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RESEARCH PAPER

Why, when and for what diseases pregnant and new mothers "should" be vaccinated

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ABSTRACT
Immunological and serological changes that occur during pregnancy can alter the susceptibility of both the mother and the fetus against various infectious diseases. The pregnant woman has an altered immune response and, for some pathologies, is at increased risk of infection and of developing complications and serious outcomes. In addition, maternal infections can result in congenital anomalies, malformations or severe neonatal diseases. Vaccination of pregnant women can therefore have a double goal: to protect the mother from diseases that could have an impact on her health and to avoid infection/disease transmission to the fetus or the newborn. Despite the potential benefits of immunization in pregnant women, it is still evident reluctance and/or refusal of vaccinations by health professionals as well as by pregnant women, who are wary of the real advantages linked to vaccines. For these reasons a group of experts has evaluated the latest scientific evidence reported in the international literature on this relevant topic.

KEYWORDS
antenatal immunizations; breastfeeding; contraindications; indications; pregnancy; precautions

Rationale of antenatal immunization

Immunological and physiological changes that occur during pregnancy can alter the susceptibility of the mother and the fetus to several infectious diseases. From the immunological point of view, the humoral adaptive immunity remains intact with an increase in the T-helper-2 antibody-mediated response. On the other hand, a selective suppression of the T-helper-1 cell-mediated immunity, which impacts on the mother's ability to respond to infection, is observed. This means that pregnant women are more prone to infections.[1] Besides, it is well known that some maternal infections can result in congenital anomalies, malformations or serious neonatal diseases (for example: congenital rubella, congenital varicella, etc.). Immunization of pregnant women could allow to achieve 2 relevant targets: the protection of the woman from infectious diseases that could seriously affect her health and to avoid the transmission of an infection and/or a disease to the fetus or newborn. As a matter of fact, maternal protective antibody concentrations can pass through the placenta to the fetus, especially during the third trimester of pregnancy. In newborns, these antibodies (Abs) usually have a half live equal to 3–4 weeks and progressively wane during the first 6–12 months of life, when immunization programs have already started.[1]

Despite the potential benefits resulting from the administration of vaccines in pregnant women, it is still evident reluctance and/or refusal of this approach both by health workers and pregnant women, who are wary of the real benefits or have unfounded fears of side effects related to vaccines and vaccinations. Formulating unanimous recommendations for immunizations of pregnant women and during breastfeeding is challenging because the evidence-base to guide decisions is extremely limited. Most of the available data concerning the safety of vaccines, in fact, come from passive surveys.[2]

The use of several vaccines (for example, against influenza, diphtheria, tetanus, pertussis) that, if administered during pregnancy, could be effective in preventing diseases in both mother and the fetus is well described in international literature.[3] However, these studies give limited results about safety, especially on the possible effects of vaccination on the fetus and the newborn. Accordingly to the Centers for Disease Control and Prevention (CDC) of Atlanta (United States of America, USA) the risk to a developing fetus from immunization of the mother during pregnancy is theoretical. Anyway, it is important to distinguish between live and inactivated vaccines. No theoretical or evidence does exist of risk to the fetus from vaccinating pregnant women or during breastfeeding with inactivated virus or bacterial vaccines or toxoids. On the other hand, live vaccines administered to a pregnant woman pose a theoretical risk to the fetus; therefore, live attenuated viral and bacterial vaccines are generally contraindicated during pregnancy. Live vaccines should be administered as soon as possible in the postpartum.[4]

Ideally, the immunization status of women who want to become pregnant should be investigated before conception and live attenuated vaccines should be administered to

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women of childbearing age with the recommendation to delay the start of a pregnancy for one month after vaccination. However, if a live attenuated vaccine is accidentally administered to a pregnant woman or if a woman becomes pregnant within 4 weeks after vaccination, does not arise any specific indication to the voluntary interruption of pregnancy. Anyway, in this latter case, it is absolutely necessary to explain to the mother the potential risks to the fetus. In any case, if a woman is at high risk for a specific disease that could have a negative impact on her health or on the health of the fetus, the benefits always dominate the potential risks related to immunization.

Medical doctors and health workers should evaluate risks and benefits related to the immunization of pregnant women, irrespective of the possibility to administer live attenuated, inactivated vaccines or vaccines containing purified antigenic components.[5,6]

Immunizing a woman during pregnancy provides important benefits to both mother and fetus/newborn. For example, tetanus toxoid administered during the 3rd trimester of pregnancy had a significant impact in preventing neonatal tetanus in industrialized countries.[7]

Besides, immunization strategies of pregnant women may offer a new approach for the prevention of infectious diseases of infants and children sustained by pathogens against which protection is desirable prior to the start and/or the completion of the primary vaccination course.[8,9]

Due to the low number of studies on vaccines' safety, in 2007 the Advisory Committee on Immunization Practices (ACIP) in the USA have discussed and published recommendations for vaccination during pregnancy and breastfeeding. The working group included members belonging to ACIP and to professional medical associations, experts in the field and CDC consultants;[2] its target was to clearly state which immunizations should be considered safe or contraindicated and which could be used with precaution.

ACIP defines "contraindication" as a condition that increases the risk of severe adverse events (SAEs) and as such not allows the administration of a vaccine. Taking into account pregnancy and breastfeeding, any SAE includes maternal, fetal and neonatal severe adverse events specifically related to a vaccine. "Precaution" is a condition of the recipient that could increase (biological plausibility) the risk of having a SAE or that could hamper the immune response to immunization. In this case, usually, immunization should be postponed; anyway, the vaccination can be performed if achievable benefits exceed potential risks.

Aim of our working group was the evaluation of the latest scientific evidence reported in international literature on this relevant topic and to give advice on indications, contraindications and precautions.

Recommended immunizations in pregnancy (Table 1)

Tetanus-diphtheria-pertussis combined vaccine (adult formulation: dTap)

As with most inactivated vaccines and toxoids, pregnancy is not a contraindication for use of diphtheria, tetanus and acellular pertussis combined vaccine with a reduced antigen content (adult formulation: dTap). A single dose of dTap in pregnancy, thanks to the maternal Abs passed through the placenta to the fetus, could protect the newborn from pertussis (and from tetanus and diphtheria as well).[7]

Table 1. Recommended immunizations in pregnancy.

Vaccine	Why	When
dTap	As with most inactivated vaccines and toxoids, pregnancy is not a contraindication for use of dTap.	Between the 27th and the 36th week of pregnancy.
Flu	WHO has identified pregnant women and infants as subjects at high risk for morbidity and mortality from influenza illness.	Inactivated influenza vaccines (QIV, TIV) can be used during all stages of pregnancy.

Legenda: dTap: Tetanus-diphtheria-pertussis combined vaccine (adult formulation); Flu: Influenza vaccine; TIV, inactivated trivalent flu vaccine; QIV, inactivated quadrivalent flu vaccine

For some time this approach was evaluated with concern as it was worried that maternal Abs could negatively affect the newborn immune response to pediatric diphtheria-tetanus-pertussis (DTP) vaccine or to combined vaccines including diphtheria and/or tetanus components. Besides, for many years pertussis immunization in pregnancy has not been performed due to the lack of data on safety. Nowadays, no increased risk of adverse events among women who received dTap vaccine during pregnancy or among their infants has been established.[10,11]

In 2008 ACIP recommended that pregnant women, not previously immunized with dTap:

- should receive dTap in the postpartum before hospital discharge;
- could receive dTap even after a 2-year interval after a previous dose of dT (adult formulation of diptheria-tetanus combined vaccine);
- should receive dT during pregnancy when indicated for the protection against diphtheria and tetanus;
- could postpone dT vaccine recommended in pregnancy and replace it with dTap in postpartum if a sufficient protection against tetanus and diphtheria is still in place.

In conclusion, in those years, even if specific contraindications to this immunization were not in place, a risk-benefit evaluation had to be performed before choosing to use dTap in pregnancy.

In 2011 a decisional model and a cost-efficacy analysis showed that dTap immunization in pregnancy could prevent more cases, hospitalizations and deaths in infants in respect to the same immunization performed in postpartum for 2 reasons:[12]

1) immunization in pregnancy is useful to both mother and child, protecting first of all the mother and, as a consequence, the baby;
2) immunization during the last period of pregnancy optimized the transfer of maternal Abs to the newborn, protecting the same soon after birth.

Accordingly to these evaluations, in 2011 ACIP recommended dTap vaccine to not previously immunized pregnant

women. dTap vaccine should be administered during the 3rd or the last part of the 2nd trimester of pregnancy (after 20th week). If the vaccine was not administered in pregnancy, it should be used immediately after delivery. In 2012 the recommendation has been extended to all pregnant women, whether or not previously immunized.[13] This approach has been chosen as protective Abs reach their maximum level one month after immunization, and decrease after one year becoming insufficient to protect the baby in his first month of life. dTap should be preferentially administered during the second-third trimester of pregnancy (particularly between 27th and 36th week), even if it has been recently demonstrated that avidity of immune globulins G (IgG) against pertussis is higher if the immunization is performed between 27th and 30th week of pregnancy.[14]

Accordingly to most recent published data, no increased risk of adverse events among women who received Tdap vaccine during pregnancy or among their infants has been registered.

Pertussis vaccination during pregnancy has recently been recommended in both the USA and United Kingdom (UK) to prevent pertussis infection in infants. While there are no apparent safety concerns about the administration of dTap vaccine during pregnancy, there are only limited safety data available. Anyway, the administration of dTap vaccine during pregnancy seems to be an appropriate strategy for reducing the burden of pertussis in infants.

Even wound management could be an opportunity to administer a dTap booster. Unimmunized pregnant women should receive 3 doses of dT (recommended schedule: 0, 4 and 6–12 months). dTap vaccine should replace 1 dose of dT, preferably between 27th and 36th week of pregnancy.[14,15]

Influenza vaccines

World Health Organization (WHO) has identified pregnant women and infants as subjects at high risk for morbidity and mortality from influenza (flu) illness. It has been demonstrated that seasonal flu increases the risk of hospitalization (especially if contracted in the 2nd or 3rd trimester of pregnancy), the birth of premature children and low birth weight for gestational age, as well as an increased risk of miscarriage. These risks are even higher if pregnant woman has any co-morbidity that itself is a recommendation for flu vaccination (diabetes, asthma, any heart disease, etc.). As it is absolutely relevant that immunization is performed well before flu season start, routine influenza vaccination is recommended for all pregnant women and women who intend to become pregnant.

Nowadays, 2 main flu vaccines are available at international level: inactivated vaccines (trivalent: TIV and quadrivalent: QIV) and live attenuated vaccine (LAIV). This latter is contraindicated in pregnancy. For many years seasonal flu vaccination has been performed using TIV vaccines containing 2 virus A subtypes and one B type.[16] More recently a QIV vaccine, containing 2 virus A and B subtypes, has become available.

In any case, after vaccination, mothers produce circulating Abs against influenza, part of which are transmitted to the fetus through the bloodstream and, after birth, through breast milk, giving protection to the newborn till the age of 6 months, when the use of flu vaccine can start.[17]

Inactivated flu vaccines can be used during all stages of pregnancy. Safety data on the use of flu vaccines in pregnancy, and in particular during the first trimester, are limited; however, no data about any fetal or maternal adverse outcomes nor about any congenital malformation attributable to immunization done during the 1st trimester have been reported. More data are available on the administration of flu vaccine during the 2nd and 3rd trimester; no worldwide data about any fetal or maternal adverse outcomes attributable to this immunization have been pointed out.[18,19]

The evidence of excess mortality during seasonal influenza, therefore, enhances the opportunity of vaccination of healthy pregnant women in the second or third trimester and of those at risk (for the presence of any co-morbidity) in any trimester. The excess mortality in pregnant women sustains also the opportunity to administer flu vaccine in any trimester during a pandemic.[20]

Vaccinations contraindicated in pregnancy (Table 2)

Measles-mumps-rubella (MMR) combined vaccine and varicella (V) vaccine

Data obtained from newborns of mothers immunized against rubella during their pregnancy have shown the presence of rubella-specific Abs. This could mean that a passive transfer of maternal Abs or that a fetal immune response against vaccinal virus strain has occurred. No cases of congenital rubella or varicella or of any malformation have never been considered attributable to fetal infection following immunization in pregnancy. Notwithstanding these reports, MMR and V immunizations, being with live attenuated viruses, are contraindicated in pregnancy.[21] Women should also be advised against the beginning of a pregnancy within 4 weeks after vaccination. Anyway, fetal malformations attributable to vaccination in pregnant women have not as yet been observed worldwide; for this reason, accidental immunization of a pregnant woman does not make necessary an abortion. A pregnancy test is not necessary before administering these vaccines; it is enough to give these vaccines during the first day of the menstrual period.[4]

Concerning the contacts of immunized subjects, there is no documented risk that attenuated virus contained in the vaccine

Table 2. Vaccinations contraindicated in pregnancy. These immunizations are contraindicated in pregnancy, mainly because are live vaccines.

Vaccine	Note
MMR and V	Women should also be advised against the beginning of a pregnancy within 4 weeks after vaccination. Anyway, fetal malformations attributable to vaccination in pregnant women have not as yet been observed worldwide; for this reason, accidental immunization of a pregnant woman does not make necessary an abortion.
OPV (Sabin)	Contraindicated since there is an inactivated vaccine
BCG	Although no adverse effects have been observed following the BCG vaccination on the fetus, more studies are needed to demonstrate its safety.
Zoster (Oka/Merck strain)	

Legenda: MMR: measles-mumps-rubella combined vaccine; V: Varicella vaccine; OPV: oral poliovirus vaccine; BCG: Bacillus Calmette–Guérin vaccine.

could be transmitted. The risk of transmission of attenuated varicella-zoster virus (VZV) is negligible; transmission has been very rarely documented from immunized subjects with a post-vaccinal rash. For these reasons, contacts of susceptible pregnant women can be immunized against varicella. If a post-vaccinal rash occurs, any lesion should be covered and contacts with susceptible pregnant women should be reduced/avoided. Health workers with post-vaccinal rash should be excluded by any chance of contact with susceptible pregnant women.

Oral live poliovirus (OPV) vaccine

Being a live attenuated vaccine, it is contraindicated in pregnant women.

Bacillus Calmette-Guérin (BCG) vaccine

BCG vaccine should not be used in pregnancy. Although no adverse effects have been observed following the BCG vaccination on the fetus, more studies are needed to demonstrate its safety.[22]

Vaccinations to be administered during pregnancy with caution (Table 3)

As a general rule, for most of these vaccines, there is not any theoretical increased risk if administered to a pregnant woman. However, the low statistical power of the studies and the lack of enough data on the follow-up of infants, suggest the need for further monitoring and to avoid their use in pregnancy.

Hepatitis B (HBV) vaccine

HBV vaccine does not contain live attenuated virus; for this reason, pregnancy and breastfeeding should not be considered a contraindication to its use. Even if specific studies are quite limited, HBV vaccination of a pregnant woman is not related to any increased risk of negative outcomes in the fetus.[23] On the other hand, it should be considered that a HBV infection in a pregnant women could imply a severe disease for the woman and the risk of a chronic disease in the newborn.

All pregnant women should be evaluated for HBV surface antigen (HBsAg); women at high risk of acquiring this infection (intravenous drug addicts, cohabitants or sexual partners of a HBsAg positive subject) should receive a complete vaccinal cycle (3 doses) in any moment, followed by the evaluation of the immune response.[24]

Hepatitis A (HAV) vaccine

HAV vaccine contains inactivated virus and, as such, can be administered to a pregnant woman at risk of acquisition of this infection.[24] The immunization schedule foresees 2 doses; the 2nd dose should be done 6 months-1 year after the 1st one. For pregnant women not previously immunized for HBV, it is available a combined vaccine (HAV-HBV) that can be administered following a primary as well as an accelerated schedule. Primary schedule implies 3 doses (0, 1 and 6 months) without any booster; the accelerated schedule foresees 3 doses (0, 7, 21–30 days) and a booster dose (after 12 months).

Table 3. Vaccines to be administered with caution during pregnancy.

Vaccine	Why is not absolutely contraindicated	When could be administered
HBV	HBV vaccine does not contain live attenuated virus; for this reason, pregnancy and breastfeeding should not be considered a contraindication to its use	Women at high risk of acquiring this infection (intravenous drug addicts, cohabitants or sexual partners of a HBsAg positive subject) should receive a complete vaccinal cycle (3 doses) in any moment.
HAV	Inactivated vaccine can be administered to a pregnant woman at risk of acquisition of this infection	The immunization schedule foresees 2 doses; the 2nd dose should be done 6 months-1 year after the 1st one
HPV	Three recombinant HPV vaccines are available. It does not exist any risk (also of malformations), related to all 3 available vaccines, to the fetus following the accidental immunization of a pregnant woman.	If an accidental administration occurs, the immunization schedule should be completed after delivery
IPV (Salk)	Inactivated vaccine	The CDC states that this vaccine may be administered, accordingly to the recommended immunization schedule for adults, to pregnant women at risk of exposure to wild poliovirus (for example, stay in endemic geographical areas)
Meningococcus (polysaccharide or conjugate)	There are no contraindications both for conjugate and polysaccharide meningococcal vaccines	Meningococcal conjugate vaccines should be taken into account if the pregnant woman travels to high risk geographical areas, for post-exposure intervention or in case of an epidemic outbreak
Pneumococcus (polysaccharide or conjugate)	There are no contraindications both for conjugate and polysaccharide pneumococcal vaccines	No data are available on the use of 13-valent conjugated and 23-valent polysaccharide pneumococcal vaccines in pregnant women; for this reason, the administration of these vaccine should be avoided during pregnancy, except in cases of a clear need or if the benefits will outweigh the risks.

Legenda: HBV: hepatitis B vaccine; HBsAg: hepatitis B surface antigen; HAV: hepatitis A vaccine; HPV: human papillomavirus vaccine; IPV: inactivated poliovirus vaccine.

Human papillomavirus (HPV) vaccine

Nowadays, 2 recombinant HPV vaccines are available; quadrivalent HPV vaccine (qHPV) able to protect against HPV-16,

−18, −6 and −11, and bivalent vaccine (bHPV) able to protect agaisnt HPV-16 and −18. A new 9-valent HPV vaccine has recently been approved in Europe to prevent HPV-related pathologies sustained by HPV sub-types 16, 18, 31, 33, 45, 52, 58, 6 and 11.

HPV vaccine is not indicated in pregnancy; anyway, being this vaccine recommended also to women of childbearing age, it is possible that an immunized woman become pregnant after the start of the immunization cycle.[25] Some randomized clinical trials have shown that does not exist any risk (also of malformations), related to all 3 available vaccines, to the fetus following the accidental immunization of a pregnant woman. In any case, if an accidental administration occurs, the immunization schedule should be completed after delivery. No pregnancy test is required before immunization, and, in case of accidental administration in a pregnant woman, this does not make necessary an abortion.[26,27,28,29]

Inactivated poliovirus (IPV) vaccine

Even if no adverse events have been reported in pregnant women and in their newborns, this immunization should not be used in pregnancy. Anyway, the CDC states that this vaccine may be administered, accordingly to the recommended immunization schedule for adults, to pregnant women at risk of exposure to wild poliovirus (for example, stay in endemic geographical areas).[30]

Meningococcal vaccines

Available data of passive surveillance studies performed on conjugate and polysaccharide meningococcal vaccines do not support any adverse event related to their use in pregnancy. However, the low statistical power of such studies and the lack of adequate follow-up data in newborns suggest the opportunity to enhance our knowledge on this specific topic.[31]

There is no theoretical reason to suppose any adverse event in the mother and the child following the administration of any meningococcal vaccine in pregnancy; for this reason, pregnancy should not preclude vaccination, if indicated, with any meningococcal vaccine (Meningococcus B vaccine included). Meningococcal conjugate vaccines should be taken into account if the pregnant woman travels to high risk geographical areas, for post-exposure intervention or in case of an epidemic outbreak; the same vaccines could be used during breastfeeding.

Pneumococcal vaccines

Every year, around the world, at least one million children die of pneumococcal infections. The development of bacterial resistance to antibiotics is added to the difficulty in treating the disease and emphasizes the need for a more focused preventive approach. The pneumococcal vaccination during pregnancy could be a way to prevent pneumococcal disease during the first months of life, before the pneumococcal vaccine administered to the infant begins to induce protection. This could be a good theoretical approach. However, at present, the evidence of the effectiveness of maternal vaccination in the child protection against pneumococcal infections is insufficient.[32] No data are available on the use of 13-valent conjugated and 23-valent polysaccharide pneumococcal vaccines in pregnant women; for this reason, the administration of these vaccine should be avoided during pregnancy, except in cases of a clear need or if the benefits will outweigh the risks.[33,34,35]

Specific cases

Yellow fever (YF) vaccine

In respect to other live vaccine that should be avoided in pregnancy, YF vaccine could be used with precaution. Pregnant women should not be routinely immunized and trips to endemic areas should be postponed after delivery. If vaccination is required only on the basis of international requirements, but no real increased risk of infection does exist, it should be granted a temporary exemption certificate. If it is not possible to postpone the trip in high-risk areas, vaccination can be performed, because the small theoretical risk of vaccination is significantly offset by the higher risk of infection. The immunogenicity of the YF vaccine administered during pregnancy may be reduced. If a woman is inadvertently vaccinated during pregnancy or within 4 weeks before the same, it does not arise any specific indication of voluntary abortion.[36]

Rabies vaccine

It is not known if the rabies vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The vaccine must be given to a pregnant woman only if the potential benefits outweigh the risks. Pre-exposure immunization can be considered in pregnancy if a substantial risk of exposure exists. Taking into account the impact of rabies and the lack of evidence of any fetal damage following this immunization, pregnancy is not considered an absolute contraindication to the post-exposure use of rabies vaccine.[37]

Accordingly to CDC: "Rabies postexposure prophylaxis with rabies immune globulin and vaccine should be administered after any moderate or high-risk exposure to rabies; preexposure vaccine may be considered for travelers when the risk of exposure is substantial."

Japanese encephalitis (JE) vaccine

No controlled study evaluated the safety, immunogenicity and effectiveness of this vaccine in pregnant women. Preclinical studies in animals (rats) have not shown any kind of harm to the mother or the fetus.[38]

Pregnant or nursing women who must travel to areas where the risk of JE infection is high, should be immunized if the risk of contracting the disease is greater than the risks (often unknown) of vaccination for the woman, the fetus or the breastfed baby.[39]

Tickborne encephalitis (TBE) vaccine

An inactivated vaccine is available. The immunization schedule consists of 3 doses (0, 1–3 and 5–12 months) plus a booster dose 3 years after the 3rd dose; after the completion of the schedule, a booster dose is recommended every 5 years. The accelerated schedule consists of 3 doses (0, 14 days, 6–12 months) plus following boosters. For inactivated TBE

vaccine, data are insufficient for use in pregnancy and lactation. Therefore the vaccine should be administered during pregnancy and in women who are breastfeeding when it is considered urgent to achieve protection against TBE infection and after careful consideration of the risk/benefit ratio.[40]

Cholera vaccines

Since 2004, an inactivated vaccine that confers specific protection to Vibrio cholerae serogroup O1, but does not protect against serogroup O139 or other species of Vibrio has been authorized in Europe.[41] The vaccine contains the B subunit of cholera toxin and this confers cross-protection from diarrhea caused by Enterotoxigenic Escherichia coli (ETEC).[42] The vaccine is administered orally and the vaccination schedule consists of 2 doses to be taken one week apart. The vaccination series should be completed one week before potential exposure. Although scientific studies have not been performed to address this issue and are not even available data on reproductive toxicity in animals, literature reports that during a mass vaccination in Zanzibar, 196 women were given this vaccine without any statistically significant evidence of harmful effects caused by immunization during pregnancy.[43]

Typhoid vaccines

Two vaccines are available against typhoid, one live attenuated that is administered orally and one polysaccharide that contains the Vi capsular antigen and is administered intramuscularly. The primary vaccination with oral vaccine involves 3 capsules to be taken on alternate days and one hour before any meal. The antimalarial chemoprophylaxis may be initiated, if necessary, 3 days after the last dose of vaccine.[44] If chloroquine, mefloquine, pyrimethamine/sulfadoxine or atovaquone/proguanil are already in use, it is possible to administer the oral vaccine without interrupting the prophylaxis. The assumption of mefloquine should be separated at least 12 hours from any dose of oral vaccine. If antimalarial prophylaxis has already started with other drugs, the same should be suspended at least 3 days before using oral typhoid vaccine. Typhoid vaccines can be co-administered with other vaccines, even live ones. No specific data are available on the use of typhoid vaccines in pregnant women. The live attenuated vaccine is contraindicated in pregnancy because animal experimental studies have shown developmental delays. Vi polysaccharide vaccine should be given to a pregnant woman only if clearly needed; it should be better to administer the vaccine 2 weeks before any potential exposure.[44]

Breastfeeding and vaccination

Neither inactivated nor live attenuated vaccines administered during lactation affect safety of mothers or their children. Although live attenuated viruses can replicate in the immunized subjects, most of them are not excreted into breast milk. The OKA strain contained in varicella vaccine, for example, has not been found in human milk. Although the rubella virus may be excreted in breast milk, usually does not infect the child; anyway, if the infection occurs, it is well tolerated because the virus is attenuated. Vaccines containing inactivated, recombinant, subunit, polysaccharide or conjugate antigens, as well as toxoids, are not a source of any risk to mothers who are breastfeeding or to their children.[24]

In addition there is no evidence that immunization during lactation can negatively affect the maternal or infant immune response. In particular, although it has been speculated that the diminished response to live and attenuated oral vaccines (OPV and rotavirus) in infants in developing countries could be attributed to maternal Abs in breast milk, recent studies show that the cause would be attributable to malnutrition and other intestinal infections and breastfeeding appears indeed to be a protective factor.[45]

Breastfeeding is not a contraindication to influenza vaccination, with either TIV or QIV.[38]

Breastfeeding women can be immunized with dT, dTap, pneumococcal, meningococcal, hepatitis A, hepatitis B, IPV, rabies, typhoid, MMR, varicella and cholera vaccines, if necessary. The HPV vaccine can be used during lactation as well.[38]

The vaccine for Japanese Encephalitis (JE) during lactation has not been studied. Its administration to nursing women and who have to travel in high-risk areas for the disease should be considered only if the risk of getting the disease is higher than that (often unknown) to develop possible adverse effects of vaccination (for both mother and the fetus/newborn).[39]

There are some cases in which vaccination is not recommended during lactation. It has been documented the probable transmission of viral strain of yellow fever vaccine from a mother to her baby through breast milk. Therefore, nursing mothers should not generally be vaccinated against yellow fever, unless they have to travel in areas where the risk of transmission is high and protection against vectors is not possible.[38,46]

It is not known whether BCG vaccine is excreted in human milk. However, the CDC states that there are no risks for either the mother or for the child if the vaccine is administered to a woman during breastfeeding.[47]

Closing remarks

This work has reviewed current evidence-based recommendations for the implementation of maternal immunization. Despite administration of vaccines to pregnant women is not a routine event and it is generally preferred to administer vaccines either prior to conception or in the postpartum period, active immunization during pregnancy is a remarkably promising strategy for maternal and neonatal health benefits. Further research in vaccination during pregnancy is warranted for the safety of the pregnant women and their newborns.[48,49]

Abbreviations

Abs	antibodies
CDC	Centers for Disease Control and Prevention
USA	United States of America
ACIP	Advisory Committee on Immunization Practices
SAE	severe adverse event
dTap	tetanus-diphtheria-pertussis combined vaccine (adult formulation)
DTP	diphtheria-tetanus-pertussis combined vaccine (pediatric formulation)
dT	diptheria-tetanus combined vaccine (adult formulation)
IgG	immune globulins G

UK	United Kingdom
WHO	World Health Organization
flu	influenza
TIV	inactivated trivalent flu vaccine
QIV	inactivated quadrivalent flu vaccine
LAIV	live attenuated flu vaccine
MMR	measles-mumps-rubella combined vaccine
V	varicella
VZV	varicella-zoster virus
OPV	oral poliovirus vaccine
BCG	Bacillus Calmette–Guérin vaccine
HBV	hepatitis B
HBsAg	hepatitis B surface antigen
HAV	hepatitis A
HPV	human papillomavirus
qHPV	quadrivalent HPV vaccine
bHPV	bivalent HPV vaccine
IPV	inactivated poliovirus vaccine
YF	yellow fever
JE	Japanese encephalitis
TBE	tickborne encephalitis
ETEC	Enterotoxigenic Escherichia coli

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