should be avoided on theoretical risks [49]. Recently, IVP vaccination combined with Tdap, has been recommended for pregnant women in the UK [50].

OPV contains live attenuated poliovirus types 1, 2, and 3 [48]. Studies of pregnant women who were advised to take OPV during outbreaks of poliomyelitis in Finland [51–53] and Israel show no association between vaccination and poor outcomes of pregnancy (e.g neonatal death, congenital malformation, premature birth, perinatal infection and neurological aberration) [54]. However, on rare occasions, OPV can lead to vaccine-associated paralytic polio (VAPP) in the general population and it is no longer licensed in some countries [55].

Japanese encephalitis vaccine

Japanese encephalitis vaccine contains inactivated Japanese encephalitis virus [56]. CDC indicates its administration to pregnant women in high risk of infection with Japanese encephalitis virus [57]. High risk groups include travelers to a country with an increased incidence of Japanese encephalitis (Japan, Korea, Cambodia, China, India, Indonesia, Malaysia, Thailand, Sri Lanka, Nepal and Vietnam) [58]. No controlled studies have assessed the safety or efficacy of the Japanese encephalitis vaccine in pregnant women [57].

Yellow fever vaccine

Yellow fever vaccine contains live yellow fever virus. CDC indicates its administration for pregnant women who cannot avoid traveling to countries with an increased incidence of yellow fever (tropical regions of South America and sub-Saharan Africa) [59]. In that case the gynecologist - obstetrician and the infectious disease specialist must be consulted [59]. A study conducted during a mass vaccination campaign in São Paulo, Brazil in 2000, in order to evaluate the possible effects of the yellow fever vaccine during pregnancy demonstrated that the frequency of malformations, miscarriages, stillbirths and premature delivery was similar to that found in the general population [60,61].

Typhoid fever vaccine

There are two types of Typhoid fever vaccine: live attenuated vaccine (Ty21a) and Vi polysaccharide vaccine [62].

Ty21a vaccine contains the live attenuated strain Salmonella typhi Ty21a and is only for oral administration [62]. Although, studies have not been conducted for the use of Ty21a vaccine in pregnant women, CDC indicates pregnancy is a contraindication to vaccination as it contains live viruses [63].

Vi polysaccharide vaccine contains Vi capsular antigen and is administrated intramuscularly [62]. Although, studies have not been conducted for the use of Vi polysaccharide vaccine during pregnancy and thus data for its safety are limited, CDC indicates its administration only for pregnant women in high risk of infection with Salmonella typhi [63]. ACIP recommends delaying vaccination until the second or third trimester to minimize the possibility of teratogenicity [64]. High risk groups include travelers to areas with low standards of hygiene or with typhoid fever outbreaks (e.g northern and western Africa, southern Asia, Indonesia and Peru), people in close contact with a typhoid carrier or laboratory workers who work with SalmonellaTyphi bacteria [62].

Smallpox vaccine

Smallpox vaccine contains live smallpox (or variola) virus. CDC indicates its administration only after direct exposure to smallpox (e.g face-to-face, household, or close-proximity contact with a smallpox patient), while pre-exposure vaccination is contra-indicated in any trimester of pregnancy [65]. In addition, its administration is contraindicated for women who might conceive within 4 weeks of vaccination [65].

A study conducted in 2014 to estimate the maternal and fetal risks of smallpox vaccination during pregnancy, didn't identify any association between smallpox vaccination and spontaneous abortion, preterm birth, or stillbirth [66]. The main concern for the vaccine is the possibility of fetal smallpox infection, which is rare but associated with increased rates of fetal or neonatal death (of 21 cases that have been recorded, only 3 survived) [66]. Apart from fetal smallpox, smallpox vaccine has not been clearly proven to cause serious birth defects or other adverse events for the fetus or neonate, such as premature birth, low birth weight, or miscarriage [67]. Inadvertent vaccination of pregnant women should not be a reason of pregnancy termination, since the risk for fetal smallpox is low [67].

Anthrax vaccine

Anthrax vaccine is an attenuated vaccine that contains antigenic proteins of Bacillus anthracis. CDC indicates its administration only after direct exposure to bacillus anthracis, while pre-exposure vaccination is not recommended in any trimester of pregnancy [68]. More particularly it can be given only after the consumption of raw or undercooked meat from an infected animal with anthrax or after the inhalation of anthrax spores in infected places (wool mills, slaughterhouses) (69).

Vaccines that should be avoided during pregnancy

Vaccines containing live attenuated viruses have the potential to pass the placental barrier and cause infection to the fetus. Their administration is contraindicated during pregnancy because of the theoretical risks to the mother and the fetus.

Measles, mumps, rubella vaccine (MMR)

MMR vaccine is a live-attenuated vaccine containing live measles, mumps and rubella viruses. CDC states that pregnancy is a contraindication to vaccination with MMR due to maternal mortality and poor prenatal outcome associated with infection with rubella and measles [70]. In addition, it should not be administered to women attempting to become pregnant [70]. Women should be counseled to avoid becoming pregnant for 28 days after receiving the MMR vaccine [70]. Inadvertent vaccination of pregnant women or women who became pregnant within 28 days of vaccination should not be a reason of pregnancy termination, as according to ACIP the risk of vaccine-associated defects is almost negligible [71,72]. In that case the gynecologist - obstetrician must be consulted about the theoretical risks to the fetus [70]. Postpartum administration of MMR vaccine is indicated to women who lack presumptive evidence of immunity to rubella [70]. ACIP reviewed combined data from rubella registries in Europe (years 1971–1990 and 2001–2004) and the USA (1971–1988) after administration of vaccines containing different attenuated rubella virus strains [73]. Among 680 live births to rubella-susceptible women, none of the infants was found to have congenital rubella syndrome (CRS) [73], which is associated with adverse events including cataracts, hearing loss, mental retardation, and congenital heart defects [70]. A follow up of vaccinated women who were unknowingly pregnant during a nationwide measles-rubella vaccination campaign in 2001, didn't document any adverse pregnancy outcomes such as stillbirth, prematurity, low birth weight, or defects compatible with CRS [74].

Varicella vaccine

Varicella vaccine is a live-attenuated vaccine containing live varicella zoster virus [75]. CDC indicates pregnancy is a contraindication to vaccination with Varicella vaccine, although the effects of the varicella virus on the fetus are unknown [75]. In addition, it should not be administered to women attempting to become pregnant [75]. Women should be counseled to avoid becoming pregnant for 28 days after receipt of Varicella vaccine [75]. In absence of immunization against varicella, pregnant women are recommended to receive the first dose of vaccine after the completion or termination of their pregnancies [75]. Inadvertent vaccination of pregnant women or women who became pregnant within 28 days of vaccination should not be a reason of pregnancy termination [75]. In that case the gynecologist - obstetrician must be consulted about the theoretical risks to the fetus [75]. A study was conducted in 1995 by a global healthcare company (Merck and Co.) in collaboration with CDC, in order to examine the maternal-fetal outcomes of pregnant women who were accidentally administered varicella vaccine 3 months before or during pregnancy [76]. During the first 10 years of the pregnancy registry no cases of congenital varicella syndrome or birth defects compatible with congenital varicella syndrome have been reported (e.g low birth weight, cutaneous scarring, limb hypoplasia, microcephaly, cortical atrophy, chorioretinitis, cataracts) [77,78]. The rate of major birth defects was similar to the rate reported in the general U.S. population (3.2%) [75]. Although the study results do not exclude the possibility of risk for women who received inadvertent varicella vaccination before or during pregnancy, the potential risk, if any, is low [75].

Bacille calmette-guérin vaccine (BCG)

BCG vaccine is a live-attenuated vaccine containing a strain of Mycobacterium bovis known as Bacillus Calmette-Guérin [79]. CDC states that pregnancy is a contraindication to vaccination with the BCG vaccine, due to the potential risk of the live pathogen [80]. So far there aren't enough data to prove its safety and therefore further studies are needed [80]. Until now no harmful effects of BCG vaccination of pregnant women have been reported on the fetus [80].

Herpes zoster (shingles) vaccine

There are currently available two types of Herpes zoster vaccine: recombinant zoster vaccine (RZV) and live zoster vaccine (ZVL) [81].

RZV contains a non-live recombinant Varicella zoster virus glycoprotein E surface antigen reconstituted in a novel liposome-based adjuvant system [82]. Its administration has not been studied in pregnant women. CDC recommends delaying vaccination with RZV for these women until completion of pregnancy [81].

ZVL contains Oka/Merck strain of live, attenuated Varicella zoster virus, the same strain used in the varicella vaccines [81]. CDC states that pregnancy is a contraindication to vaccination with ZVL, since the vaccine contains live, attenuated Varicella-zoster virus and thus has the potential to cause congenital varicella syndrome [82]. In addition, CDC recommends that pregnancy should be avoided for three months following vaccination with Herpes zoster vaccine [82].

Other vaccines

Human papillomavirus (HPV) vaccine

There are currently available three types of HPV vaccine. All of them are composed of a major capsid protein of HPV, L1 protein, which is expressed by using recombinant DNA technology to produce noninfectious virus-like particles (VLPs) [83]. Quadrivalent HPV vaccine (HPV4) contains four HPV type-specific VLPs prepared from the L1 proteins of HPV 6, 11, 16, and 18 [83]. Bivalent HPV vaccine (HPV2) contains two HPV type-specific VLPs prepared from the L1 proteins of HPV 16 and 18 [83]. 9-valent HPV vaccine (HPV9) contains nine HPV type-specific VLPs prepared from the L1 proteins of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 [84].

Although ACIP recommends routine vaccination for females up to 26 years old [83], HPV vaccines are not recommended for use in pregnant women of these ages because of limited information about their safety [85]. If a woman is found to be pregnant after initiating the vaccination series, the vaccination should be delayed until completion of pregnancy [85,86]. Inadvertent vaccination of pregnant women should not be a reason of termination [85,86]. The vaccines have not been associated with adverse outcomes of pregnancy or adverse events in the developing fetus [83], including spontaneous abortion, late fetal death and congenital anomalies [87].

In a clinical review of non-manufacturer reports received in VAERS between June 2006 and December 2013, there were 147 reports of HPV4 administered to pregnant women [88]. This analysis did not find unexpected patterns of fetal adverse effects after HPV4 vaccination [88]. Moreover, a cohort study included all the women in Denmark who had a pregnancy between October 2006 and November 2013 and compared women who had vaccine exposure during the prespecified time window with women who had not been vaccinated at the same time [89]. The conclusion of the study was that HPV4 vaccination during pregnancy was not associated with a statistically significantly higher risk of adverse pregnancy outcomes compared with exposure [89]. Outcomes included spontaneous abortion, stillbirth, major birth defect, small size for gestational age, low birth weight, and preterm birth [89]. A single center study that was conducted in Costa Rica, found no evidence that HPV2 vaccination affects the risk of miscarriage for pregnancies conceived less than 90 days after vaccination [90]. Hence, data regarding the safety the of HPV9 during pregnancy is limited but reassuring.

Vaccines and breastfeading

According to ACIP, neither inactivated nor live-virus vaccines administered to lactating women affect the safety of breastfeeding for women or their infants as they are not excreted into milk with the exception of smallpox and yellow fever vaccines [91]. CDC recommends that if a woman received smallpox vaccine during pregnancy or breastfeeding, she should avoid breastfeeding, because of the theoretical risk for contact transmission from mother to infant [92]. However, a study conducted to evaluate whether the varicella vaccine virus is detected in breast milk after vaccination of breastfeeding women found no evidence of varicella vaccine virus excretion in breast milk [93]. Participating women were varicella seronegative during routine prenatal screening and received the first dose of varicella vaccine at least 6 weeks postpartum and the second dose at least 4 weeks later [93]. Breast milk samples were collected after each vaccine dose and tested for varicella zoster virus by polymerase chain reaction (PCR) [93]. Varicella DNA was not detected by PCR in any of the 217 post vaccination breast milk specimens. None of the infants was seropositive [93]. Yellow fever vaccine should be avoided in breastfeeding women, because 2 cases of yellow-fever vaccine associated with acute neurotropic disease have been detected in infants whose mothers were vaccinated [60].

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