CLINICAL GUIDANCE FOR USE OF LIVE ATTENUATED CHIKUNGUNYA VACCINE AMONG PREGNANT AND BREASTFEEDING INDIVIDUALS

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Clinical guidance for use of live attenuated chikungunya vaccine in pregnant individuals

Presentation of chikungunya among pregnant persons

- Clinical disease similar to non-pregnant persons

Outcomes of chikungunya virus infection during pregnancy

- Adverse outcomes such as fetal loss, stillbirth, or preterm birth documented but rare
  - Mouse studies and examination of placentas from infected women suggest placenta is refractory to chikungunya virus infection[1,2]

- Infection commonly results in adverse neonatal outcomes if pregnant individual infected around time of delivery
  - In these cases, intrapartum transmission occurs in ~30%–50% cases[3–6]
  - Mechanism considered to be transplacental transmission with hypothesis that maternal blood enters fetal circulation by placental barrier breaches from uterine contractions during labor

1. Fritel X et al, Emerg Infect Dis 2010; 2. Couderc T et al, PLoS Pathog 2008; 3. Gerardin P et al, PLoS Medicine 2008; 4. Ramful D et al, Ped Infect Dis J 2007; 5. Torres JR et al, Int J Infect Dis 2016; 6. Senanayake MP et al, Ceylon Med J 2009.

Disease in neonates infected via intrapartum transmission

- Severe and sometime fatal illness
  - In one prospective study 53% (10 of 19 neonates) had severe disease[1]
- Presentations include encephalopathy, sepsis-like illness, cardiac, dermatologic, and hemorrhagic manifestations
- Neurocognitive outcomes often poor, particularly if initial clinical presentation with encephalopathy

Bin S et al, Clin Case Rep 2023

Jebain J et al, ID Cases 2020

Villamil-Gomez W et al, J Trop Ped 2015

1. Gerardin P et al, PLoS Medicine 2008

Chikungunya and young infants

- Young infants infected via mosquito-borne transmission also at risk for severe disease, particularly during the first few months of life
- Clinical presentations similar to those with neonatal infections

Valamparampil JJ et al, Ind J Ped 2009

Gupta D et al, Ind J Ped 2015

Vaccination during pregnancy: Immunogenicity

- No data available on immunologic response to chikungunya vaccine administered to pregnant individual

- General principles and experience with other vaccines
  - Transplacental transfer of antibodies after maternal immunization demonstrated to confer protection with most vaccines
  - Examples of benefits include decreased rates of hospitalization in infants born to vaccinated women (e.g., influenza, COVID-19, RSV vaccines) and decreased risk for preterm birth (e.g., COVID-19 vaccine)

Vaccination during pregnancy: Safety

- Data are insufficient to determine whether any safety risks from vaccination during pregnancy
  - Pregnancy was an exclusion criteria in clinical trials
  - Only two pregnant persons inadvertently vaccinated during pregnancy
- Two pregnant persons vaccinated during 1st trimester
  - 36-year-old: spontaneous abortion 59 days after vaccination at gestational age ~10–14 weeks
  - 23-year-old: anembryonic pregnancy noted at 53 days, spontaneous abortion at 55 days after vaccination at ~8 weeks gestation
- General notes on cases
  - Anembryonic pregnancies generally result from chromosomal problem at conception
  - Estimated 20%–25% of all pregnancies lead to pregnancy loss, with highest rates in 1st trimester and increasing rates with increasing maternal age

Key language related to pregnancy in package insert[1]

- Noted under “Warnings and Precautions”
  - Vertical transmission of wild-type chikungunya virus from pregnant individuals with viremia at delivery is common and can cause potentially fatal chikungunya virus disease in neonates. Vaccine viremia occurs in the first week following administration of chikungunya vaccine….it is not known if the vaccine virus can be vertically transmitted and cause fetal or neonatal adverse reactions

- Noted under “Use in Specific Populations”
  - A decision to administer chikungunya vaccine during pregnancy should take into consideration the individual’s risk of wild-type chikungunya virus infection, gestational age, and risks to the fetus or neonate from vertical transmission of wild-type chikungunya virus....If neonates are born within 14 days of their mother receiving chikungunya vaccine, closely monitor them after birth for potential disease due to vaccine virus

1. FDA. Package Insert – IXCHIQ. Available at: https://www.fda.gov/vaccines-blood-biologics/ixchiq

Viremia after vaccination

- In Phase 1 clinical trial
  - Viremia after vaccination assessed by quantitative reverse transcription-polymerase chain reaction (qRT-PCR)
  - Plasma tested on days 3, 7, and 14 after vaccination
- Among 30 subjects vaccinated with vaccine dose with equivalent amount of attenuated chikungunya virus as in licensed vaccine, viremia detected in
  - 90% on day 3
  - 17% on day 7
  - 0% on day 14

Live, attenuated vaccines and pregnancy: ACIP General Best Practice Guidelines for Immunization

- For many live vaccines, pregnancy is <u>contraindication</u>
  - Theoretical risk to fetus from maternal viremia and viral transmission to fetus
  - MMR and varicella vaccines contraindicated during pregnancy, although no cases of congenital rubella or varicella syndrome or abnormalities attributable to fetal infection observed among infants born to women inadvertently vaccinated during pregnancy
- For some live vaccines, pregnancy is <u>precaution</u>
  - Vaccines can be used after considering the risks of disease and risks and benefits of vaccination
  - Yellow fever, dengue vaccines

Kroger A et al. General Best Practice Guidance for Immunization (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html)

Groups for whom clinical guidance will be relevant

- Travelers and laboratory workers
- Persons in U.S. territories and states with risk of chikungunya virus transmission

Objectives of vaccinating pregnant individuals

- Protect pregnant person from chikungunya virus infection
- Avoid maternal infection around time of delivery to prevent intrapartum virus transmission and severe disease in newborn
- Transplacental transfer of antibodies might also protect young infant from mosquito-borne transmission and severe disease

Proposed clinical guidance for use of chikungunya vaccine in pregnant individuals (1)

Pregnant individuals should avoid the risk for chikungunya virus infection, if possible (e.g., by avoiding travel to an area with virus transmission particularly during an outbreak).

Proposed clinical guidance for use of chikungunya vaccine in pregnant individuals (2)

Pregnancy is a precaution for vaccination with the live attenuated chikungunya vaccine. In general, vaccination should be deferred until after delivery. However, when the risk of infection is high and exposure cannot be avoided, a health care provider should discuss with a pregnant person the potential risks of chikungunya virus infection and the potential benefits and risks of vaccination so that vaccination can be considered.

Proposed clinical guidance for use of chikungunya vaccine in pregnant individuals (3)

If pregnant persons choose to be vaccinated, out of caution vaccination should generally be avoided during the 1st trimester (until 14 weeks gestation) and after the 36th week of gestation.

- Avoiding vaccination during the 1st trimester is preferred for two reasons. Firstly, pregnancy loss has been reported in two individuals vaccinated during the 1st trimester, although one was an anembryonic pregnancy. In addition, the vaccine is reactogenic and can cause fever, and fever has been linked to birth defects in the 1st trimester.
- Avoidance of vaccination after the 36th week of gestation is to limit the risk of vaccine-induced viremia occurring in the intrapartum period and thus to reduce the theoretical risk for perinatal transmission and potential adverse outcomes.*

*Vaccine viremia is considered to occur in most individuals in the first few days after vaccination and to decrease thereafter; viremia was no longer detectable in any clinical trial subjects at 14 days after vaccination.

Proposed clinical guidance for use of chikungunya vaccine in pregnant individuals (4)

In line with common practice following vaccination with live vaccines, non-pregnant vaccine recipients should generally wait 4 weeks before becoming pregnant. If a pregnant person is inadvertently vaccinated outside of the preferred period or becomes pregnant within 4 weeks after chikungunya vaccination, this should not be considered a reason to terminate the pregnancy.

This guidance is intended to maximize the benefits of vaccination while minimizing risks associated with vaccination during pregnancy.

Guidance that maximizes benefits of vaccination while minimizing risks associated with vaccination during pregnancy

1. Avoid risk if possible
2. In general, defer vaccination until after delivery
3. If exposure risk high, consider vaccination given risk for severe adverse outcomes of infection particularly if intrapartum transmission occurs
4. If consider vaccination, where possible avoid 1st trimester and after 36th week of gestation

Clinical guidance for use of live attenuated chikungunya vaccine in breastfeeding individuals

Chikungunya and breastfeeding

- Chikungunya viral ribonucleic acid (RNA) detected in breast milk on very rare occasions[1,2]
  - No studies have reported detection of replicating virus

- Case report describing mother with chikungunya and chikungunya virus RNA detected in her breast milk was breastfeeding her 3-month-old infant[1]
  - No symptoms or laboratory evidence of infection in infant

1. Campos GS et al, Pediatr Infect Dis J 2017; 2. De Paula Souza et al, Transl Res 2023.

Chikungunya vaccine and breastfeeding

- No human data on whether chikungunya vaccine virus or antibodies are present in breast milk after vaccination
- Neonates and other infants aged <1 year are at risk for severe disease if infected with wild-type chikungunya virus
  - Vaccine virus is attenuated, but outcome if chikungunya vaccine virus was transmitted by breastfeeding unknown

Key language related to lactation in package insert[1]

- Breastfeeding is neither contraindication nor precaution for vaccination
- Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for the vaccine and any potential adverse effects on the breastfed child from the vaccine or from the mother’s susceptibility to chikungunya
- Vaccine viremia occurs after vaccination…the potential for transmission of vaccine virus from mother to infant through breastmilk is unknown

1. FDA. Package Insert – IXCHIQ. Available at: https://www.fda.gov/vaccines-blood-biologics/ixchiq

Live attenuated vaccines and breastfeeding: ACIP General Best Practice Guidelines for Immunization

- Although live viruses in vaccines can replicate in mother, majority of live viruses in vaccines have been shown not to be excreted in milk
  - Varicella vaccine virus has not been detected in human milk
  - Rubella vaccine virus has been detected in human milk, but virus usually does not infect infant, and if infection occurs, the attenuated virus is well tolerated

- Live vaccines considered to be safe for administration to breastfeeding individuals with two exceptions:
  - Yellow fever vaccine: three breastfed infants developed encephalitis after mother vaccinated
  - Smallpox vaccine (ACAM2000): theoretical risk for contact transmission from mother to infant

Kroger A et al. General Best Practice Guidance for Immunization (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html)

ACIP breastfeeding guidance for other live vaccines

- MMR: Not a precaution or contraindication
- Varicella: Not a precaution or contraindication
- Yellow fever: Precaution
- Smallpox (ACAM2000): Contraindication

Groups for whom clinical guidance will be relevant

- Travelers and laboratory workers
- Persons in U.S. territories and states with risk of chikungunya virus transmission

Objectives of vaccinating breastfeeding individuals

- Protect breastfeeding individual
- Added benefit might be reduction in risk for infant through transfer of protective antibodies in breast milk

Proposed clinical guidance for use of chikungunya vaccine in breastfeeding individuals

Breastfeeding individuals and their infants should avoid the risk for chikungunya virus infection, if possible (e.g., by avoiding travel to an area with transmission particularly during an outbreak).

In the absence of data, breastfeeding is a precaution for vaccination. When the risk of infection is high (e.g., during an outbreak) and exposure cannot be avoided, a health care provider should discuss with a breastfeeding individual the developmental and health benefits of breastfeeding for the infant, the risks of chikungunya virus infection, and the potential benefits and risks of vaccination, and offer the vaccine to the breastfeeding person. At the current time, the data are insufficient to make a recommendation to defer breastfeeding for any period after vaccination.

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