Review Article

Vaccination in Pregnancy

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Summary

<u>Background:</u> Vaccination during pregnancy can protect both the expecting mother and the unborn and newborn child from infectious diseases.

<u>Methods:</u> This review is based on publications retrieved by a selective literature search on the immunological particularities of infectious diseases affecting pregnant women, unborn children, and neonates, with particular attention to the guidelines of the German Standing Committee on Vaccinations (Ständige Impfkommission, STIKO) and the pertinent guidelines.

Results: Vaccination during pregnancy protects the expecting mother from a severe course of a number of different infectious diseases. Vaccination with inactivated vaccines against influenza, tetanus, and pertussis is effective, safe, and well tolerated. Women who are pregnant or of child-bearing age should be immunized against tetanus according to the STIKO recommendations. All pregnant women from the second trimester onward should receive an inactivated quadrivalent influenza vaccine. The immunity acquired after vaccination with an acellular pertussis vaccine is present only for a limited time. In a cohort study involving 72,781 pregnant women, pertussis vaccination during pregnancy was found to yield 91% protection against pertussis for their subsequently born children in the first three months of life. Further types of vaccine can also be given during pregnancy if indicated. Additional reasonable measures to protect the health of mother and child include the vaccination of other persons in close contact as well as the closure of relevant vaccination gaps among young adults, particularly women of child-bearing age. Treating physicians play a crucial role in encouraging vaccine acceptance by their patients.

<u>Conclusion:</u> Maternal immunization is a safe and effective strategy for giving neonates passive immune protection against life-threatening infections by the vertical transmission of maternal antibodies until they are able to build up their own adaptive immunity.

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ue to specific features of their immune system, pregnant women, fetuses and newborns are particularly susceptible to infectious diseases, including vaccination-preventable diseases which are associated with significant morbidity and mortality. Vaccination in pregnancy can protect pregnant women as well as their unborn and newborn children against infectious diseases. Physicians involved in their care play a key role in the efforts to increase vaccination acceptance.

This article discusses the mechanism of action, the evidence related to the expected effects, contraindications, and potential side effects of vaccination in pregnancy. This review is based on pertinent publications retrieved from a selective literature search with special consideration of the current recommendations of the German Standing Committee on Vaccination (STIKO, Ständige Impfkommission).

Special features of the immune system in pregnancy

Immune tolerance to the semiallogeneic fetus by the maternal immune system is a key requirement for a successful pregnancy. The complex adaptive changes needed to create this tolerance increase the risk of a severe course of an infectious disease, for example of influenza, even in immunocompetent pregnant women (1–3). The fetus is at risk for infection-related diseases acquired in utero or perinatally (4). In general, pregnant women are as capable of mounting an immune response to natural infections and vaccinations as nonpregnant women (5). However, increasing levels of the sex hormones estradiol and progesterone result in changes in the equilibrium of pro-inflammatory and anti-inflammatory reactions which varies over the course of pregnancy (1). As a consequence, more antibodies are formed, while the specific T cell-mediated maternal protection, which is directed against cells infected by a virus, wanes (2, 5, 6).

The placenta is an immunologically active organ capable of interacting with pathogens and modulating the maternal immune response (1). Trophoblast cells are resistant to infection by a variety of viruses and are able to transfer this resistance to other cells via paracrine signaling (7). In addition, a significant transfer of immunoglobulin G (IgG) from the maternal blood to the fetus occurs by means of transcytosis. The active transplacental IgG transfer starts at 13 weeks' gestation and continues to increase over the course of pregnancy. The largest portion of antibodies is received by the fetus during the last four weeks of pregnancy (8).

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Congenital viral syndromes	Rubella* ¹ Varicella* ¹	Maternal antibodies/passive immunity due to: Standard vaccinations for infants Preconceptional vaccination of women of childbearing potential in case of gaps in the vaccination status
Chronic disease by vertical transmission	Hepatitis B	 Standard vaccination of infants Catch-up vaccination up to age 17 years Preconceptional vaccination of adult women in risk groups*² Vaccination in pregnancy, if required
Risk of severe maternal in-	Influenza	Vaccination in pregnancy
fection	Varicella* ¹ Measles* ¹	Standard vaccination of women during infancy Preconceptional vaccination of women of childbearing potential with gaps in the vaccination status
Risk to newborns from exposure to infections in their environment	Pertussis/influenza	Vaccination in pregnancy
	Measles*1	Maternal antibodies/passive immunity due to:
	Pertussis (measles, influenza)	Cocoon strategy/environment: Indication vaccinations and closure of gaps in the vaccination status of household contacts

 $^{^{\}star 1}$ Live vaccination \rightarrow robust immune response, long-term protection

The immunological status of newborns and infants

Due to the functional immaturity of the adaptive immune system, the newborn's immune system characteristically lacks reactivity to multiple (including non-pathogenic) microorganisms in order to prevent excessive inflammatory responses (9). The placental transfer of maternal immunoglobulins to the fetus is a specific adaptation mechanism, compensating to a certain degree for the newborn's deficits in antibody production during the first months postpartum and providing newborns and infants with temporary passive immunity. In addition, when breastfeeding, secretory IgA antibodies and other immunologically active substances in breast milk are passed to the suckling infant (e1). According to the STIKO immunization schedule, active immunization of infants starts at the age of two months.

Goals of vaccination in pregnancy, vaccines and principles of administration

Protection against the effects of vaccinationpreventable infectious diseases on female reproductive health and on the health of their offspring requires timely administration of the recommended standard vaccines from birth as well as avoidance of gaps in the vaccination status of women of childbearing potential (10) (*Tables 1 and 2*). Active immunizations during pregnancy are intended to provide direct individual protection against the corresponding infectious disease and its adverse effects on the course of pregnancy as well as optimum passive immunity for the newborn and young infant.

Monovalent and multivalent live vaccines and inactivated vaccines are available for immunization. Live vaccines contain attenuated viruses or bacteria which typically do not cause illness in immunocompetent vaccinated persons. Immunization requires multiplication of these pathogens in the vaccinated person. Live attenuated vaccines are contraindicated in pregnancy because the vaccine virus could spread to the unborn child and, theoretically, put the fetus at risk. After vaccination with live vaccine, pregnancy should be avoided for one month. However, accidental vaccination in early pregnancy is not an indication for termination of pregnancy. Based on vaccinationrelated adverse event data from surveillance programs (11) and a systematic review of epidemiological studies including more than 3500 documented vaccinations with monovalent rubella, measles-rubella and measles-mumps-rubella (MMR) vaccines, no case of rubella embryopathy related to the vaccine virus was identified (e2). As a rule, live vaccines can be administered to breastfeeding women; however, after yellow fever vaccination of nursing mothers, isolated cases of meningoencephalitis have been reported among breastfed infants (e3).

Inactivated vaccines contain inactivated pathogens, immunogenic components of pathogens or detoxified bacterial toxins (toxoids). Some of these vaccines are less immunogenic than live attenuated vaccines and typically require booster vaccinations for lasting

^{12 1.} People in whom a severe course of hepatitis B is expected because of an existing or expected immune deficiency or suppression or due to an existing disease, e.g., patients infected with HIV and/or hepatitis C, dialysis patients

People with an increased non-occupational exposure risk, e.g., through contact with HBsAg carriers in the family/living community, through sexual behavior with high risk of infection, intravenous drug consumers, detainees and prisoners, potentially patients in psychiatric institutions (see Epidemiological Bulletin 34/2020. Tab. 2).

TABLE 2						
Vaccination recom	Vaccination recommendations for women with regard to vaccination-preventable diseases with impact on pregnancy-associated health of the mother and/or child*	l to vaccination-preventable dis	seases with impact on pr	egnancy-associated health of	the mother and/or	child*
Vaccination-pre- ventable disease	Cause of the pregnancy-associated risk for the mother and/or child	Disease in pregnant women	Risk to the unborn child	Risk to the young infant	Vaccine type	STIKO vaccination recommendation for pregnant women
Influenza	Pregnancy-induced changes in immune response and cardiopulmonary adaption; lack of passive immunity	Pneumonia with severe course in pregnancy (especially in the second and third trimester), increased risk of hospital- ization, need of intensive care treatment, death	Abortions, preterm births and stillbirths	Increased complication, hospitalization and mortality rates among infants aged <6 months	Inactivated split virus vaccines or subunit vaccines	Vaccination with a quadrivalent IIV with current, WHO-recommended antigen combination for all pregnant women from second trimester, in case of increased health risk due to an underlying disease from first trimester
Pertussis	Missing or low passive immunity in infants	Not influenced by pregnancy	Dependent on the severity of the maternal disease	Increased risk of serious complications, hospitalization, death in newborns and infants aged < 6 months	Inactivated combination vaccine (Tdap, Tdap-IPV)	Vaccination in each pregnancy between WG 28 and 32; if increased risk of preterm delivery, in the second trimester
Measles	First infection in pregnancy; lack of passive immunity	Potentially increased complication rate in pregnancy (pneumonia, hepatitis, encephalitis; anecdotal case reports)	Potentially increased risk of abortions and preterm births (anecdotal case reports)	Neonatal measles, increased risk of complications and SSPE (especially with early postnatal disease)	Live attenuated vaccine (MMR)	Contraindicated in pregnancy
Rubella	Vertical transplacental transmission	Not influenced by pregnancy	Spontaneous abortion, preterm birth, stillbirth	Congenital rubella syndrome (malformations), developmental disorders, late sequelae	Live attenuated vaccine (MMR)	Contraindicated in pregnancy
Varicella	First infection in pregnancy; vertical transplacental transmission	Complicated by varicella pneumonia, severe course in pregnancy (anecdotal case reports)	Spontaneous abortion, stillbirth (anecdotal case reports)	Congenital varicella syndrome/ embryofetopathy with skin changes, neurological, ocular and skeletal anomalies, as well as other malformations; neonatal varicella with severe course and high mortality in case of peripartum infection	Live attenuated vaccine	Contraindicated in pregnancy

*Adapted from (2, 10, 40)
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*IV, inactivated polio vaccine; MMR, measles-mumps-rubella; SSPE, subacute scierosing panencephalitis, WG, weeks' gestation; STIKO, Standing Committee on Vaccination; WHO, World Health Organization

immunity. Provided they are not very reactogenic, inactivated vaccines are considered safe for pregnant women and the fetus (12). During the first trimester of pregnancy, only urgently indicated vaccinations should be performed in order to avoid that spontaneous abortions, which commonly occur in this period, are perceived as vaccination-related.

Vaccination in pregnancy: Tetanus

The most extensive experience with maternal immunization has been made with tetanus vaccination. By immunizing pregnant women or women of childbearing potential with at least two doses of tetanus toxoid, neonatal tetanus mortality was reduced by 94% (95% confidence interval [80; 98]) (13). In Germany, less than 15 cases per year have been recorded in the last years, most of which were older adults (e4).

Vaccination in pregnancy: Influenza

Due to the impaired maternal immune defense to viral pathogens and the physiological pregnancy-related changes in the cardiopulmonary system (increase in stroke volume and oxygen consumption, decrease in lung volume), which increase over the course of pregnancy, influenza is associated with an increased risk of pneumonia in pregnant women (2, 3, 6, 14). In a case-control study covering 17 influenza seasons, more than 4300 women of childbearing potential hospitalized for influenza or pneumonia were compared to a control group of almost 22 000 women. The risk of hospitalization was found significantly increased in pregnant women; the odds ratio (OR) increased from 1.44 [0.97; 2.15] in women between 14 and 20 weeks' gestation to 4.67 [3.42; 6.39] in women between 37 and 42 weeks' gestation (15).

An analysis of the data of 17 548 022 hospitalized pregnant women from a nationwide US hospital database, covering ten influenza seasons, found that pregnant women with respiratory symptoms were at an increased risk of preterm delivery (adjusted OR [aOR] 3.82 [3.53; 4.14]), cesarean delivery (aOR 3.47 [3.22; 3.74]) and stillbirth (aOR 2.50 [1.97; 3.18]) (16). Furthermore, newborns and infants contracting an influenza infection during the first six months of life have an increased risk of complications such as fever (febrile convulsion), severe generalized disease, and the highest annual incidence of influenza-related deaths in children (17). Influenza vaccines approved in Germany are only to be used in children aged six months and older.

According to STIKO recommendations, all pregnant women should receive an inactivated quadrivalent vaccine with the current antigen combination, as recommended by the World Health Organization (WHO), from the second trimester—in case of increased health risks due to an underlying condition already from the first trimester. Even though some studies found reduced immunogenicity in pregnant women, there is no evidence of reduced clinical efficacy (5).

Studies evaluating maternal and infant endpoints showed that the influenza vaccination is safe, well tolerated and effective (18–20); here, it should be taken into account that in general the effectiveness of influenza vaccines varies greatly between seasons. According to calculations by the Centers for Disease Control and Prevention (CDC), influenza vaccine efficacy with regard to preventing laboratory-confirmed, influenza-related medical consultations was between 20% and 60% (median 48%) between 2009 and 2019 for all age groups (e5).

A randomized, double-blind, placebo-controlled study from 2011 and 2012 showed a vaccine efficacy against laboratory-confirmed influenza of 50.4% [14.5; 71.2] for HIV-negative pregnant women and of 48.8% [11.6; 70.4] for their infants up to an age of 24 weeks; vaccine efficacy in HIV-positive pregnant women was 57.7% [0.2; 82,1] (18).

In a retrospective cohort study, the number of preterm births among pregnant women vaccinated in the influenza season was significantly reduced (aOR 0.60 [0.38; 0.94]) (19). A large cohort study found 70% fewer cases of influenza-like illness (relative risk [RR] 0.30 [0.19; 0.46]) and 81% fewer hospitalizations (RR 0.19 [0.06; 0.60]) among infants aged six months or under of vaccinated mothers (20).

Vaccination in pregnancy: Pertussis

The gram-negative rod bacterium Bordetella pertussis is responsible for causing whooping cough. It is transmitted by airborne droplets and highly contagious. With an annual incidence between 10 and 40 cases per 100 000 population, pertussis is a common infectious disease, typically taking several weeks to months to clear (21). Pertussis primarily affects children and adolescents, but is often diagnosed in adults too.

The immunity achieved with acellular pertussis vaccine is only temporary; however, even pertussis infection does not leave lifelong immunity. Frequently, long-lasting mild cough is the only symptom observed in infected adolescents and adults. They are the most common source for the transmission of Bordetella pertussis to unvaccinated infants. Between 2014 and 2018, the adjusted mean incidences of pertussis and pertussis-related hospitalization during the first three months of life were 111.3 and 70.1 of 100 000 infants, respectively (22). Of the hospitalized infants, up to 61% can experience apnea, 23% pneumonia, about 1% seizures, and 0.3% encephalopathy (23)

In March 2020, the STIKO decided to recommend pertussis vaccination for every pregnancy. The safety evaluation was based on three randomized controlled trials and eleven non-randomized studies with a total study population of 1.4 million pregnant women. The efficacy was determined based on four cohort studies and four case-control studies with a total study population of 855 546 mother-child pairs. The assessed safety endpoints were fever \geq 38 °C, preeclampsia, chorioamnionitis, preterm birth, and stillbirth, low

fficacy endpoints	Study design, population and vaccine efficacy			NNV (= 1/[incidence*VE]) based on: - The mean incidence from 2014 to 2018 - The high-incidence year 2017
aboratory-confirmed vertussis in infants iged 0 to 3 months	Cohort study Cohort study Case-control study Case-control study		VE 91% [84; 95] VE 91% [88; 94] VE 91% [57; 98] VE 69% [13; 89]	987 (mean incidence) 716 (high-incidence year 2017) Calculation basis VE 91%
aboratory-confirmed pertussis-related oppitalization in infants ged 0–2 and 0–3 months, respectively	Case-control study Case-control study (age ≤ 2 months)	n = 74; n = 6252	VE 94% [59; 99] VE 91% [65; 97]	1 518 (mean incidence) 1 021 (high-incidence year 2017) Calculation basis VE 94%
boratory-confirmed pertussis-related aths ed 0 to 3 months	Cohort study	n = 243;	VE 95% [79 ; 100]	

^{*} Adapted from (22, appendix)

NNV, number needed to vaccinate; VE, vaccine efficacy

birth weight, congenital malformations, as well as intensive care treatment, sepsis and death of newborns within seven and 28 days postpartum, respectively.

The vaccination is generally well tolerated. Six additional cases of fever after vaccination per 100 000 vaccinated women are to be expected. According to the results of a UK cohort study with 72 781 pregnant women, pertussis vaccination in pregnancy protects infants aged three months or under against pertussis in 91% of cases (24). A case-control study with 6252 pregnant women found a vaccine efficacy against pertussis-related hospitalization in infants aged two months or under of 91% (25) (*Table 3*).

Pertussis vaccines are not monovalent but only available as combination vaccines (together with tetanus toxoid [T] and reduced diphtheria toxoid [d] as the Tdap vaccine or with additional inactivated polio vaccine (IPV) component as the Tdap-IPV vaccine). According to the STIKO recommendation, every pregnant women should be vaccinated against pertussis using the Tdap(-IPV) vaccine during the gestational weeks 28 to 32—those at an increased risk of preterm birth should already be vaccinated in the second trimester. If a mother did not receive the vaccination in pregnancy, she should preferentially be vaccinated in the first days after giving birth. The incidence of vaccination-related side effects did not increase if the Tdap vaccine was repeated when a minimum interval of four weeks to the previous Td vaccination was observed (26, 27). Likewise, the co-administration of influenza vaccine, which is also recommended in pregnancy, is not associated with an increased risk of side effects (28).

According to the STIKO recommendations, close household contacts of the newborn should also receive a dose of pertussis vaccine, ideally up to four weeks prior to the birth of the child, if they have not been vaccinated against pertussis in the last ten years.

In most women vaccinated prior to pregnancy, antibody titers are too low to afford optimum protection of the newborn by placental transmission of antibodies (29, 30). By contrast, vaccination of pregnant women with an ap-containing vaccine resulted in high levels of antibodies in the blood of the expectant mothers and the newborns (31).

Since after maternal immunization the desired, passively transferred maternal antibodies against pertussis are present at the time of the first pertussis vaccination of infants, these could temporarily affect the serologically detectable immune response of the vaccinated infants. After the fourth dose of a DTaP-containing vaccine, however, most studies found no significant differences between the antibody levels measured in children of vaccinated compared to unvaccinated mothers (23).

Vaccination in pregnancy: Hepatitis B

Globally, hepatitis B (HB) is one of the most common viral diseases. In Germany, altogether 4507 cases of hepatitis B were reported in 2018, including five infections among children aged one year or under (e6). Vertical transmission from the typically chronically infected mother to the child is the primary cause of viral hepatitis B in infected children (32); if the virus is contracted perinatally, the infection takes a chronic course in about 90% of the affected children (e7). Of the patients with chronic HBV infection, 20 to 30% later develop liver cirrhosis and/or liver cancer (33).

In order to reduce the risk of perinatal transmission, screening for HBsAg should be performed after 32 weeks' gestation according to the maternity guideline of the German Federal Joint Committee (G-BA, Gemeinsamer Bundesausschuss). In case of a positive screening result, simultaneous active and passive immunization of the newborn is initiated within twelve hours after delivery. With this

approach, vertical HBV transmission can almost always be prevented in newborns of mothers with low-level viremia in pregnancy, while in mothers with high-level viremia the transmission rate can be reduced significantly (34).

Measures to improve vaccination acceptance

Despite the evidence in support of the benefits for mother and child as well as the safety and efficacy of vaccination in pregnancy, the currently data available show a rather low acceptance of vaccination in pregnancy. The seasonal influenza vaccination rates in pregnancy were at just above 10%, based on nationwide outpatient claims data of statutory health insurance physicians for the years 2009 to 2015 (35). In a survey by the Robert Koch Institute (RKI), however, 41% of the surveyed pregnant women stated that they would get vaccinated in pregnancy against pertussis, if this vaccination was recommended by STIKO (36).

Physicians play a key role in the communication of vaccination-related information. In a survey of women after delivery, personal recommendation of vaccination against seasonal influenza by a gynecologist/obstetrician was stated as the most important reason for making the decision to get this vaccination (37). Vilca and Esposito (38) also highlight the critical role of gynecologists/obstetricians especially with regard to vaccination in pregnancy and recommend to routinely integrate maternal immunization in prenatal care

In a study conducted by the Robert Koch Institute (39), 87% of the surveyed community-based gynecologists stated that they would want to vaccinate their patients during pregnancy if this is recommended by the STIKO. 95.2% of the gynecologists regarded the inclusion of the STIKO-recommended vaccinations for pregnant women in the maternity guideline and the documentation in the German maternity record ("Mutterpass") for a suitable measure to improve vaccination rates in pregnancy.

Vaccinations before and during pregnancy will continue to gain importance in the future. Currently, new vaccines to protect unborn and newborn children from infection with respiratory syncytial virus, group B streptococcus, herpes simplex virus, and cytomegalovirus are being developed (e8).

Maternal immunization is a safe and effective strategy to provide young infants with passive immunoprotection against life-threatening infections by means of vertical transmission of maternal antibodies until they have established adaptive immunity of their own. Further useful measures to protect the health of mother and child include timely administration of the recommended standard vaccinations starting from birth, the vaccination of close contacts (cocoon strategy) as well as closing relevant immunization gaps in young adults, especially in women of childbearing potential.

Key messages

- Infection-related morbidity and mortality are increased in pregnant women, fetuses and infants due to special features of the immune system in these groups.
- The goals of vaccination in pregnancy are, on the one hand, to directly protect the
 pregnant woman by active immunization and, on the other hand, to indirectly protect
 fetuses, newborns and young infants by providing passive immunity conferred by
 transplacentally transmitted antibodies.
- The efficacy and safety of vaccination in pregnancy is well established for inactivated vaccines against tetanus, influenza and pertussis; vaccinations with live attenuated vaccines are contraindicated due to theoretical risks for the fetus.
- For their own protection and that of the child, pregnant women should not be excluded from an indicated vaccination; the expectant mother's interest in the health of her future child should be adequately taken into account.
- Future regular documentation of STIKO-recommended vaccinations in the maternity record could increase vaccination awareness both in pregnant women and among doctors and midwifes, strengthen the key communicative role of gynecologists, and increase vaccination acceptance.

Conflict of interest statement

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Prof. Liese received consultancy fees from GSK, Pfizer, Sanofi-Pasteur, and MSD. He received honoraria for conducting contract clinical trials for GSK and Pfizer.

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References

- Mor G, Aldo P, Alvero AB: The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol 2017; 17: 46.
- Kourtis AP, Read JS, Jamieson DJ: Pregnancy and infection. N Engl J Med 2014: 370: 2211–8.
- 3. Raj RS, Bonney EA, Phillippe M: Influenza, immune system, and pregnancy. Reprod Sci 2014; 21: 1434–51.
- Neu N, Duchon J, Zachariah P: TORCH infections. Clin Perinatol 2015: 42: 77–103.
- 5. Omer SB: Maternal immunization. N Engl J Med 2017; 376: 1256-67.
- Memoli MJ, Harvey H, Morens DM, Taubenberger JK: Influenza in pregnancy. Influenza Other Respir Viruses 2013; 7: 1033–9.
- Delorme-Axford E, Donker RB, Mouillet JF, et al.: Human placental trophoblasts confer viral resistance to recipient cells. Proc Natl Acad Sci USA 2013; 110: 12048–536.
- Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M: IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol 2012; 2012: 985646.
- Ulas T, Pirr S, Fehlhaber B, et al.: S100 alarmin-induced innate immune programming protects newborn infants from sepsis. Nat Immunol 2017; 18: 622–32.
- Röbl-Mathieu M: Impfungen bei Frauen mit Kinderwunsch. Umwelt Hygiene – Arbeitsmed 2018; 23: 301–10.
- Keller-Stanislawski B, Englund JA, Kang G, et al.: Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. Vaccine 2014; 32: 7057

 –64.
- 12. Munoz FM, Jamieson DJ: Maternal immunization. Obstet Gynecol 2019; 133: 739–53.
- Blencowe H, Lawn J, Vandelaer J, Roper M, Cousens S: Tetanus toxoid immunization to reduce mortality from neonatal tetanus. Int J Epidemiol 2010; 39: i102–i9.

- 14. Rasmussen SA, Jamieson DJ, Bresee JS: Pandemic influenza and pregnant women. Emerg Infect Dis 2008; 14: 95–100.
- Neuzil KM, Reed GW, Mitchel EF et al.: Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998: 148: 1094–102.
- Cox S, Jamieson DJ, Whiteman MK, et al.: Respiratory illness hospitalizations among pregnant women during influenza season 1998–2008. Matern Child Health J 2013: 17: 1325–31.
- Shang M, Blanton L, Brammer L, et al.: Influenza-associated pediatric deaths in the United States 2010–2016. Pediatrics 2018; 141: e20172918.
- Madhi SA, Cutland CL, Kuwanda L, et al.: Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014; 371: 918–31.
- Omer SB, Goodman D, Steinhoff MC, et al.: Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. Plos Med 2011; 8: e1000441
- Shakib JH, Korgenski K, Presson AP, et al.: Influenza in infants born to women vaccinated during pregnancy. Pediatrics 2016; 137: e20152360.
- Liese JG, Heininger U, Hellenbrand W, Riffelmann M: Pertussis. In: DGPI Handbuch – Infektionen bei Kindern und Jugendlichen. 6th edition. Stuttgart-New York: Georg Thieme 2013; 434–39.
- AG Pertussis der Ständigen Impfkommission (STIKO): Wissenschaftliche Begründung für die Empfehlung der Pertussisimpfung mit einem Tdap-Kombinationsimpfstoff in der Schwangerschaft. Epid Bull 2020; 13: 3–34
- 23. Liese J. Pertussis. In: DGPI Handbuch Infektionen bei Kindern und Jugendlichen. Stuttgart: Georg Thieme; 2018: 669–75.
- Amirthalingam G, Campbell H, Ribeiro S, et al.: Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. Clin Infect Dis 2016; 63: 236-43.
- Skoff TH, Blain AE, Watt J, et al.: Impact of the US maternal tetanus, diphtheria, and acellular pertussis vaccination program on preventing pertussis in infants < 2 months of age: A case-control evaluation. Clin Infect Dis 2017;65: 1977–83.
- Beytout J, Launay O, Guiso N, et al.: Safety of tdap-lpV given one month after td-lpVbooster in healthy young adults: a placebocontrolled trial. Hum Vaccin 2009; 5: 315–21.
- Fortner KB, Swamyb GK, Broderc KR, et al.: Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women. Vaccine 2018; 36: 6354–60.
- Sukumaran L, McCarthy NL, Kharbanda EO, et al.: Safety of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis and influenza vaccinations in pregnancy. Obstet Gynecol 2015; 126: 1069–74.

- Healy CM, Munoz FM, Rench MA, Halasa N, Edwards KM, Baker CJ: Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis 2004: 190: 335–40.
- Shakib JH, Ralston S, Raissy HH, Stoddard GJ, Edwards KM, Byington CL: Pertussis antibodies in postpartum women and their newborns. J Perinatol 2010; 30: 93–7.
- 31. Gall SA, Myers J, Pichichero M: Maternal immunization with tetanus–diphtheria–pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol 2011; 204: 334.e1–e5.
- Chen HL, Lin LH, Hu FC, et al.: Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology 2012; 142: 773–81.
- Von Laer A, Simeonova Y, Harder T, Zimmermann R, Dudareva-Vizule S: Virushepatitis B und D im Jahr 2016. Epid Bull 2017; 31: 297–308.
- Lee C, Gong Y, Brok J, Boxall EH, Gluud C: Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database Syst Rev 2006: CD004790.
- 35. Bätzing-Feigenbaum J, Schulz M, Dammertz L, Goffrier B: Impfung gegen saisonale Influenza in der Schwangerschaft gemäß STIKO-Empfehlung – Analyse anhand von Schwangerschaftskohorten 2010 bis 2014. Zentralinstitut für die kassenärztliche Versorgung in Deutschland (Zi). Versorgungsatlas-Bericht Nr. 17/06. Berlin 2017
- Bödeker B, Walter D, Reiter S, Wichmann O: Cross-sectional study on factors associated with influenza vaccine uptake and pertussis vaccination status among pregnant women in Germany. Vaccine 2014; 32: 4131–9.
- Blanchard-Rohner G, Meier S, Ryser J, et al.: Acceptability of maternal immunization against influenza: the critical role of obstetricians. J Matern Fetal Neonatal Med 2012; 25: 1800–9.
- 38. Vilca ML, Esposito S: The crucial role of maternal care providers as vaccinators for pregnant women. Vaccine 2017; 36: 5379–84.
- Böhm S, Röbl-Mathieu M, Scheele B, Wojcinski M, Wichmann O, Hellenbrand W: Influenza and pertussis vaccination during pregnancy – attitudes, practices and barriers in gynaecological practices in Germany. BMC Health Serv Res 2019; 19:616.
- 40. Volz-Zang C: Sicherheit von Impfungen während der Schwangerschaft. Bulletin zur Arzneimittelsicherheit 2014; 4: 16–20.

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► Supplementary material

eReferences:

www.aerzteblatt-international.de/m2021.0020

Questions on the article in issue 15/2021:



Vaccination in Pregnancy

The submission deadline is 15 April 2022. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

During pregnancy, a significant amount of antibodies is transferred from maternal blood to the fetus. To what class of immunoglobulins do these antibodies belong?

- a) Class A
- b) Class M
- c) Class E
- d) Class D
- e) Class G

Question 2

Which vaccination is contraindicated in pregnancy?

- a) Hepatitis B
- b) Influenza
- c) Diphtheria
- d) Varicella
- e) Tetanus

Question 3

According to STIKO recommendations, what is the best time period in pregnancy for pertussis vaccination with Tdap(-IPV)?

- a) Prior to conception
- b) Within the first 12 weeks' gestation
- c) At 28-32 weeks' gestation
- c) At 32-36 weeks' gestation
- e) On the day of delivery, during the first contractions

Question 4

According to the maternity guideline of the German Federal Joint Committee (G-BA), screening for hepatitis B antigens (HBsAg) is performed after 32 weeks' gestation. What measures should be taken if the test result is positive?

- a) Active immunization of the mother between 36 and 38 weeks' gestation
- b) Passive immunization of the mother between 36 and 38 weeks' gestation
- c) Initiation of passive immunization of the newborn within 12 hours postpartum
- c) Initiation of active and passive immunization of the newborn within 12 hours postpartum
- e) Initiation of passive immunization of the mother during delivery (placental transmission)

Question 5

What is the vaccine efficacy (VE) of pertussis vaccination in pregnancy with regard to pertussis-related hospitalization in a case-control study (more than 6000 cases) with infants aged 0-2 months?

- a) 68 %
- b) 73%
- c) 79%
- d) 85%
- e) 91%

Question 6

In pregnancy, the immune system of the woman undergoes complex adaptive changes. What are the implications for the immune response?

- a) An immune response to viral infection cannot be mounted.
- b) There is increased formation of antibodies.
- c) The strength of T-cell-mediated protection increases.
- d) Vaccination-induced immunity from the period before pregnancy loses its effect.
- e) Immunity conferred by antibodies and T cells increases in strength.

Question 7

Which type of vaccine is contraindicated in pregnancy?

- a) Inactivated combination vaccine
- b) Subunit vaccine
- c) Live attenuated vaccine
- d) Split vaccine
- e) Inactivated combination vaccine

Question 8

At what time does the active process of transplacental secretion of antibodies start?

- a) At 6 weeks' gestation
- b) At 13 weeks' gestation
- c) At 16 weeks' gestation
- c) At 17 weeks' gestation
- b) At 22 weeks' gestation

Question 9

What is the annual incidence of pertussis in Germany?

- a) 10-40 per 100 000 population
- b) 5-10 per 100 000 population
- c) 40-60 per 100 000 population
- d) 0-5 per 100 000 population
- b) 60-75 per 100 000 population

Question 10

In addition to passive immunity, the newborn can be protected against specific diseases by vaccination of contacts (cocoon strategy). For which vaccination-preventable disease is this strategy particularly recommended?

- a) Tetanus
- b) Influenza
- c) FSME
- d) Pertussis
- e) Pneumococcal disease

Supplementary material to:

Vaccination in pregnancy

by Marianne Röbl-Mathieu, Ariane Kunstein, Johannes Liese, Thomas Mertens, and Michael Wojcinski

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eReferences

- e1. Rouw E, von Gartzen A, Weißenborn A: Bedeutung des Stillens für das Kind. Bundesgesundheitsblatt 2018; 61: 945–51.
- e2. Mangtani P, Evans SJW, Lange B, et al.: Safety profile of rubella vaccine administered to pregnant women: a systematic review of pregnancy related adverse events following immunisation, including congenital rubella syndrome and congenital rubella infection in the foetus or infant. Vaccine 2020; 38: 963–78.
- e3. Imbert P, Moulin F, Mornand P, Mechai F, Rapp C: Should yellow fever vaccination be recommended during pregnancy or breastfeeding? Med Trop (Mars) 2010; 70: 321–4.
- e4. Robert Koch-Institut: DOI 10.17886/EpiBull-2016–47 https://edoc.rki.de/handle/176904/2362.
- e5. Wei CJ, Crank MC, Shiver J et al.: Next-generation influenza vaccines: opportunities and challenges. Nat Rev Drug Discov. 2020; 19: 239–52.
- e6. Robert Koch-Institut. Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten für 2018, Berlin 2019, ISBN: 978–3–89606–297–0. DOI: 10.25646/5978.
- e7. Fattovich G, Bortolotti F, Donato F: Natural history of chronic hepatitis B: Special emphasis on disease progression and prognostic factors. J Hep 2008; 48: 335–52.
- Vojtek I, Dieussaert I, Doherty TM, et al.: Maternal immunization: where are we now and how to move forward? Ann Intern Med 2018; 50: 193–208.