

**Guiding Principles for Development of ACIP Recommendations for
Vaccination during Pregnancy and Breastfeeding**

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**Advisory Committee on Immunization Practices
Workgroup on the Use of Vaccines during Pregnancy and Breastfeeding**

Guiding principles for developing ACIP recommendations for vaccination during pregnancy and breastfeeding

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Formulating policy to guide vaccination of women during pregnancy and breastfeeding is challenging because the evidence-base to guide decisions is extremely limited. In the past, ACIP has not provided guidance to workgroups on either the process to formulate policy for this population or the format and language for recommendations. As a result, workgroups have taken a variety of approaches to considering and presenting the issues, resulting in a diversity of recommendations that vary in clarity and underlying rationale. The principles presented here provide guidance to help standardize both the process of policy formulation and the format and language of recommendations for pregnant and breastfeeding women. All ACIP statements about vaccines and other biologics for use in adolescents or adults should include a background section on vaccination during pregnancy and breastfeeding and provide explicit pregnancy and breastfeeding recommendations using standardized language as outlined below. To arrive at pregnancy and breastfeeding recommendations, ACIP workgroups or subject matter experts charged with developing vaccine statements should review the process suggestions outlined below. These suggestions, while similar to the process generally followed by workgroups, focus specifically on issues related to pregnancy, breastfeeding and decision making in the absence of a strong evidence-base.

1. This document and appendix provide a brief overview of specific issues related to vaccination during pregnancy and breastfeeding
2. Guidance for the pregnancy and breastfeeding **background** section
 - a. Title: “Vaccination of women during pregnancy and breastfeeding”
 - b. Scope: This section should address the following core topics with a narrow focus on the vaccine product/s in question
 - i. Disease burden: pregnant women, fetus, newborns and young infants
 - ii. Vaccination during pregnancy
 1. Objective and rationale: (clear statement of the primary objective(s): to protect mother and/or fetus and/or neonate and/or young infant)
 2. Immunogenicity data (mother; neonate and young infant if available)
 3. Efficacy data (mother; neonate and young infant if available)
 4. Safety data (mother; fetus, neonate and young infant if available)
 5. Pregnancy trimester-specific issues (safety, efficacy, other)
 - iii. Vaccination during breastfeeding
 1. Objective and rationale: (clear statement of the primary objective(s): to protect mother and/or neonate and/or young infant and/or future offspring)
 2. Efficacy
 3. Safety
 4. Timing (eg, immediately post-partum or later in infancy; with respect to the infant/childhood vaccine series)

- iv. Cost-effectiveness (only if there are unique issues related to vaccine use during pregnancy/breastfeeding)
 - v. Alternatives or adjuncts to vaccination during pregnancy
 - vi. Logistics (eg, vaccination record) and coadministration with other vaccines
 - vii. Areas for future research (could highlight important, feasible studies that would assist vaccine policy decisions)
 - c. Length: the section should be short for most vaccine products
 - d. Data sources: indicate types of studies including well controlled clinical trials, observational studies, reviews of published literature, and unpublished data
3. Guidance for the pregnancy/breastfeeding **recommendations**
- a. These recommendations should be integrated into the recommendations section of the document rather than presented separately (as suggested for the pregnancy/breastfeeding background). Explicit recommendations should be provided both for vaccination during pregnancy and during breastfeeding
 - b. Recommendations should reference the pregnancy/breastfeeding background section for rationale and other details
 - c. Pregnancy and breastfeeding recommendations should appear in the “special populations” section of the recommendations. If pregnancy or breastfeeding are deemed precautions or contraindications, recommendations should instead appear in the “precautions/contraindications” section, and the special populations section should refer readers to the precautions/ contraindications section.
 - d. Recommendations should specify
 - i. Precautions/contraindications for the pregnant and breastfeeding populations
 - ii. Timing of vaccination
 - 1. During pregnancy: pregnancy trimester
 - 2. During breastfeeding: any specific time periods to aim for or avoid
 - iii. Minimum time period between vaccination and becoming pregnant, if vaccination is a precaution or contraindication
4. Guidance on language to reduce unnecessary variation across statements
- a. Pregnancy/breastfeeding background section
 - i. For each topic heading listed in 2b, lack of data should be stated explicitly where it applies.
 - ii. For safety, absence of adequate study/surveillance/follow up should be distinguished clearly from absence of adverse events
 - b. Recommendations section:
 - i. General
 - Distinguish clearly between contraindications and precautions. ACIP definitions are as follows:
Contraindication: A condition in a recipient that increases the risk for a serious adverse reaction. *A vaccine will not be administered when a contraindication is present*

Precaution: A condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity. *Under usual circumstances, vaccination should be deferred. However, vaccination might be indicated because benefits outweigh risks*

In the context of pregnancy and breastfeeding, serious adverse reaction includes maternal, fetal or neonatal serious adverse events linked to the vaccine. Contraindication means that there is direct evidence or strong biologic plausibility and suggestive evidence that the risk of severe adverse event is elevated for at least one of these groups. Precaution means there is no supporting evidence but there is some biologic plausibility; precaution may also mean that there is a lack of data to support safety.

- ii. Standard language: Choose which best applies and modify language only if necessary
 1. Pregnancy recommendations
 1. “Vaccination of pregnant women is recommended; all pregnant women should be vaccinated”
Illustrative examples: Inactivated influenza vaccine
 2. “Pregnancy is not a contraindication or precaution to vaccination; routine vaccination recommendations should be applied to pregnant women”
Illustrative examples: Tetanus-diphtheria (Td), Hepatitis B, Meningococcal polysaccharide
 3. “Pregnancy is a precaution and under normal circumstances vaccination should be deferred; vaccine should only be given when benefits outweigh risks”
Illustrative examples: Hepatitis A , IPV, or yellow fever (in case of travel to an area where exposure is likely); rabies (eg, after a possible exposure)
 4. “Pregnancy is a contraindication to vaccination; vaccine should not be administered to pregnant women. Vaccination with contraindicated vaccines during pregnancy is not ordinarily a reason for pregnancy termination”
Illustrative examples: MMR, varicella, live-attenuated influenza vaccine
 2. Timing of vaccination during pregnancy
 1. “Vaccination can be given at any time during pregnancy”
 2. “Vaccination should be deferred until X trimester of pregnancy unless there is a specific indication for vaccination early in pregnancy that outweighs risks”
 3. “Vaccine should not be administered during X trimester of pregnancy”

4. *For vaccines where pregnancy is a contraindication:*
“Women should avoid becoming pregnant until 28 days after vaccination”
 - i. Note: 28 days is the time period that applies to most currently contraindicated vaccines; however if for a particular vaccine product there is evidence for a shorter or longer time period, the 28 days may be modified as needed.
3. Breastfeeding recommendations
 1. “Breastfeeding is not a contraindication or precaution to vaccination; routine vaccination recommendations should be applied”
Illustrative examples: Current recommendations appear to place all vaccines except smallpox in this category (although the language is not clear)
 2. “Breastfeeding is a precaution and under usual circumstances vaccination should be deferred; vaccine should only be given when benefits outweigh risks”
 3. “Breastfeeding is a contraindication to vaccination; vaccine should not be administered to breastfeeding women.”
Illustrative example: smallpox vaccine
4. Timing of vaccination during breastfeeding
 1. “Vaccination is recommended before postpartum hospital discharge for all women whether or not they intend to breastfeed”
 2. “Vaccine may be administered at any time postpartum, for all women whether or not they intend to breastfeed”
 3. “Where possible, vaccination of breastfeeding women should be deferred until X period postpartum, unless benefits outweigh risks”
 4. “For breastfeeding women, vaccine should not be administered during X period postpartum”
5. Suggestions to aid policy decision-making in the absence of adequate data
 - a. Review any unpublished or pre-licensure data available (eg, from accidental vaccinations of pregnant women)
 - b. Assess whether there will be adequate data in the future and on what timeline
 - c. Review the decisions of other professional organizations/ other countries and the underlying rationale
 - d. Review “ACIP precedents” with regards to vaccination during pregnancy and breastfeeding
 - i. Vaccination during breastfeeding is contraindicated only for smallpox vaccine
 - ii. Live vaccines pose theoretical concern more often than inactivated vaccines

- iii. When risk of maternal infection is high and risk of a poor outcome is high, vaccination is recommended (eg, rabies, yellow fever)
- iv. In the absence of adequate safety and efficacy data, direct protection of mother provides a stronger basis than indirect protection of neonate/young infant for a recommendation of vaccination during pregnancy
- v. There is more comfort with second and third trimester vaccination than first trimester (not based on safety data, but based on public perception)
- e. Evaluate safety checks in place in case the pregnancy/breastfeeding recommendations for the product in question result in unintended adverse consequences
 - i. Is post-licensure data on safety (passive, or active, or special studies) likely to detect important adverse events?
 - ii. Are there registries or other sources that would allow for detection of safety or efficacy concerns?
 - iii. If there are concerns about maternal antibody inhibition of infant response to a similar vaccine or fetal antigen tolerance with subsequent diminished postnatal responsiveness, is any system in place to monitor those outcomes?
 - iv. Are there any sentinel events of concern that warrant particular attention?
- 6. Suggestions on how to standardize the gathering of expert opinion
 - i. Areas of expertise that should be represented in workgroup deliberations:
 1. Disease burden (all relevant populations (eg, pregnant women, neonates, young infants))
 2. Vaccine product: efficacy, safety for pregnant women, fetus, newborn/infant as relevant
 3. Maternal/neonatal immunology if concerns about maternal antibody inhibition of infant immune response to same or related vaccine are relevant
 4. Consider: target population representation (eg, pregnant woman; a representative of infants who have been affected by the disease in question)
 5. Scientific leader from obstetric clinical community
 6. Scientific leader from pediatric clinical community
 7. Consider: inclusion of someone with expertise in health law
 - ii. Strategies for obtaining input
 1. If some members are particularly vocal or stifling of free conversation, consider solicitation of written input through a standard set of key questions from all members
 2. Consider pulling in additional targeted experts if a particular issue stands out as complex or controversial
 - iii. Suggestion of procedures to follow when expert opinion cannot reach consensus
 1. Present pros and cons as options to the full ACIP, with a summary of supporting evidence, and let them vote

2. Allow the workgroup to draft a dissenting opinion and present both positions to ACIP before they vote

Appendix: Brief overview of issues related to vaccination during pregnancy and breastfeeding

1. Vaccination during pregnancy
 - a. Vulnerable populations
 - i. Pregnant women
 1. Altered immune response
 2. Increased risk of some infections
 3. Increased risk of severe outcomes (maternal, fetal or both) of some infections
 - ii. Fetus, newborn, young infant
 1. Immature immune response
 2. Increased risk of some infections
 3. Increased risk of severe outcomes of some infections
 4. Infection sequelae can result in lifelong disability
 - b. The promise of vaccination during pregnancy (any or all of the below)
 - i. Protection of mother
 - ii. Protection of fetus
 - iii. Protection of neonate
 - iv. Protection of young infant
 - v. In the US there are approximately 4 million live births each year
 - vi. In the US >98% of women have at least 1 prenatal visit, providing a health care opportunity for vaccination
 - c. Concerns about vaccination of pregnant women
 - i. Lack of data to make evidence-based decisions
 1. No or limited well-controlled trials to establish efficacy of vaccines in pregnant women or their offspring
 2. No or limited post-licensure studies of efficacy or safety (eg, from registries, VAERS, Vaccine Safety Datalink)
 3. No or limited animal data
 4. No or limited data on burden of illness
 - Key aspects of interest: incidence, severity, sequelae, time period of most vulnerability to infection
 - Key target populations: pregnant woman, fetus, newborn, young infant
 - ii. Theoretical concerns about efficacy (woman, fetus, newborn)
 1. Will altered immune status of pregnant woman reduce response to vaccine?
 2. Will sufficient maternal antibody be transferred to fetus to confer protection (to fetus, newborn)?
 3. Will half life of maternal antibody be sufficient to protect fetus/newborn during relevant period of vulnerability?
 - iii. Theoretical concerns about safety (woman, fetus, newborn)
 1. Vaccine type
 - Live vaccines (eg, viral antigen) historically have been viewed as more risky than inactivated and toxoid vaccines

- i. There is evidence of fetal vaccinia infection following smallpox vaccination during pregnancy
 - ii. There is no direct evidence of any live vaccine resulting in a fetal or neonatal serious adverse event
 - o Even more limited data on newer vaccine types
 - i. Unclear that generalizations about live vs. inactivated vaccines can be applied to new or future vaccine antigen types and technologies
 - ii. Unclear that generalizations about live parenteral vaccines can be applied to live mucosal vaccines
 2. Additives/adjuvants/preservatives (eg, thimerosal)
 - o Limited or no safety data on exposure of pregnant women, fetus and newborn to these
 3. Timing of vaccination
 - o Safety risks may vary with time period of vaccination during pregnancy (eg, early pregnancy vs. late pregnancy; immediately post-partum vs. later)
- iv. Concerns about impaired newborn/infant immune response to childhood series
 1. Primary concern is inhibition of newborn or infant response to active vaccination due to high concentrations of passively acquired maternal antibodies
 2. Evidence that transplacental transfer of maternal antibody can interfere with infant response to childhood vaccine series
 - o naturally-acquired or vaccine-induced maternal measles antibody interferes with infant response to measles vaccine
 3. Theoretic concern that vaccination during pregnancy could similarly impair response to routine childhood series
 - o Extent of inhibition depends on multiple factors (eg, type of maternal and infant vaccine antigen, concentration and avidity of maternal antibody, timing and doses in infant series)
 - o Priming of the infant immune system can occur despite presence of maternal antibody
 4. In addition to concerns about maternal antibody inhibition of infant postnatal responses to infant immunization series, there are also theoretical concerns that the fetus could develop antigen tolerance *in utero* which may result in diminished postnatal responsiveness to the infant immunization series.
- v. Lack of harmonization with FDA labeled indications (*see Table for a description of FDA pregnancy categories*)
 1. Label subject to federal regulations
 - o 21 CFR 201.56 (General) and 201.57 (Specific)
 2. One currently licensed vaccine (HPV) is pregnancy category B
 3. One currently licensed vaccine (anthrax) is pregnancy category D
 4. All other licensed vaccines are currently labeled as category C

- vi. Public perception/risk communication
 1. Temporal association between vaccine and adverse pregnancy events
 2. Principle of avoiding any unnecessary exposures during pregnancy
 - vii. Legal liability
 1. National Childhood Vaccine Injury Act
 - If covered vaccine properly prepared and accompanied by proper directions and warnings, manufacturer cannot be held liable for injuries.
 - Law clearly covers vaccine directly administered to child
 - Statute is silent on *in utero* transmission (eg, adverse effect in fetus whose mother is vaccinated); case law is unclear
 - viii. Logistical concerns
 1. Most obstetric offices do not have the infrastructure (eg, proper storage refrigerator, tracking of administration documentation required by law) to administer vaccines and obstetric providers often do not view vaccination as their primary responsibility
 2. There is no good vaccine record keeping system for adult vaccination (eg, to avoid problem of repeat vaccination)
 3. Providers who care for pregnant women are often most concerned about the woman and fetus and may be less educated/aware about infectious risks to the neonate and young infant
 4. Vaccine recommendations for pregnant women have a history of lack of clarity
 - d. Alternatives or supplements to vaccination during pregnancy: Depending on the infection, some or all of the below may be effective as adjuncts or as alternatives
 - i. Routine infection control (eg, hand hygiene, respiratory etiquette)
 - ii. Vaccination of household contacts of newborns/pregnant women (“cocoon strategy” for pertussis and influenza) but limited data on efficacy
 - iii. Postpartum vaccination (See section 2 below)
 1. Eg, rubella and Tdap vaccination recommendation
 2. Avoids safety concerns of vaccination during pregnancy
 3. Only confers fetal protection in subsequent pregnancies (assuming maternal antibody levels persist at adequate concentrations)
 4. Only confers maternal protection after the time of vaccination (eg, misses vulnerable time window of that pregnancy and early postpartum period)
2. Vaccination during breastfeeding
- i. Objectives
 1. Protect mother from vaccine-preventable diseases
 2. Indirect protection of neonate/ infant by preventing infection in mother (“cocoon strategy”; see 1d)
 3. Confer protection in subsequent pregnancies (eg, rubella)
 4. Transfer of protective antibody to neonate/ infant
 - Antibody in human milk is >90% secretory IgA
 - Offers surface protection in the mouth

- Unclear whether offers additional protection (eg, against respiratory infection)
 - Transfer of circulatory IgG to infant has not been documented
- ii. Concerns
1. Interruption of breastfeeding (which has known, important benefits)
 2. Interference of antibody transferred via human milk with neonate/infant direct response to childhood series
 - A particular issue for orally administered vaccines
 - Evidence from rotavirus and poliovirus vaccines suggest this may be overcome by administering >1 dose
 3. Transmission of vaccine virus in the case of live vaccines
 - Evidence from smallpox, MMRV, MMR
 4. Consistency with FDA labels
 - Majority of labels state “Because many drugs are excreted in human milk, caution should be exercised when administering vaccine to a nursing woman”

Table. Food and Drug Administration pregnancy categories*. Regulation requires that each product be classified under one of five pregnancy categories (A, B, C, D, or X), on the basis of risk of reproductive and developmental adverse effects or, for certain categories, on the basis of such risk weighed against potential benefit.

Pregnancy category A	Adequate and well controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimester), and the possibility of fetal harm appears remote.
Pregnancy category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester (and there is no evidence of risk in later trimesters)
Pregnancy category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks OR Animal reproduction studies have not been conducted and there are no adequate and well-controlled studies in humans
Pregnancy category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

*Note: As of January, 2008, FDA is in the process of developing a new pregnancy labeling system. This new system is under consideration and has not yet been instituted.

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This document can be found on the CDC website at:

<http://www.cdc.gov/vaccines/recs/acip/downloads/preg-principles05-01-08.pdf>