Evidence to Recommendations and proposed recommendations for use of virus-like particle chikungunya vaccine among adolescent and adult travelers

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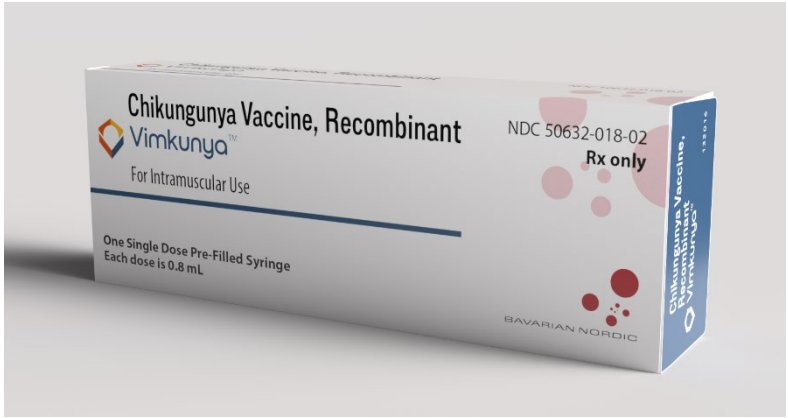
Virus-like particle chikungunya vaccine (CHIK-VLP) and its licensure

CHIK-VLP

- Manufactured by Bavarian Nordic (trade name: VIMKUNYA™)
- Licensed in United States on February 14, 2025
- Indicated for use in persons aged ≥12 years
- Single dose primary schedule



Licensure

- Licensed through Accelerated Approval pathway used for products for **serious conditions** and that fill **unmet medical need**
  - Traditional approval challenging as efficacy trial difficult when outbreaks unpredictable and duration can be short, and no established immunologic correlate of protection
- **Effectiveness** demonstrated based on adequate and well-controlled trials showing vaccine has effect on surrogate endpoint reasonably likely to predict clinical benefit
  - CHIK-VLP surrogate was chikungunya neutralizing antibody titer threshold preventing viremia in non-human primates challenged with virus
- Regardless of licensure pathway, **safety** must be assessed in adequate and well-controlled studies with appropriate safety sample size

Post-marketing study

- Under FDA regulations, post-marketing clinical trial required to confirm clinical benefit
- Randomized, double-blind, placebo-controlled study planned to evaluate efficacy, safety, and immunogenicity of CHIK-VLP

Evidence to Recommendations for use of CHIK-VLP among travelers aged ≥12 years

Policy question

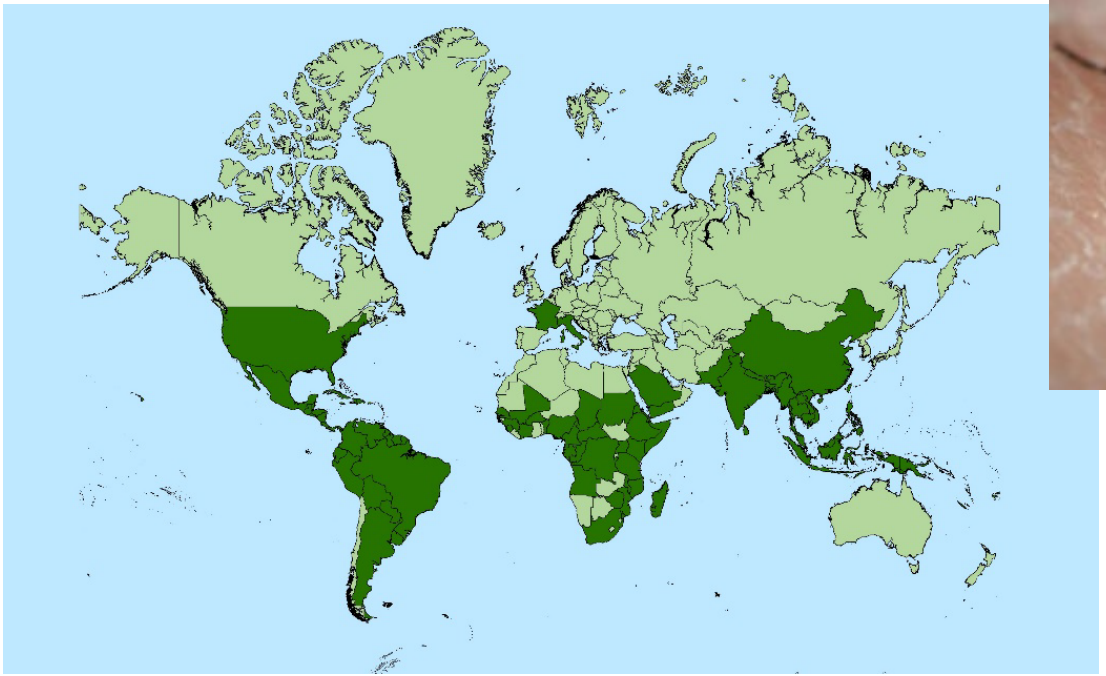
Should CHIK-VLP be recommended for use in persons aged ≥12 years traveling to areas with risk of chikungunya virus transmission?

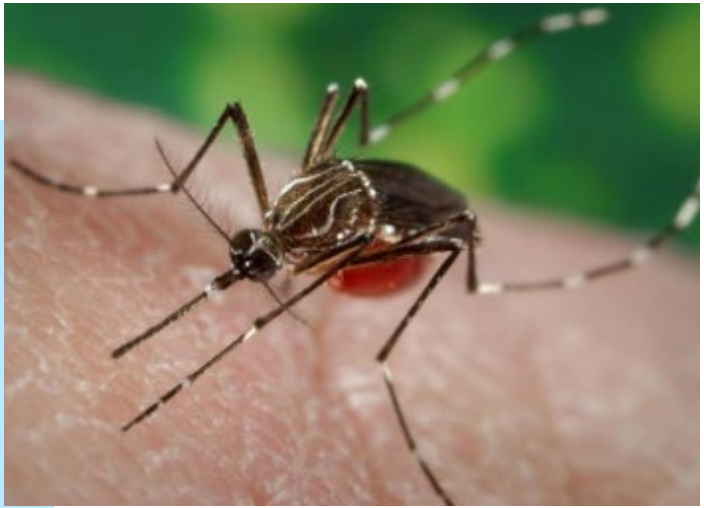
EtR framework

EtR Domain	Question
Public health problem	• Is the problem *(chikungunya)* of public health importance?
Benefits and harms	• How substantial are the desirable anticipated effects of CHIK-VLP? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects? • What is the overall certainty of this evidence for the critical outcomes?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcomes?
Acceptability	• Is the intervention acceptable to key stakeholders?
Resource use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?
Feasibility	• Is the intervention feasible to implement?

Domain 1: Public Health Problem

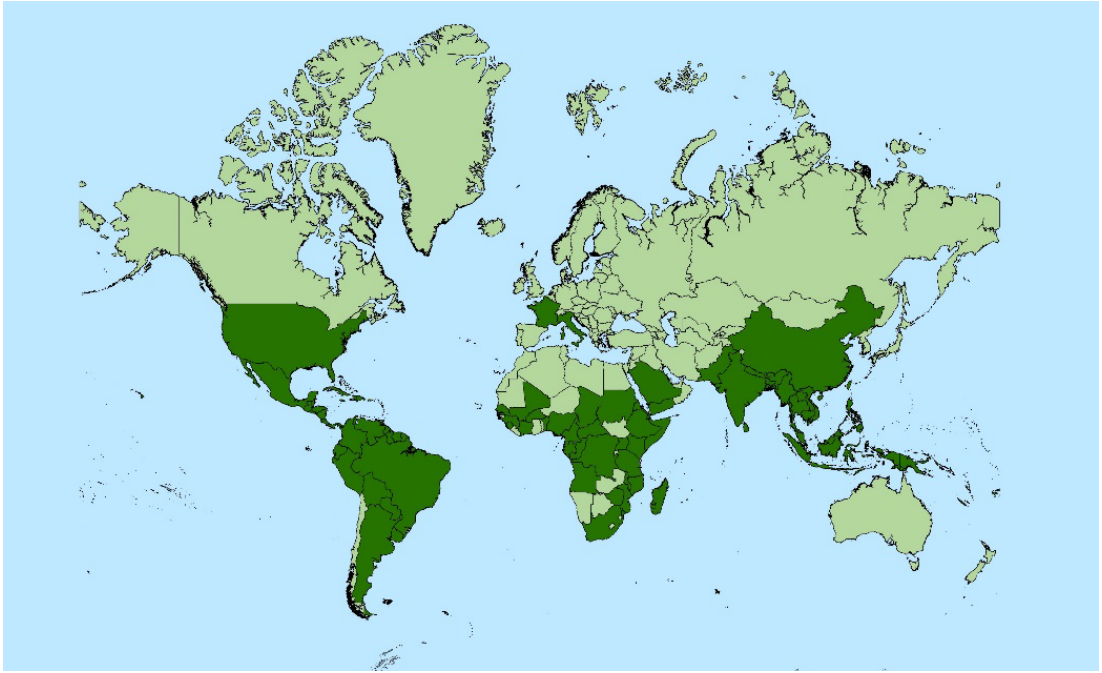
Chikungunya virus transmission





Countries and territories with current or past transmission of chikungunya virus

Chikungunya virus disease cases



Countries and territories with current or past transmission of chikungunya virus

Globally, ~620,000 cases reported in 2024 but likely underestimate

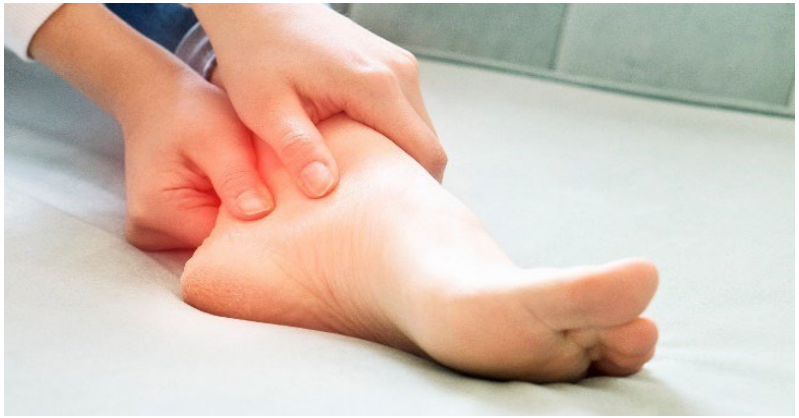
Outbreaks can be large and explosive

- One-third to three-quarters of population affected
- Substantial morbidity
- Stresses healthcare capacity

Impact of acute illness

- Fever and polyarthralgia
  - Arthralgia often severe and can be debilitating
  - Multiple joints involved, most commonly hands and feet
- Other symptoms include headache, myalgia, fatigue, rash, abdominal pain, and vomiting
- No anti-viral treatment
  - Supportive management

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



Impact of disease: severe presentations

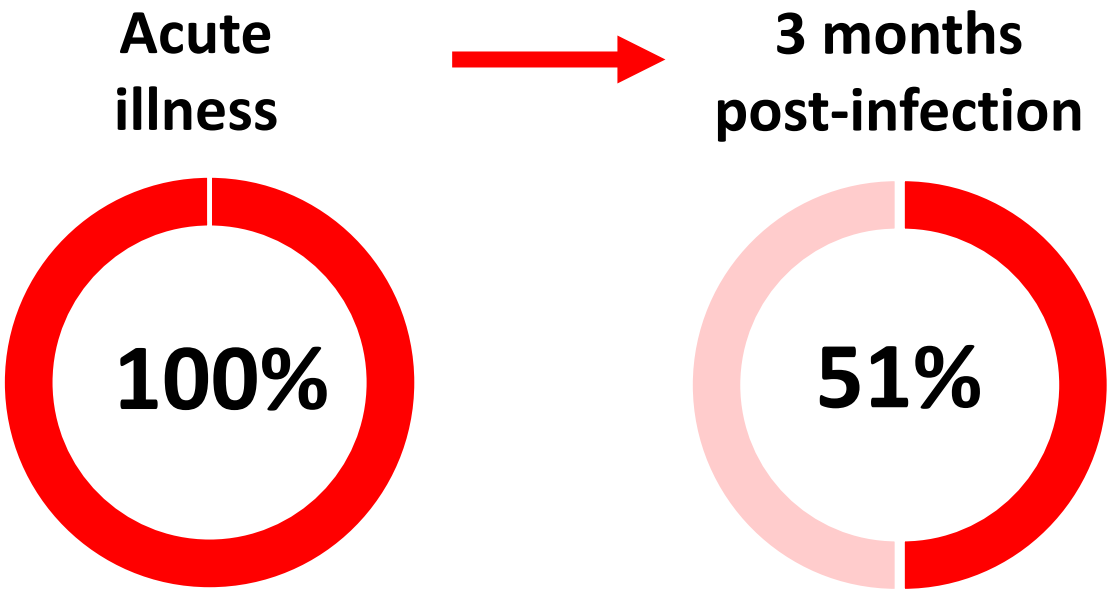
- Cases of severe illness uncommon
  - **Infection-related** (e.g., encephalitis, myocarditis)
  - **Exacerbation of underlying medical conditions**
- Rare deaths
  - Case fatality rate: 0.01%–0.5%
  - Mostly in **older adults**, particularly those with comorbidities, and **young infants** infected through intrapartum transmission or by mosquito bites

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

Impact of disease: Arthralgia that persists or recurs

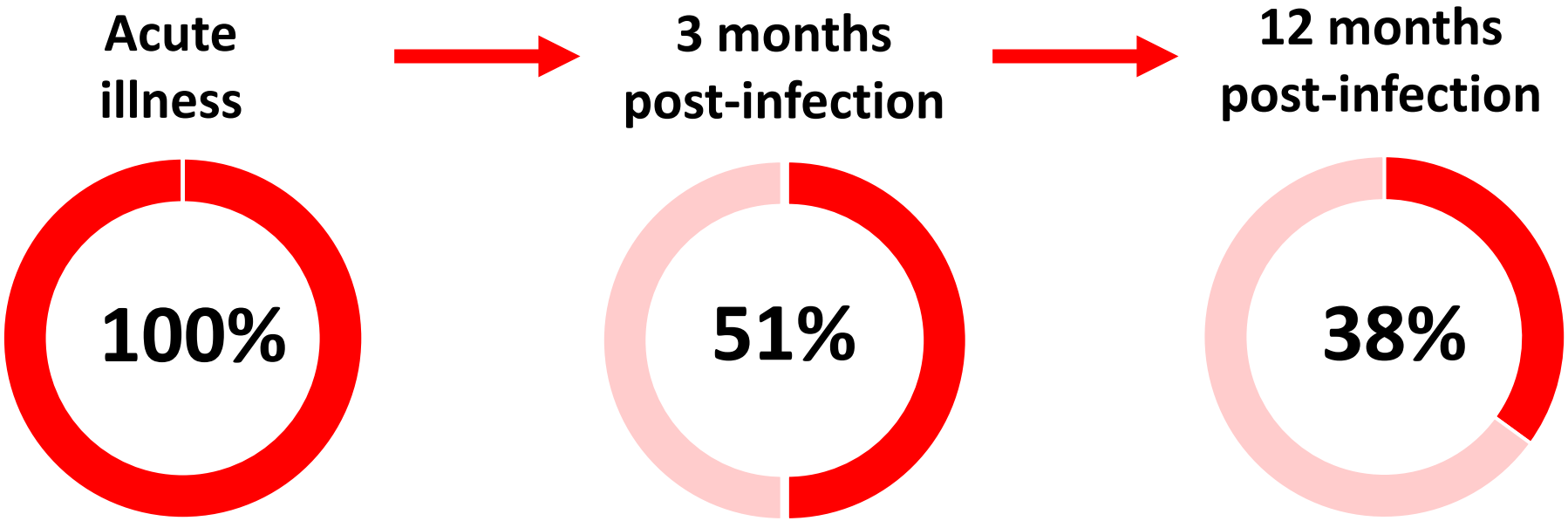
- Most patients have arthralgia that resolves in 7–10 days
- Arthralgia sometimes persists or relapses with other symptoms e.g., fatigue
- Rates of ongoing arthralgia vary based on several factors e.g., severity of acute illness, age, pre-existing joint problems

Impact of disease: Arthralgia that persists or recurs



Based on recent meta-analysis (Lindsey N. Chronic arthralgia after chikungunya. US Advisory Committee on Immunization Practices meeting, June 2023)*

Impact of disease: Arthralgia that persists or recurs

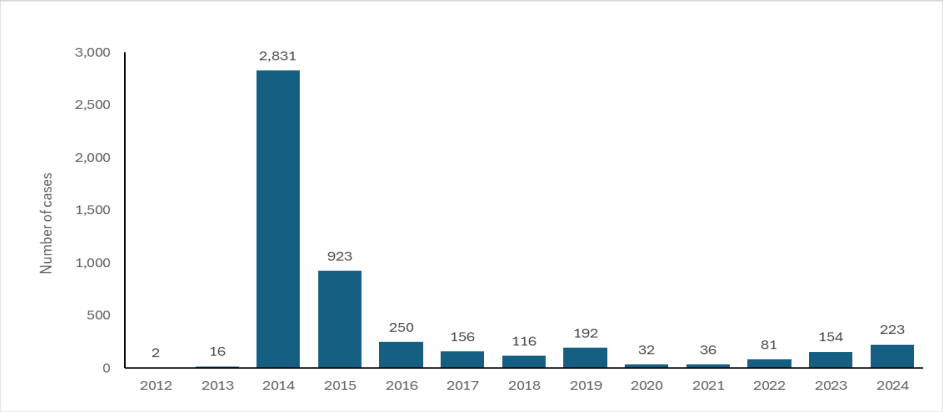


Based on recent meta-analysis (Lindsey N. Chronic arthralgia after chikungunya. US Advisory Committee on Immunization Practices meeting, June 2023)*
*Rates likely overestimated as background rate of arthralgia in the population could not be taken into account

Is chikungunya a problem of public health importance for US travelers?

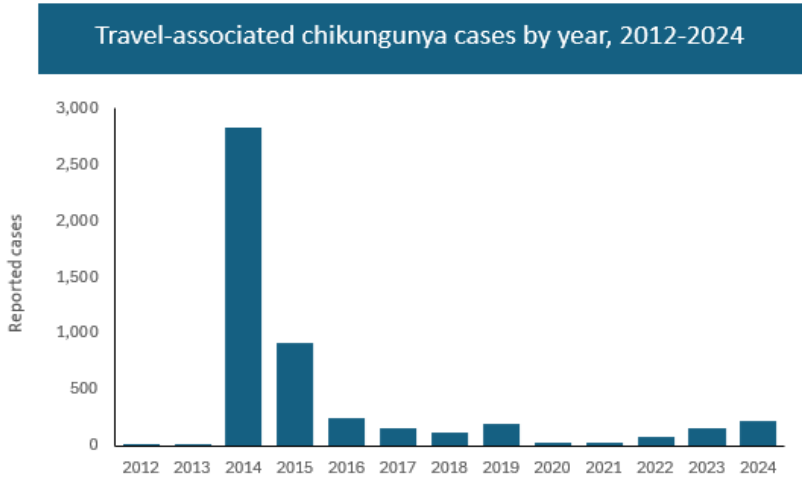
- Risk highly variable from location-to-location and from year-to-year
- 2014–2015: High case load during outbreak in the Americas
- 2022–2024: 100–200 US traveler cases/year although extent of underdiagnosis and underreporting unknown

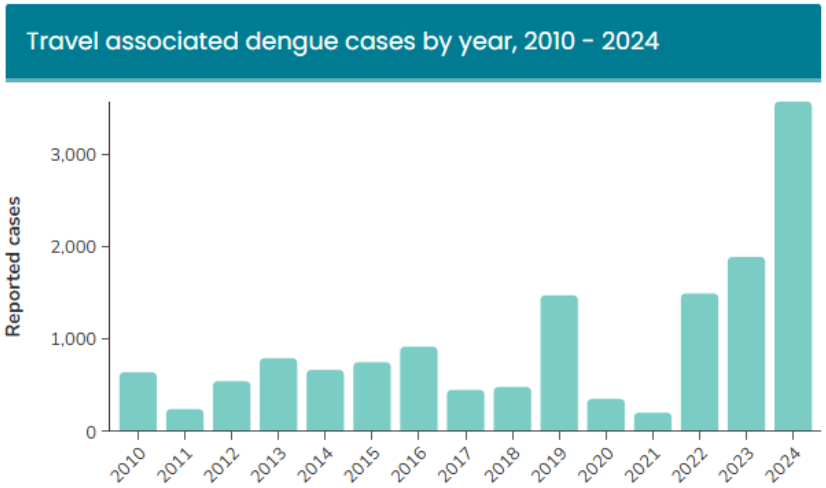
Chikungunya cases in US travelers reported to CDC, 2012–2024 (N=5,012)*



*2024 data are provisional

Comparison of chikungunya vs. dengue cases among travelers





Except during 2014–2015, **3–18 times <u>fewer</u> chikungunya** cases reported annually as dengue cases

Chikungunya risk estimates for travelers for 1 week travel to outbreak or non-outbreak area*

- Travelers to **outbreak** area for **1 week**
  - Clinical disease: 667 cases per 100,000
  - Hospitalization: 27 cases per 100,000
  - Chronic arthralgia of any severity at 12 months: 253 cases per 100,000

*Based on unpublished data gathered during outbreaks in Puerto Rico and United States Virgin Islands with potential limitations and calculations requiring assumptions

Chikungunya risk estimates for travelers for 1 week travel to outbreak or non-outbreak area*

- Travelers to **outbreak** area for **1 week**
  - Clinical disease: 667 cases per 100,000
  - Hospitalization: 27 cases per 100,000
  - Chronic arthralgia of any severity at 12 months: 253 cases per 100,000
- Travelers to **non-outbreak** area for **1 week**
  - Clinical disease: 6.7 cases per 100,000
  - Hospitalization: 0.3 cases per 100,000
  - Chronic arthralgia of any severity at 12 months: 2.5 cases per 100,000

*Based on unpublished data gathered during outbreaks in Puerto Rico and United States Virgin Islands with potential limitations and calculations requiring assumptions

Chikungunya risk estimates for travelers to non-outbreak area for 1 week or 6 months*

- Travelers visiting **non-outbreak** area for **1 week**
  - Clinical disease: 6.7 cases per 100,000
  - Hospitalization: 0.3 cases per 100,000
  - Chronic arthralgia of any severity at 12 months: 2.5 cases per 100,000
- Travelers visiting **non-outbreak** area for **6 months**
  - Clinical disease: 176 cases per 100,000
  - Hospitalization: 7 cases per 100,000
  - Chronic arthralgia of any severity at 12 months: 67 cases per 100,000

*Based on unpublished data gathered during outbreaks in Puerto Rico and United States Virgin Islands with potential limitations and calculations requiring assumptions

Question: Is chikungunya of public health importance?

- ☐ No
- ☐ Probably no
- ☐ Probably yes
- ☐ Yes
- ☐ Varies
- ☐ Don’t know

- For **US travelers**
  - **Most important** factor is **level of chikungunya virus transmission at destination**
  - Additional factors are **travel duration** and **other considerations** (e.g., age, underlying medical conditions)

Domain 2: Benefits and Harms of CHIK-VLP

Desirable anticipated effects of vaccination

Critical GRADE outcomes	Comment
Short-term vaccine efficacy (i.e., at 21 days) against disease	Immunogenicity data only
Long-term vaccine efficacy (i.e., at 12 months) against disease	Immunogenicity data only

- No established immunologic correlate of protection
  - Surrogate marker of protection based on neutralizing antibody titer estimated from validated non-human primate model

Seroresponse rate at 21 days after vaccination*

- Key results from two randomized controlled trials
  - Adolescents and adults aged 12–64 years (N=2,559 subjects with results in vaccine arm)
  - Older adults aged ≥65 years (N=189 subjects with results in vaccine arm)

- **Seroresponse rate 97% overall**
  - 98% in ages 12–64 years vs. 87% in ages ≥65 years

*Percent of subjects with anti-chikungunya virus 80% serum neutralizing antibody titer ≥100

Seroresponse rate at 12 months after vaccination*

- Long-term results from Phase 3 study not yet available
- Results from one Phase 2 study with data collection at 11 months
  - Adults aged 18–45 years (N=46 subjects with results)
  - Seroresponse rate 91%
- Given limited data, also reviewed Phase 3 study results at 6 months
  - Adolescents and adults aged 12–64 years: seroresponse rate 85% (1967/2301)
  - Older adults aged ≥65 years: seroresponse rate 76% (139/184)

*Percent of subjects with anti-chikungunya virus 80% serum neutralizing antibody titer ≥100

Question: How substantial are the desirable anticipated effects?

- ☐ Minimal
- ☐ Small
- ☐ Moderate
- ☐ Large
- ☐ Varies
- ☐ Don’t know

Undesirable anticipated effects of vaccination

Critical outcomes	
Serious adverse events (SAEs)	All SAEs and related SAEs
Arthralgia/arthritis	All arthralgia, severe arthralgia, persistent arthralgia, and arthritis

SAEs within 6 months

- **SAE**
  - 0.9% (27 of 2,996) vaccinated subjects in 2 randomized trials
  - 0.6% (4 of 671) placebo recipients*

- **Related SAE**
  - 1 event (0.03%) considered possibly vaccine-related by site investigator
    - Retinal detachment in subject with history of seeing black spots in same eye 1 month pre-study#

*Not significantly different; #Considered unrelated by Safety Monitoring Committee Chair

Arthralgia and arthritis after vaccination

- Results from 3 randomized studies
- **Arthralgia within 7 days**
  - **7%** (221 of 3,019) vaccinated vs. **6%** (52 of 866) placebo recipients*
- **Severe arthralgia[#] within 7 days**
  - **0.2%** (7 of 3,019) vaccinated vs. **0.2%** (2 of 866) placebo recipients*
- **Persistent arthralgia commencing within 7 days and with duration >15 days**
  - **0.03%** (1 of 3,019) vaccinated vs. **0%** (0 of 866) placebo recipients*
- **Arthritis within 28 days**
  - **0.03%** (1 of 3,048) vaccinated vs. **0%** (0 of 723) placebo recipients*

*Not significantly different; [#]Event that prevented daily activity in accordance with US FDA toxicity grading scale

Question: How substantial are the undesirable anticipated effects?

- ☐ Minimal
- ☐ Small
- ☐ Moderate
- ☐ Large
- ☐ Varies
- ☐ Don’t know

- Rates of SAEs and all arthralgia/arthritis outcomes not significantly different in vaccine and placebo groups
- Unclear determination of relatedness for SAE reported as related

Do the desirable effects outweigh the undesirable effects?

Very good short-term seroresponse rates and similar rates of adverse events in vaccine and placebo groups

Can prevent acute illness that can be severe, rare serious complications, and long-term arthralgia

Possibility of rare SAEs; with safety results from ~3,000 subjects, post-marketing safety surveillance important

Do the desirable effects outweigh the undesirable effects?

- ☐ Favors intervention
- ☐ Favors comparison
- ☐ Favors both
- ☐ Favors neither
- ☐ Varies
- ☐ Don’t know

- Risk varies substantially and inversely with chikungunya virus transmission intensity
- Risk-benefit assessment favorable **if vaccine used in line with proposed recommendations which target higher risk travelers**

Overall certainty of evidence from GRADE analysis for critical outcome of prevention of disease

Critical outcome	Certainty of evidence	Rationale
Short-term vaccine efficacy at 21 days	Low	Downgraded for very serious indirectness • No effectiveness data, immunogenicity data used • No established immunologic correlate of protection • Surrogate endpoint approved for licensure has FDA requirement for post-licensure controlled trials to confirm clinical benefit

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Short-term vaccine efficacy at 21 days	Low	Downgraded for very serious indirectness • No effectiveness data, immunogenicity data used • No established immunologic correlate of protection • Surrogate endpoint approved for licensure has FDA requirement for post-licensure controlled trials to confirm clinical benefit
Long-term vaccine efficacy at 12 months	Very low	Downgraded for very serious indirectness and imprecision • Indirectness factors as above • Results from Phase 3 trial not yet available so used data from Phase 2 study (N=46 subjects with results) supplemented by Phase 3 studies 6-month data

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GRADE summary of certainty: Low (short-term) and very low (long-term)

Summary statements on short- and long- term prevention of chikungunya by CHIK-VLP

- For short-term disease prevention, based on large effect and low certainty in the evidence
  - *CHIK-VLP might result in large increase in short-term protection against chikungunya*
- For long-term disease prevention, based on large effect and very low certainty in the evidence
  - *CHIK-VLP might result in large increase in long-term protection against chikungunya but the evidence is very uncertain*

Overall certainty of evidence from GRADE analysis for critical outcome of potential adverse events

Critical outcome	Certainty of evidence	Rationale
Any or related SAEs	Low	Downgraded for very serious imprecision • Fragility of estimate as sample size insufficient to detect rare events • 95% confidence intervals (CI) for effect estimates include potential for possible benefits or harms

Overall certainty of evidence from GRADE analysis for critical outcome of potential adverse events

Critical outcome	Certainty of evidence	Rationale
Any or related SAEs	Low	Downgraded for very serious imprecision • Fragility of estimate as sample size insufficient to detect rare events • 95% confidence intervals (CI) for effect estimates include potential for possible benefits or harms
Any, severe, or persistent arthralgia, or arthritis	Moderate	Downgraded for serious imprecision • 95% CI for effect estimate includes potential for possible benefits or harms (arthralgia) • Fragility of estimate as sample size insufficient to detect rare events (severe or persistent arthralgia, arthritis)

Overall certainty of evidence from GRADE analysis for critical outcome of potential adverse events

Critical outcome	Certainty of evidence	Rationale
Any or related SAEs	Low	Downgraded for very serious imprecision • Fragility of estimate as sample size insufficient to detect rare events • 95% confidence intervals (CI) for effect estimates include potential for possible benefits or harms
Any, severe, or persistent arthralgia, or arthritis	Moderate	Downgraded for serious imprecision • 95% CI for effect estimate includes potential for possible benefits or harms (arthralgia) • Fragility of estimate as sample size insufficient to detect rare events (severe or persistent arthralgia, arthritis)

GRADE summary of certainty: Low (based on outcome with lowest certainty level)

Summary statements on safety of CHIK-VLP

- For SAEs and related SAEs, based on small but important effect and low certainty in the evidence
  - *CHIK-VLP might result in slight increase in SAEs and related SAEs when compared with placebo*
- For arthralgia/arthritis outcomes, based on no effect and moderate certainty in the evidence
  - *CHIK-VLP probably results in little to no difference in arthralgia, severe arthralgia, persistent arthralgia, and arthritis after vaccination compared with placebo*

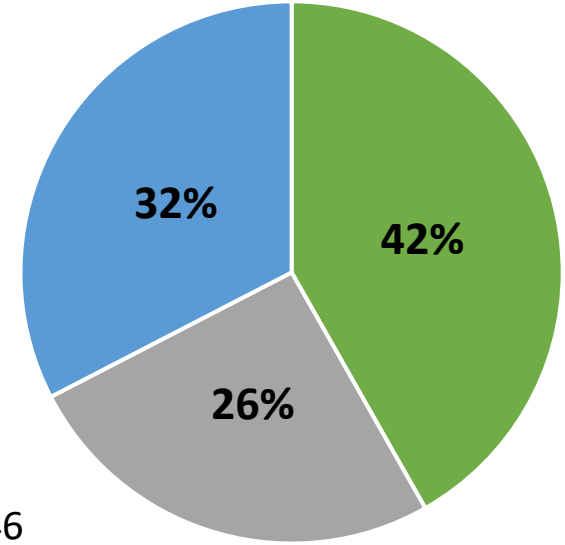
Domain 3: Values and Preferences

Perceptions of US adults aged ≥18 years of chikungunya disease and value of chikungunya vaccination

- Online CDC 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

Perceptions of US adults aged ≥18 years of chikungunya disease and value of chikungunya vaccination

Outbreak (disease risk of 1 in 150)



N=4,146

Likely* Unsure Unlikely**

*Includes very and somewhat likely responses

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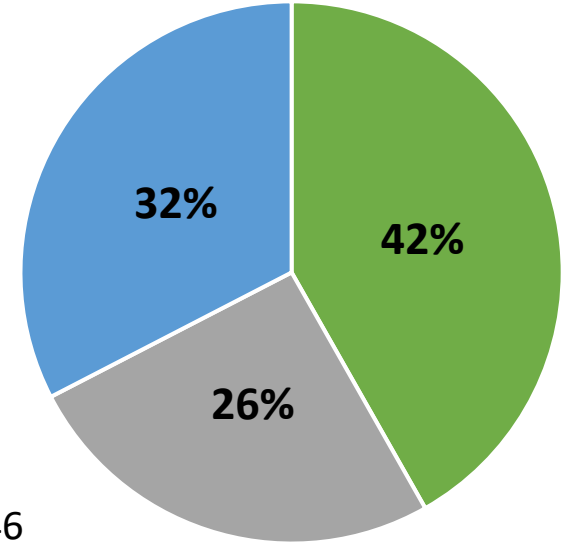
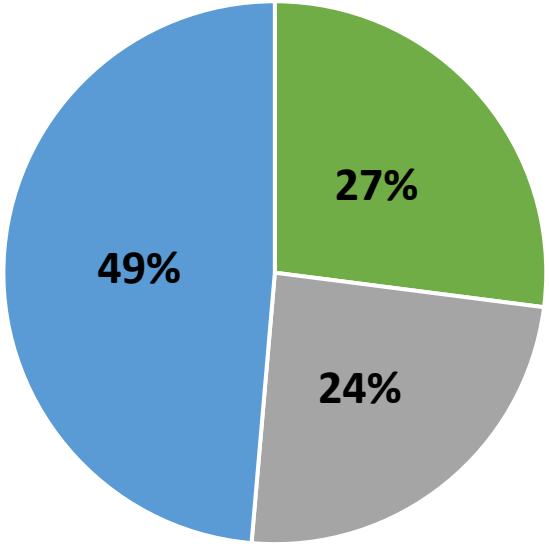


N=4,146

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



N=4,138

Likely* Unsure Unlikely**

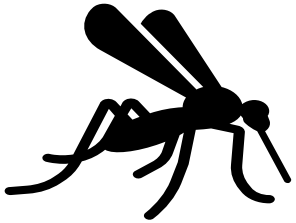
*Includes very and somewhat likely responses

**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

Avoiding long-term joint pain

Vaccine cost

Question: Does the target population feel that the desirable effects of vaccination are large relative to undesirable effects?

- ☐ No
- ☐ Probably no
- ☐ Probably yes
- ☐ Yes
- ☐ Varies
- ☐ Don’t know

- Level of **disease risk** key factor in determining likelihood of vaccination

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

- ☐ Important uncertainty or variability
- ☐ Probably not important uncertainty or variability
- ☐ No important uncertainty or variability
- ☐ No known undesirable outcomes

Domain 4: Acceptability

Acceptability to key stakeholders

- Travel medicine and other healthcare providers
  - Vaccine is tool for disease prevention in addition to guidance for mosquito bite prevention measures

- Travelers
  - Vaccine provides option to protect from disease that can cause severe acute illness and potentially long-term joint pain
  - Vaccine recommendations might allow insurance coverage

Question: Is the intervention acceptable to key stakeholders?

- ☐ No
- ☐ Probably no
- ☐ Probably yes
- ☐ Yes
- ☐ Varies
- ☐ Don’t know

Domain 5: Resource Use

Resource use considerations

- Cost-effectiveness analysis for chikungunya vaccination of travelers has not been published
- Past analyses conducted for travel vaccines indicate most travel vaccines are not cost-effective
  - Number of travelers needed to be vaccinated to prevent one case often high
- Resource use considerations less relevant for travel vaccine as not paid for by public funding
- Travelers make individual decisions based on their willingness to pay and perceptions and tolerance of risk

Question: Is the intervention a reasonable and efficient allocation of resources?

- ☐ No
- ☐ Probably no
- ☐ Probably yes
- ☐ Yes
- ☐ Varies
- ☐ Don’t know

- **Vaccine recommendations targeted to higher risk travelers** so financial implications of vaccine purchase and most benefit will be for travelers at highest risk of disease

Domain 6: Equity

Health equity considerations

- Vaccine paid for out of pocket by most travelers
  - Some travelers will have financial means to allow vaccination and others will not

Question: What would the impact be on health equity?

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

- Chikungunya vaccine recommendations cannot address this issue

Domain 7: Feasibility

Feasibility considerations

- Easy to administer in healthcare setting because of single dose primary schedule
- Resources to guide implementation will be available on CDC website, including information on areas with outbreaks and with elevated risk for US travelers
  - Possible challenge is need to regularly refer to website for current information
- Delays in recognizing outbreaks could impact implementation of outbreak recommendation and put travelers at risk
  - Risk-benefit assessment does not favor vaccinating all travelers to address this issue
- Potential challenges with availability of two chikungunya vaccines with some different indications for use, so clear information will be needed

Question: Is the option 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 CHIK-VLP for ACIP's consideration

Acknowledgment of ACIP Chikungunya Vaccines Work Group members' hard work and decision-making challenges for finalizing vaccine recommendations

Draft recommendations for CHIK-VLP

ACIP recommends virus-like particle chikungunya vaccine for persons aged ≥12 years traveling to a country or territory where there is a chikungunya outbreak.[#]

In addition, virus-like particle chikungunya vaccine may be considered for persons aged ≥12 years traveling or taking up residence in a country or territory without an outbreak but with elevated risk for US travelers[#] if planning travel for an extended period of time e.g., 6 months or more.

[#]Resources will be available on CDC website

Specifying areas with outbreaks and risk for US travelers for purposes of recommendations

- **Outbreak**
  - Defined as occurring when CDC posts information on outbreak on CDC website
- **Country or territory without an outbreak but with elevated risk for US travelers**
  - Median of ≥1 US traveler case during last 5 years with at least 1 confirmed case based on molecular testing or presence of IgM and neutralizing antibodies*

*Excludes probable cases with IgM antibodies alone because high proportion are false positive results

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Acknowledgments

ACIP Chikungunya Vaccines Work Group

Arboviral Diseases Branch, CDC

- Erin Staples

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov