PROPOSED POLICY OPTIONS FOR CHIKUNGUNYA VACCINE USE AMONG U.S. ADULT TRAVELERS

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Chikungunya virus and transmission

- Alphavirus
- Key vectors are *Aedes aegypti* and *Aedes albopictus* mosquitoes
- Mainly feed in daytime with peak activity early morning and late afternoon

Other uncommon transmission modes

Intrauterine

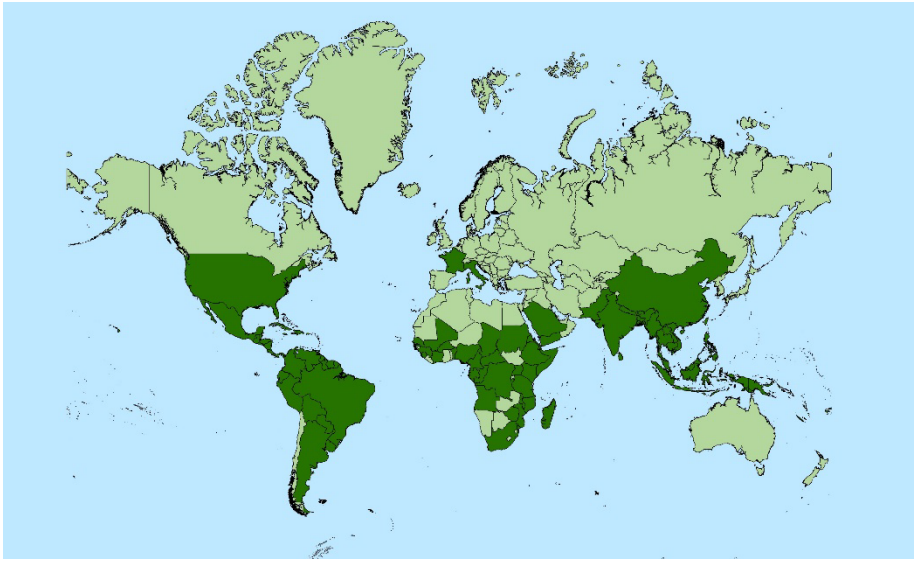
Intrapartum

Bloodborne

Laboratory exposure

Distribution and disease burden in endemic areas

- Typically tropical and subtropical regions
- Periodically causes large outbreaks
  - Often high attack rates
- Virus transmission usually highest during wet season
- Large numbers of cases reported annually



Countries and territories with current or past transmission of chikungunya virus

Clinical features of acute chikungunya virus infection

- Febrile illness with typically severe arthralgia, can be debilitating
- Joint symptoms involve multiple joints, most commonly hands and feet
- Other symptoms include headache, rash, myalgia, anorexia
- No anti-viral treatment available

Image above from : https://www.paho.org/en/topics/chikungunya

Complications of chikungunya

- Rare serious complications (e.g., myocarditis, hepatitis, acute renal disease, neurologic illness)
- Deaths rare and reported mostly in
  - Older adults, particularly those with comorbidities
  - Young infants infected perinatally or by mosquito bites

Debilitated. This man was so weakened by chikungunya that he needed a wheelchair. Adults over 65 and people with pre-existing conditions are at higher risk of serious illness and require closer follow-up.

Infected at birth. This newborn girl contracted chikungunya from her mother during childbirth. Such babies require close follow-up and should not stop breastfeeding.

Images from : https://www.paho.org/en/topics/chikungunya

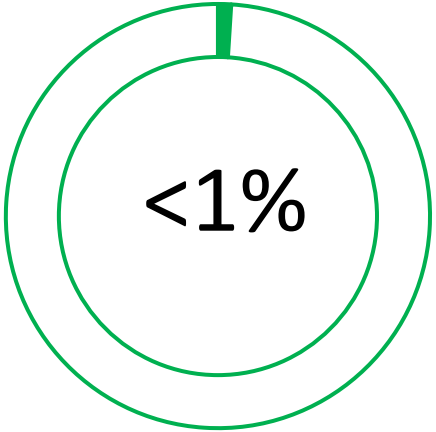
Chronic arthralgia following chikungunya

- Acute symptoms usually resolve in 7–10 days
- Some patients have continuation or relapse of symptoms
- Studies reported variable proportions of patients with persistent symptoms and likely varies with
  - Severity of acute illness
  - Age
  - Preexisting joint problems
- Ongoing arthralgia of variable severity possibly present in up to ~50% at 3 months and up to ~30% at 12 months

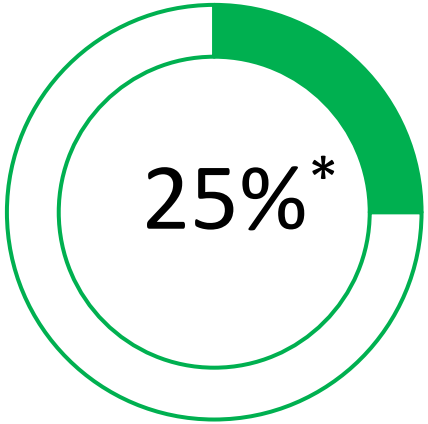
Chikungunya among U.S. travelers

- Approximately 100–200 reported cases annually
- Infection most commonly acquired in locations in Asia and Americas
- Greatest risk factor for travelers is traveling to area with outbreak

Example of higher risk during outbreak: Risk for travelers to Paraguay in 2023



Percentage of all U.S. persons traveling to areas with chikungunya risk visiting Paraguay



Percentage of all reported U.S. traveler chikungunya cases who indicated they had traveled to Paraguay

*20 of 80 travelers with destination data, preliminary ArboNET data, 2023

Chikungunya vaccine

- Live attenuated vaccine
- Single dose schedule
- Administered intramuscularly
- Licensure based on data from
  - ~620 subjects for immunogenicity
  - ~3,500 subjects for safety (including ~3,100 in pivotal clinical trial)

Short- and long-term protection (seroresponse rates)

- Short-term protection (28 days after vaccination)
  - 98% (611 of 622) combined seroresponse rate from two studies
- Long-term protection (12 months after vaccination)
  - 99% (356 of 360) seroreponse rate from one study
- **Work Group summary**
  - Although data are limited, vaccine highly immunogenic

Vaccine safety (1)

- Pivotal Phase 3 clinical trial included 3,082 adults in vaccine arm and 1,033 in placebo arm
- Solicited local reactions within 10 days after vaccination
  - 15% in vaccinees vs 11% in placebo recipients
- Solicited systemic adverse events (AE) within 10 days after vaccination
  - 50% in vaccinees vs 27% in placebo recipients
  - Most common were headache, fatigue and myalgia in ~25%–30% of vaccinees
- Any related severe systemic AEs*
  - 1.9% in vaccinees vs 0.1% in placebo recipients
  - Commonest were fever (1.3%), arthralgia (0.3%), myalgia (0.3%)

*Prevented daily activity or required medical attention or fever ≥39°C (102.1°F)

Vaccine safety (2)

- Serious adverse events within 6 months of vaccination
  - 1.5% in vaccinees vs 0.8% of placebo recipients
  - Two events in vaccinated subjects considered vaccine-related

- Arthralgia/arthritis
  - Any arthralgia within 10 days in 17% vaccinees vs 5% placebo recipients
  - Severe arthralgia, persistent arthralgia, arthritis, and new onset or worsening osteoarthritis not reported in significantly higher percentage of vaccinees vs placebo recipients

Chikungunya-like adverse reactions: Background

- Safety outcome of interest has been chikungunya-like illness after vaccination
- Work Group had reviewed data on “adverse events of special interest” defined by manufacturer
- FDA-requested reanalysis based on revised case definition that was less restrictive in terms of timing of onset of events, clustering of symptoms, and duration of events
  - Revised FDA definition was fever* and ≥1 of arthralgia or arthritis, myalgia, headache, back pain, rash, lymphadenopathy, or certain neurological, cardiac or ocular symptoms that occurred within 30 days after vaccination

* Fever ≥100.4°F

Chikungunya-like adverse reactions: Results per reanalysis

- Chikungunya-like adverse reactions
  - 11.7% (361 of 3,082) vaccine recipients and 0.6% (6 of 1,033) placebo recipients
  - Most symptoms mild or moderate
- Severe reactions that prevented daily activity or required medical intervention, or fever ≥102.1°F (39°C)
  - 1.6% (n=48) vaccine recipients vs 0% of placebo recipients
- Prolonged reactions with duration ≥30 days
  - 0.5% (n=14) vaccine recipients vs 0% of placebo recipients

Chikungunya-like adverse reactions: Work Groups conclusions

- Already considered reactogenic nature of vaccine
- Looked closely at similar events when conducting GRADE analysis
- Noted some other reactogenic vaccines have similar rates of adverse events
- In Evidence to Recommendations framework when considering if desirable effects outweighed undesirable effects of vaccination had noted risk-benefit assessment
  - Will vary substantially depending on chikungunya virus transmission intensity and other factors
  - Was likely favorable if used in line with our proposed recommendations
- No change in Work Group assessment

Vaccine safety: Work Group summary

- Reactogenic vaccine
- Will be important to continue to monitor vaccine safety post-licensure

Summary of Work Group considerations

- Disease that can result in severe arthralgia during the acute illness, rare serious complications, and sometimes long-term arthralgia
- Highest risk for severe outcomes is among older adults, particularly those with comorbidities, and neonates and young infants
- Moderate disease burden among US travelers with 100-200 cases reported annually
- Substantially higher risk for infection if travel during an outbreak
- Immunogenic but reactogenic vaccine

Draft recommendations for ACIP's consideration

Draft recommendations

- Chikungunya vaccine is recommended for persons aged ≥18 years traveling to a country or territory where there is a chikungunya outbreak

- In addition, chikungunya vaccine may be considered for the following persons traveling to a country or territory without an outbreak but with evidence of chikungunya virus transmission among humans within the last 5 years
  - Persons aged >65 years, particularly those with underlying medical conditions, who are likely to have at least moderate exposure* to mosquitoes, OR
  - Persons staying for a cumulative period of 6 months or more

Providing clarity on chikungunya outbreaks

- For the purposes of the recommendation, an outbreak will be defined as occurring when CDC posts information on an outbreak on CDC website

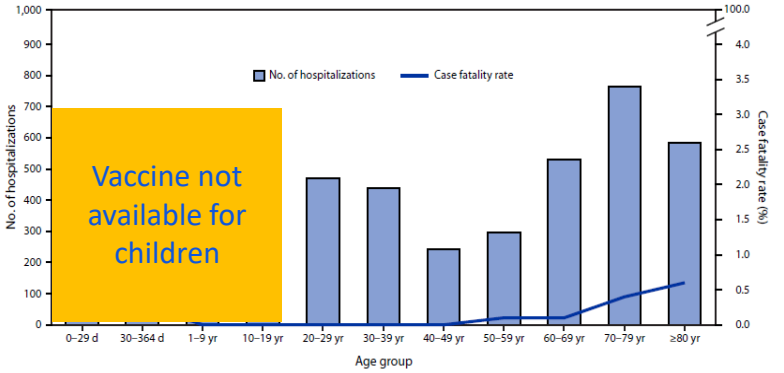
Shared clinical decision-making recommendation for persons aged >65 years or traveling for a longer duration

- More uncertainty in risk-benefit assessment in these cases
- Likely to be circumstances where some individuals might reasonably choose vaccination or some providers might wish to recommend it
- Appropriate to hold conversation between healthcare provider and patient about the risks and benefits including
  - likelihood of exposure based on factors including activities, time of year, duration of travel
  - disease and potential severity
  - vaccine efficacy
  - possibility of vaccine-associated adverse events
- Takes into account traveler's personal perceptions and tolerance of risk

Persons >65 years, particularly those with underlying medical conditions

- Key risk factors for severe disease include older age and underlying medical conditions (e.g., diabetes, cardiac disease, hypertension)
- Key risk factors for chronic arthralgia are older age and pre-existing joint problems
- Risk for higher morbidity and mortality in older persons supported by data from recent outbreak in Paraguay[1]

FIGURE. Number of hospitalizations (N = 4,604) and case fatality rate* among probable and confirmed chikungunya cases, by age group — Paraguay, October 1, 2022–March 11, 2023



* Deaths per 100 cases.

1. Torales M, et al. MMWR Morb Mortal Wkly Rep 2023

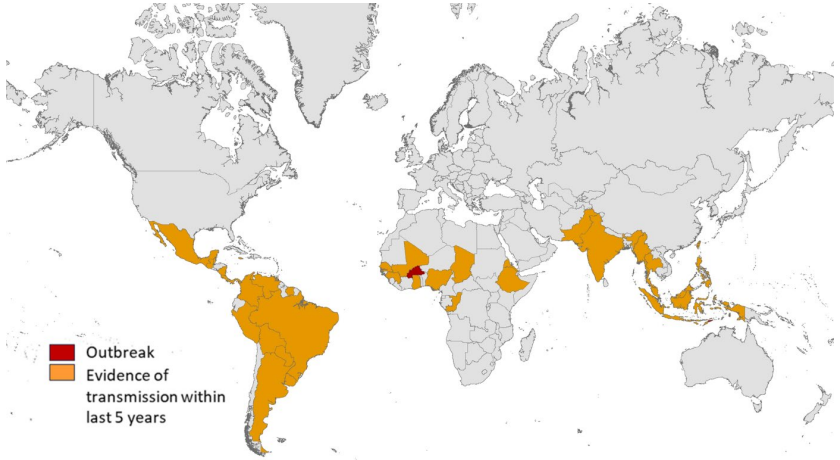
Travel for cumulative period of ≥6 months

- Key risk factor for chikungunya virus infection is intensity of transmission
  - If equivalent transmission, cumulative duration of exposure important
- Transmission patterns can be unpredictable over longer term and likely some seasonal variation in mosquito activity impacting risk
- Expatriates in location with risk might not have access to vaccine if risk increased or outbreak began

Providing clarity on evidence of chikungunya virus transmission among humans within the last 5 years

- Rationale: 5-year time frame provides interval that allows reasonable confidence there is transmission or insufficient transmission to be concern for travelers

- Tool: Map that shows countries with chikungunya virus transmission among humans reported during last 5 years, posted on CDC website



Mock-up map to demonstrate transmission of chikungunya virus among humans during last 5 years

Providing clarity on moderate exposure

- Travelers who might have at least 2 weeks (cumulative) of exposure to mosquitoes in indoor and/or outdoor settings
- Does not include travelers who might have limited exposure to mosquitoes (e.g., those traveling for business and likely to be mainly in mosquito-protected indoor settings)

Work Group deliberations when developing recommendations

- Aim to balance desirable and undesirable effects of vaccination
  - “Recommended”: for travelers with highest risk
  - “May be considered”: some individuals might reasonably choose vaccination and some providers might wish to recommend it

Draft recommendations

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  - Persons aged >65 years, particularly those with underlying medical conditions, who are likely to have at least moderate exposure* to mosquitoes, OR
  - Persons staying for a cumulative period of 6 months or more

*Moderate exposure could include travelers who might have at least 2 weeks (cumulative) of exposure to mosquitoes in indoor and/or outdoor settings