Chikungunya: Epidemiology and Risk Groups

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Centers for Disease Control and Prevention

Fort Collins, Colorado, USA

Product Development for Vaccines Advisory Committee Meeting

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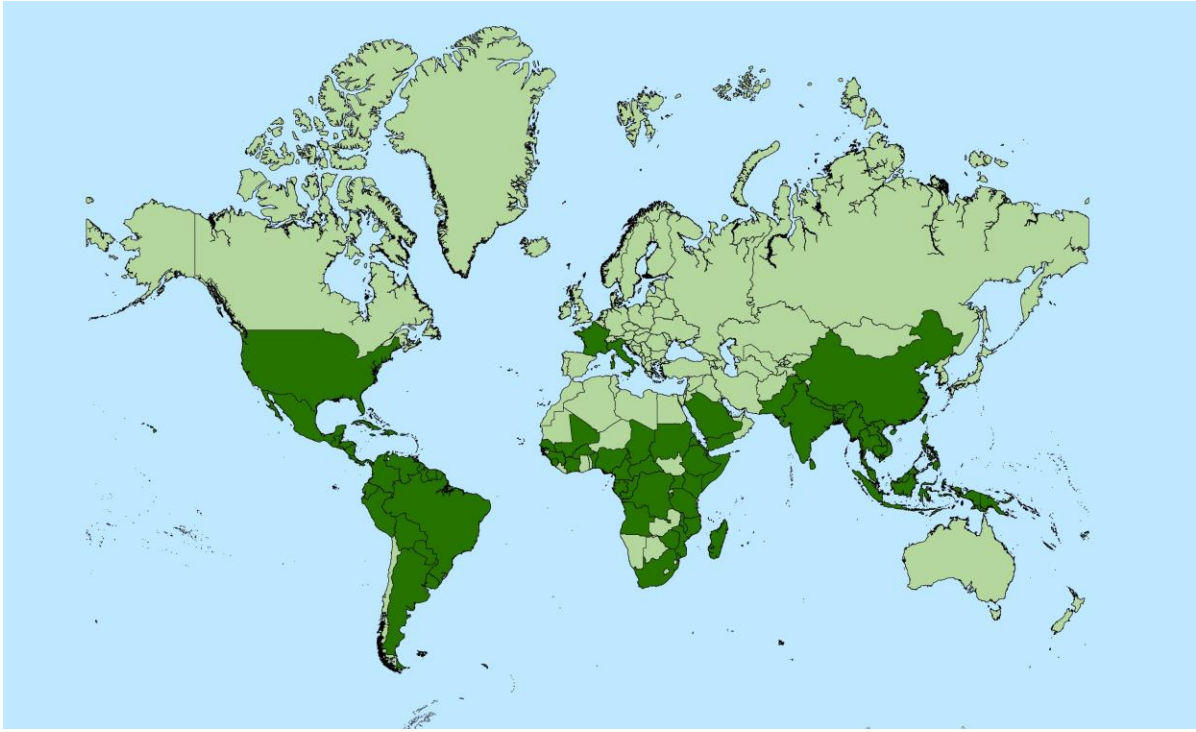
Chikungunya virus

- Alphavirus
- Primarily transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes
  - Lay eggs in containers that hold water
- Uncommon modes of transmission
  - Intrauterine and intrapartum
  - Bloodborne
  - Laboratory exposure

Distribution and disease patterns

- Virus transmission in tropical and subtropical regions of world
- Sporadic cases and periodic outbreaks
- Outbreaks can be explosive and result in high attack rates

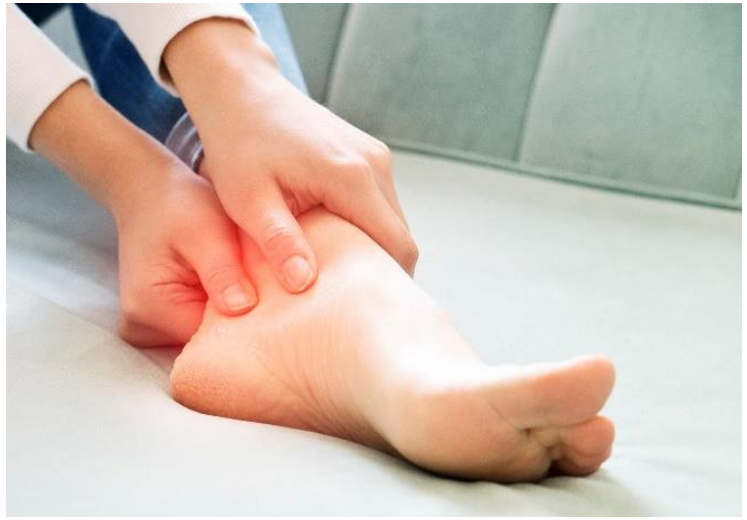
Countries with current or past transmission of chikungunya virus



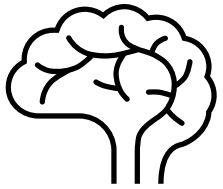
https://www.cdc.gov/chikungunya/geo/index.html

Clinical features of chikungunya

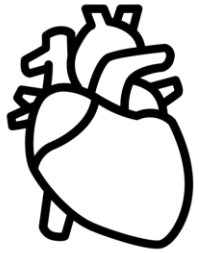
- High fever and arthralgia which is often severe and debilitating
- Multiple joints involved
  - Arthralgia most common in hands and feet
- No anti-viral treatment available



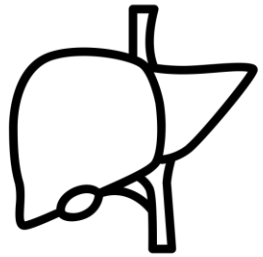
Rare complications



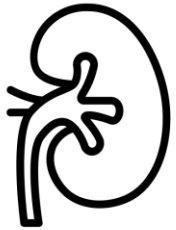
Neurologic disease



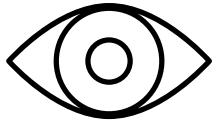
Myocarditis



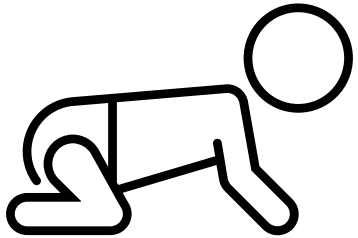
Hepatitis



Acute renal disease



Ocular disease



Severe bullous lesions

Mortality rate low 0.02% – 0.8%

Chronic arthralgia after chikungunya

- Multiple studies but variability in methodologies, symptoms assessed, definitions and ascertainment of symptoms, characteristics of patient in cohorts
- Recent meta-analysis*estimated
  - About **one-half** have arthralgia at **3 months**
  - About **one-third** have arthralgia at **12 months**
- However, proportions likely somewhat overestimate rates of chronic arthralgia in patients overall as studies
  - Almost exclusively included persons who sought health care (i.e., likely more severe disease)
  - Do not account for background rate of arthralgia in population

*Lindsey N. Chronic arthralgia after chikungunya. US Advisory Committee on Immunization Practices meeting, June 2023.

Risk factors for severe disease

- Age >65 years
- Age <1 year
- Underlying medical conditions (e.g., diabetes, heart disease, hypertension)
- Infection in neonate following intrapartum transmission

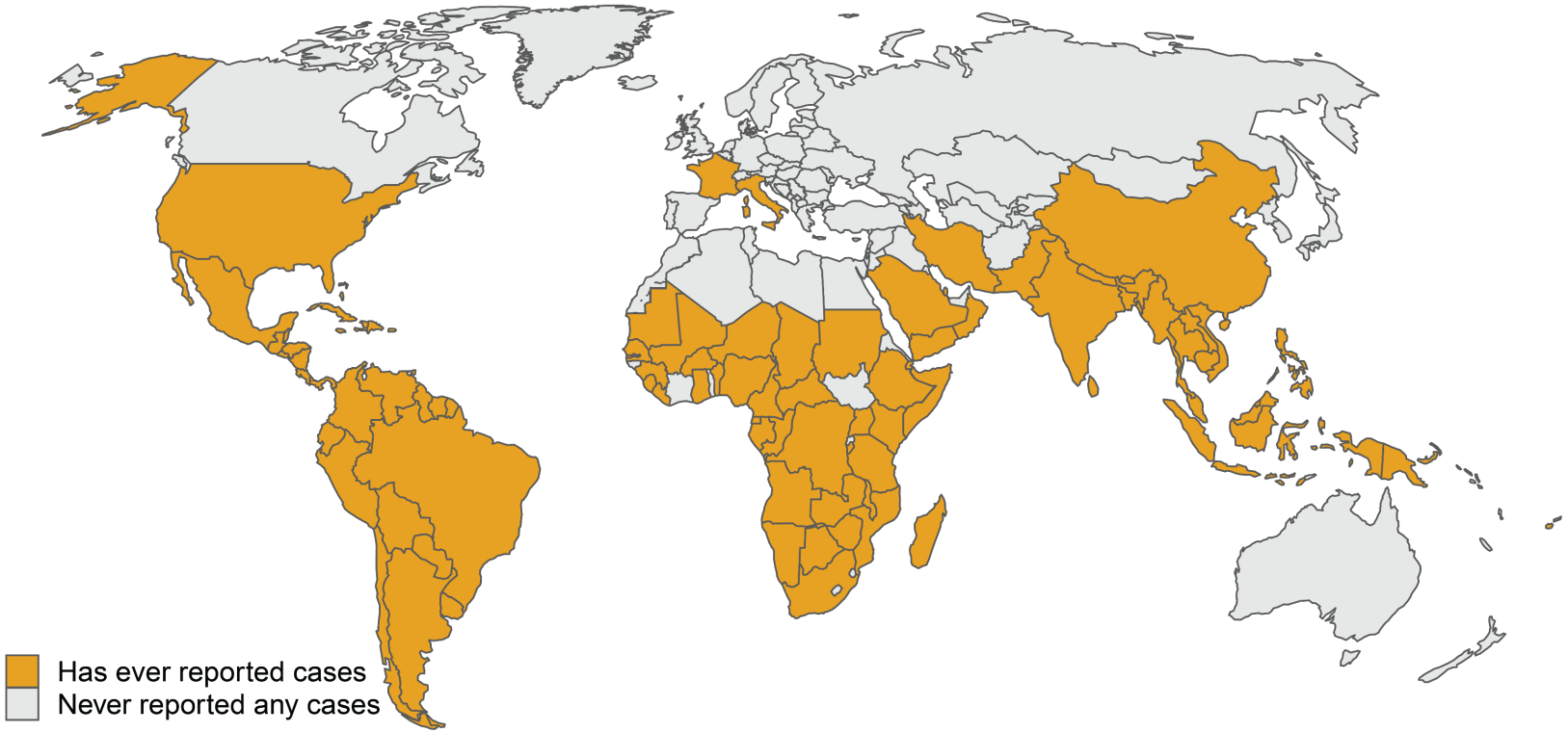
Thank you

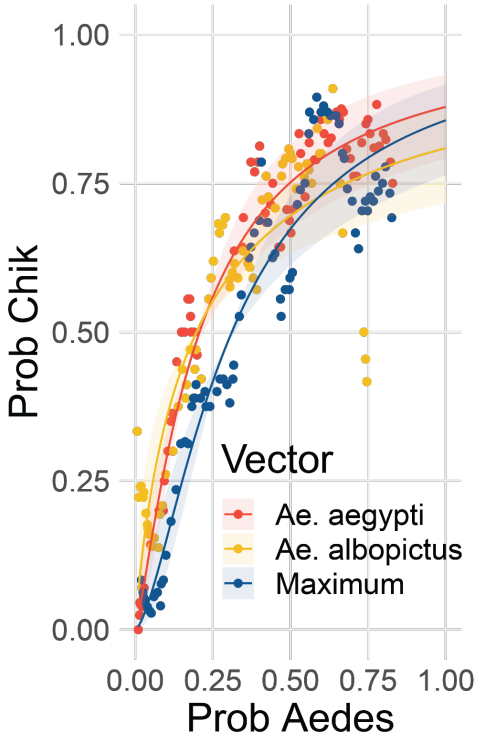
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Susan Hills (shills@cdc.gov)

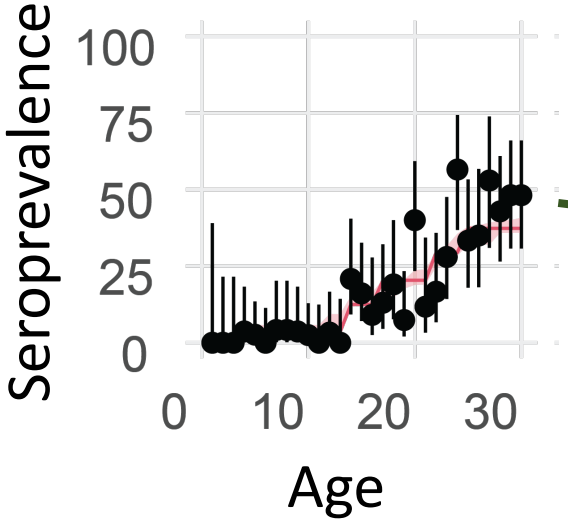
Underlying global epidemiology of chikungunya

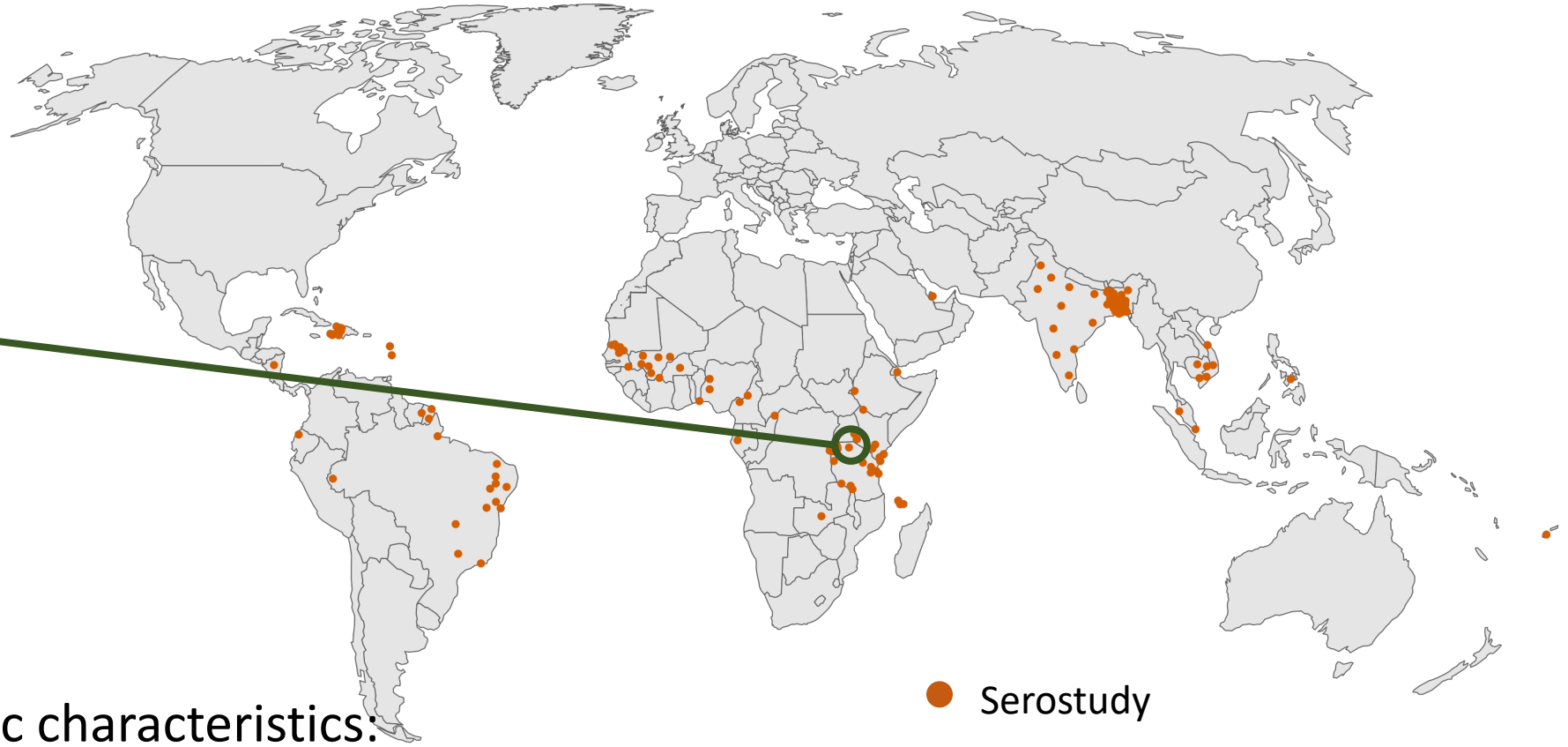
- Most tropical/sub-tropical countries have experienced CHIKV transmission
- Strong relationship between history of transmission with vector presence





- For vaccine strategy, need to understand frequency and size of outbreaks
- Outside South America, many outbreaks are missed
- Cannot rely on case reporting
- Serostudies combined with models can help





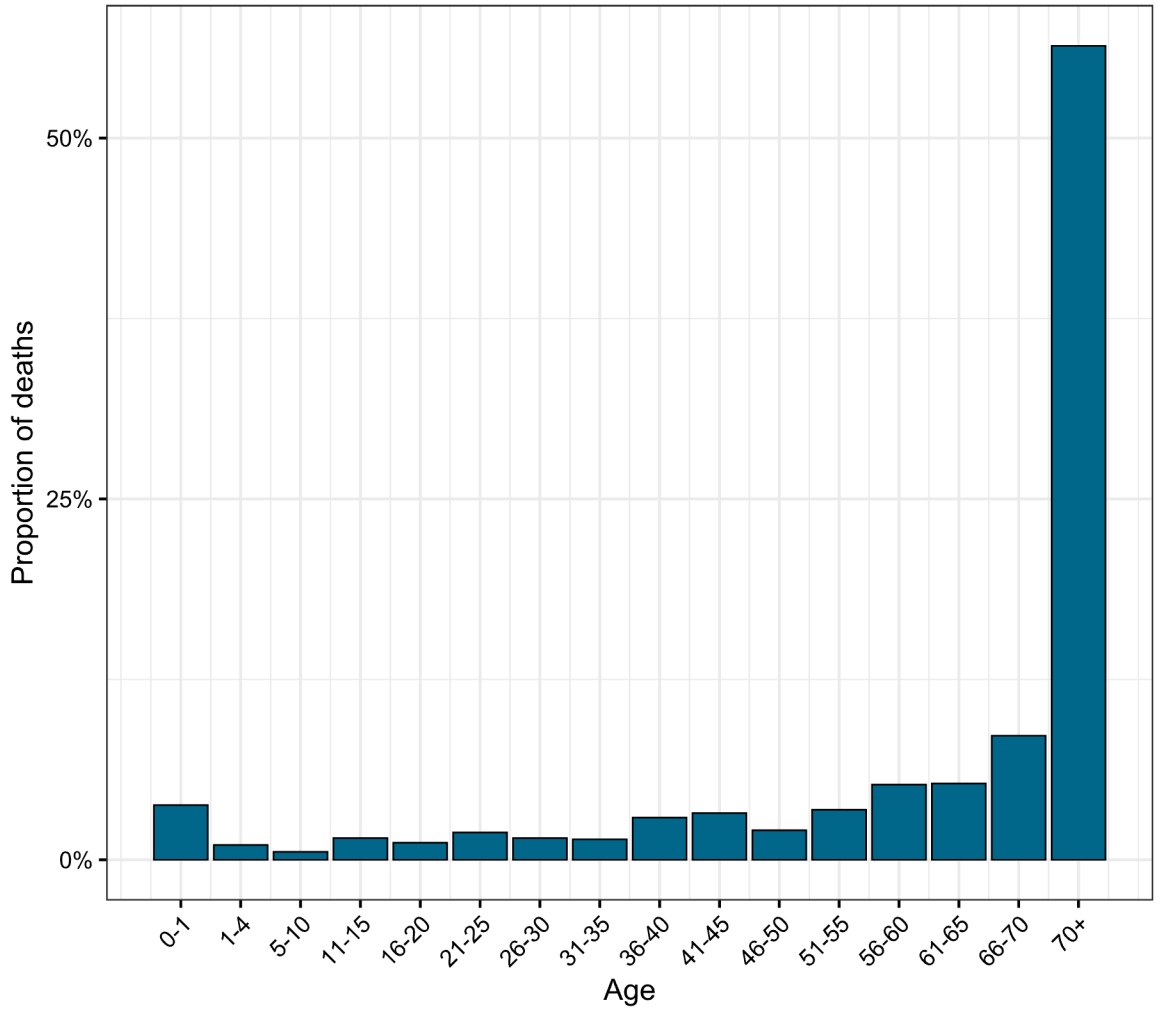
<u>Estimated mean epidemic characteristics:</u>

- One outbreak every ~8 years
- ~10% of population infected per outbreak

Vaccine use strategies

- Two main approaches:
  - Reactive campaigns using stockpiles
  - Regular immunization

- Optimal strategy depends on:
  - Underlying epidemiology
  - Vaccine characteristics – VE, infection vs disease blocking, duration of protection
  - Target population – especially by age
  - Ability to detect and respond to outbreaks

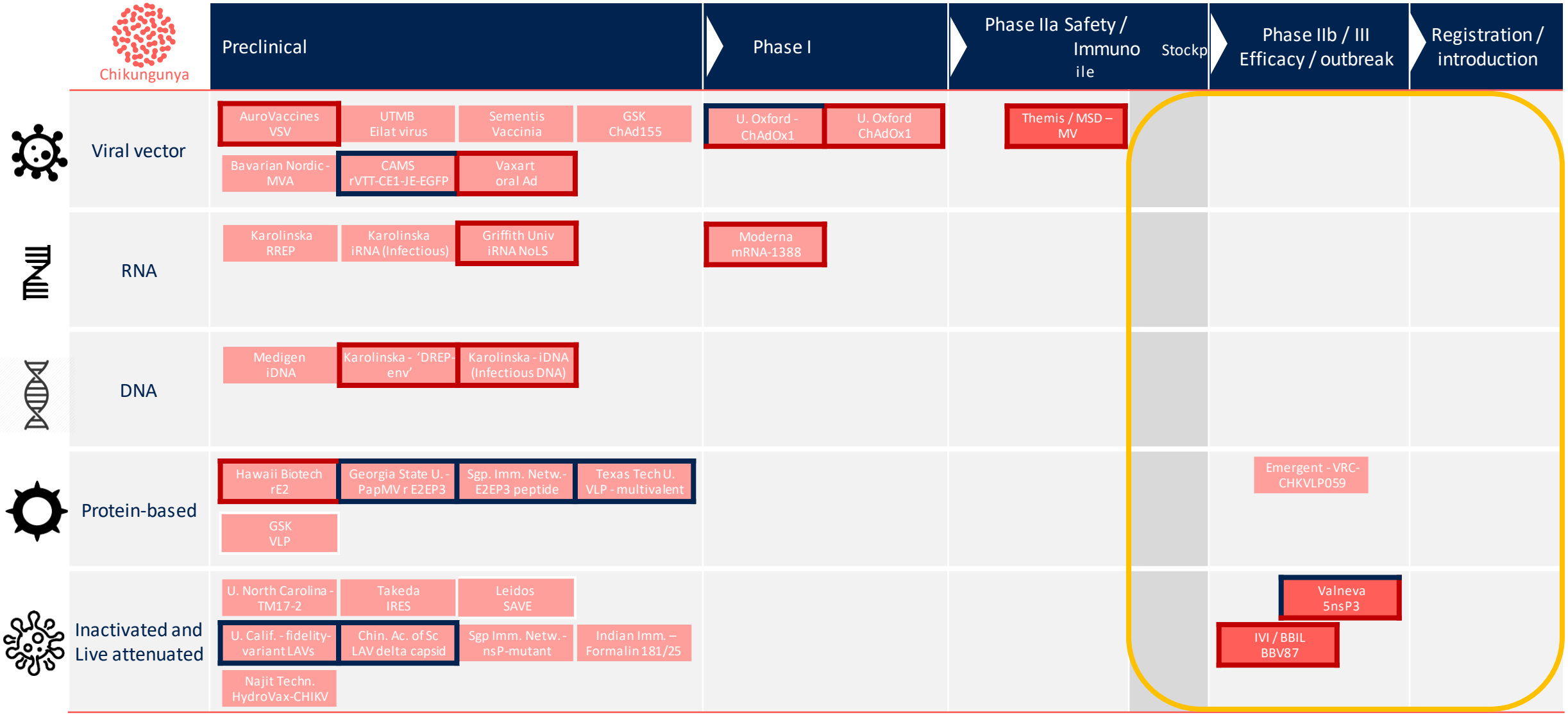


CEPI

CEPI's Chikungunya Vaccine Development Program

Timothy Endy MD, MPH
CEPI CHIKV Program Leader

Chikungunya vaccine development landscape



CEPI

CEPI-funded CHIK project

Non-CEPI-funded active CHIK project

Projects progressing to the pipeline

Platform used for COVID-19

Target awardees for CfP-3iii

CEPI 1.0 VS CEPI 2.0 CHIK grant objectives

CHIKV CfP-3i EC grant:

- For CHIKV vaccines, to support the rapid progression of the most advanced clinical CHIKV vaccine candidates through mid-stage and late-stage clinical development, and to support activities enabling future efficacy testing, including identification of correlates of protection and their validation that can facilitate future regulatory approval.

CHIKV CfP-3iii EC grant: The focus of this grant submission is on assessing the long-term safety, durability of protection and facilitating access and registration of CHIKV vaccines in CHIKV endemic countries to potentially include technology transfer. The specific aims and objectives are:

1. Supporting developers with a CHIKV vaccine program that is currently in Phase 3 studies and near national regulatory licensure or licensed by a national regulatory agency to support the execution of extended Phase 3 human clinical trials and/or Phase 4 studies to establish long-term safety of the vaccine, durability of a surrogate marker of protection based on neutralizing antibody titers and /or vaccine effectiveness by utilizing surveillance for virologically confirmed disease.

2. Supporting developers with a CHIKV vaccine program that is in Phase 3 human clinical trials with near licensure by a national regulatory agency or with licensure by a national regulatory agency to support additional human clinical trials (Phase 2 studies) in special subgroup populations to include age de-escalation into pediatric populations, pregnant women and those who are immunocompromised.

CEPI-funded Portfolio Snapshot

Chikungunya	Valneva	IVI / Bharat
Development phase	Phase IV	Phase II/III
Platform	Live Attenuated	Inactivated + Alum
Antigen	CHIKV 5nsP3	Whole virion BBV87
Dose schedule	1	2
Route of administration	IM	IM
Clinical trial sites	USA, BRA	IND, THA, COL, COR, GUT, PAN
Regulatory pathway	FDA, EMA, ANVISA, WHO PQ	DCGI, INVIMA, Thai FDA, WHO PQ

New Portfolio in Due Diligence

	valneva / INSTITUTO BUTANTAN A serviço da vida	International Vaccine Institute / BHARAT BIOTECH	BAVARIAN NORDIC
Platform	LAV (VLA 1555/1553) La Reunion ECSA strain	IAV (BBV87) Indian ECSA strain	CHIKV VLP WA stain
Development Phase	Ph 4	Ph 3 (Pending start)	Ph 3 completed
Phase 4 plan	Effectiveness & Post approval safety	Effectiveness RCT	Ph 3b/4 efficacy study
Expansion study	Ph 2 dose range + Ph 3 PIP	Ph 2b HIV+ cohort Ph 2b in pregnant women	Ph 3 PIP Ph 3 Adolescent study Ph 3 Infants
Licensure route	US licensed, EMA, ANVISA	DCGI	US, EMA

Valneva’s live-attenuated, single-dose chikungunya virus vaccine candidate (VLA1553)

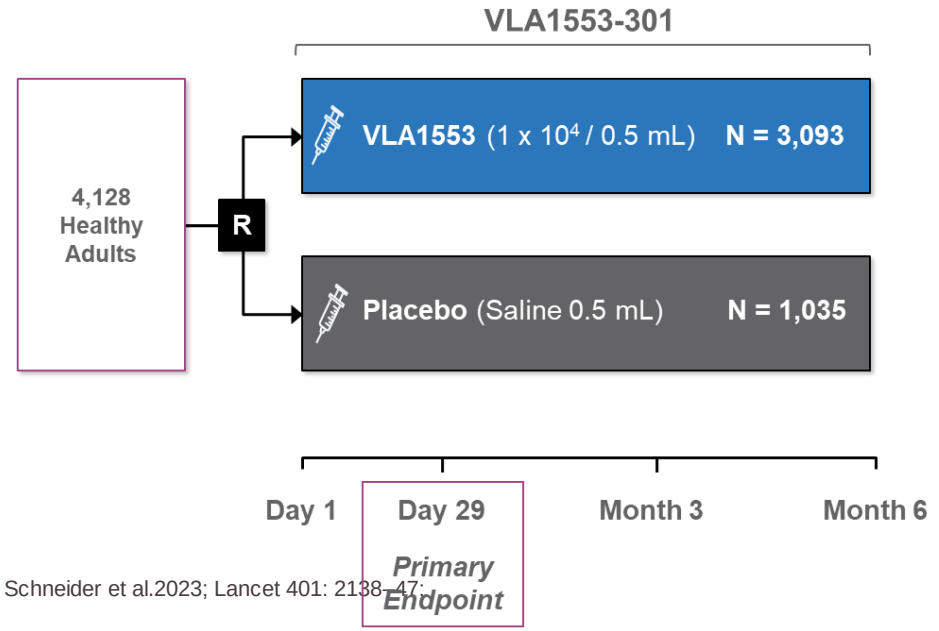
Phase 3 Results and Antibody Persistence Data
Slide deck provided by Valneva for external use

valneva

Pivotal Clinical Trial VLA1553-301

Provided safety and immunogenicity data as the basis for licensure

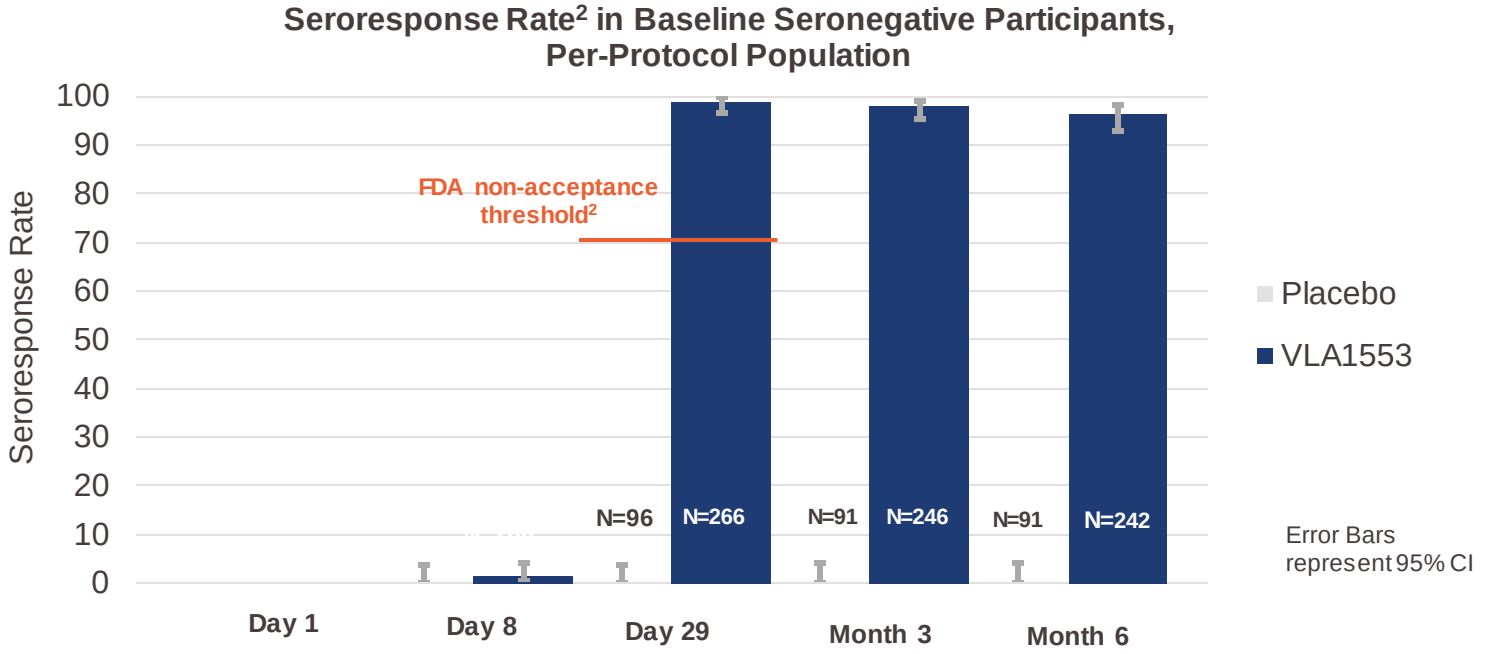
- Multicenter, randomized, placebo-controlled double-blind Phase 3[1] clinical trial in adults conducted in US
- 4,128 healthy adults, ≥ 18 years old, were randomized 3:1 to receive a single vaccination of VLA1553 or a saline control
- **Primary endpoint: rate of participants achieving seroresponse** (or CHIKV-specific neutralizing antibody titers ≥ 150) after single vaccination of VLA1553, in a subset



N = number of participants in the intention-to-treat population 1 Schneider et al.2023; Lancet 401: 2138–47.

VLA1553-301 Primary Endpoint met

Seroresponse[1] in 99% of Participants

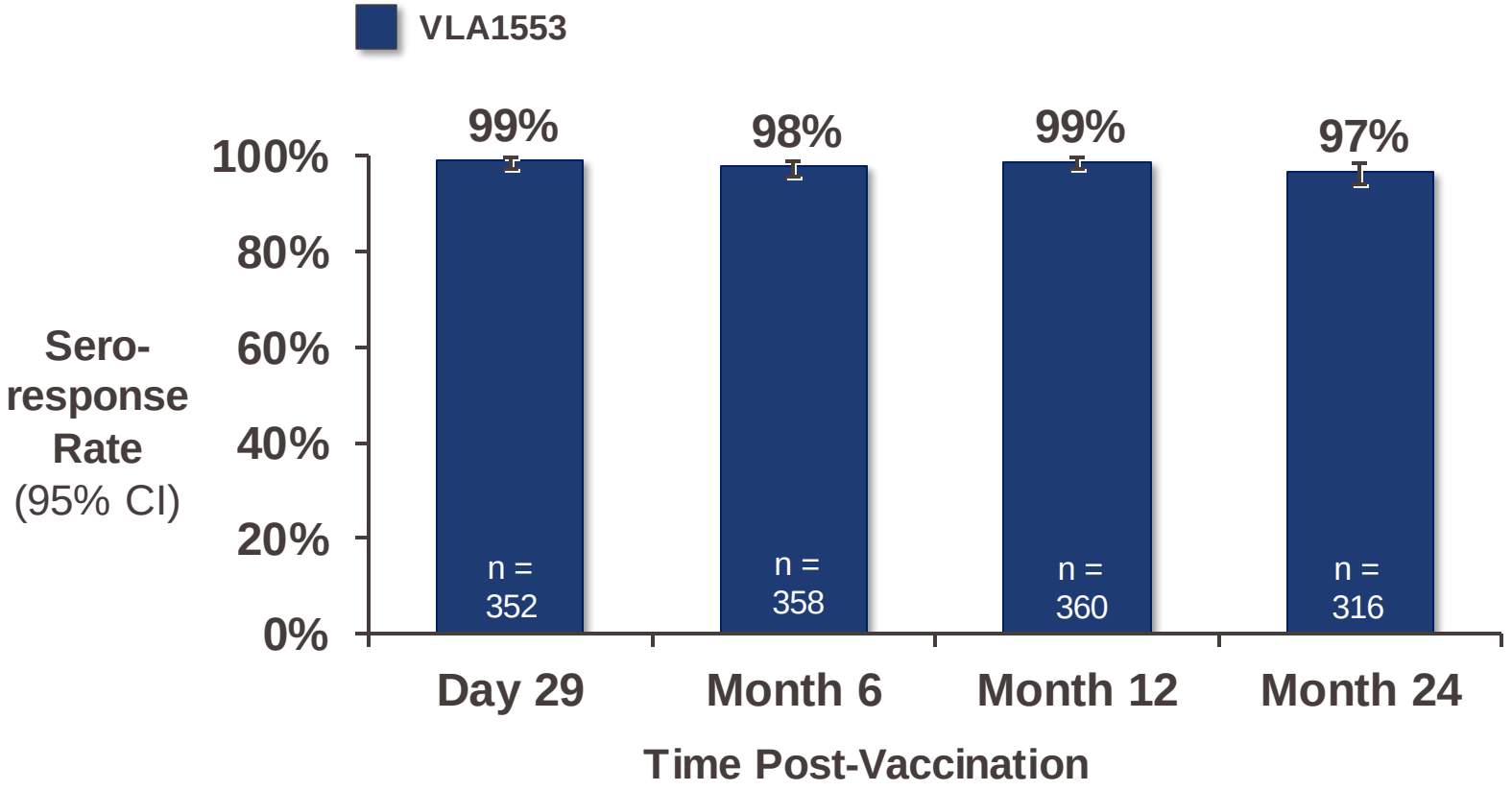


- **Per-Protocol population: 362 / 462 participants from immunogenicity set**
- **Day 29 Seroresponse rate (SRR):**
  - **98.9% (263/266, 95% CI: 96.7- 99.8) vs placebo 0% (0/96, 95%CI 0.0 - 3.8)**
- **High SRR was maintained after six months at 96.3% (233/242, 95% CI: 93.1 - 98.3)**

1 CHIKV neutralizing antibody titer ≥150 by $\mu PRNT_{50}$; 2 Schneider et al.2023; Lancet 401: 2138–47;

VLA1553-303: seroresponse in 97% of Participants Retained After 24 Months[1,2]

Data support the anticipated long-term durability of the immune response after a single dose

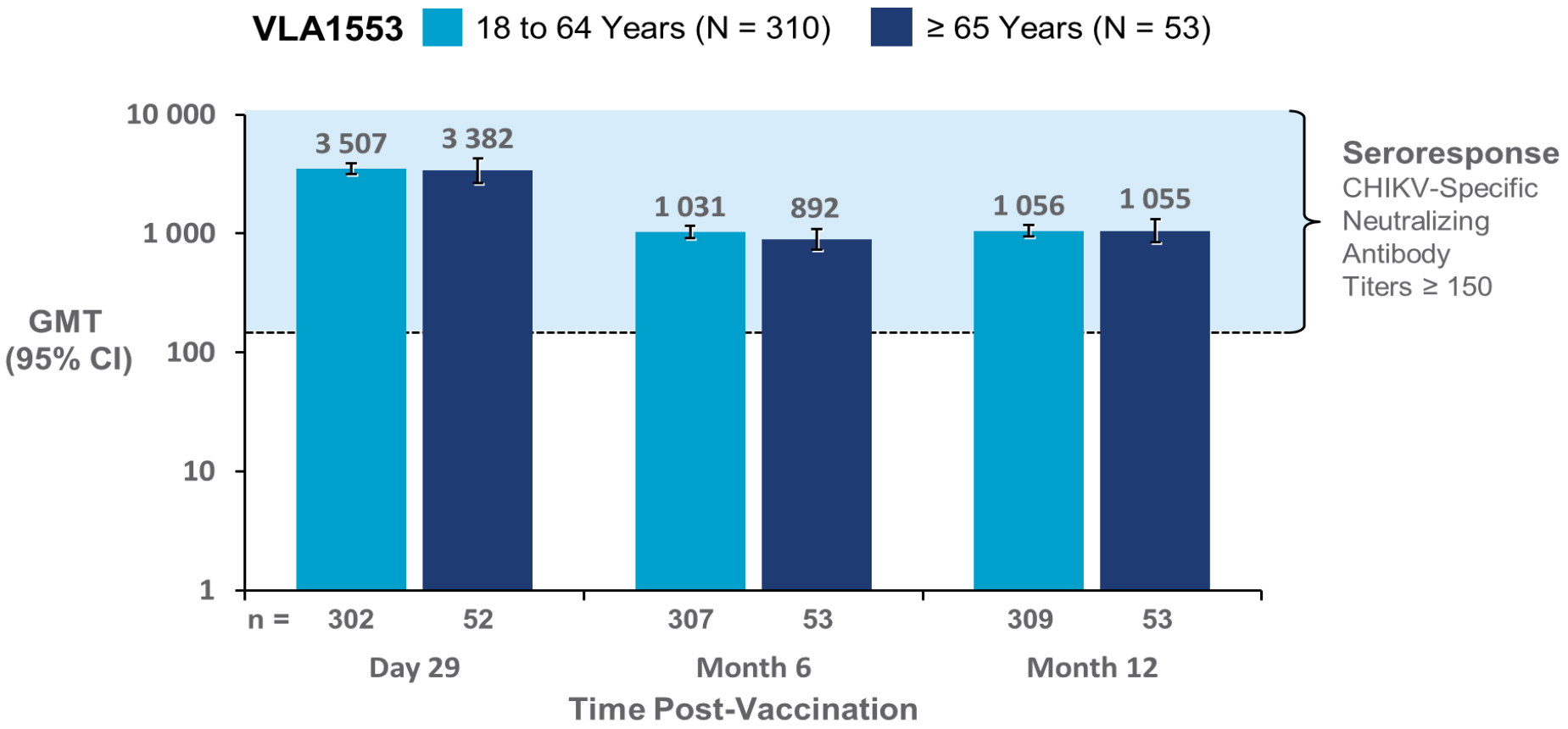


Seroresponse = CHIKV-specific neutralizing antibody titers ≥ 150

1 Buerger et at, presented at CISTM 2023; 2 Valneva Press Release Dec 4, 2023 https://valneva.com/press-release/valneva-reports-positive-24-month-antibody-persistence-data-for-its-single-shot-chikungunya-vaccine-ixchiq/

VLA1553-303: Equal level of neutralizing antibodies in both age groups[1]

In older adults aged ≥ 65 years, antibody persistence was similar to younger



Whole Sample Population

Seroresponse = CHIKV-specific neutralizing antibody titers ≥ 150

1 Buerger et at, presented at CISTM 2023

Pathways: Options when Clinical Efficacy Trials are Challenging – Chikungunya Virus Vaccines

U.S. FOOD & DRUG ADMINISTRATION

Robin Levis, PhD
Deputy Director, Division of Viral Products, OVRR/CBER
U.S. Food and Drug Administration

December 13, 2023

Getting to Licensure: Pathways and Requirements

Requirements for Licensure	Traditional Approval	Accelerated Approval	Animal Rule
Safe: "relative freedom from harmful effect..."	✓	✓	✓
Potent: "specific ability of product … to effect a given result" (effectiveness)"	**Endpoint that directly demonstrates clinical benefit**	**Surrogate endpoint that is reasonably likely to predict clinical benefit**	**Efficacy demonstrated in animal model(s), with requirements to assure that animal studies establish reasonable likelihood of clinical benefit in humans**
Pure: "relative freedom from extraneous matter in the finished product..."	✓	✓	✓
Manufactured: consistently according to Current Good Manufacturing Practices (cGMPs) to ensure continued safety and effectiveness	✓	✓	✓

Accelerated Approval

Qualifying criteria	
A drug that treats a **serious condition** AND	*A disease or condition associated with morbidity that has substantial impact on day-to-day functioning, survival, or likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one*
Generally provides a meaningful advantage over **available therapies** AND	• *Is approved or licensed in the United States for the same indication being considered for the new drug and* • *Is relevant to current U.S. standard of care for the indication*
Demonstrates an effect on a **surrogate endpoint that is reasonably likely to predict clinical benefit** or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	• *For vaccines, can be an immune marker that is not scientifically established, but is reasonably likely, to predict protection against disease*

Clinical Disease Endpoint Efficacy Trials for Chikungunya Vaccines – Traditional Approval

- In the absence of a scientifically well-established immune marker that predicts protection against CHIKV disease, traditional approval would require a clinical disease endpoint efficacy trial
  - A randomized controlled, double blind, trial to demonstrate vaccine effectiveness against virologically-confirmed CHIKV infection and disease
- Feasibility of being able to conduct a field efficacy trial is low
  - Disease outbreaks are irregular and unpredictable
  - Require an established infrastructure to conduct the trial in an outbreak setting
    - Difficult to pre-position this infrastructure
    - Timing of study implementation is critical

Accelerated Approval for Chikungunya Vaccines

- Approaches to identify immune markers reasonable likely to predict protection against virologically confirmed disease:
  - Sero-epidemiological studies
  - Cynomolgus Macaque Model
  - Passive transfer of vaccinee sera to NHP

Sero-Epidemiological Studies

- Sero-epidemiological studies were proposed as an approach to identify an immune marker reasonably likely to predict protection
- Prospective, sero-epidemiological studies in CHIKV endemic regions could employ active surveillance and serologic/virologic testing methods to identify cases of CHIKV infection, with correlation of baseline antibody titers (e.g., CHIKV-neutralizing antibodies) at enrollment with infection and disease outcomes during the surveillance period
- Considerations for sero-epidemiologic studies include:
  - Reliability of surveillance and testing methods to identify clinical cases that reflect established features of CHIKV disease and epidemiology
  - Subject recruitment methods to avoid potential selection bias
  - Proper validation of serologic assays to quantify antibody titers
  - Measured immune marker may correlate with, but not be responsible for protection against CHIKV disease

Cynomolgus Macaque Model of CHIKV Infection and Disease

- A NHP model of CHIKV infection and disease has been proposed to identify an immune marker reasonably likely to predict protection in humans
- A cynomolgus macaque model recapitulates several features of human CHIKV disease including fever, rash, viremia (tissue dissemination), and abnormal blood chemistry
- Considerations regarding the relevance of this model to human disease include:
  - Differences in disease features during subacute and chronic phase observed between cynomolgus macaques and humans
  - A challenge dose of CHIKV representative of natural infection in humans (10^3 PFU) induces fever, which may be accompanied by rash, but no overt signs of arthritis
  - Higher challenge doses (>10^7 PFU) of CHIKV induce inflammation and effusion in joints and results in meningoencephalitis and death in cynomolgus macaques

Passive Transfer of Human Antibodies to Non-Human Primates (NHPs)

- Passive transfer of pooled human sera or purified IgG from vaccinees into NHPs prior to CHIKV challenge to identify an immune marker reasonably likely to predict protection
- Considerations regarding the utility of passive transfer studies in NHPs include:
  - Will an immune marker derived using pooled human serum or purified IgGs (prepared from pooled serum) accurately predict protection from CHIKV disease in humans?
  - Are there clinically meaningful differences in antibody quality that may influence protective capacity between a certain titer in a vaccinated human and the same titer resulting from dilution during passive transfer?
- What would be the optimal timing for collecting post-vaccination human serum to be used in passive transfer studies?
- Will other factors in human serum, besides antibodies (e.g., cytokines), contribute to protection against CHIKV infection and disease?

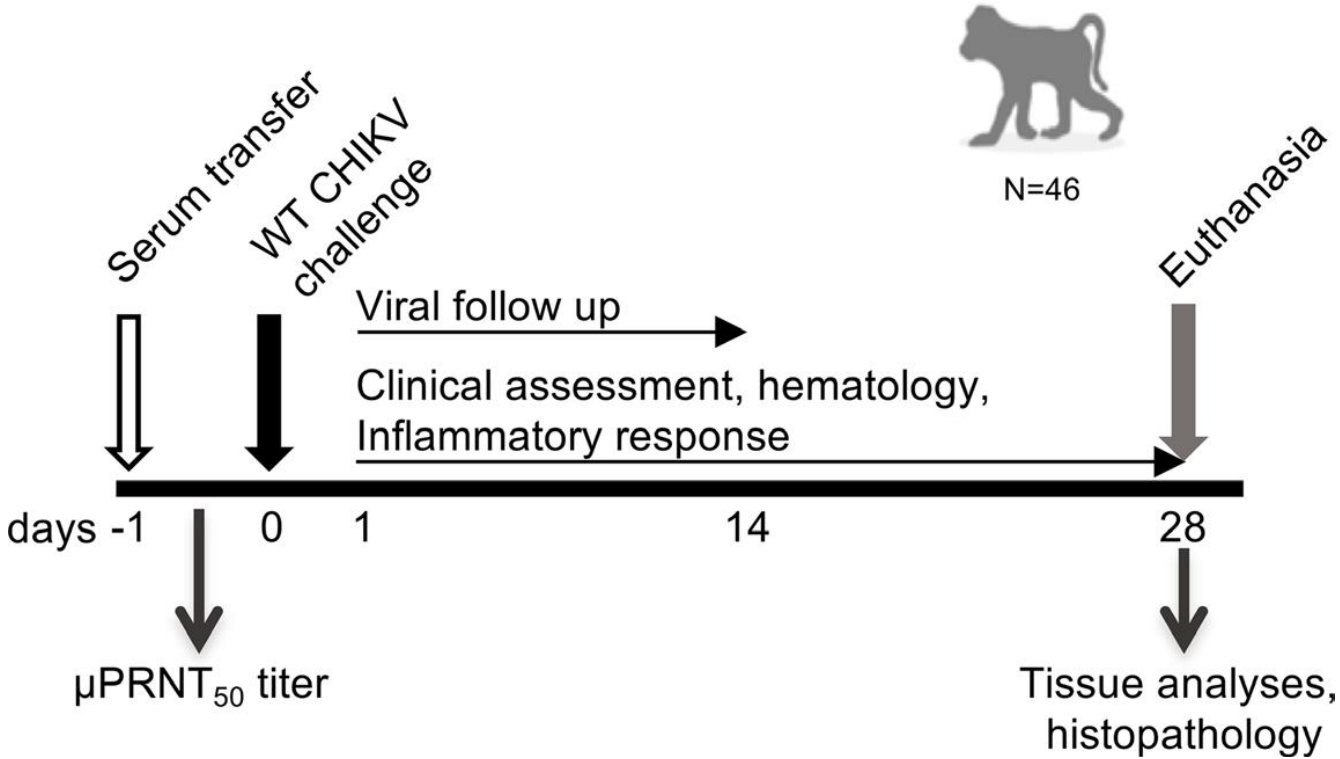
2019 VRBPAC to Discuss Chikungunya Vaccine Licensure

- Considerations for clinical studies to assess effectiveness of CHIKV vaccines:
  - Feasibility of randomized, controlled clinical disease endpoint efficacy trials
  - Role of sero-epidemiologic data in identifying an immune marker reasonably likely to predict vaccine effectiveness
- Utility of the non-human primate (NHP) challenge model to assess effectiveness of CHIKV vaccines, including:
  - Effectiveness endpoints, such as viremia, arthritis-related endpoints or other essential endpoints
  - Role of passively transferred sera or purified IgG from vaccinated humans in identifying an immune marker reasonably likely to predict vaccine effectiveness

Review and Licensure of Chikungunya Virus Vaccines

- Agreement reached at VRBPAC related to acceptable licensure pathway.
- Determined that FDA will review NHP data supporting proposed correlates of protection to be used as a primary end point in Phase 3 trials.
  - These data will be used on a case-by-case basis to support accelerated approval of Chikungunya vaccines
  - Data will be generated using the passive transfer of vaccinee sera in an NHP challenge model
  - Each sponsor performed independent studies to define an endpoint that is reasonably likely to predict clinical benefit
- FDA will also review post approval study protocols for the confirmatory study to assess effectiveness of Chikungunya vaccines

Design of Valneva Passive Transfer Study



https://doi.org/10.1172/jci.insight.160173

Valneva Accelerated BLA Approval: 09 –November – 2023

"Effective this date, we have approved your BLA for Chikungunya Vaccine, Live, under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the regulations for accelerated approval, 21 CFR 601.41. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Chikungunya Vaccine, Live under your existing Department of Health and Human Services U.S. License No. 1909. **Chikungunya Vaccine, Live is indicated for active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years of age and older who are at increased risk of exposure to Chikungunya virus."**

Post-Marketing Requirements to Confirm Efficacy (1)

Test-negative observational study to assess effectiveness of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with IXCHIQ in the adolescent and adult population (12 years of age and older) in endemic areas of Brazil.

- Final Protocol Submission: May 31, 2025
- Study Implementation Readiness Verification Submission: June 30, 2025
- Study Initiation: March 1, 2026
- Study/Trial Completion: March 1, 2028
- Final Report Submission: September 30, 2028

Post-Marketing Requirements to Confirm Efficacy (2)

Pragmatic randomized controlled trial to assess the effectiveness and safety of IXCHIQ vaccination in the prevention of symptomatic, laboratory confirmed Chikungunya after a single vaccination with IXCHIQ in adults in an endemic country.

- Final Protocol Submission: September 30, 2024
- Study Implementation Readiness Verification Submission: June 30, 2025
- Study Initiation: October 1, 2025
- Study/Trial Completion: July 31, 2029
- Final Report Submission: December 31, 2029

Post-Marketing Pediatric Requirements

- Deferred pediatric study under PREA (VLA1553-321) to evaluate safety and immunogenicity of IXCHIQ in adolescents 12 to <18 years of age.
  - Final Report Submission: November 30, 2024
- Deferred pediatric study under PREA (VLA1553-221) to evaluate dose-finding safety and immunogenicity of IXCHIQ in children 1 to <12 years of age.
  - Final Report Submission: January 31, 2026
- Deferred pediatric study under PREA (VLA1553-322) to evaluate safety and immunogenicity of IXCHIQ in children 1 to <12 years of age.
  - Final Report Submission: June 30, 2027
- Deferred pediatric study under PREA (VLA1553-222) to evaluate dose-finding safety and immunogenicity of IXCHIQ in neonates and infants <1 year of age.
  - Final Report Submission: February 28, 2029
- Deferred pediatric study (VLA1553-323) to evaluate safety and immunogenicity of IXCHIQ in neonates and infants <1 year of age.
  - Final Report Submission: October 31, 2030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