



EVIDENCE TO RECOMMENDATIONS FOR CHIKUNGUNYA VACCINE USE AMONG ADULT TRAVELERS

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Chikungunya virus and transmission

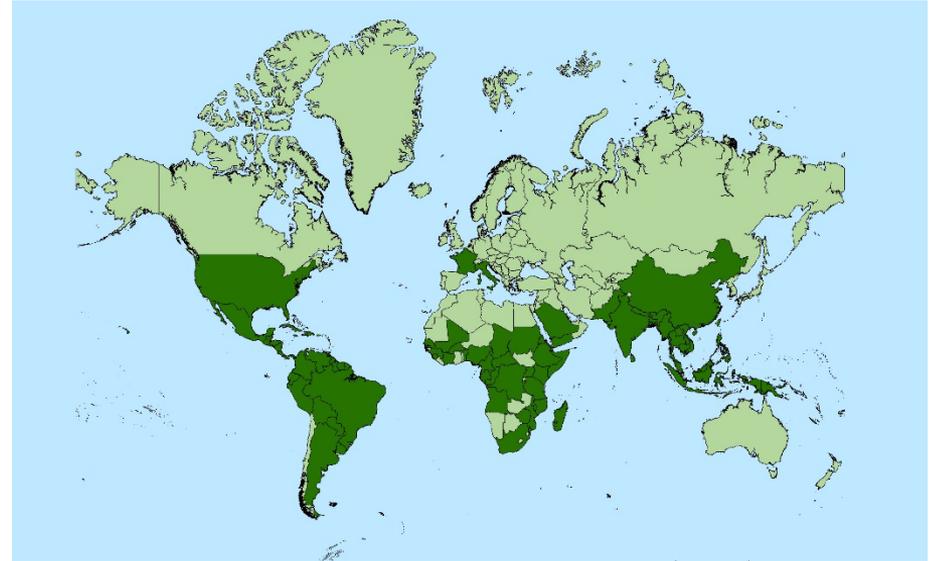
- Alphavirus
- Primarily transmitted by *Aedes aegypti* and *Aedes albopictus*
- Uncommon modes of transmission
 - Laboratory exposure
 - Intrauterine and intrapartum
 - Bloodborne transmission through needlestick



Distribution

- Tropical and subtropical regions
- Large outbreaks have occurred in most parts of the world
 - Often high attack rates

Countries and territories with current or past transmission of chikungunya virus



<https://www.cdc.gov/chikungunya/geo/index.html>

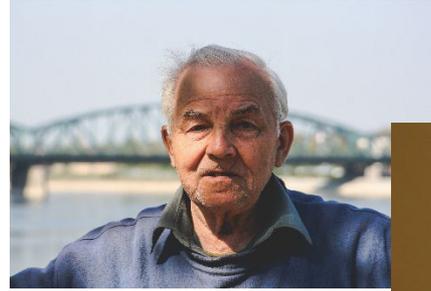
Clinical features of acute chikungunya virus infection

- Febrile illness with arthralgia which is often severe and debilitating
- Rare serious complications (e.g., neurologic illness, myocarditis, hepatic or renal disease)
- No anti-viral treatment



Risk factors for severe disease

- Age >65 years
- Age <1 year
- Underlying medical conditions (e.g., diabetes, heart disease, hypertension)
- Intrapartum transmission



Chikungunya vaccine

- Live attenuated vaccine manufactured by Valneva
- Single dose primary schedule
- Initial licensure for adults aged ≥ 18 years
- Currently under consideration by US Food & Drug Administration
- Not yet licensed anywhere in world
- No existing vaccine recommendations from ACIP or other vaccine advisory groups

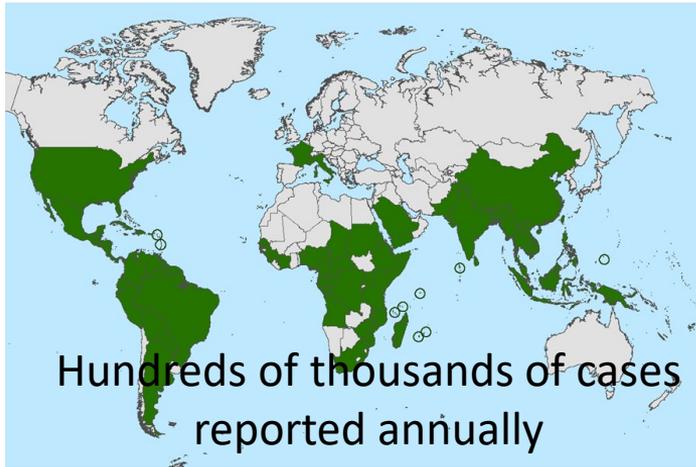
Evidence to Recommendations for chikungunya vaccination for travelers

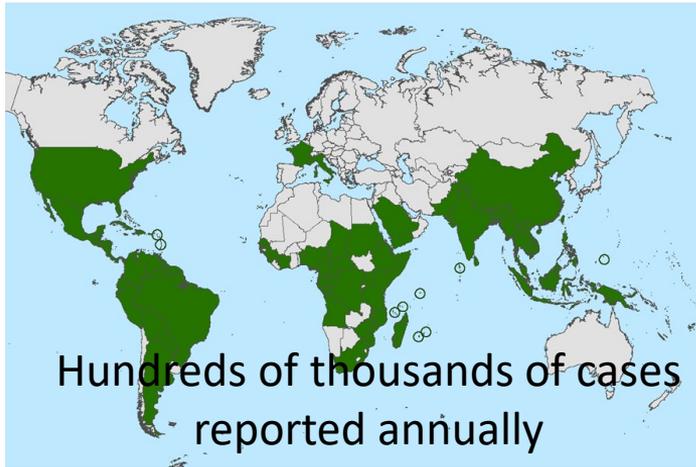
Policy question

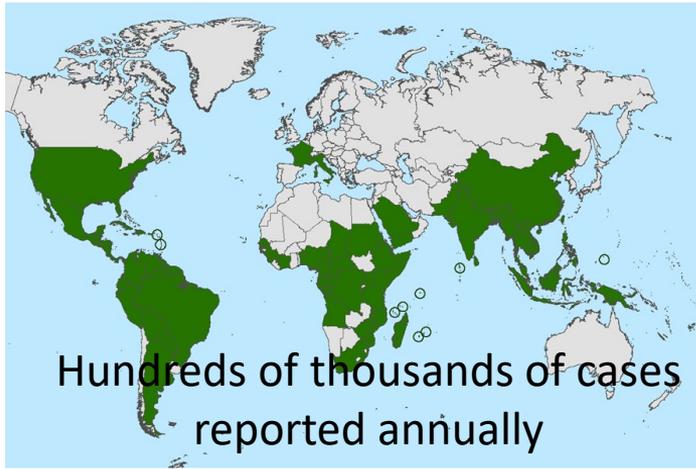
Should chikungunya vaccine be recommended for use in persons aged ≥ 18 years traveling to areas with risk of chikungunya virus transmission?

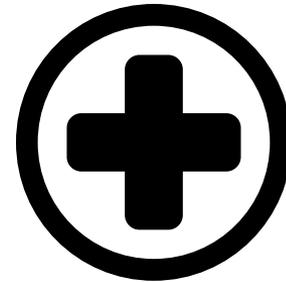
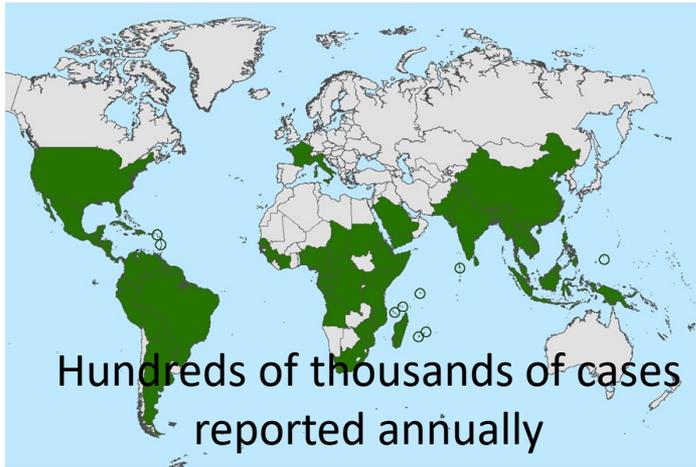
Domain 1. Public health problem

Is chikungunya of public health importance?









Mortality <1%

Public health problem

Is chikungunya of public health importance?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Domain 2: Benefits and harms of chikungunya vaccine

How substantial are the desirable anticipated effects?

Short-term and long-term protection from disease

- No efficacy data so immunogenicity data reviewed
 - No correlate of protection
- Licensure through Accelerated Approval pathway
 - Effectiveness demonstrated by clinical trials showing vaccine has effect on surrogate endpoint reasonably likely to predict clinical benefit
 - Vaccine effectiveness will need to be confirmed in post-licensure field studies
- Marker of protection based on neutralizing antibody titer estimated from validated non-human primate model

Seroresponse at 28 days after vaccination

- Two studies
 - One randomized controlled trial
 - One lot-to-lot consistency study with no placebo group
- Total of 622 subjects
- Seroresponse at 28 days: $\geq 98\%$
- None of 96 subjects in placebo arm of randomized controlled trial had seroresponse

Seroresponse at 12 months after vaccination

- One study with 360 subjects
- Seroresponse at 12 months: 99%

How substantial are the desirable anticipated effects?

- Minimal Small Moderate Large Varies Don't know

How substantial are the undesirable anticipated effects?

Serious adverse events (SAE) within 6 months

■ SAE

- 51 (**1.5%**) of 3,490 **vaccinated** subjects in 2 trials reported SAE
- 8 (**0.8%**) of 1,033 **placebo** recipients in randomized controlled trial reported SAE*

■ Related SAEs

- 2 events (**0.1%**) considered vaccine-related by study investigators
 - Hospitalization for severe myalgia
 - Hospitalization for myalgia, high fever, syndrome of inappropriate antidiuretic hormone excretion, and atrial fibrillation

*No significant difference from vaccine group; 46 (1.5%) of 3,082 vaccinated subjects in randomized, controlled trial

Arthralgia and arthritis in randomized controlled trial*

	Vaccinated group (N=3082)		Placebo group (N=1033)		Risk ratio	(95% CI)
	n	(%)	n	(%)		
Any arthralgia within 10 days [#]	520	(17%)	50	(5%)	3.5	(2.6, 4.6) [‡]
Severe arthralgia within 10 days ^{#,€}	9	(0.3%)	0	(0%)	6.0	(0.4, 104.2)
Persistent arthralgia [‡]	9	(0.3%)	4	(0.4%)	0.8	(0.2, 2.4)
Arthritis within 6 months [£]	5	(0.2%)	2	(0.2%)	0.8	(0.2, 4.3)
New onset or worsening osteoarthritis within 6 months [£]	12	(0.4%)	2	(0.2%)	2	(0.5, 9.0)

[#]Solicited adverse event; [‡]Significant difference; [€]Severe arthralgia defined as an event that prevented daily activity;

[‡]Commencing within 10 days and with duration >15 days; [£]Unsolicited adverse event

*Similar percentage of events in vaccinated subjects in lot-to-lot consistency study (N=408) without placebo control group

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How substantial are the undesirable anticipated effects?

- Minimal Small Moderate Large Varies Don't know

Do the desirable effects outweigh the undesirable effects?



Balance of desirable and undesirable effects

- High seroresponse rates through at least 1 year after vaccination
- No serious safety concerns identified in trials performed to date
- Prevents disease that can result in severe arthralgia during acute illness, rare serious complications, and sometimes long-term arthralgia
- Healthcare provider should discuss desirable and undesirable effects of vaccination and individual risk based on disease risk at destination, activities, and personal factors
 - For some travelers, even low probability of SAE might be higher than disease risk
 - Target vaccine to travelers at higher risk for disease

Do the desirable effects outweigh the undesirable effects?

Favors
intervention

Favors
comparison

Favors
both

Favors
neither

Varies

Don't
know

What is the overall certainty of the evidence for the critical outcomes?



What is the overall certainty of the evidence for protection from chikungunya?

No studies found Very low Low Moderate High

- No vaccine efficacy data, no immunologic correlate of protection, protection based on surrogate endpoint reasonably likely to predict clinical benefit and requiring confirmation by post-licensure vaccine effectiveness studies



What is the overall certainty of the evidence for safety of chikungunya vaccination?

No studies found Very low Low Moderate High

- Number of subjects in trials insufficient to detect rare adverse events, confidence intervals indicated potential for benefit or harm, and/or suboptimal method for collection of specific outcome information



Domain 3. Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

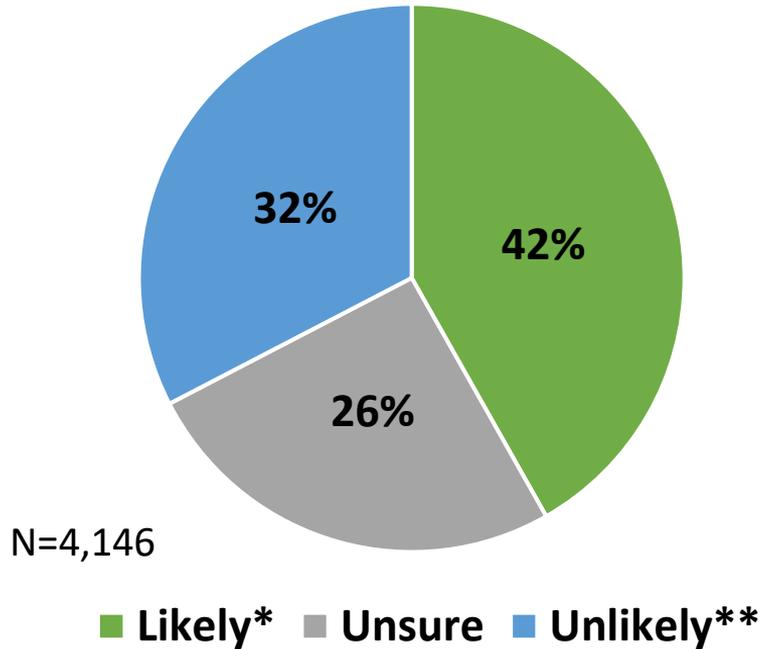
Is there important uncertainty about or variability in how much people value the main outcomes?

Perceptions among US adults aged ≥ 18 years of the value of a chikungunya vaccine (CDC study)

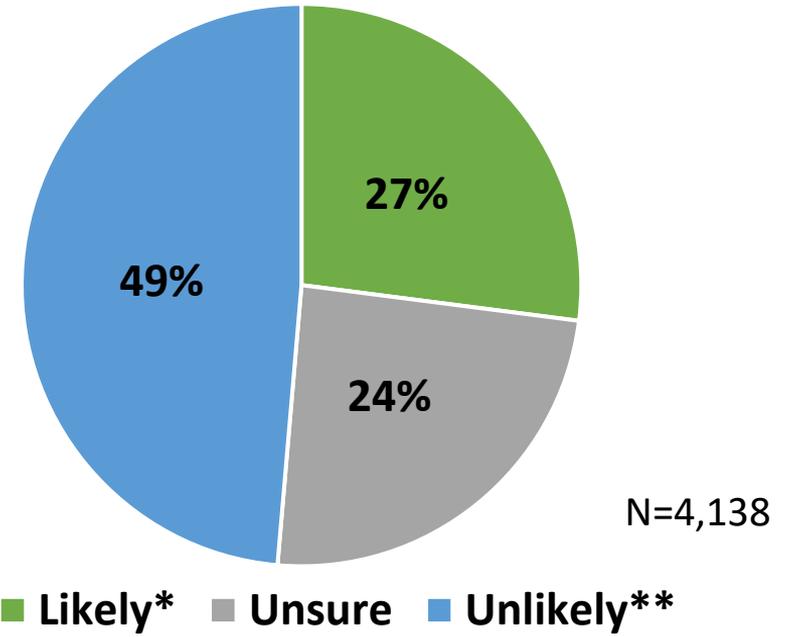
- Online survey conducted in 2022
- Participants provided information on
 - Risk for disease with travel during outbreak or non-outbreak periods
 - Rates of chronic arthralgia after chikungunya
 - Vaccine cost

Results

Outbreak period (risk of 1 in 150)



Non-outbreak period (risk of 1 in 15,000)



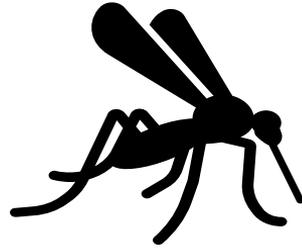
*Includes very and somewhat likely responses

**Includes very and somewhat unlikely responses

Variability in responses

- Lower likelihood of vaccination
 - Persons aged 18–29 years
 - Lower education
 - Lower household income
 - Black race

Important factors in decision-making



Risk of disease



Vaccine side effects



Avoid risk of long-term joint pain



Vaccine cost

Perceptions among US adults aged ≥ 18 years of value of chikungunya vaccine (Valneva study)

- Online survey conducted in 2021
- 2,002 US residents who had traveled internationally during last 3 years or planned to do so within next 3 years
- Limited information about participants provided but anyone who self-identified as 'anti-vaccination' excluded

Results

- After being provided basic information on chikungunya and its sequelae
 - 72% were very or somewhat likely to ask healthcare provider about a vaccine
 - 81% were very or somewhat likely to be vaccinated if recommended by healthcare provider

Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Important uncertainty or variability

Probably important uncertainty or variability

Probably not important uncertainty or variability

No important uncertainty or variability

No known undesirable outcomes

Domain 4. Acceptability

Is chikungunya vaccine acceptable to key stakeholders?

Acceptability to key stakeholders



- Travel medicine and other healthcare providers
 - Online survey in 2021 (Valneva) among 158 US healthcare providers who routinely provide travel health services indicated 87% were very or somewhat likely to recommend vaccine if recommended by ACIP



- Travelers
 - Option for protection from a disease that can cause severe arthralgia and potentially long-term joint pain

Acceptability

Is the intervention acceptable to key stakeholders?

- No Probably no Probably yes Yes Varies Don't know

Domain 5. Resource use

Is chikungunya vaccination a reasonable and efficient allocation of resources?

Cost-effectiveness considerations

- No cost-effectiveness analysis (CEA)
 - Most travel vaccines are not cost-effective
 - Chikungunya vaccine for travelers is not likely to be cost-effective
- CEA less relevant for travel vaccine
 - Decision is for individual traveler and not for population
 - Vaccine paid for by traveler and generally not covered by insurance
- Vaccine recommendations targeting higher risk travelers probably reasonable allocation of resources
 - Financial implications borne by travelers most at risk and who benefit most

Resource use

Is chikungunya vaccination a reasonable and efficient allocation of resources?

- No Probably no Probably yes Yes Varies Don't know

Domain 6. Equity

What would be the impact on health equity?

Health equity considerations

- Vaccine primarily paid for out of pocket
 - Some travelers not have resources to pay for vaccine
- Travel medicine providers likely have better awareness of disease and vaccine availability than non-specialist providers
 - People with fewer resources less likely to attend travel medicine provider
- Chikungunya vaccine recommendations cannot address these issues

Equity

What would be the impact on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know

Domain 7. Feasibility

Is the intervention feasible to implement?

Feasibility considerations

- Single dose primary series allows administration in pre-travel consultation
- Disease risk highest, and vaccination most of benefit, during outbreaks
 - Challenge with delay in awareness of outbreaks
 - CDC will post information on website once aware of outbreaks

Feasibility

Is the intervention feasible to implement?

- No Probably no Probably yes Yes Varies Don't know

Balance of consequences

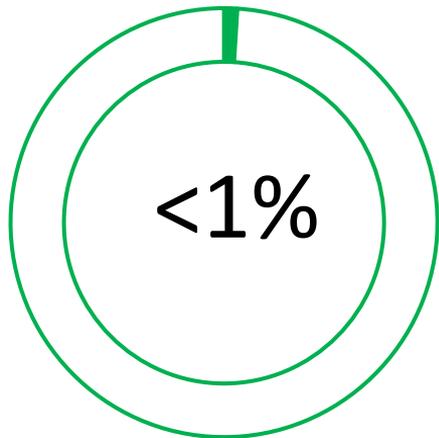
- Undesirable consequences *clearly outweigh* desirable consequences in most settings
- Undesirable consequences *probably outweigh* desirable consequences in most settings
- The balance between desirable and undesirable consequences *is closely balanced or uncertain*
- Desirable consequences *probably outweigh* undesirable consequences in most settings
- Desirable consequences *clearly outweigh* undesirable consequences in most settings
- There is insufficient evidence to determine the balance of consequences

Draft recommendations for ACIP's consideration

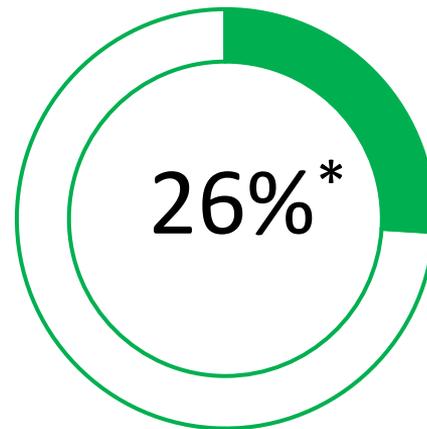
Draft recommendations

- 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
 - Older persons (e.g., >65 years), particularly those with underlying medical conditions, who are likely to have at least moderate exposure to mosquitoes
 - Persons staying for a cumulative period of 6 months or more during a 2-year period

Example of data supporting recommendation: Substantially higher risk for travelers during outbreak, Paraguay 2023



Percentage of all US persons traveling to areas with chikungunya risk visiting Paraguay



Percentage of all reported US traveler chikungunya cases whose travel destination was Paraguay

*18 of 69 travelers with destination data, preliminary ArboNET data, 2023

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

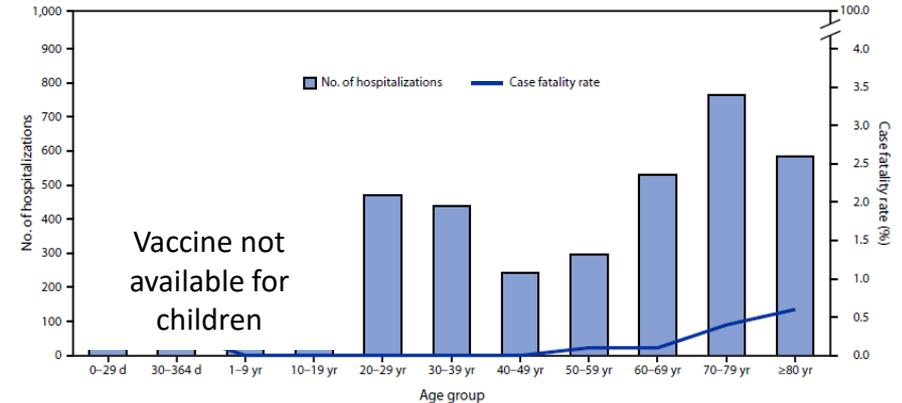
Shared clinical decision-making recommendation

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Older persons, particularly those with underlying medical conditions?

- Key risk factors for severe disease
 - Older age
 - Underlying medical conditions
- Key risk factors for chronic arthralgia
 - Older age
 - Presence of pre-existing joint problems
- Risk for higher morbidity and mortality in older persons supported by data from recent outbreak in Paraguay¹

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



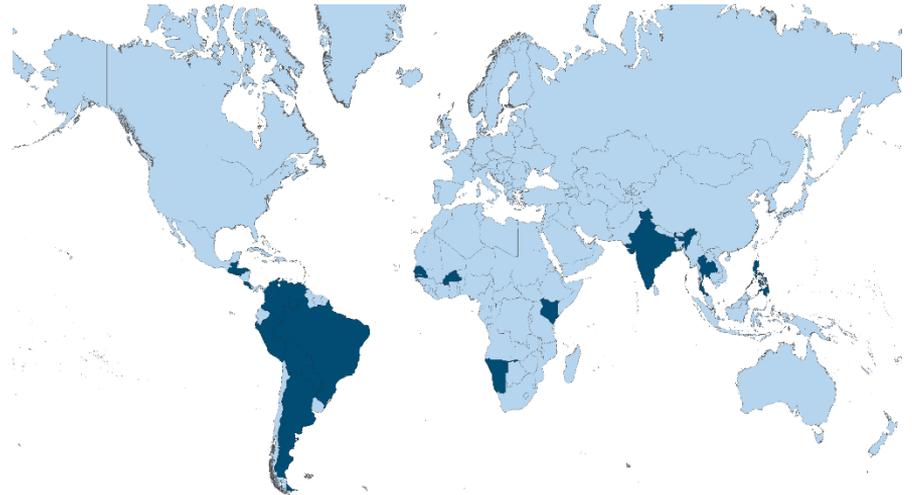
Cumulative period of ≥ 6 months during 2-year period*

- 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 the longer term and likely to be some seasonal variation in mosquito activity that might impact risk

*2-year period based on immunogenicity data showing high seroresponse rate (99%) at one year after vaccination suggesting good protection at least through second year but no longer-term data

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

Moderate exposure

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

General considerations*

- All persons who travel to areas with possible chikungunya virus transmission should be advised to take precautions to avoid mosquito bites

- The risk for chikungunya for most US travelers to countries or territories with evidence of transmission is low. However, some travelers are at increased risk for infection or more severe disease. In the discussion between the healthcare provider and traveler on the need for vaccination, consideration should be given to
 - 1) whether there is a recognized outbreak or ongoing disease activity
 - 2) the duration of travel or residence, including likelihood of future travel to an area with chikungunya virus transmission
 - 3) the likelihood of exposure to Aedes mosquitoes
 - 4) older age (e.g., >65 years)
 - 5) underlying medical conditions that increase the risk for severe disease (e.g., diabetes, cardiac disease, hypertension)
 - 6) underlying conditions that increase the risk for chronic arthralgia after infection (e.g., existing joint disease)
 - 7) an individual's personal perception and tolerance of risk

* Provided in background materials

Draft recommendations

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 - Older persons (e.g., >65 years), particularly those with underlying medical conditions, who are likely to have at least moderate exposure* to mosquitoes
 - Persons staying for a cumulative period of 6 months or more during a 2-year period

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