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Review

Vaccines and pregnancy: Past, present, and future

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S U M M A R Y

Vaccination during pregnancy with certain vaccines can prevent morbidity and mortality in pregnant women and their infants. However, previous recommendations often focused on the potential risks of vaccines to the fetus when used during pregnancy. In recent years, additional data have become available on the absence of increased risks for adverse events associated with vaccines when administered during pregnancy and on their benefits to mothers and infants. Currently two vaccines – (i) inactivated influenza, and (ii) tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) – are recommended for use by all pregnant women by the United States Advisory Committee on Immunization Practices. Here we review the history of vaccination during pregnancy, the current status of recommendations for vaccination during pregnancy in the USA, and the potential for future advances in this area, including key barriers that must be overcome to accommodate these advances.

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1. Introduction

Vaccinations have had a substantial impact on decreasing morbidity and mortality in the USA and the world, and because of this impact, vaccinations are considered one of the top ten public health achievements in the twentieth century [1]. Vaccination during pregnancy has the potential to protect not only the mother, who may be at increased risk of morbidity and mortality from infectious disease, but also her infant through maternal antibodies that are transferred across the placenta during the second half of pregnancy. In addition, mothers vaccinated during pregnancy are less likely to transmit an infection to their infant after birth. Because of their immature immune systems, young infants are often particularly vulnerable to infectious diseases, and their ability to mount an immune response to vaccinations is often inadequate [2]. Past discussions regarding the use of vaccines during pregnancy often focused on potential risks to the infant, rather than on their benefits. In recent years, data have accumulated on the benefits of certain vaccines to infants when given to their mothers during pregnancy and on the absence of increased risks for adverse events associated with administration of vaccines during pregnancy. Here we review the history of the use of vaccines during pregnancy, what is known about the risks and benefits of vaccines during pregnancy on the mother and her infant, and the increasing emphasis in recent years on the benefits of certain vaccines when given during pregnancy. We also discuss future advances in the area of vaccines and pregnancy with the potential to improve maternal and infant health.

2. Past

The concept that vaccination during pregnancy could protect a newborn infant is not a new one. As early as 1879, it was recognized that newborn infants born to mothers who received 'Jennerian vaccination' (smallpox vaccination) during pregnancy were protected from vaccinia virus early in life [3]. The protective effect of maternally transferred antibodies on offspring was shown in 1892 using a mouse model [4]. In humans, it was recognized early in the twentieth century that many infants were resistant to some common infectious diseases during the first few months of life, especially if the mother was known to have had the disease [5], and this

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protection was correlated with the presence of maternal antibodies that were passed transplacentally from mother to the fetus [6].

Vaccination with tetanus toxoid during pregnancy has been used for many years to protect infants born to women in developing countries from neonatal tetanus. Observational studies in the 1960s provided evidence that neonatal tetanus could be prevented with tetanus toxoid vaccination during pregnancy, and a double-blind controlled trial subsequently provided confirmation: the neonatal tetanus death rate was 7.8 deaths per 100 births among infants born to mothers in the control arm, compared to no deaths among infants born to mothers who received two or three injections with tetanus toxoid more than 6 weeks apart [7]. These results subsequently led to the World Health Organization's Maternal and Neonatal Tetanus Elimination Initiative, a program focused on tetanus toxoid vaccination of pregnant and childbearing age women and promotion of hygienic deliveries. This initiative has resulted in a 93% reduction in neonatal deaths due to tetanus [8].

Much of the previous guidance on vaccinations during pregnancy emphasized concerns that vaccine exposure could place the fetus or infant at risk or could be perceived as doing so; however, as additional data on benefits of vaccines during pregnancy and on the absence of increased risks for adverse events after maternal vaccination have accumulated, that emphasis has changed. The history of recommendations by the Advisory Committee on Immunization Practices (ACIP), a group of experts that develops recommendations on use of vaccines in the USA [9], related to influenza vaccination during pregnancy is illustrative. Inactivated influenza vaccination of pregnant women and other groups at increased risk for influenza-associated complications was first recommended by the Surgeon General in 1960 [10], but many subsequent recommendations were less supportive. In 1990, the ACIP noted that an increased risk of influenza-associated complications in pregnant women had not been documented, except during pandemics. Thus, only pregnant women with underlying conditions were recommended to receive influenza vaccination, and waiting to vaccinate until after the first trimester was 'a reasonable precaution to minimize any concern over the theoretical risk of teratogenicity' [11]. In 1995, based on case reports and other studies, the ACIP recommendation was extended to women without underlying conditions, but only during the third trimester of pregnancy [12]. In 1997, after a study had shown an increased risk of influenza-associated hospitalizations among pregnant women during interpandemic periods, especially during the second and third trimesters [13], ACIP recommended second and third trimester vaccination [14]. The 1997 recommendations noted that many experts considered influenza vaccination to be safe in all trimesters of pregnancy, but that delaying vaccination until after the first trimester would avoid 'coincidental association' of the vaccine with first trimester spontaneous abortions [14]. In 2004, ACIP extended influenza vaccination to all pregnant women regardless of pregnancy trimester [15]. This recommendation followed the severe 2003–2004 influenza season during which many cases of severe influenza among pregnant women were reported and missed opportunities for vaccination were identified [16,17].

3. Present

Current ACIP recommendations regarding vaccination during pregnancy (Table 1) are based on considerations of the benefits of vaccination during pregnancy to mother and infant and the potential risks. Because of concerns about possible harm to the fetus, pregnant women have been typically excluded from premarketing clinical trials of medications and vaccines; thus, most data become available through postmarketing observational studies [43]. In developing recommendations for pregnant women, ACIP considers whether the vaccine is inactivated or live: inactivated viral or bacterial vaccines or toxoids have been considered to be safe during pregnancy, whereas live vaccines are considered potentially to be of concern because of the theoretical risk of transmission of the live vaccine component to the fetus [18].

3.1. Vaccines recommended for all pregnant women by ACIP

ACIP currently recommends two inactivated vaccines for all pregnant women, inactivated influenza vaccine and the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. For both vaccines, evidence suggests that vaccination during pregnancy provides protection to the infant in early life because of maternally transferred antibodies [44,45].

Pregnant women are at increased risk for complications associated with seasonal and pandemic influenza because of changes in their immune, respiratory, cardiovascular and other systems during pregnancy [2,46]. Infants aged <6 months are also at increased risk of influenza-associated complications [2] and are unable to receive influenza vaccine because they fail to mount an adequate immune response; thus, maternal vaccination also protects these vulnerable infants from influenza [47]. Finally, infants born to women who become severely ill with influenza during pregnancy are at increased risk of adverse birth outcomes, such as low birth weight, small for gestational age, and preterm birth [47]. Consistent with these findings, recent studies have suggested that infants born to women who received inactivated influenza vaccine during pregnancy have a lower risk of these adverse birth outcomes, compared with infants born to unvaccinated women or to women who received another vaccine [47].

Although influenza vaccination has been recommended for pregnant women regardless of trimester since 2004, an increased focus has recently been placed on the importance of influenza vaccination during pregnancy. The finding that pregnant women were at higher risk for influenza-associated complications during the 2009 H1N1 pandemic likely played a role in this change in focus [48,49]. Shortly before the pandemic, results from a randomized controlled trial in Bangladesh were published that demonstrated a 63% reduction in influenza illness in infants in the first 6 months of life following maternal influenza vaccination during pregnancy, compared with infants born to women who had received pneumococcal polysaccharide vaccine [44].

Observational studies conducted to assess potential risks to the mother or infant associated with inactivated influenza vaccination (including with 2009 H1N1 vaccine) during pregnancy have been reassuring: no safety concerns have been identified among mothers or their infants [50–53]. However, data from the first trimester are limited; thus, future research should concentrate on these early pregnancy exposures [51,52].

After the introduction of vaccination against pertussis, the number of pertussis cases in the USA reported to the US Centers for Disease Control and Prevention (CDC) dropped substantially to fewer than 10 000 by 1965. However, gradual increases in the numbers of cases occurred in the 1980s, and in 2012, 48 277 cases were reported, the highest number since 1955 [54]. The highest incidence is reported in infants aged <1 year; among the 20 reported deaths in 2012, 16 were in infants aged <1 year and 15 were in infants aged <3 months [54].

Following licensure of Tdap vaccine by the US Food and Drug Administration (FDA) in 2005, ACIP recommended that women receive Tdap before pregnancy; for women not vaccinated before pregnancy, a dose of Tdap in the immediate postpartum period was recommended. ACIP also recommended vaccination of persons who have or who anticipate having close contact with an infant aged <12 months (a strategy called 'cocooning') as an approach to

Table 1
Summary of current US Advisory Committee on Immunization Practices (ACIP) recommendations for use of vaccines during pregnancy (adapted from the Centers for Disease Prevention and Control [18]).

Vaccine	Indication (routine, travel, other) [19–21]	Type [22]	ACIP recommendation[a]
Recommended for all pregnant women			
Inactivated influenza vaccine	Routine	Inactivated viral	Women who are or will be pregnant during influenza season should receive inactivated influenza vaccine [23].
Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap)	Routine	Inactivated bacterial	Health care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap. Optimal timing for Tdap administration is between 27 and 36 weeks of gestation although Tdap may be given at any time during pregnancy [24].
Allowed during pregnancy by ACIP in some circumstances			
Anthrax – post-event	Other	Inactivated bacterial	In a post-event setting that poses a high risk for exposure to aerosolized *Bacillus anthracis* spores, pregnancy is neither a precaution nor a contraindication to post-exposure prophylaxis. Pregnant women at risk for inhalation anthrax should receive anthrax vaccine [25].
Hepatitis A	Routine	Inactivated viral	The safety of hepatitis A vaccination during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated hepatitis A virus (HAV), the theoretical risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who might be at high risk for exposure to HAV [26].
Hepatitis B	Routine	Inactivated viral (recombinant)	Pregnancy is not a contraindication to vaccination. Limited data suggest that developing fetuses are not at risk for adverse events when hepatitis B vaccine is administered to pregnant women. Available vaccines contain non-infectious hepatitis B virus surface antigen and should cause no risk of infection to the fetus [27].
Japanese encephalitis (JE)	Travel	Inactivated viral	Practitioners should use caution when considering the use of JE vaccine in pregnant women. Vaccination with JE vaccines usually should be deferred because of a theoretical risk to the developing fetus. However, pregnant women who must travel to an area in which risk for JE is high should be vaccinated if the benefits outweigh the risks of vaccination to the mother and developing fetus [28].
Meningococcal conjugate (MCV4/MenACWY)	Routine	Inactivated bacterial	Pregnancy should not preclude vaccination with MenACWY if indicated [29].
Meningococcal polysaccharide (MPSV4)	Travel	Inactivated bacterial	Pregnancy should not preclude vaccination with MPSV4, if indicated [29].
Inactivated polio vaccine (IPV)	Routine	Inactivated viral	Although no adverse effects of IPV have been documented among pregnant women or their fetuses, vaccination of pregnant women should be avoided on theoretical grounds. However, if a pregnant woman is at increased risk for infection and requires immediate protection against polio, IPV may be administered in accordance with the recommended schedules for adults [30,31].
Pneumococcal polysaccharide (PPSV23)	Routine	Inactivated bacterial	The safety of pneumococcal polysaccharide vaccine during the first trimester of pregnancy has not been evaluated, although no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy [18,32].
Rabies	Travel/other	Inactivated viral	Because of the potential consequences of inadequately managed rabies exposure, pregnancy is not considered a contraindication to postexposure prophylaxis. Certain studies have indicated no increased incidence of abortion, premature births, or fetal abnormalities associated with rabies vaccination. If the risk for exposure to rabies is substantial, pre-exposure prophylaxis also might be indicated during pregnancy [33].
Smallpox (vaccinia) – post-event setting	Other	Live viral	Pregnant women who have had a definite exposure to smallpox virus and are, therefore, at high risk for contracting the disease, should be vaccinated [34].
Tetanus and diphtheria (Td)	Routine	Inactivated bacterial toxoids	Wound management: if a Td booster is indicated for a pregnant woman, health care providers should administer Tdap. Unknown or incomplete tetanus vaccination: to ensure protection against maternal and neonatal tetanus, pregnant women who never have been vaccinated against tetanus should receive three vaccinations containing tetanus and reduced diphtheria toxoids. The recommended schedule is 0, 4 weeks, and 6–12 months. Tdap should replace one dose of Td, preferably between 27 and 36 weeks of gestation to maximize the maternal antibody response and passive antibody transfer to the infant [24].
Yellow fever (YF)	Travel	Live viral	Pregnancy is a precaution for YF vaccine administration, compared with most other live vaccines, which are contraindicated in pregnancy. If travel is unavoidable, and the risks for YF vaccine

(*continued on next page*)

Table 1 (*continued*)

Vaccine	Indication (routine, travel, other) [19–21]	Type [22]	ACIP recommendation[a]
			exposure are felt to outweigh the vaccination risks, a pregnant woman should be vaccinated. If the risks for vaccination are felt to outweigh the risks for YF virus exposure, pregnant women should be issued a medical waiver to fulfill health regulations. Although no specific data are available, a woman should wait 4 weeks after receiving YF vaccine before conceiving [35].
No specific recommendation			
Haemophilus influenzae type b (Hib)	Routine	Inactivated bacterial	ACIP has not published pregnancy recommendations for Hib at this time [20].
Pneumococcal conjugate (PCV13)	Routine	Inactivated bacterial, conjugate	ACIP has not published pregnancy recommendations for PCV13 at this time. Use of PCV13 is limited among women of childbearing age [18].
Typhoid	Travel	Two vaccines available: live bacterial and inactivated bacterial forms	No data have been reported on the use of any of the three typhoid vaccines among pregnant women [36].
Not recommended or contraindicated during pregnancy			
Anthrax – pre-event	Other	Inactivated bacterial	In a pre-event setting, in which the risk for exposure to aerosolized *Bacillus anthracis* spores is presumably low, vaccination of pregnant women is not recommended and should be deferred until after pregnancy [25].
Bacillus Calmette–Guérin (BCG)	Other	Live attenuated	Although no harmful effects to the fetus have been associated with BCG vaccine, its use is not recommended during pregnancy [37].
Human papillomavirus (HPV)	Routine	Inactivated viral	HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose series should be delayed until completion of pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed [38].
Live-attenuated influenza (LAIV)	Routine	Live attenuated viral	LAIV is not recommended for use during pregnancy [23].
Measles–mumps–rubella (MMR)	Routine	Live attenuated viral	MMR vaccine and its component vaccines should not be administered to women known to be pregnant or attempting to become pregnant. Because of the theoretical risk to the fetus when the mother receives a live virus vaccine, women should be counseled to avoid becoming pregnant for 28 days after receipt of MMR vaccine [39].
Smallpox (vaccinia) – pre-event setting	Other	Live viral	Because of the limited risk but severe consequences of fetal infection, smallpox vaccine should not be administered in a pre-event setting to pregnant women or to women who are trying to become pregnant. Before vaccination, women of childbearing age should be asked if they are pregnant or intend to become pregnant in the next 4 weeks; women who respond positively should not be vaccinated [40].
Varicella	Routine	Live viral	Because the effects of the varicella virus vaccine on the fetus are unknown, pregnant women should not be vaccinated. Non-pregnant women who are vaccinated should avoid becoming pregnant for 1 month after each injection [41].
Zoster	Routine	Live viral	Zoster vaccine is not recommended for use in pregnant women, although these women are unlikely to be in the vaccine target age group. The effects of the live, attenuated varicella zoster virus-based vaccine on the fetus are unknown. Women should avoid becoming pregnant for 4 weeks following zoster vaccination [42].

[a] Recommendations are verbatim from ACIP references.

protect infants from pertussis [55]. However, cocooning has been challenging to implement, and a decision analysis showed that Tdap vaccination during pregnancy would avert more infant pertussis cases, hospitalizations, and deaths than postpartum vaccination or cocooning strategies [56]. Thus, in 2011, after review of data on the risks and benefits, ACIP recommended Tdap vaccination during pregnancy, preferably during the third or late second trimester (after 20 weeks gestation), for women who had not previously been vaccinated [45].

Based on further review of data, including information that pertussis antibody levels wane after a year, ACIP altered their recommendation in 2012 to recommend Tdap vaccine during each pregnancy, regardless of previous vaccination [24]. Although ACIP noted that Tdap vaccine may be administered any time during pregnancy, third trimester vaccination (at least 2 weeks before birth to allow time for an adequate maternal immune response) was recommended to allow the highest levels of maternal antibodies to be transferred across the placenta to provide infant protection [24]. Whereas review of limited safety data on Tdap vaccination during pregnancy has not identified concerns related to adverse maternal or infant outcomes [57], no data are available on repeat vaccination, although reassuring data were available for use of tetanus toxoid-containing vaccines during pregnancy [24]. However, ACIP noted that the benefits of Tdap vaccination during every pregnancy outweighed the potential risks for adverse events [24]. Enhanced adverse event monitoring for administration of Tdap vaccination during each pregnancy is ongoing [24].

3.2. *Vaccines contraindicated or not recommended for use during pregnancy by ACIP*

In contrast to the two inactivated vaccines that are recommended for all pregnant women, most live vaccines are specifically contraindicated or not recommended for use during pregnancy by

ACIP (Table 1). These include Bacillus Calmette–Guérin (BCG) vaccine (sometimes recommended for children in countries with a high prevalence of tuberculosis), live attenuated influenza vaccine (LAIV), measles–mumps–rubella (MMR) vaccine, varicella vaccine, zoster vaccine, and smallpox vaccine in a pre-event setting. In addition, because of the theoretical risk of infection with the live attenuated virus in live vaccines, ACIP recommends that pregnancy should be avoided for the month following vaccination for several of these vaccines (i.e. MMR, smallpox, varicella and zoster vaccines) [39–42]. Prenatal screening for evidence of immunity to rubella and varicella is recommended, given the risks of adverse fetal effects associated with rubella and varicella, and increased risk of varicella-associated complications during pregnancy. Women without evidence of rubella or varicella immunity should be vaccinated postpartum before discharge from the health care facility, with a second dose of varicella vaccine provided 4–8 weeks later. Although live vaccines are believed to pose a theoretical risk, the actual observed risks appear to be low, based on limited observational data of exposures to LAIV, MMR, and varicella vaccines [39,50,58,59]. Data from an ongoing pregnancy registry of women exposed to varicella zoster virus-containing vaccines are reassuring; no cases of congenital varicella syndrome and no increased risk for other birth defects have been observed. However, the small sample size of exposed women in the registry does not allow exclusion of risk [60,61].

Of the live vaccines, only smallpox vaccine has been clearly associated with fetal infection when the vaccine was administered during pregnancy. However, even though millions of pregnant women received smallpox vaccine during prior large-scale vaccination programs, only ~50 cases of fetal vaccinia following smallpox vaccination during pregnancy were reported [62]. Additionally, data on smallpox vaccine exposures during pregnancy, collected in a pregnancy registry after the USA initiated smallpox vaccination programs among military and certain civilian workers in 2003, were also reassuring. Among 376 women who inadvertently received smallpox vaccine during pregnancy or who became pregnant within 28 days of vaccination (most were vaccinated near the time of conception), no cases of fetal vaccinia and no increased risks for other adverse pregnancy outcomes were observed [59].

Two inactivated vaccines, human papillomavirus (HPV) vaccine and anthrax vaccine (in a pre-event setting), are not recommended for use during pregnancy by ACIP, in both cases because of the absence of immediate benefit to a pregnant woman and her infant. HPV is a sexually transmitted virus that can cause genital warts and cervical and other cancers. FDA has licensed two types of HPV vaccines (bivalent and quadrivalent). ACIP recommends routine vaccination with three doses of the HPV vaccine over a 6-month period for females aged 11 or 12 years and for females aged 13–26 years of who did not receive any or all of the series when they were younger [38]. Even though both HPV vaccines are inactivated vaccines, they are not recommended during pregnancy because of the lack of immediate benefit to the woman or her infant when given during pregnancy. However, data regarding inadvertent pregnancy exposures to HPV vaccine from pre-licensure clinical trials and from post-licensure pregnancy registries are reassuring [63]. If pregnancy is recognized after initiating the vaccination series, the remainder of the series should be delayed until after pregnancy, but no intervention is needed if HPV vaccine was given during pregnancy [38]. A pregnancy registry has been established to collect data on pregnancy exposures to the quadrivalent HPV vaccine [60].

Although anthrax can rarely occur naturally after exposure to animals or their tissues infected with *Bacillus anthracis*, the anthrax cases that occurred in the USA in 2001 following exposures distributed through the mail demonstrate anthrax's potential as a bioterrorism agent. Anthrax vaccine adsorbed (AVA) vaccine is currently approved for use in the USA for pre-exposure prophylaxis and contains no live or dead bacteria. AVA is approved as a five-dose regimen for pre-exposure prophylaxis, and can also be used as a component of a post-exposure prophylaxis regimen under an Emergency Use Authorization [25].

Because of the low risk for anthrax in a pre-event setting, ACIP does not recommend vaccination during pregnancy. A study of 3465 infants born to women in the military inadvertently exposed to AVA vaccine during the first trimester of pregnancy showed that first trimester exposure was associated with slightly higher odds of birth defects, compared with women who were vaccinated later during pregnancy. However, the finding was statistically significant only when alternative referent groups (women who were never vaccinated or vaccinated after pregnancy) were used. When specific birth defects were evaluated, only one birth defect, atrial septal defect (ASD), was associated with AVA exposure; however, the code used to identify ASD also included patent foramen ovale, an obligatory opening in the atrial septum in the fetus that may persist after birth, especially in preterm infants. This finding was no longer statistically significant when preterm infants with ASD as the only reported defect were excluded from the analysis [64]. ACIP review of these data concluded that AVA is not associated with an increased risk for birth defects and can be administered during pregnancy, but that vaccination should be deferred until after pregnancy unless a woman has an exposure that places her at immediate risk of disease [25].

3.3. *Vaccines allowed during pregnancy by ACIP in some circumstances*

According to ACIP, many vaccines (Table 1) may be used in certain situations in which the benefits to the pregnant woman are believed to outweigh the potential risks. In these situations, the risks of maternal infection and of a poor outcome if the woman becomes infected are believed to be high, and no evidence of harm from the vaccine is available. Vaccines in this category include several routinely recommended vaccines [hepatitis A and B, meningococcal conjugate and meningococcal polysaccharide, inactivated polio, rabies, pneumococcal polysaccharide (PPSV23), and tetanus and diphtheria (Td) vaccines] and two vaccines recommended for travelers (Japanese encephalitis and yellow fever vaccines). As discussed previously, two vaccines, anthrax and smallpox, are recommended for use during pregnancy only in the post-event setting, when risks for maternal illness are significant [25,34].

Nearly all vaccines that are allowed by ACIP in some circumstances are inactivated; although information regarding safety of these vaccines is limited, the available data are reassuring [65,66]. Collection of data through pregnancy exposure registries is ongoing for hepatitis B and meningococcal vaccines [60].

However, one vaccine allowed by ACIP in some circumstances, yellow fever (YF) vaccine, is a live vaccine. The YF virus is transmitted to humans from the bite of an infected mosquito; YF is endemic in sub-Saharan Africa and tropical South America. Illness with YF ranges from mild febrile illness to severe disease with hepato-renal dysfunction; case fatality among persons with severe disease is 20–50%. Because of the risk for severe disease, YF vaccine is recommended for persons aged ≥9 months who are traveling to or living in areas with a risk of YF transmission, and is required for entry into certain countries [35]. The most up-to-date information regarding vaccines for travelers is located at the CDC website [19].

The limited data available on use of YF vaccine during pregnancy suggest that YF virus may be transmitted across the placenta, albeit rarely, based on the presence of IgM antibodies to the YF virus in

the cord blood of one of 81 infants whose mothers had received YF vaccine during pregnancy [35]. A recent systematic review identified eight studies (four using active and four using passive surveillance methods) of YF vaccine during pregnancy [67]. Among 1381 women included in the studies using active surveillance, no increased risk for adverse outcomes was observed. Three of the four studies using passive surveillance methods were reassuring; the fourth showed a higher rate of spontaneous abortions in a small study ($n = 39$) of women vaccinated with YF vaccine during pregnancy, but this finding was not statistically significant [67].

Given that YF vaccine is a live vaccine and that limited data are available, ACIP considers pregnancy to be a precaution for YF vaccine administration; vaccination is recommended during pregnancy if travel is unavoidable and the risks for contracting YF (based on issues such as location of travel, season, and anticipated activities while traveling) are felt to outweigh the potential risks of vaccination. Similar to most other live vaccines, non-pregnant women receiving YF vaccine are recommended to wait 4 weeks before conceiving [35].

YF vaccine effectiveness among pregnant women may be less than that among nonpregnant women and appears to vary by pregnancy trimester, with later pregnancy appearing to be associated with lower rates of seroconversion. Thus, serologic testing should be considered for women vaccinated during pregnancy [35].

3.4. No specific recommendations for use during pregnancy by ACIP

For a few vaccines, ACIP has not made specific recommendations during pregnancy because of inadequate data or limited use during pregnancy. These include *Haemophilus influenzae* type b (Hib) conjugate, pneumococcal conjugate (PCV13), and typhoid vaccines. Hib vaccine is not routinely recommended for persons aged >5 years. However, it is recommended under certain circumstances, that is, among persons aged >5 years of age who are unvaccinated or partially vaccinated with Hib vaccine and have leukemia, malignant neoplasms, anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus infection, or other immunocompromising conditions [20]. PCV13 is recommended in a four-dose series for children aged <2 years, and its use among women of childbearing age is limited; recommendations for adolescent and adult age groups are limited to persons who have not previously received PCV13 and who have certain medical conditions (i.e. sickle cell disease, HIV infection or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leak) [20]. Two types of typhoid vaccines are available in the USA, an oral live-attenuated vaccine and an injectable inactivated vaccine [68]. These vaccines provide some protection against typhoid fever, a sometimes severe illness caused by the bacterium *Salmonella enterica* serotype Typhi acquired by consumption of contaminated food or water. The vaccine is recommended for travelers to developing countries, including parts of Asia, Africa, the Caribbean, and Central and South America [19]. ACIP has not published typhoid vaccine recommendations specifically for pregnant women; however, avoiding live attenuated vaccine seems prudent, given theoretical concerns associated with vaccination with live vaccines.

4. Future

Future areas of importance in the area of vaccines and pregnancy include: (i) improving uptake for vaccines currently recommended for all women during pregnancy; (ii) improving the availability of information about the safety of vaccines administered during pregnancy (including both pre-licensure and post-licensure data); and (iii) advancing the development and use of other vaccines that could protect mothers and their infants.

To improve the uptake of vaccines that are currently recommended for all women during pregnancy, future work needs to identify and address barriers to pregnant women receiving recommended vaccinations. Despite ACIP recommendations, inactivated influenza and Tdap vaccination coverage among pregnant women is considerably lower than desired. In recent years, significant improvements in influenza vaccination coverage among pregnant women have been observed, from 11% during the 2001–2002 influenza season to 38–50% during the 2010–2011 influenza season, depending on the survey tool used [69]. However, substantial efforts will be needed to reach the Healthy People 2020 goal of 80% of pregnant women vaccinated with influenza vaccine each year [70]. Given that ACIP recommendations regarding Tdap vaccine during pregnancy are recent, estimates of coverage following these recommendations are scant, but appear to be quite low: in an Internet panel survey of 1231 women conducted following the 2011 ACIP recommendation, only 2.6% of women reported receiving Tdap vaccine during their recent pregnancy [71].

Offer and recommendation of vaccines by a health care provider have been shown to be critical to vaccine uptake; for example, pregnant women whose health care providers recommended and offered influenza vaccination are more likely to report being vaccinated (73.6%) compared with pregnant women who received only a recommendation but no offer of vaccination (47.9%) and women who received neither a recommendation nor an offer (11.1%) [72]. Several strategies have been recommended to improve vaccine coverage for recommended vaccines during pregnancy. These include: reminder/recall systems; standing orders; entry of vaccine administration information into immunization information systems; review of immunization status at patient visits; ongoing education of health care providers who administer vaccines; ensuring that health care providers receive reimbursement for vaccine administration; assessment of immunization coverage rates in provider practices; and increasing vaccine demand by improving public and provider awareness [73,74]. A recent American College of Obstetricians and Gynecologists Committee Opinion discusses the importance of integrating immunizations into clinical practice [75]. This document and the organization's website [76] provide guidance to obstetrician-gynecologists about becoming routine vaccinators, and have great potential for improving uptake of recommended vaccines in the future.

Monitoring for adverse events associated with vaccines among all populations is important to detect rare adverse events that might not be observed in pre-licensure clinical trials [77]; however, post-licensure monitoring is especially important for pregnant women who are often excluded from clinical trials [43]. This monitoring addresses vaccine safety concerns that are often raised by pregnant women and their health care providers. Several strategies have been established for vaccine safety monitoring among pregnant women in the USA. The Vaccine Adverse Event Reporting System (VAERS) is a spontaneous reporting surveillance system administered by the CDC and FDA since 1990. Through VAERS, reports are collected from vaccine manufacturers, health care providers, and vaccine recipients to identify possible safety concerns; however, most of the time, VAERS cannot determine whether a vaccine is the cause of an adverse event. VAERS has been used to monitor adverse events associated with several vaccines when used during pregnancy [57,78–80]. Another method used to assess vaccine safety is the Vaccine Safety Datalink, a collaborative effort between the CDC and nine health care systems across the USA. This system can be used to identify a large retrospective cohort of women vaccinated and not vaccinated with a particular vaccine during pregnancy; this system has been used to assess the effects of inactivated influenza vaccine during pregnancy [53,81,82]. Another system recently established to better understand the effects of

vaccines during pregnancy is the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) [83]. VAMPSS uses two complementary study designs, a prospective cohort and a case–control study. The prospective cohort arm compares pregnancy outcomes of women who received a vaccine or medication to women who were not exposed for a variety of pregnancy outcomes (e.g. spontaneous abortion, fetal death, preterm birth, small for gestational age, pre-eclampsia, and presence of a malformation). The case–control study design focuses on infants with birth defects identified through hospitals and birth defects surveillance systems: mothers of babies with and without birth defects are interviewed regarding their pregnancy exposures and potential confounding factors. VAMPSS has recently been used to analyse the prenatal effects of 2009 H1N1 monovalent and trivalent inactivated influenza vaccines [84,85]. The Clinical Immunization Safety Assessment (CISA) project is a collaboration between CDC and seven medical centers that conducts post-licensure vaccine safety clinical research and provides consultation to healthcare providers with vaccine safety questions about patients residing in the USA, including pregnant women [86,87].

Another important area of future progress in vaccines and pregnancy is to include pregnant women in pre-licensure clinical trials for vaccines that are likely to be recommended during pregnancy. In the past, pregnant women have been excluded from clinical trials of medications and vaccines because of the potential risk to the fetus [43]. However, this leaves women and their health care providers without data to guide use of these agents during pregnancy, and collecting these data following licensure often takes many years [88]. For these reasons, most vaccines (and most medications) are listed as FDA pregnancy category C (i.e. no adequate and well-controlled studies in pregnant women are available), including several types of inactivated influenza vaccine [18]. In 2010, a meeting was convened by the National Institutes of Health (NIH) to address ethical, regulatory, and scientific issues raised by inclusion of pregnant women in clinical research studies [89]. In addition, NIH also recently held a series of meetings to guide the development of future clinical trial protocols of vaccines in pregnant women [90,91]. From these meetings, it is expected that future studies of vaccines and medications that are intended for use among pregnant women will include pregnant women and will be conducted in an ethical and scientifically valid manner.

Identification of other vaccines that might protect infants early in life from infectious disease morbidity and mortality if administered during pregnancy is another key area for the future. For example, young infants are particularly vulnerable to the effects of group B streptococcus (GBS). GBS is the leading cause of sepsis and meningitis among newborns in the first week of life ('early-onset GBS') in the USA. Infants with GBS aged 7–89 days ('late-onset GBS') present more often with meningitis, with lower mortality than that seen with early-onset disease, but with a significant risk of long-term sequelae. Although maternal screening and intrapartum antibiotic prophylaxis treatment for GBS has decreased the number of cases of early-onset GBS disease in the USA by 80% [92], GBS continues to present a significant burden on infant health, and development of antibiotic-resistant GBS strains is of concern [93]. Development of a GBS vaccine for use during pregnancy could have substantial public health impact: modeling data suggest that maternal GBS vaccination could potentially prevent 4% of preterm births, more than 60% of early-onset GBS and 70% of late-onset GBS disease [94]. Ongoing research on the development of a safe, effective GBS vaccine for use has shown promising results [93]. Several other vaccines are under investigation for use during pregnancy, including meningococcal polysaccharide, pneumococcal conjugate and polysaccharide, Hib conjugate and polysaccharide, and respiratory syncytial virus vaccines [93,95].

Healy [93] has identified a number of factors to be considered before implementation of a maternal immunization program with a new vaccine, including safety, immunogenicity, timing of immunization, biological considerations (including whether maternal immunization will decrease the infant's immune response to vaccines), and implementation (education of health care providers and the public, acceptability of vaccines during pregnancy, and logistics and financing). Regulatory issues and concerns about litigation pose significant barriers to the use of currently recommended vaccines and to the development of new vaccines for use during pregnancy [96]. Unfortunately, the question of whether the National Vaccine Injury Compensation Program – a program established by the National Childhood Vaccine Injury Act of 1986 to provide no-fault monetary awards for adverse events caused by covered vaccines – includes in-utero injuries that occur following vaccination of pregnant women has not yet been resolved [97].

In summary, benefits of maternal vaccination for preventing maternal and infant morbidity and mortality have been demonstrated, in particular, with maternal vaccination with influenza and tetanus toxoid vaccines. This strategy has been expanded to pertussis, and could be beneficial to prevent other diseases, especially those with a substantial burden in the first few months of life. Several barriers to developing vaccines for administration during pregnancy and to optimally implementing maternal vaccination programs remain. However, recent progress – in terms of additional data on safety and effectiveness of vaccines during pregnancy, improved integration of maternal vaccination into clinician practice, and advances toward including pregnant women in clinical trials for relevant vaccines – hold promise for the future of vaccination during pregnancy.

Practice points

- Health care providers who care for pregnant women should review their vaccination history as part of routine prenatal care, and should recommend and offer appropriate vaccines.
- All women who are or will be pregnant during the influenza season should receive inactivated influenza vaccine regardless of trimester.
- All pregnant women should receive a dose of Tdap vaccine during each pregnancy, regardless of prior history of vaccination. Ideally the vaccine is administered between 27 and 36 weeks of gestation although it may be given at any time during pregnancy.

Research directions

- Although safety data from inactivated influenza vaccine in pregnancy have been reassuring, data from vaccination in the first trimester of pregnancy are limited, and therefore additional safety data from use early in pregnancy are needed.
- Patient and health care provider barriers to receiving recommended vaccines in pregnancy need to be explored in order to develop more effective interventions to increase adherence to vaccination recommendations.
- In addition to safety data, more information is needed about the potential for new and existing vaccines to protect infants early in life from infectious disease morbidity and mortality.

Conflict of interest statement

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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