Phase IV post-approval studies in the context of vaccines approved through accelerated procedures: Case study, CHIKUNGUNYA vaccines.

Purpose of the meeting:

Present and update regulators with the recent developments and regulatory processes in the licensing of chikungunya vaccines, and to address the design, feasibility and conduct of post-approval studies for the NRAs to be prepared in the event of requests for market authorization by chikungunya developers.

Agenda

Wednesday, March 19th 2025		
8:00-8:45	Registration of participants	45'
8:45-9:30	Opening remarks and general introduction of participants. ANVISA and CEPI	45'
Introduction of chikungunya disease and epidemiology		
Purpose: Set the scene for chikungunya disease globally and regionally. Present the symptoms, disease, and treatment, case definition of chikungunya and diagnosis, and recent developments.		
9:30-10:45	Chikungunya disease: clinical and diagnosis. André Ribas Freitas, Brazil	20'
	Epidemiology of Chikungunya disease: • PAHO (Thais dos Santos, PAHO/WHO), • Colombia (Fernando de la Hoz, UNC) • India (Nivedita Gupta, ICMR) (*virtual*) • Kenya (George Warimwe, KWTRP and Uof Ox) • Thailand (Apinya Niramitsantipong, DDC/MOH)	40'
	Modelling of chikungunya disease. Henrik Salje, University of Cambridge, UK	15'
10:45-11:00	Coffee break	15'
11.00-11:10	Feasibility of clinical efficacy studies for chikungunya vaccines. André Ribas Freitas, Brazil	10'
11:10-12:10	Country perspectives on the feasibility of predicting outbreaks • Colombia (Fernando de la Hoz, UNC) • Kenya (George Warimwe, KWTRP and U of Ox) • Thailand (Apinya Niramitsantipong, DDC/MOH)	60'
Update on vaccine development		
Purpose: Developers will present a brief description of the vaccine developments and the planned or ongoing regulatory processes.		
12:15-12:30	• Valneva/Butantan • Bavarian-Nordic	45"

12:45-13:45	Lunch	60’
Immune correlates/surrogates and update on regulatory status of chikungunya vaccines		
Purpose: Conducting Phase 3 randomized clinical trials with disease outcomes is challenging with some vaccines, either because trials require very large sample sizes, or because of the unpredictability of outbreaks. This session will discuss generalities of the use of correlates of protection in the assessment of vaccine efficacy, and NRAs where vaccine has been licensed will present a brief description of the use of correlates and other criteria and regulatory elements used for the licensing of the CHIKV vaccine. Two panels will follow, one panel of NRAs will discuss if correlates of protection can be or are considered in their current regulations, and a second panel will discuss feasibility of licensing vaccine with current data.		
13:45-14:05	Use of correlate/surrogate of protection to assess vaccines (Debbie Ferguson, MHRA)	20’
14:05-15:15	Updates from Regulators on licensing of ChikV vaccines • FDA David Kaslow (virtual) • Health Canada, Richard Siggers • ANVISA, Brenda Valente • CDSCO-India, Rubina Bose • EMA, Marco Cavaleri	70’
15:15-15:30	• Q&A	15’
15:30-16:00	Coffee break	30’
16:00-16:45	Panel discussion of NRAs on use of Correlates of Protection (1). • ANMAT (Argentina), Gabriela Beatriz Bravo • CDSCO-India, Rubina Bose • PPB-Kenya, Mikal Ayiro • Ghana-FDA, Ernest Agyei-Kwame • AVAREF, Kwasi Nyarko	45’
16:45-17:30	Panel discussion of NRAs on feasibility of licensing vaccines with current data (2) • Rwanda-FDA, Jean Pierre Nsanzimfura • SRS-El Salvador, Rosa María Morales Rivas • DINAVISA-Paraguay, Marlene Esquivel. • Badan POM-Indonesia, Diah Puspitasari, • PPB-Kenya, Mikal Ayiro	45’
17:30-17:35	Housekeeping reminders for in-person attendees	5’

CHIKUNGUNYA
Phase IV

São Paulo, Brazil March 2025

CEPI

ANVISA
Agência Nacional de Vigilância Sanitária

Introduction of chikungunya disease and epidemiology

Purpose: Set the scene for chikungunya disease globally and regionally. Present the symptoms, disease, and treatment, case definition of chikungunya and diagnosis, and recent developments.

Chikungunya Disease: Clinical and Diagnosis

André Ricardo Ribas Freitas, MD PhD
Medical Epidemiologist
São Leopoldo Mandic School of Medicine
Dr. Mário Gatti Municipal Hospital

Chikungunya Meeting, March 19-20, 2024, São Paulo, SP/BRA

Declaration of No Conflict of Interest

Professional Affiliations:

- Assistant Physician at the Mário Gatti Municipal Hospital, Campinas
- Professor at São Leopoldo Mandic Medical School, Campinas and Araras (SP/Brazil)
- Member of the Working Group for the evaluation of the efficacy and safety of vaccines for Chikungunya, Dengue, and Zika at the Technical Chamber for the Registration of Medications (CATEME, ANVISA)
- Member of the Technical Advisory Committee on Arboviruses (CTA-Arboviruses), Ministry of Health
- Representative of the National Council of Municipal Health Departments (CONASEMS) at the Public Health Emergency Operations Center for Dengue and other Arboviruses (Centro de Operações de Emergências para Dengue e outras Arboviroses, COE-ARBOVIROSES)
- Volunteer Physician of the National Force of the Unified Health System (Força Nacional do SUS), Ministry of Health

Conflict of Interest Statement:

- I declare that I have no ties to any vaccine manufacturer and affirm that I have no conflicts of interest related to this presentation or research.

Chikungunya Virus (CHIKV) – Key Characteristics

- **Family & Genus:**
  - **Togaviridae**, **Alphavirus** genus
  - Enveloped, **positive-sense, single-stranded RNA virus (~11.8 kb)**
- Three main lineages:
  - **West African (WA)**
  - **East/Central/South African (ECSA)**
  - **Asian lineage**
- **ECSA strain mutations (A226V, E1-K211E, E2-V264A) enhanced Aedes albopictus transmission**, contributing to **rapid global spread**

- **Transmission & Vectors:**
  - Primarily transmitted by **Aedes aegypti** and **Aedes albopictus** mosquitoes
  - Efficient urban and sylvatic transmission cycles
- **Immunity & Vaccine Development:**
  - **Single serotype**, but **lifelong immunity after infection**
  - **Several vaccines in late-stage clinical trials**
- **Global expansion** driven by **vector fitness, climate change, and rapid urbanization**

Historical Aspects of Break-bone Fever

- Chikungunya virus (CHIKV) is believed to have been responsible for **epidemics of break-bone fever in the 18th and 19th centuries**, then named as dengue.
  - Possible pandemics periods: 1779-1780; 1823-1828; 1870-1880; 1901-1907
- During the early 20th century, a significant confusion existed regarding **dengue-like febrile illnesses**. At the time, two distinct syndromes were commonly reported:
  - **"Dengue" (now likely chikungunya):** Recurrent outbreaks of severe febrile illness with intense **polyarthritis and prolonged joint symptoms** were often categorized as dengue, particularly in the Indian subcontinent and Southeast Asia.
  - **"Seven Days Fever" (now recognized as dengue):** This term was used to describe febrile illnesses lasting about a week, typically associated with a biphasic fever, rash, and **absence of long-term joint symptoms**—matching the clinical profile of dengue.

*Christie J. (1881). On Epidemics of Dengue Fever: Their Diffusion and Etiology. *Glasgow medical journal*, *16*(3), 161–176.
*Carey D. E. (1971). Chikungunya and dengue: a case of mistaken identity?. Journal of the history of medicine and allied sciences, 26(3), 243–262.
*Halstead S. B. (2015). Reappearance of chikungunya, formerly called dengue, in the Americas. Emerging infectious diseases, 21(4), 557–561.

Historical Confusion Between Dengue and Chikungunya

- The distinction between these two syndromes remained unclear for decades, as both diseases were transmitted by **Aedes mosquitoes** and often co-circulated in the same regions*.
- Dengue virus (DENV) was identified in the 1940s and later classified into four serotypes, while chikungunya virus (CHIKV) was first isolated during the 1952 Tanzania outbreak, confirming it as a distinct entity.

Possible consequences:

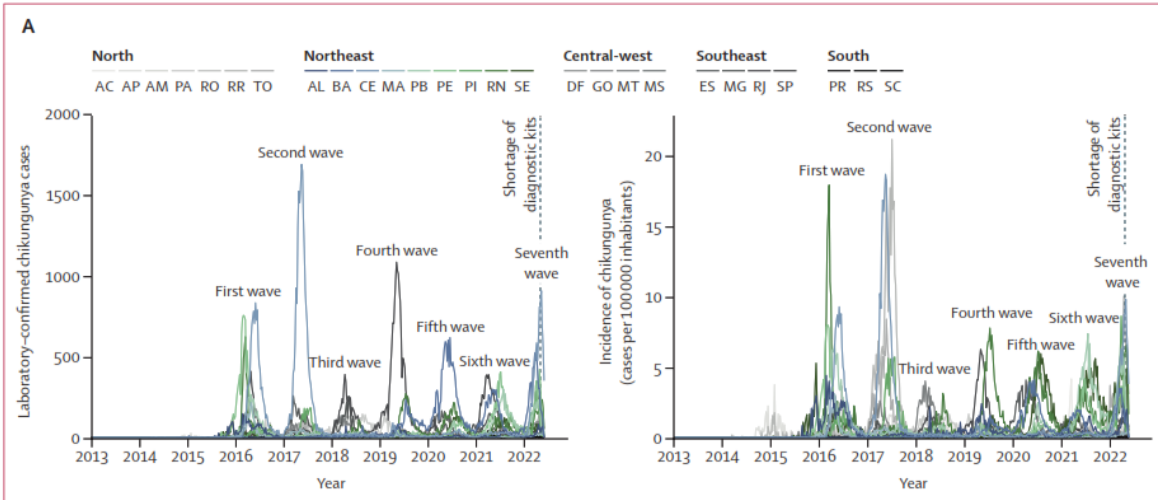
- This historical misclassification has had lasting consequences, including **underestimation of chikungunya's burden** and misinterpretation of past epidemiological data.
- Even today*, misdiagnosis remains a challenge, particularly in areas where dengue outbreaks dominate public health discussions.

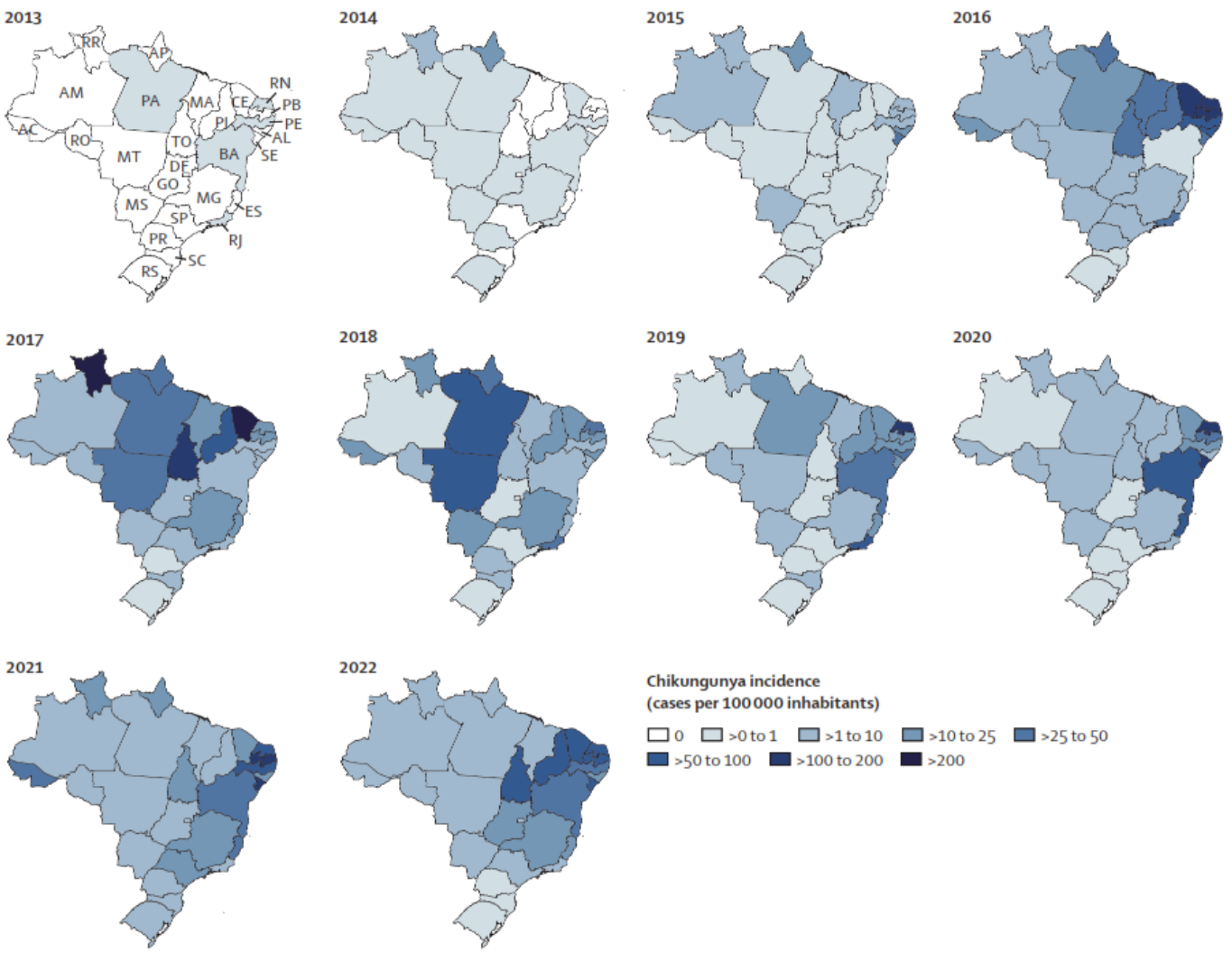
*Ribas Freitas, AR et al. (2024) How much of the current serious arbovirus epidemic in Brazil is dengue and how much is chikungunya? The Lancet Regional Health – Americas, Volume 34, 100753

Global Expansion and Emergence in the 21st Century

- **2005:** The virus expanded its transmission area, leading to **explosive outbreaks on islands in the Indian Ocean** (e.g., Réunion, Mauritius, Seychelles).
- **2006-2011:** CHIKV spread further, causing **major outbreaks in the Pacific region**, including **New Caledonia and the Philippines**.
- **2013:** First identification of CHIKV in **Western Hemisphere:**
  - **2014-2015:** The virus caused **intense epidemics** in the **Caribbean Region**, rapid spread and high attack rates of CHIKV (**Jamaica**, **80.4% of the population seroconverted within a year)**, followed by low circulation or detection
  - **2015-today:** Other Regions of the Americas, continuous and recurrent transmission: Epidemics often affect **a large proportion of the population in small region** within a short time.

Dynamics of chikungunya transmission in Brazil (laboratory confirmed cases)





Souza, W M *et al*. Spatiotemporal dynamics and recurrence of chikungunya virus in Brazil: an epidemiological study.The Lancet Microbe, Volume 4, Issue 5, e319 - e329

Clinical Presentation of Chikungunya

- High fever (usually >38.5°C) lasting 3–5 days.
- Polyarthralgia (sometimes polyarthritis) affecting multiple joints, often bilateral and symmetrical, leading to significant functional impairment.
- Maculopapular rash appearing in 40–50% of cases, typically on the trunk and limbs.

Severe Cases:

Leading to Hospitalizations and Deaths in Chikungunya

- **Neurological involvement:** Encephalitis, meningoencephalitis, myelitis, and Guillain-Barré syndrome.
- **Cardiovascular manifestations:** Myocarditis, heart failure, arrhythmias, and hemodynamic instability.
- **Hepatic dysfunction:** Transaminitis and fulminant hepatitis, particularly in neonates and immunocompromised individuals.
- **Hematologic**: Coagulopathy, severe thrombocytopenia
- **Multi-organ failure.**
- Increased risk of death associated with other illnesses within 84 days of the onset of symptoms.[1]

[1]Cerqueira-Silva, T *et al*. (2024). Risk of death following chikungunya virus disease in the 100 Million Brazilian Cohort, 2015-18: a matched cohort study and self-controlled case series. *The Lancet. Infectious diseases*, *24*(5), 504–513. https://doi.org/10.1016/S1473-3099(23)00739-9

Severe Forms of Chikungunya

🛑 Higher Risk Groups

- **Infants** – Particularly neonates infected perinatally
- **Elderly** – Increased risk due to frailty and comorbidities
- **Individuals with Pre-existing Conditions** – Hypertension, diabetes, cardiovascular diseases, immunosuppression

⚠️ Not Exclusive to These Groups

- Severe cases occur in **young adults (25% <52ys[1]; 23% <60 years[2])**
- **No pre-existing conditions among 17%[1] - 61%[2]** of severe and fatal cases
- Previously healthy adults can also develop **life-threatening complications**

Chikungunya severity is often underestimated.

[1]Crosby L, et al. Severe manifestations of chikungunya virus in critically ill patients during the 2013-2014 Caribbean outbreak. Int J Infect Dis. 2016;48:78-80
[2]Tandale BV et al. (2009) Systemic involvements and fatalities during chikungunya epidemic in India, 2006. Journal of Clinical Virology 46, 145–149

NECROPSIA DE 68 CASOS FATAIS DE CHIKUNGUNYA CONFIRMADOS (RT-PCR (53%), IMUNO-HISTOQUÍMICA (41%) E/OU IGM (63%), CEARÁ/BR, 2017

Mediana de idade = 51 anos

Presença de:

- Febre, 65% (44/68)
- Artralgia, 43% (29/67)
- Comorbidades, 46% (20/44)

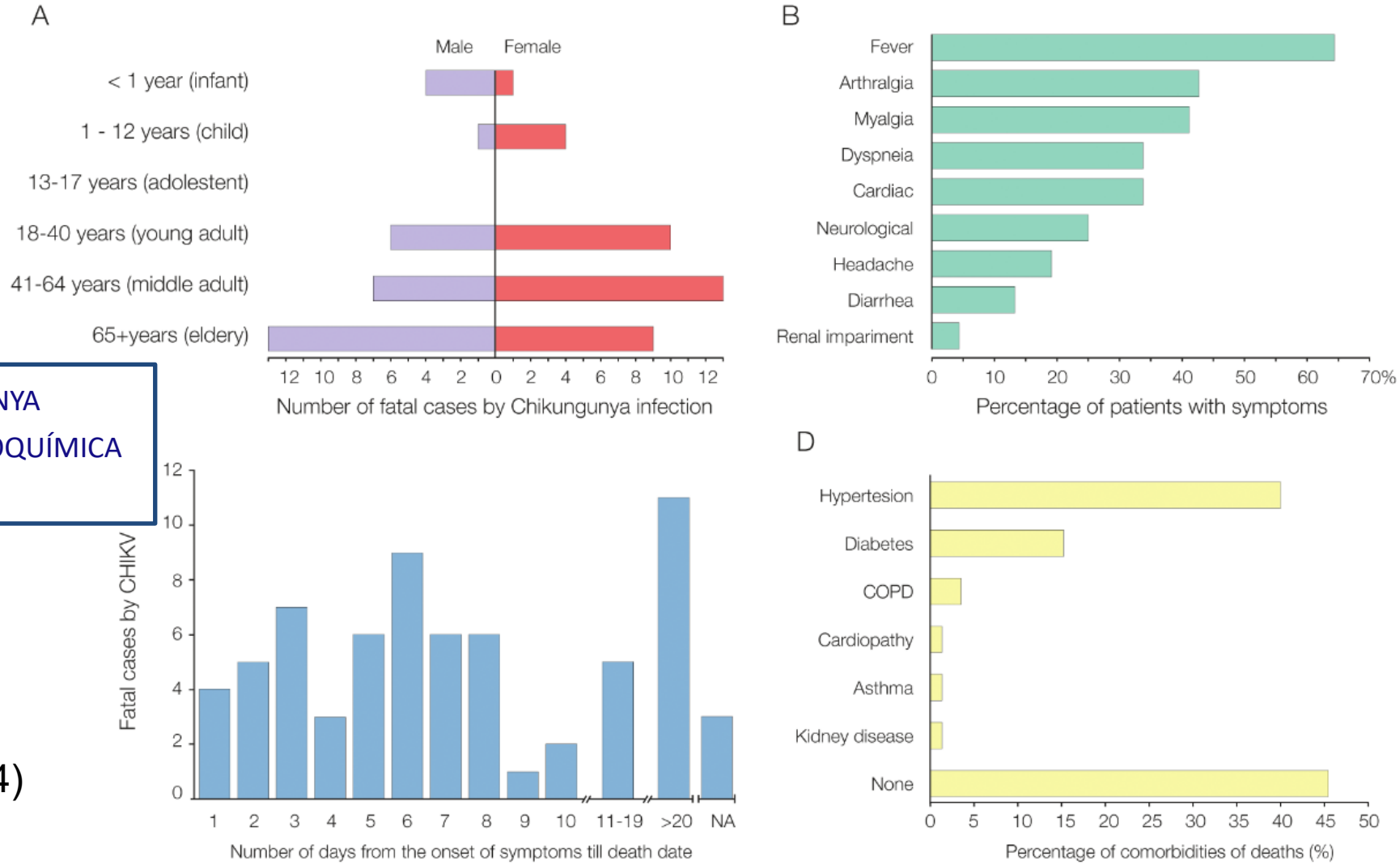
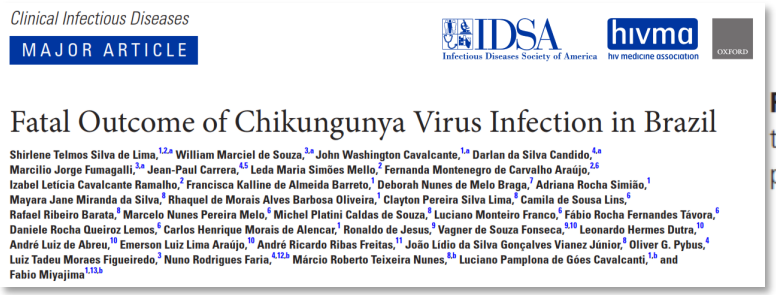


Figure 2. Demographics, symptoms, and comorbidities of 68 chikungunya deaths from Ceará state, Brazil. *A*, Age range and sex. *B*, Clinical characteristics. *C*, Days from the onset of symptoms of individuals till death. *D*, Comorbidities associated with chikungunya deaths. Abbreviations: CHIKV, chikungunya virus; COPD, chronic obstructive pulmonary disease; NA, not available.


Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Fatal Outcome of Chikungunya Virus Infection in Brazil

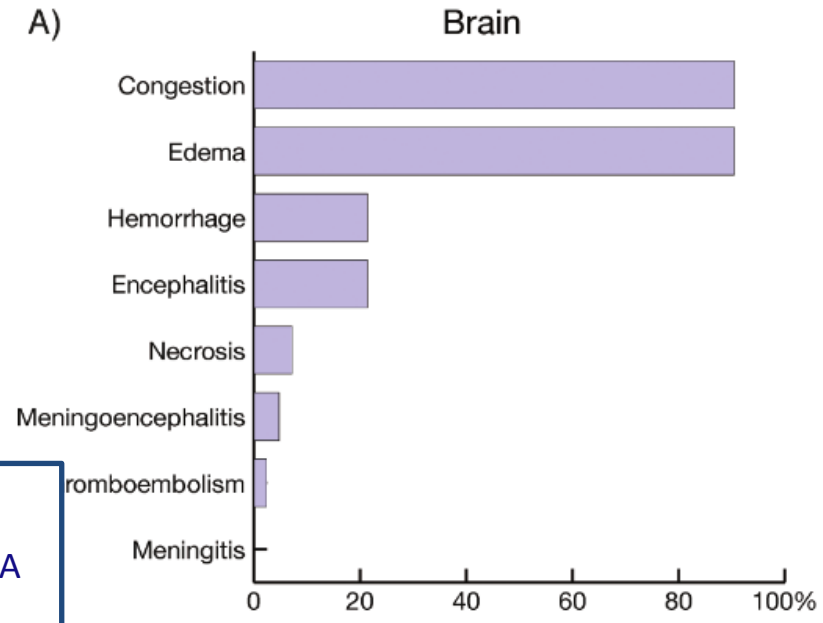
Shirlene Telmos Silva de Lima,[1,2,a] William Marciel de Souza,[3,a] John Washington Cavalcante,[1,a] Darlan da Silva Candido,[4,a] Marcilio Jorge Fumagalli,[5,a] Jean-Paul Carrera,[4,5] Leda Maria Simões Mello,[2] Fernanda Montenegro de Carvalho Araújo,[2,6] Izabel Letícia Cavalcante Ramalho,[2] Francisca Kalline de Almeida Barreto,[1] Deborah Nunes de Melo Braga,[7] Adriana Rocha Simião,[1] Mayara Jane Miranda da Silva,[8] Rhaquel de Morais Alves Barbosa Oliveira,[1] Clayton Pereira Silva Lima,[8] Camila de Sousa Lins,[6] Rafael Ribeiro Barata,[8] Marcelo Nunes Pereira Melo,[6] Michel Platini Caldas de Souza,[8] Luciano Monteiro Franco,[6] Fábio Rocha Fernandes Távora,[6] Daniele Rocha Queiroz Lemos,[6] Carlos Henrique Morais de Alencar,[1] Ronaldo de Jesus,[9] Vagner de Souza Fonseca,[9,10] Leonardo Hermes Dutra,[10] André Luiz de Abreu,[10] Emerson Luiz Lima Araújo,[10] André Ricardo Ribas Freitas,[11] João Lídio da Silva Gonçalves Vianez Júnior,[9] Oliver G. Pybus,[4] Luiz Tadeu Moraes Figueiredo,[3] Nuno Rodrigues Faria,[4,12,b] Márcio Roberto Teixeira Nunes,[8,b] Luciano Pamplona de Góes Cavalcanti,[1,b] and Fabio Miyajima[1,13,b]

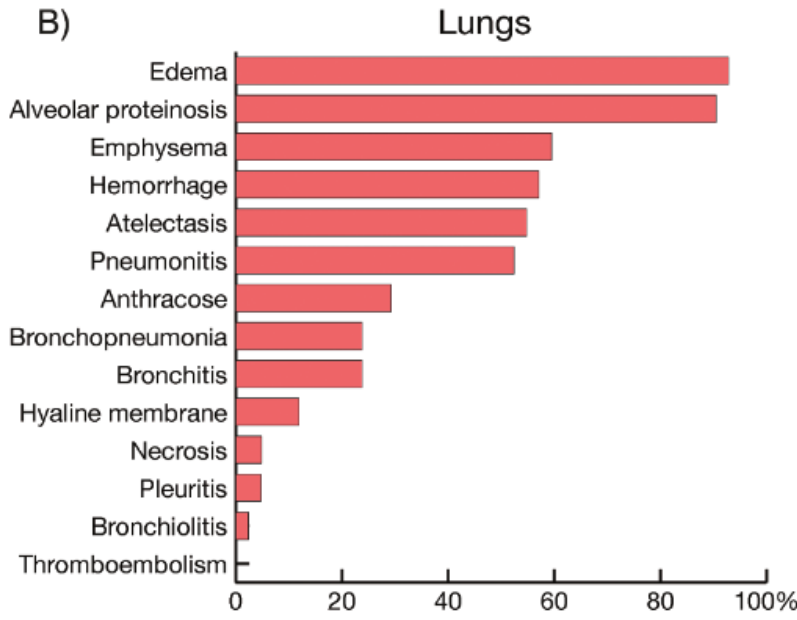
CONASEMS
Conselho Nacional de Secretarias Municipais de Saúde

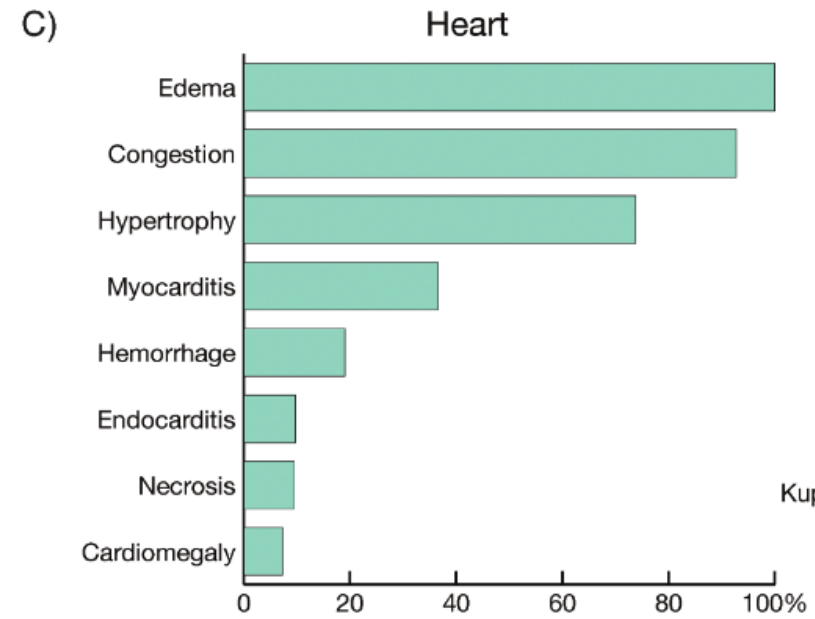
NECROPSIA DE 68 CASOS FATAIS DE CHIKUNGUNYA CONFIRMADOS (RT-PCR (53%), IMUNO-HISTOQUÍMICA (41%) E/OU IGM (63%), CEARÁ/BR, 2017

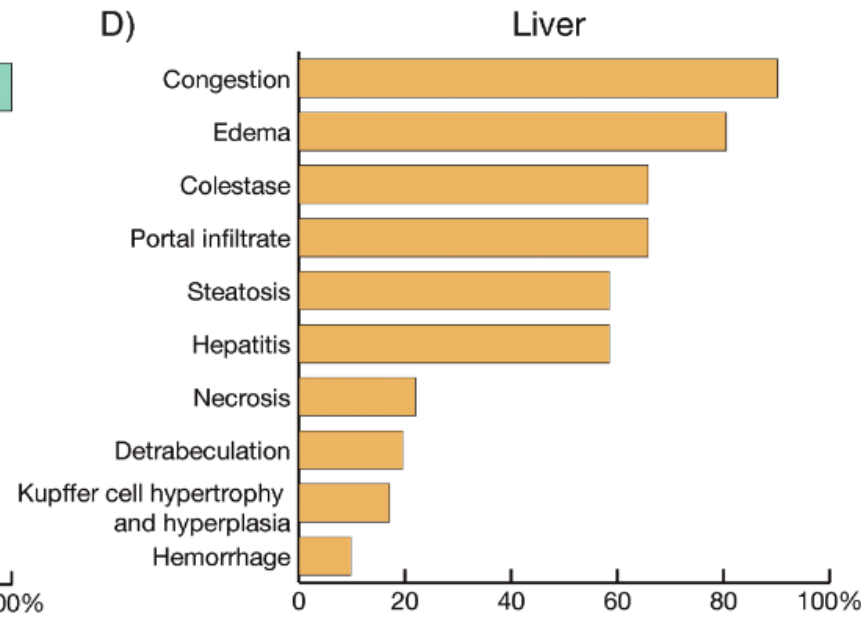
Órgãos vitais afetados

- Cérebro
- Pulmões
- Coração
- Fígado









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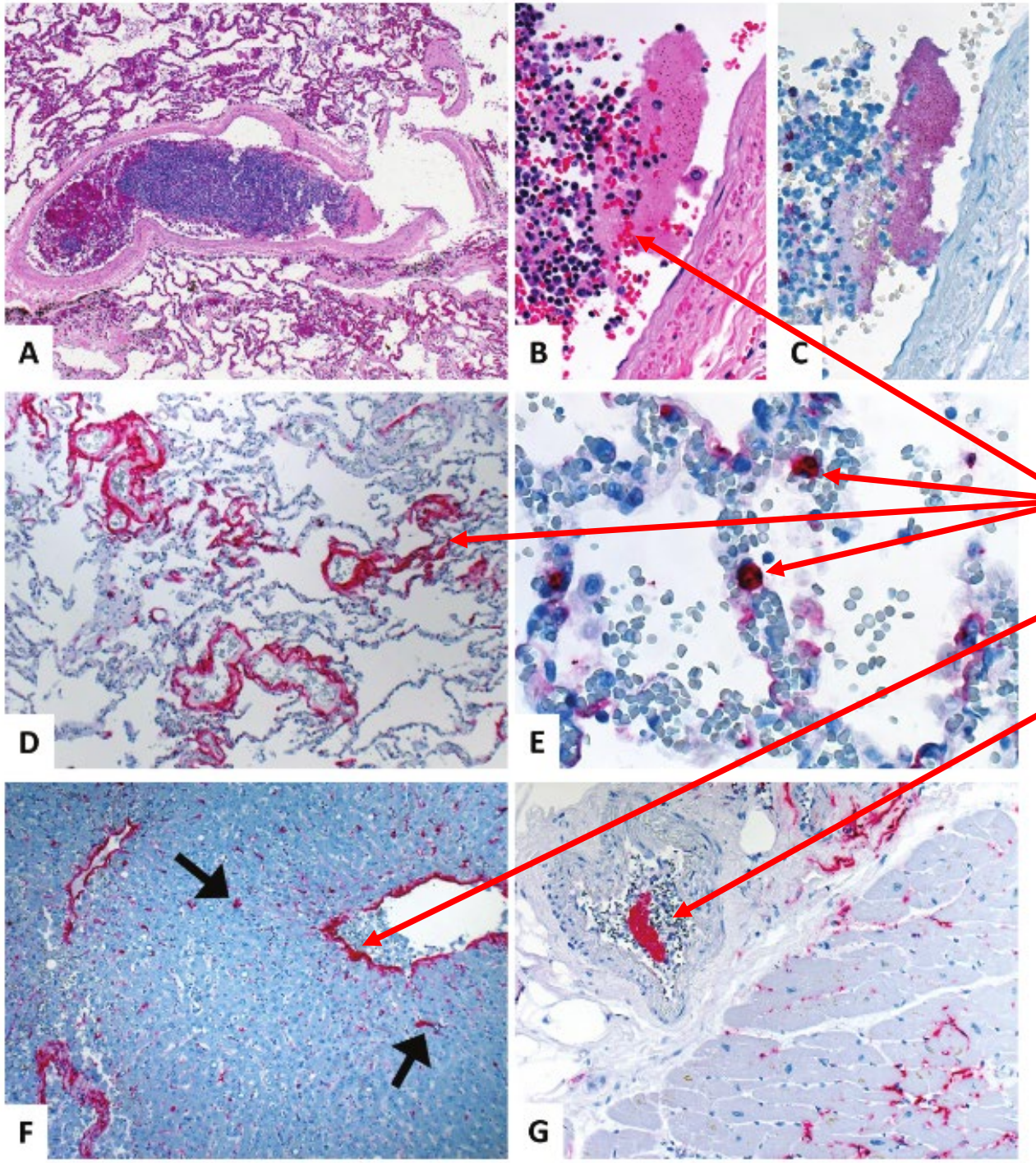
CONASEMS
Conselho Nacional de Secretarias Municipais de Saúde

Extenso infiltrado leucocitário pulmonar



Imunohistoquímica (antígenos de CHIKV em vermelho)

- Pulmão (C – E)
- Fígado (F)
- Coração (G).

Clinical Infectious Diseases

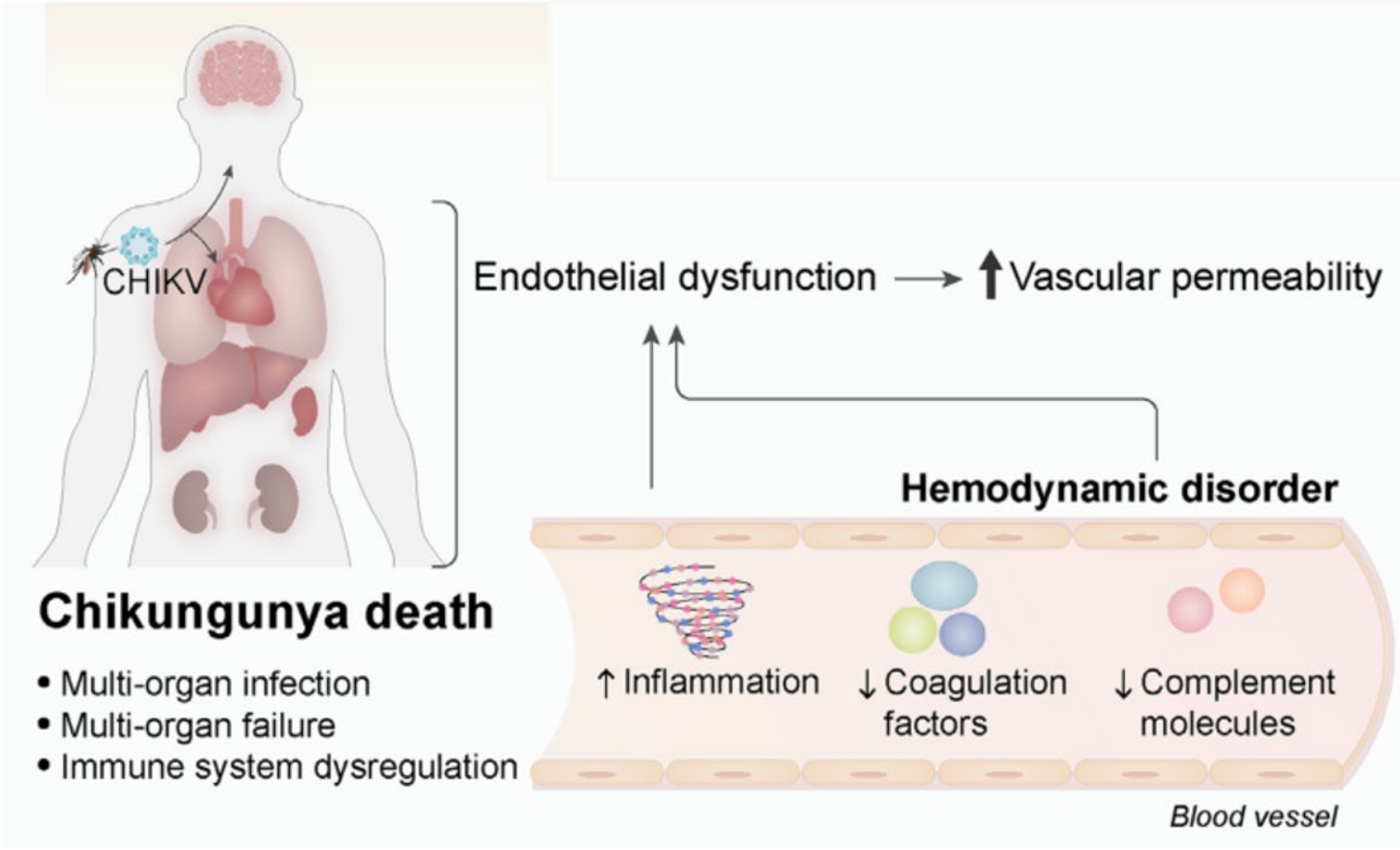
MAJOR ARTICLE

Clinical Characteristics, Histopathology, and Tissue Immunolocalization of Chikungunya Virus Antigen in Fatal Cases

Tyler M. Sharp,[1,2,a,©] M. Kelly Keating,[3,a] Wun-Ju Shieh,[3] Julu Bhatnagar,[3] Brigid C. Bollweg,[3] Rebecca Levine,[2,3] Dianna M. Blau,[3] Jose V. Torres,[4] Aidsa Rivera,[1] Janice Perez-Padilla,[1] Jorge Munoz-Jordan,[1] Dario Sanabria,[4] Marc Fischer,[2,5] Brenda Rivera Garcia,[6] Kay M. Tomashek,[1,2] and Sherif R. Zaki[3]

[1]Centers for Disease Control and Prevention, Dengue Branch, San Juan, Puerto Rico, USA, [2]US Public Health Service, Silver Springs, Maryland, USA, [3]Centers for Disease Control and Prevention, Infectious Diseases Pathology Branch, Atlanta, Georgia, USA, [4]Puerto Rico Institute of Forensic Sciences, Medicolegal and Toxicological Investigation Division, San Juan, Puerto Rico, USA, [5]Centers for Disease Control and Prevention, Arboviral Diseases Branch, Fort Collins, Colorado, USA, and [6]Puerto Rico Department of Health, San Juan, Puerto Rico, USA

PATHOPHYSIOLOGY OF FATAL CHIKUNGUNYA CASES



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Pathophysiology of chikungunya virus infection associated with fatal outcomes

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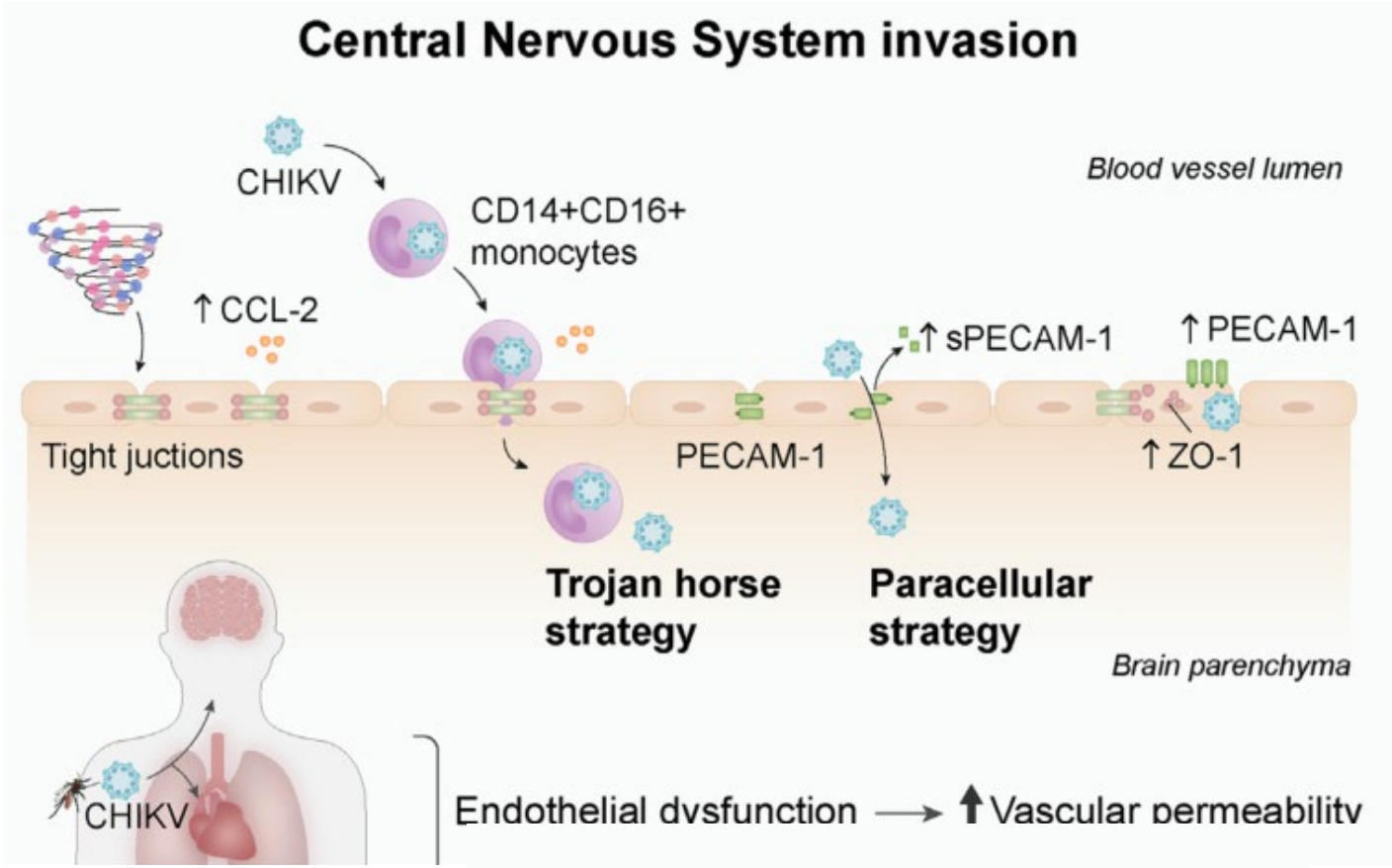
Epidemiological analyses were performed in R studio (version 1.3.1073). The correlation between suspected CHIK-deaths per year and suspected CHIK cases per year in Brazil was determined by Pearson's correlation coefficients. The cumulative case-fatality ratio for the country and states was also calculated.

Sample collection, clinical information, histopathological analysis, and ethics statement

Sera, cerebrospinal fluid (CSF), and tissue samples were collected from a cohort of CHIK-deaths (n = 32) in Brazil, as previously reported.[12] Briefly, these cases were investigated by the Central Public Health Laboratory and the Death Verification Service during the chikungunya outbreak in Ceará State in 2017. Additional blood samples were collected from patients with acute CHIK who survived (n = 39) during the CHIK epidemics between 2016 to 2019 in Brazil. Samples from blood donors and healthy individuals were included in the study, all of whom were negative for CHIKV RNA by RT-qPCR and non-reagent for IgM and IgG against CHIKV (n = 15). All residual samples were stored at -80°C for subsequent investigation. Tissue samples from CHIK-deaths were conserved in formalin-fixed blocks for histopathological analysis. Basic clinical and demographic data were collected through a questionnaire filled out by the patients or their relatives.

DE SOUZA, W. M. et al. Pathophysiology of chikungunya virus infection associated with fatal outcomes. Cell Host & Microbe. abr. 2024.

Central Nervous System Invasion



DE SOUZA, W. M. et al. Pathophysiology of chikungunya virus infection associated with fatal outcomes. Cell Host & Microbe. abr. 2024.

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Pathophysiology of chikungunya virus infection associated with fatal outcomes

Chikungunya Mortality: A Neglected Complication

Underreporting of Fatal Cases – Key Factors

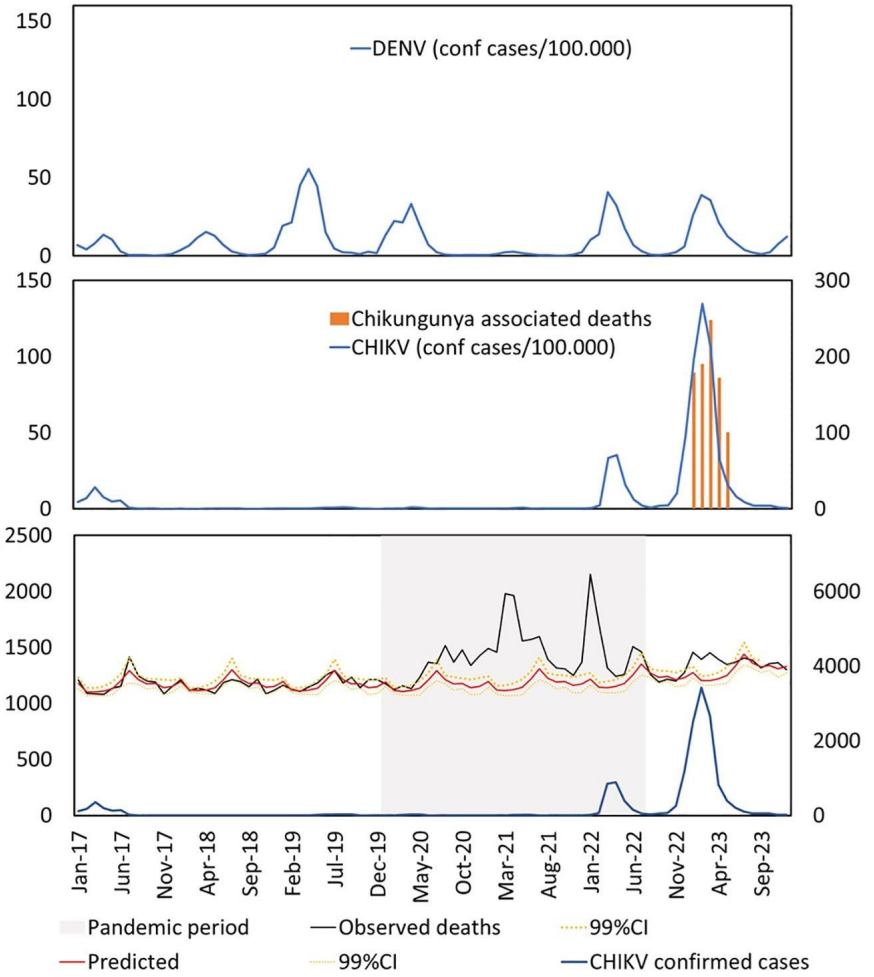
- **Lack of knowledge about severe forms among health professionals**
- Sometimes the deaths occurring **weeks after acute infection** make causality harder to establish.
- **Multisystem Involvement Masking Diagnosis**
  - **Cardiovascular, neurological, renal, and hepatic complications** complicate clinical recognition.
- **Limited Diagnostic Resources in Endemic Countries**

Conclusion:

- **Chikungunya-related mortality is significantly underestimated in many settings.**
- Improved awareness and training about severe clinical forms and improvements in surveillance are essential to understand the true impact.

Underestimation of fatal chikungunya cases Minas Gerais, Brazil (2023)

- In 2023, a major chikungunya epidemic occurred in Minas Gerais, one of the most populous states in the country.
- We analyzed the North and Northeast Health Macroregions of Minas Gerais, with 2.5 million inhabitants, with only 15 confirmed chikungunya deaths
- Excess deaths were calculated by comparing observed deaths with model estimates during the epidemic period.
- During the epidemic, there were 890 excess deaths attributed to chikungunya, translating into a mortality rate of 35.1/100,000 inhabitants.
- The excess mortality rate was significantly 60 times higher than the deaths reported by surveillance.
- The correlation between excess deaths and laboratory-confirmed chikungunya cases was strong, while the correlation with dengue and COVID-19 was not statistically significant.



Ribas Freitas, AS Lima Neto, R Rodrigues, E Alves de Oliveira. (2024). Excess mortality associated with chikungunya epidemic in Southeast Brazil, 2023. Frontiers in Tropical Diseases 5, 1466207

UNDERESTIMATION OF FATAL CHIKUNGUNYA CASES (OTHER EXAMPLES)

Local	Year	Pop	Reported deaths	Excess deaths	Proportion detected	Excess mort rate	Probable lineage	Source
Reunion	2006	770	254	260	98%	33.8	ECSA (IOL)	Euro Surveill, 2007
Ahmedabab (India)	2006	3,800	0	2,944	0%	77.5	ECSA (IOL)	EID, 2008
Port Blair	2006	136	0	86	0%	63.2	ECSA (IOL)	Epid & Infect, 2011
Mauritius	2006	1,250	0	743	0%	59.4	ECSA (IOL)	EID, 2008
Martinica e Guadaloupe	2014	783	160	639	23%	81.6	Asian	Epid & Infect, 2018
Puerto Rico	2014	3,688	31	1,310	2%	35.5	Asian	EID, 2018
Dominican Republic	2014	10,400	6	4,925	0%	47.4	Asian	TRSTMH 2018
Jamaica	2014	2,720	0	2,499	0%	91.9	Asian	Pat & Glob Health, 2019
Pernambuco	2016	9,410	94	4,505	2%	47.9	ECSA	PLoS Currents, 2017
Rio Grande do Norte	2016	3,474	64	1,478	4%	42.5	ECSA	PLoS Currents, 2017
North and Northeast (Minas Gerais. BR)	2023	2,535	15	819	2%	32.3	ECSA	Present study

Deaths/100,000 population.

Ribas Freitas, AS Lima Neto, R Rodrigues, E Alves de Oliveira. (2024). Excess mortality associated with chikungunya epidemic in Southeast Brazil, 2023. Frontiers in Tropical Diseases 5, 1466207

Chikungunya in Pregnancy & Neonatal Period

Viremia During Pregnancy

- No strong evidence of increased risk for **fetal death or miscarriage**.

Peripartum Viremia (7 Days Before to 2 Days After Birth)

- **Vertical transmission rate:** ~50%.
- **Severe neonatal infections:** ~50% of infected newborns.
- **High fatality rate** in severe cases.

Severe Neonatal Manifestations

- **Bleeding & blistering skin lesions**.
- **Multi-organ failure**.
- **Hyperalgesic syndromes**.
- **Neurological complications (~50% of severe cases)**:
  - **Encephalitis & severe CNS involvement**.
  - ~50% of neurological cases show **delayed neurodevelopment**.
  - ~10% of all **perinatal infections** lead to long-term neurodevelopmental delays.

Gérardin et al PloS Med 2008;
Gérardin et al PLoS Negl Trop Dis 2014

Laboratory Diagnosis

Direct Detection (Best for Early Diagnosis)

- **RT-PCR (qPCR/Conventional PCR)**
- **Most sensitive** method in the first **7 days** of symptoms.
- Detects **viral RNA** before the immune response develops.

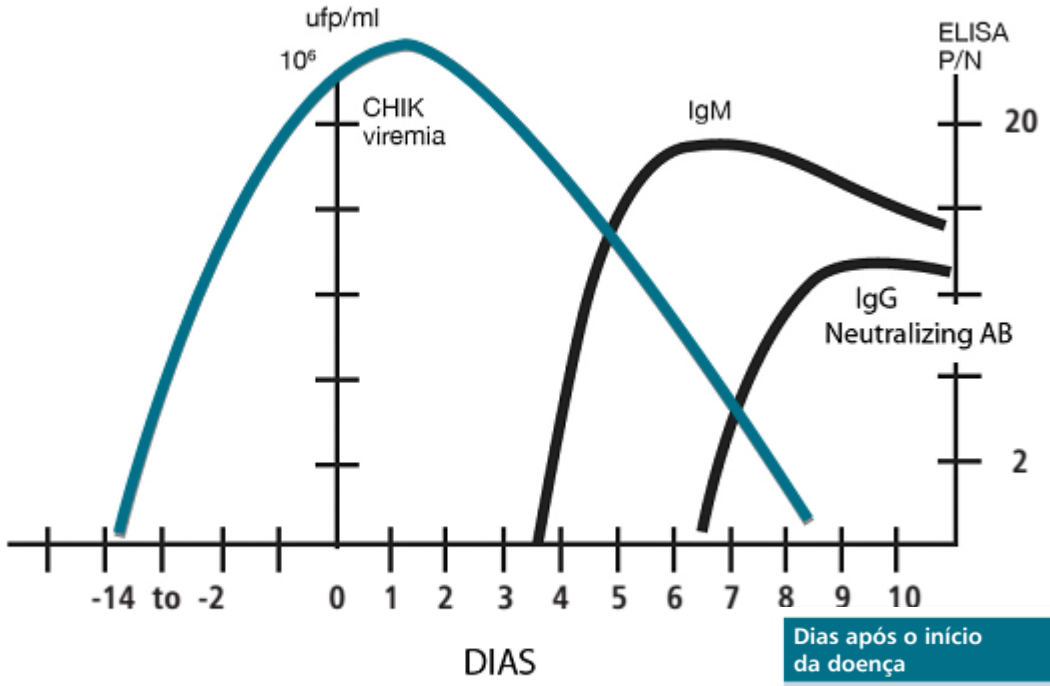
Serological methods (IgM/IgG ELISA, PRNT)

- **IgM detection** – Useful after **day 5**, but can cross-react with other alphaviruses.
- **IgG detection** – Indicates **past exposure**, not active infection.

Viral Isolation (Cell Culture)

- Used mainly in research or reference labs.
- Confirms the presence of **infectious virus**.

LABORATORY DIAGNOSIS



Fonte: Centres for Disease Control and Prevention/CDC e Organização Pan-Americana da

Fonte: Preparación y respuesta ante la eventual introducción del virus chikungunya en las Américas. Organización Panamericana de la Salud. Washington, D.C.: OPS, © 2011

Dias após o início da doença	Teste de vírus	Teste de anticorpos
Dia 1-3	RT-PCR = Positivo Isolamento = Positivo	IgM = Negativo PRNT = Negativo
Dia 4-8	RT-PCR = Positivo Isolamento = Negativo	IgM = Positivo PRNT = Negativo
>Dia 8	RT-PCR = Negativo Isolamento = Negativo	IgM = Positivo PRNT = Positivo

Fonte: Centres for Disease Control and Prevention/CDC e Organização Pan-Americana da Saúde.

Importance of Laboratory Diagnosis

Clinical Overlap with Other Arboviruses

- Chikungunya presents with **fever, polyarthritis, and rash**, similar to dengue and Zika.
- **Clinical diagnosis alone is unreliable**, especially during co-circulating outbreaks.

Laboratory Confirmation is Essential

- Helps distinguish chikungunya from **dengue, Zika, and other febrile illnesses**.
- Guides **case management, surveillance, and outbreak response**.

Misdiagnosis Risks

- Delayed or incorrect treatment.
- Underreporting of chikungunya cases and deaths.
- Misclassification as dengue, leading to **inaccurate epidemiological data**.

UNDERESTIMATION OF CHIKUNGUNYA CASES

BELO HORIZONTE, MINAS GERAIS, BRAZIL, 2023

SÃO LEOPOLDO MANDIC

- Unlike dengue, a case of chikungunya is only recognized with more rigorous clinical suspicion
- Chikungunya is not well known by most healthcare professionals, leading to a bias in clinical suspicion, contributing to many cases of chikungunya being reported as dengue.
- During epidemics, the majority of patients do not undergo confirmatory tests and, therefore, end up being considered dengue fever.
- This reinforces the false idea that chikungunya continues to be a rare disease in Brazil.
- Minas Gerais (MG) largest states in Brazil and concentrated 25% of the cases that occurred in 2023.
- MG surveillance structure systematically performs Multiplex RT-qPCR for etiological diagnosis of a large proportion of patients, regardless of the initial clinical suspicion.

UNDERESTIMATION OF CHIKUNGUNYA CASES

BELO HORIZONTE, MINAS GERAIS, BRAZIL, 2023

SÃO LEOPOLDO MANDIC

Official Case Numbers Underestimate Chikungunya

- Official reports show 2.4x more "probable dengue" cases than chikungunya in BH and 5x more in MG.

Higher Positive Tests for Chikungunya (absolute number and proportion)

- **BH:** 3.8x more positive chikungunya tests than dengue.
- **MG:** 1.4x more positive chikungunya tests than dengue.
- Test positivity for chikungunya was **2.1–5.1x higher** than for dengue in both direct (RT-qPCR) and indirect (IgM) methods

Conclusion:

- Adjusted estimates suggest a significantly higher chikungunya burden.
- Testing data contradict official dengue-chikungunya case ratios.
- Surveillance gaps may lead to chikungunya underestimation, impacting public health responses.

Chikungunya cases would be 3.3 times higher
Dengue cases would be 67% lower

	Officially reported clinical cases		Multiplex RT-qPCR			Enzyme immunoassay (IgM) tests			Total positive tests (RT-qPCR and IgM)	Overall test positivity [(c) + (e)]/[(b) + (d)]	Rough estimate of real clinical cases[a]
	Suspects[c] (a)	Probable[c]	Performed[d] (b)	Positives[d] (c)	Test positivity (c)/(b)	Performed[d] (d)	Positives[d] (e)	Test positivity (e)/(d)			
Belo Horizonte (BH)											
Dengue	53,405	14,050	8200	520	6.3%	3464	388	11.2%	908	7.8%	4769
Chikungunya	7861	5962	8198	1989	24.3%	2553	1472	57.7%	3461	32.2%	19,723
Arbovirus[b] (total)	61,266	20,012							4932		24,492
Minas Gerais (MG)											
Dengue	699,559	413,307	83,206	9007	10.8%	65,447	17,878	27.3%	26,885	18.1%	149,868
Chikungunya	129,095	83,330	83,242	24,324	29.2%	21,808	12,344	56.6%	36,668	34.9%	289,244
Arbovirus[b] (total)	828,654	496,637							63,553		439,112

[a]The estimate of real clinical cases was calculated by multiplying the number of suspected arboviruses by the overall positivity of laboratory tests. [b]There may be patients who have been notified twice, for dengue and chikungunya. [c]Sources: http://tabnet.datasus.gov.br (accessed on 03/19/2024). [d]Sources: https://www.saude.mg.gov.br/aedes/painelvigilancialaboratorial (accessed on 03/19/2024).

Table 1: **Number of officially reported clinical cases, diagnostic tests performed in official laboratories and estimated clinical cases (State of Minas Gerais and Belo Horizonte, Brazil, 2023).**

*Ribas Freitas, AR et al. (2024) How much of the current serious arbovirus epidemic in Brazil is dengue and how much is chikungunya? The Lancet Regional Health – Americas, Volume 34, 100753

Challenges in Endemic Regions

- **Limited access to diagnostics** – Many regions rely solely on clinical diagnosis.
- **Cost barriers** – RT-PCR and ELISA tests may not be widely available.
- **Infrastructure gaps** – Poor lab capacity and trained personnel shortages.

Impact of Limited Testing

- Underestimation of chikungunya **burden and mortality**.
- Failure to detect **new outbreaks early**.
- **Underestimation of chikungunya cases and daeths and overestimation of dengue cases** due to syndromic diagnosis.

Need for Expanded Diagnostic Access

- Investment in **point-of-care** tests for rapid identification.
- Strengthening laboratory networks in **low-resource settings**.

THANKS!

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Chikungunya Disease in the Americas

Thais H. dos Santos

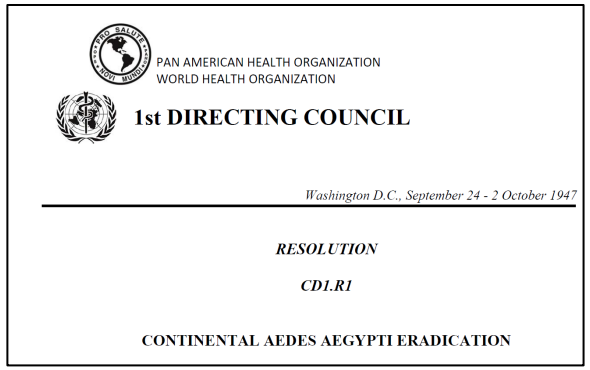
Regional Advisor, Surveillance and Control of Arboviral Diseases

OPS Organización Panamericana de la Salud

Organización Mundial de la Salud
Oficina Regional para las Américas

Arboviral Disease Surveillance in the Americas: resolutions

CD1.R1
Continental *Aedes aegypti* eradication, (Sep-1947)



PAN AMERICAN HEALTH ORGANIZATION
WORLD HEALTH ORGANIZATION

1st DIRECTING COUNCIL

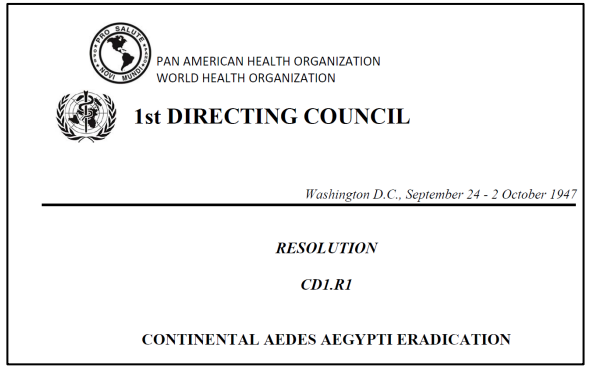
Washington D.C., September 24 - 2 October 1947

RESOLUTION

CD1.R1

CONTINENTAL AEDES AEGYPTI ERADICATION

CD43.R4
Dengue and dengue hemorrhagic fever (Sep-2001)



PAN AMERICAN HEALTH ORGANIZATION
WORLD HEALTH ORGANIZATION

1st DIRECTING COUNCIL

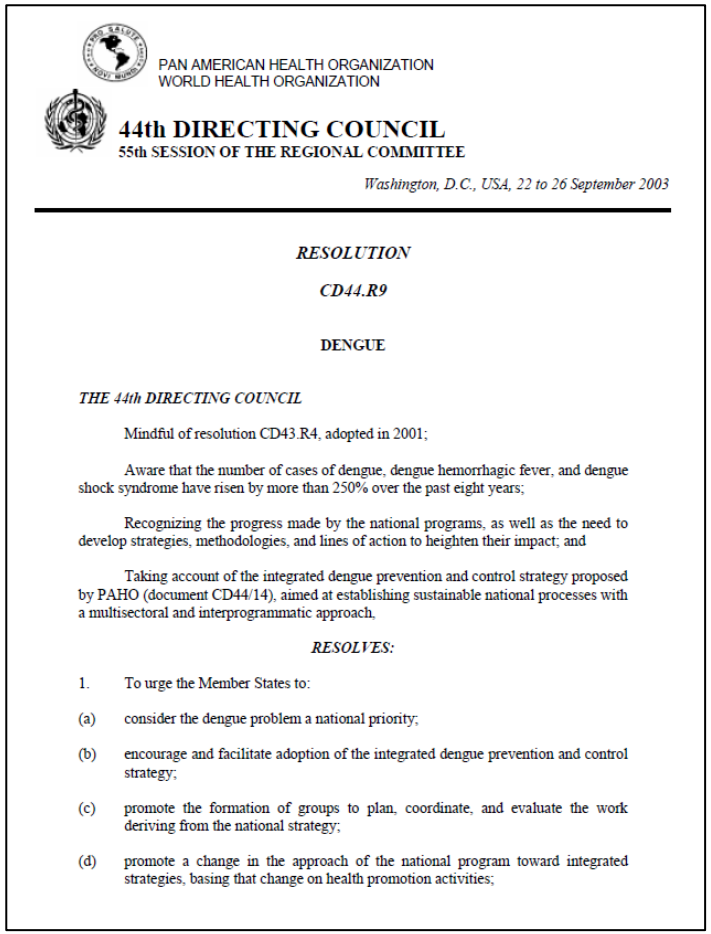
Washington D.C., September 24 - 2 October 1947

RESOLUTION

CD1.R1

CONTINENTAL AEDES AEGYPTI ERADICATION

CD44.R9
Dengue (Sep-2003)



PAN AMERICAN HEALTH ORGANIZATION
WORLD HEALTH ORGANIZATION

44th DIRECTING COUNCIL
55th SESSION OF THE REGIONAL COMMITTEE

Washington, D.C., USA, 22 to 26 September 2003

RESOLUTION

CD44.R9

DENGUE

THE 44th DIRECTING COUNCIL

Mindful of resolution CD43.R4, adopted in 2001;

Aware that the number of cases of dengue, dengue hemorrhagic fever, and dengue shock syndrome have risen by more than 250% over the past eight years;

Recognizing the progress made by the national programs, as well as the need to develop strategies, methodologies, and lines of action to heighten their impact; and

Taking account of the integrated dengue prevention and control strategy proposed by PAHO (document CD44/14), aimed at establishing sustainable national processes with a multisectoral and interprogrammatic approach,

RESOLVES:

1. To urge the Member States to:

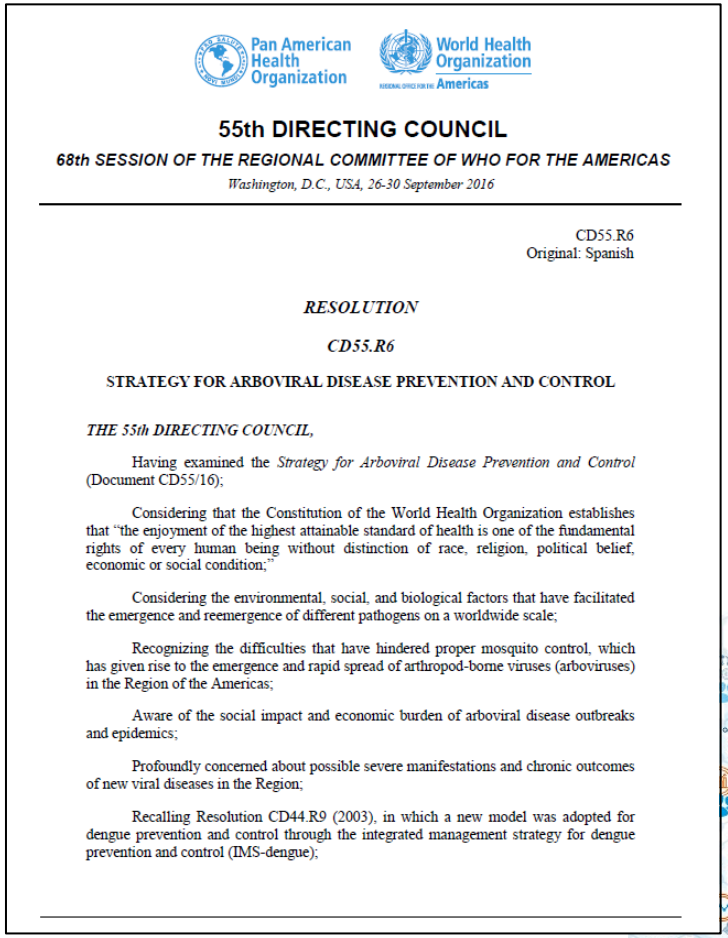
(a) consider the dengue problem a national priority;

(b) encourage and facilitate adoption of the integrated dengue prevention and control strategy;

(c) promote the formation of groups to plan, coordinate, and evaluate the work deriving from the national strategy;

(d) promote a change in the approach of the national program toward integrated strategies, basing that change on health promotion activities;

CD55.R6
Strategy for Arboviral Disease Prevention and Control (Sept-2016) IMS-Arbovirus



Pan American Health Organization
World Health Organization Americas

55th DIRECTING COUNCIL

68th SESSION OF THE REGIONAL COMMITTEE OF WHO FOR THE AMERICAS

Washington, D.C., USA, 26-30 September 2016

CD55.R6
Original: Spanish

RESOLUTION

CD55.R6

STRATEGY FOR ARBOVIRAL DISEASE PREVENTION AND CONTROL

THE 55th DIRECTING COUNCIL,

Having examined the *Strategy for Arboviral Disease Prevention and Control* (Document CD55/16);

Considering that the Constitution of the World Health Organization establishes that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition;"

Considering the environmental, social, and biological factors that have facilitated the emergence and reemergence of different pathogens on a worldwide scale;

Recognizing the difficulties that have hindered proper mosquito control, which has given rise to the emergence and rapid spread of arthropod-borne viruses (arboviruses) in the Region of the Americas;

Aware of the social impact and economic burden of arboviral disease outbreaks and epidemics;

Profoundly concerned about possible severe manifestations and chronic outcomes of new viral diseases in the Region;

Recalling Resolution CD44.R9 (2003), in which a new model was adopted for dengue prevention and control through the integrated management strategy for dengue prevention and control (IMS-dengue);

Collaborative Surveillance

"systematic strengthening of capacity and collaboration among diverse stakeholders...with the ultimate goal of enhancing public health intelligence and **improving evidence for decision-making**."

PAHO Pan American Health Organization World Health Organization Americas Region

Source: WHO. Defining Collaborative Surveillance
https://apps.who.int/iris/bitstream/handle/10665/367927/9789240074064-eng.pdf?sequence=1&isAllowed=y

What do we want with the VCS?

PAHO Pan American Health Organization World Health Organization Americas Region

What are VCS?

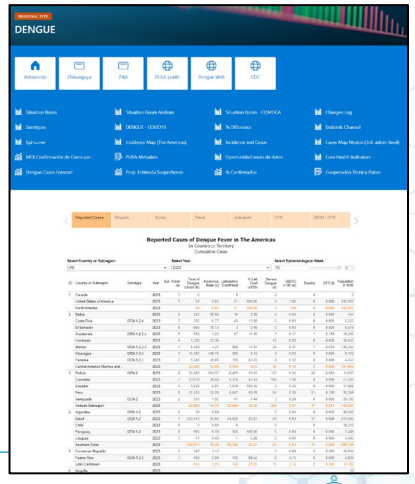
Virtual Collaboration Spaces (VCS) are the mechanism through which we operationalize collaborative surveillance. They facilitate communication, collaboration and technical cooperation of the different arbovirus work groups (Country/PAHO). They also facilitate the publication of information to support decision making on the adoption of control measures

Main characteristics

They are flexible and dynamic spaces that can easily modify their structure and content based on the needs of the users. They are constantly changing and developing.

Tailored based on country needs

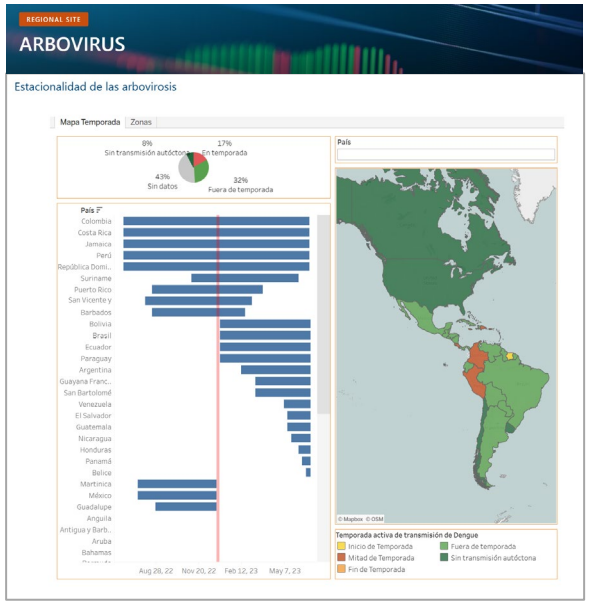
Developed with information security and confidentiality in mind. Transparency facilitates partners' trust



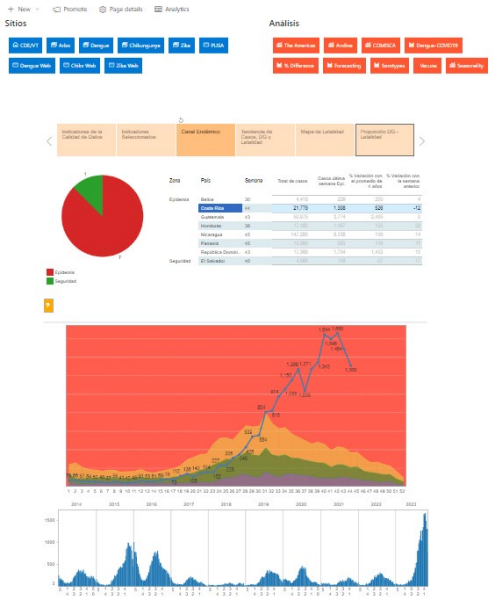
PAHO Pan American Health Organization World Health Organization Americas Region

Different VCS for Different Users

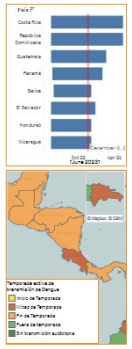
Regional Level

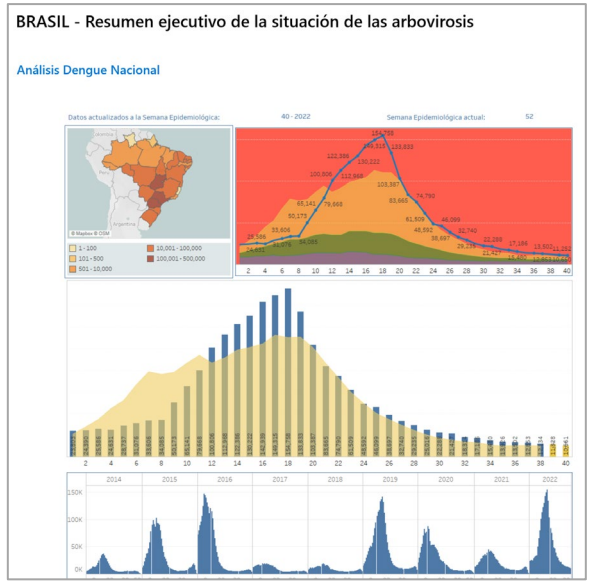


Sub-regional

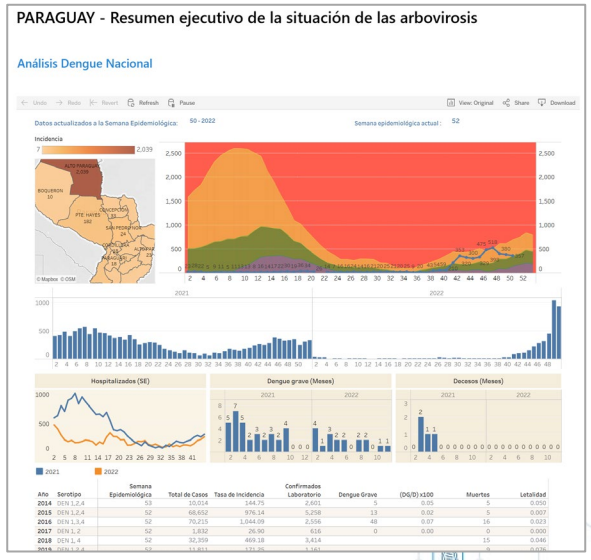


Country level





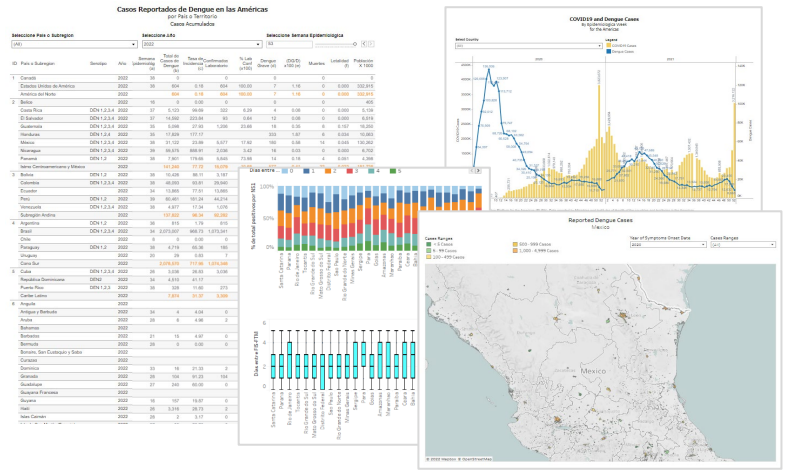
Sub-national level



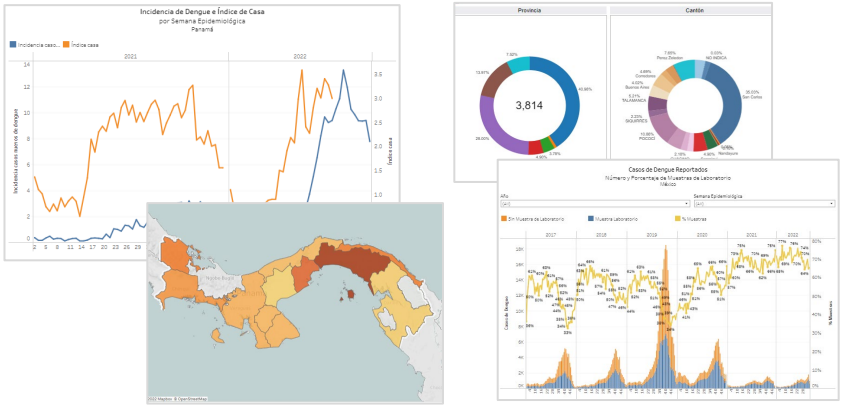
PAHO Pan American Health Organization
World Health Organization Americas Region

42 years of Dengue Data, 10 years of Chikungunya data, 8 years of Zika data available through interactive visualizations

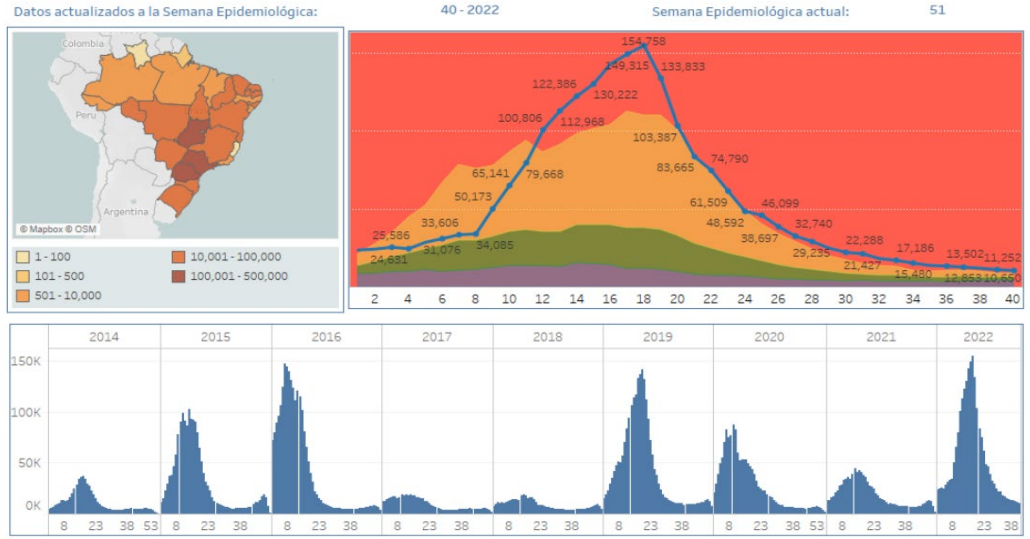
More than 800 visualizations

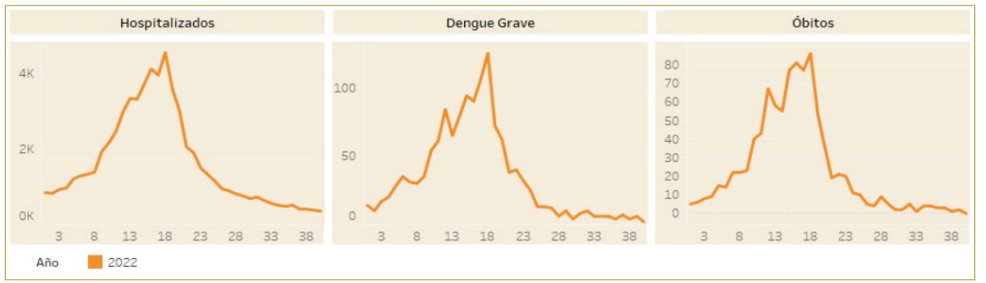


Includes entomologic and virologic surveillance data



Dashboards and “situation rooms”





Año	Serotipo	Semana Epidemiológica	Total de Casos	Tasa de Incidencia	Confirmados Laboratorio	Dengue Grave	(DG/D) x100	Muertes	Letalidad
2014	DEN 1,2,3,4	40	538,077	266.33	213,980	666	0.12	397	0.074
2015	DEN 1,2,3,4	40	1,523,039	747.85	465,153	1,529	0.10	843	0.055
2016	DEN 1,2,3,4	40	2,142,496	1,022.34	1,019,348	904	0.04	692	0.032
2017	DEN 1,2,3,4	40	447,880	214.00	145,605	255	0.06	135	0.030
2018	DEN 1,2,3,4	40	385,944	183.03	153,457	290	0.08	145	0.038
2019	DEN 1,2,3,4	40	2,119,860	1,016.74	1,237,682	1,411	0.07	800	0.038
2020	DEN 1,2,3,4	40	1,395,986	669.55	752,589	810	0.06	544	0.039
2021	DEN 1,2	40	874,203	408.52	386,239	344	0.04	230	0.026
2022	DEN 1,2,3,4	40	2,182,229	1,019.77	1,141,264	1,364	0.06	929	0.043

PAHO Pan American Health Organization
World Health Organization Americas Region


United States
Mexico
Colombia
Peru
Brazil
Argentina
Spain
December
2013


Colombia
Spain
December
2014

Introduction of Chikungunya Virus in the Americas

December 6, 2013: **The confirmation of two autochthonous transmission cases of the Chikungunya virus** on the island of Saint Martin was reported to PAHO/WHO.

Organización Panamericana de la Salud
Organización Mundial de la Salud
Américas

Alerta Epidemiológica

Fiebre por Chikungunya

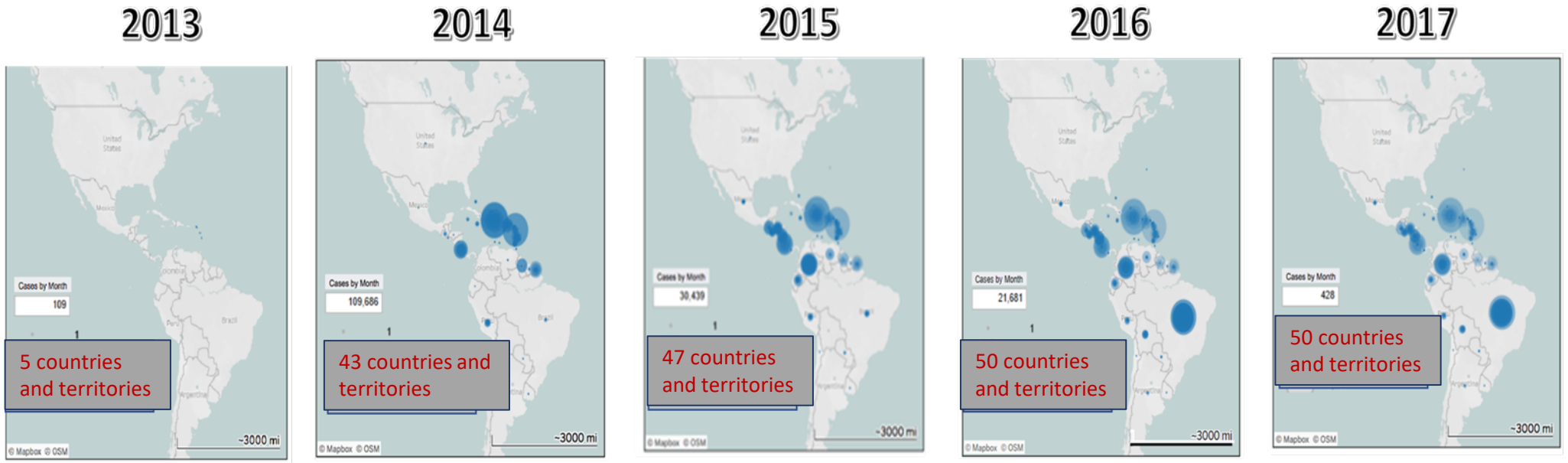
9 de diciembre 2013

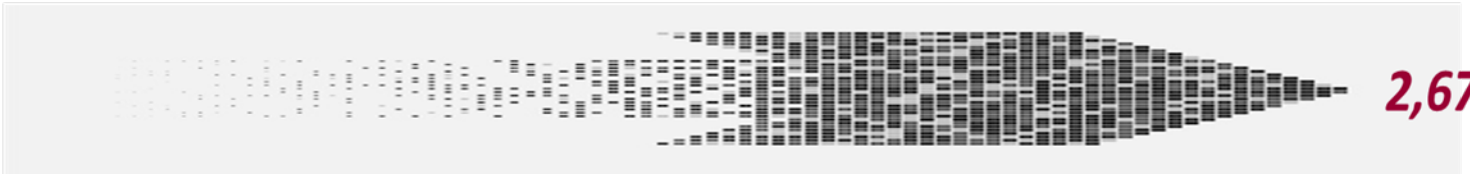
Ante la detección de los primeros casos de transmisión autóctona de fiebre por chikungunya en las Américas, la Organización Panamericana de la Salud (OPS) / Organización Mundial de la Salud (OMS) recomienda a los Estados Miembros que establezcan y mantengan la capacidad para detectar y confirmar casos, manejar pacientes, implementar una efectiva estrategia de comunicación con el público para reducir la presencia del vector, en especial en las áreas en las que está presente el mosquito transmisor de esta enfermedad.

OPS Organización Panamericana de la Salud Organización Mundial de la Salud Américas

https://www.paho.org/es/documentos/definiciones-caso-clasificacion-clinica-fases-enfermedad-dengue-chikunguna-zika

Spread of Chikungunya in the Americas

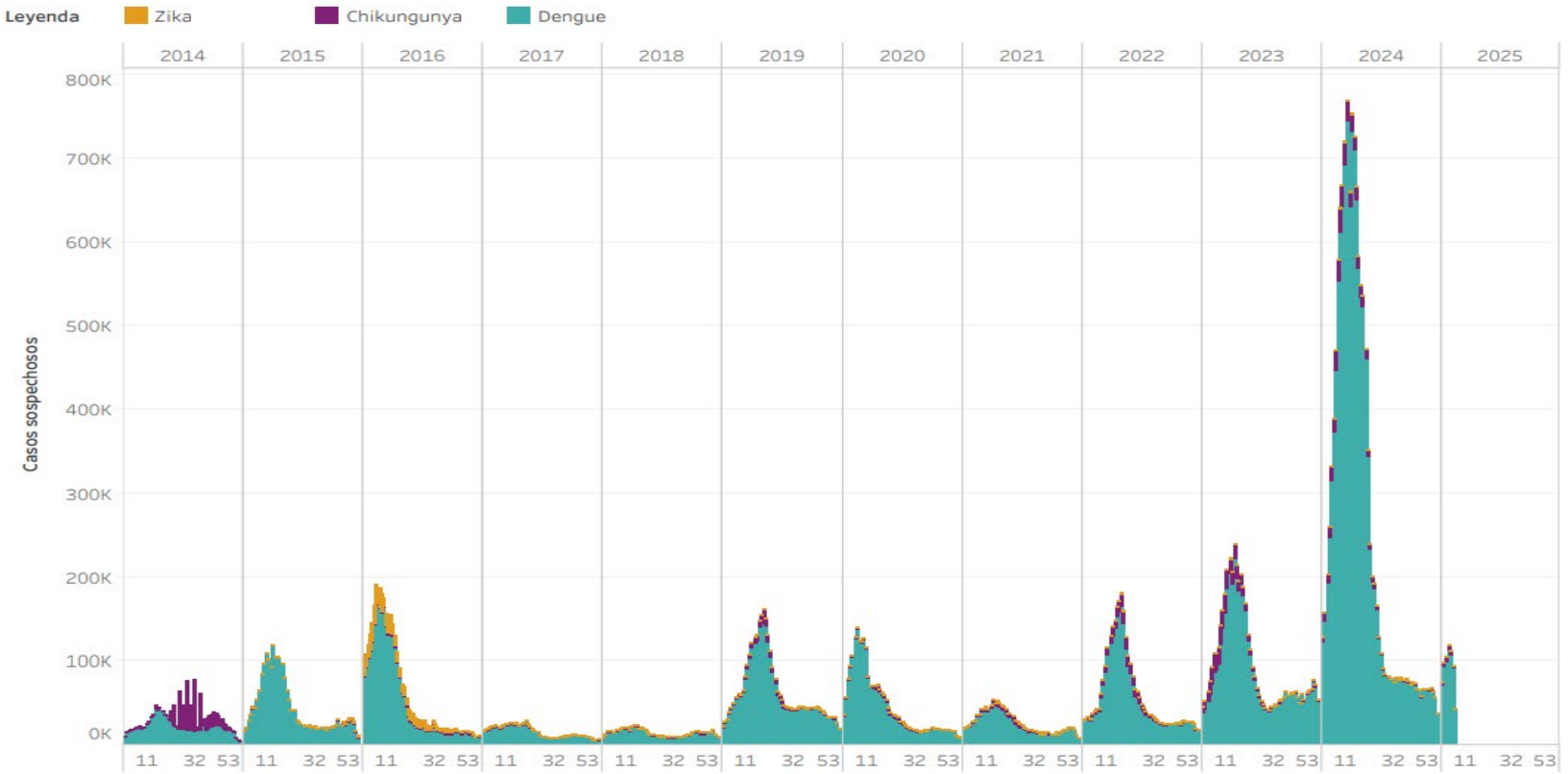




2,673,671 casos

https://www.paho.org/es/documentos/definiciones-caso-clasificacion-clinica-fases-enfermedad-dengue-chikunguna-zika

Dengue, Chikungunya, and Zika Cases in the Americas 2014-2025[&] SE 10



- **Dengue:** It is the most prevalent, 2014 to 2025 reported 35,928,361 cases (87%)
- **Chikungunya:** 2014–2025, 4,342,033 cases. The second most important arbovirus.
- **Zika:** 2015-2024: 1,018,756 cases

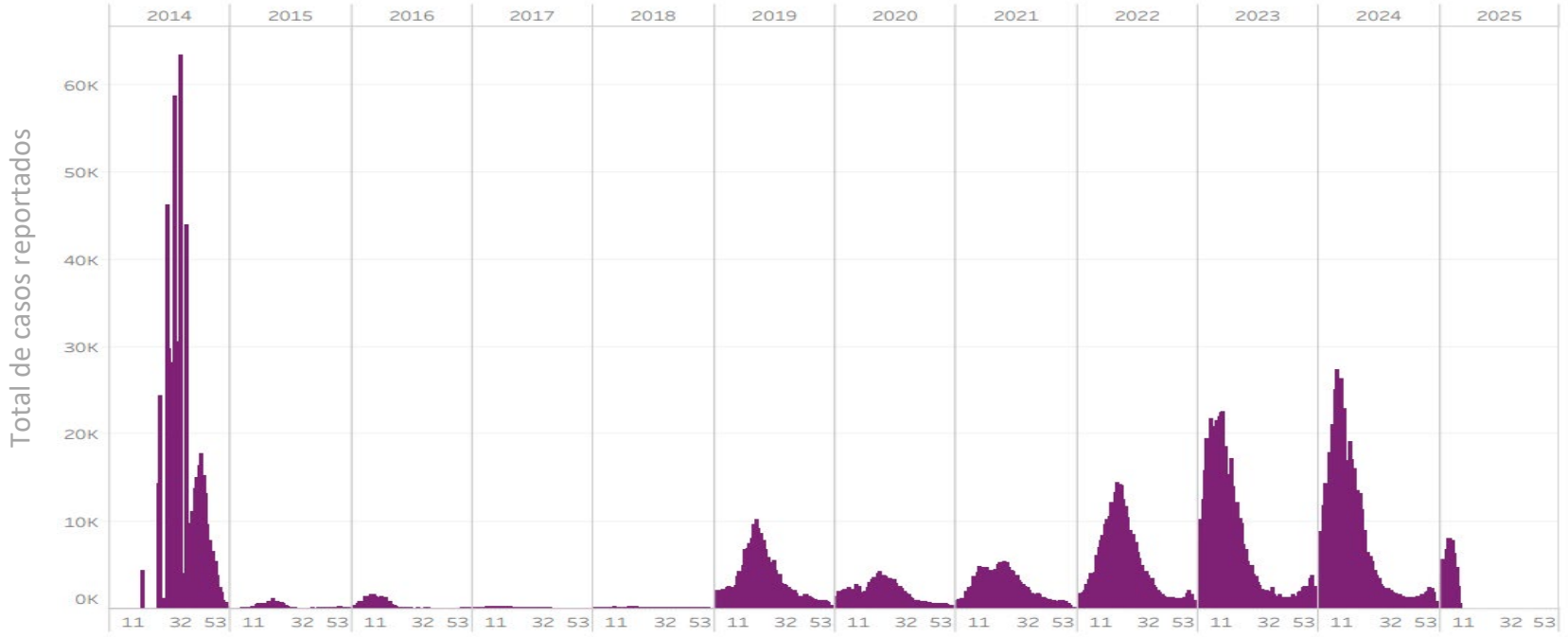
Contribution of Chikungunya (2014-2024): 4,342,033 cases (10.5%)

Contribution of Zika (2015-2024): 1,018,756 cases (2.5%)

Source: PAHO/WHO Health Information Platform (PLISA)
& Preliminary information

Weekly Chikungunya Cases in the Americas 2025[&] SE 10

Region	Suspected cases	Cumulative incidence *	Confirmed cases	Deaths/CFR
The Americas	54,511	5	25,672 (47%)	27/ 0.049%

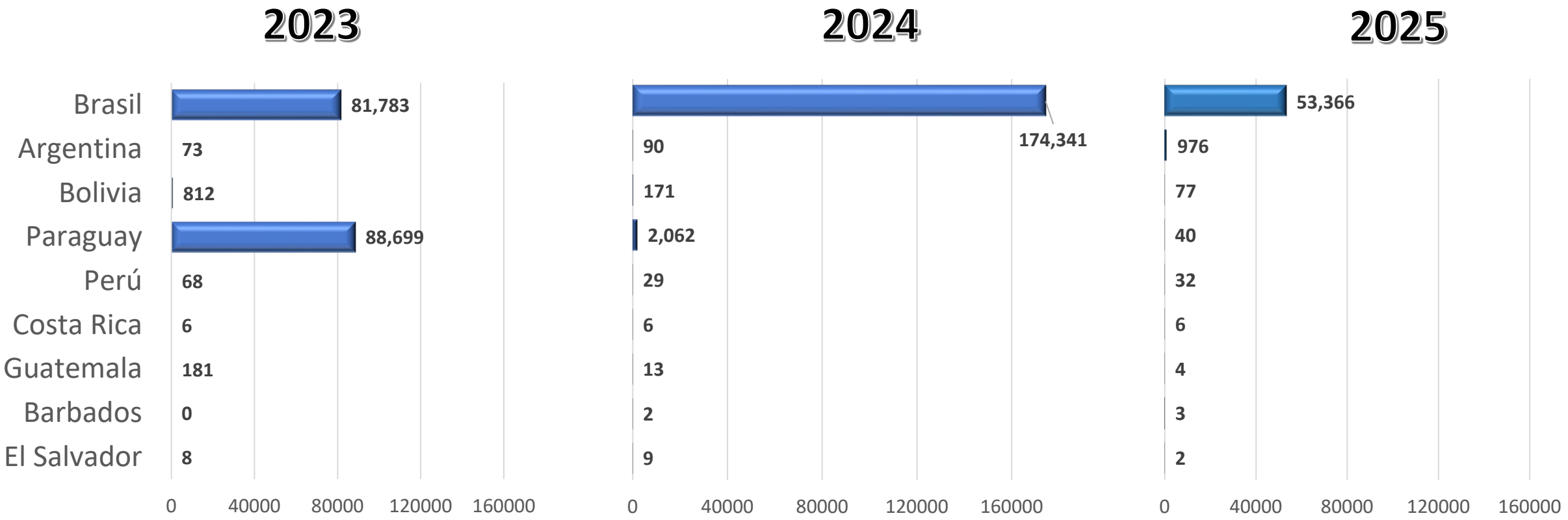


2025 Observations:

- **69% decrease compared to the same week in 2024**
- **58% increase compared to the median of the last seven years**

Source: PAHO/WHO Health Information Platform (PLISA)
* Per 100,000 pop
& Preliminary information

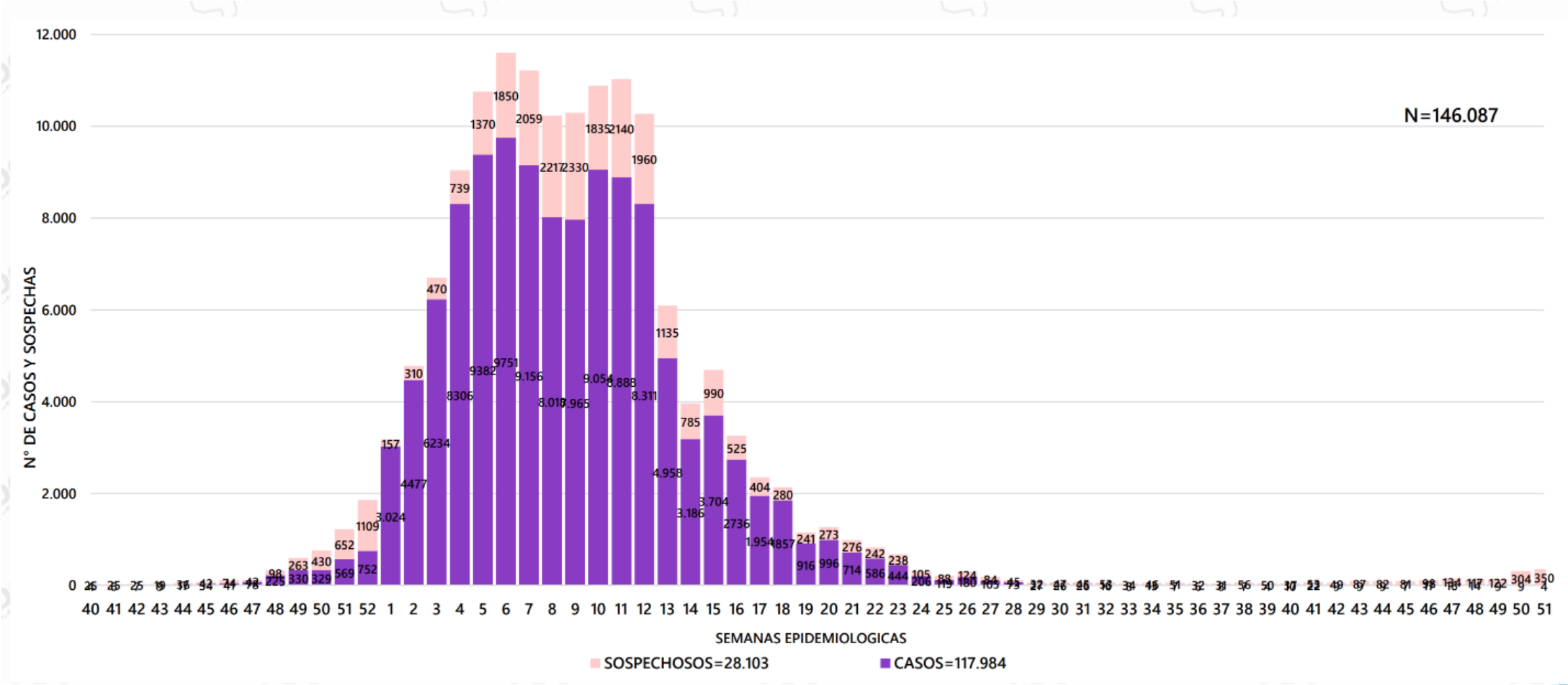
Chikungunya Cases 2023–2025[&] in the Americas (as of EW 10 of each year)



Source: PAHO/WHO Health Information Platform (PLISA)
& Preliminary information

Chikungunya Outbreak in Paraguay, 2023

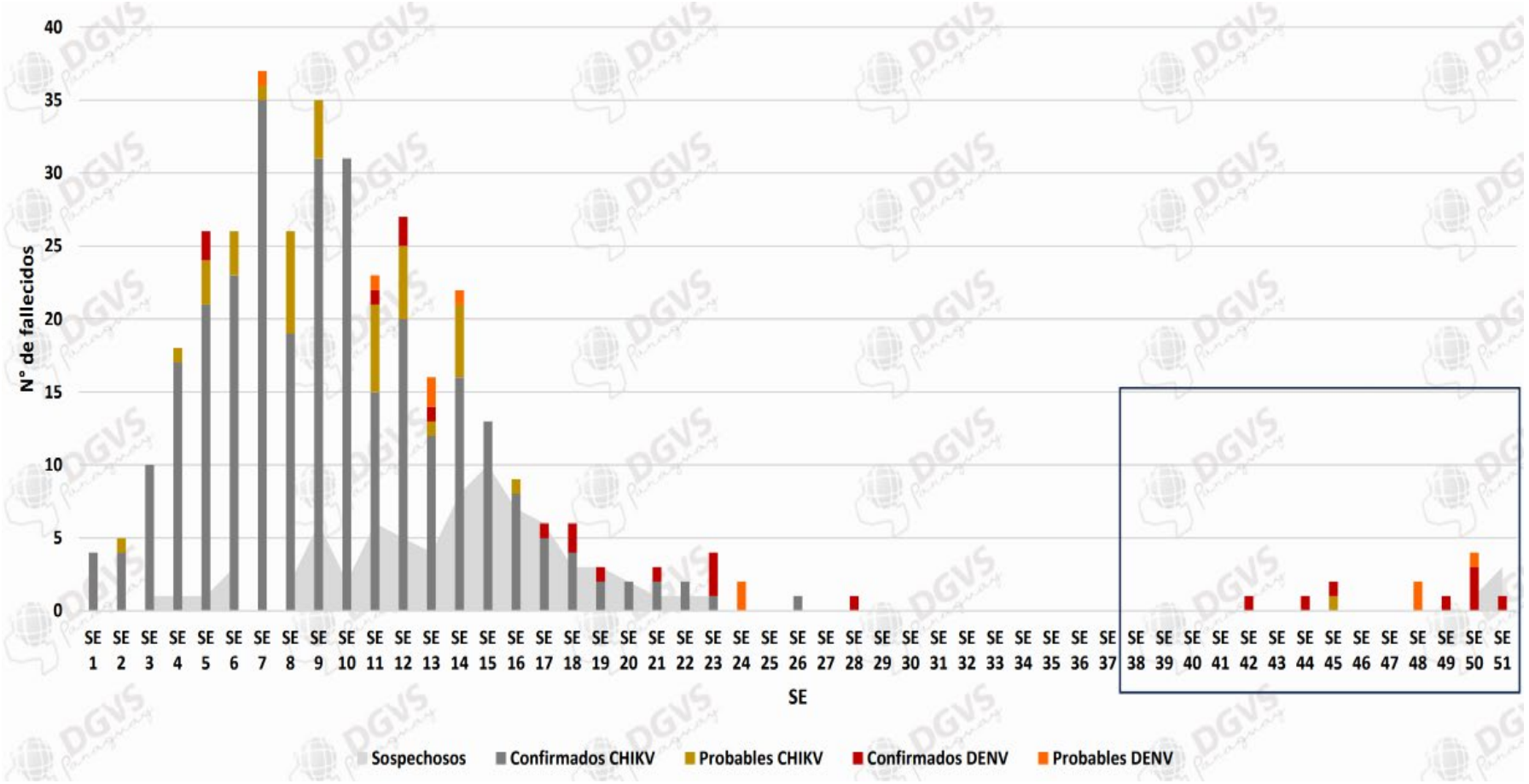
Suspected cases of chikungunya in Paraguay, 2023



Source: General Directorate of Health Surveillance. Directorate of Health Surveillance and Emergency Response. Paraguay 2023

Chikungunya Outbreak in Paraguay, 2023

Reported deaths from arboviruses in Paraguay, 2023



337 fallecidos por Chikungunya
298 Confirmados
39 Probables

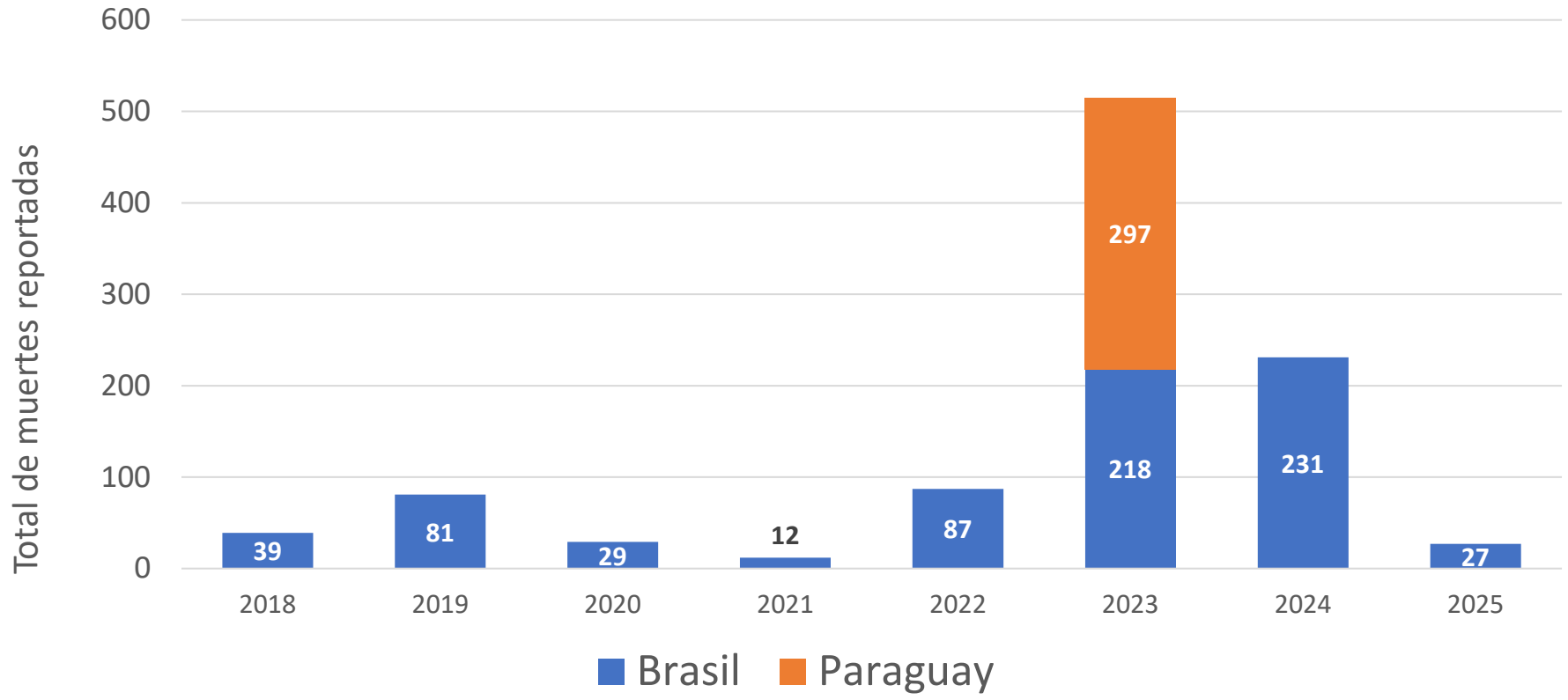
33 fallecidos por Dengue
23 Confirmados
10 Probables

1253 defunciones **descartadas**

82 defunciones en **investigación**

Source: General Directorate of Health Surveillance. Directorate of Health Surveillance and Emergency Response. Paraguay 2023

Chikungunya Deaths in the Americas, 2018-2025[&], SE 10



- In the period **1,021 deaths** were reported, 71% of which were in Brazil.

Source: PAHO/WHO Health Information Platform (PLISA)
& Preliminary information

Final considerations

- The Americas has had an unprecedented two years of arboviral transmission (dengue, chik), now adding oropouche to the mix
- Enormous gains have been made in improving the resolution of arboviral disease data through the implementation of a collaborative surveillance strategy, making analytical products available to a wider base of public health practitioners
- Surveillance data catalyze the integration of the response through the integration of different data streams, providing a more comprehensive analysis of risk and facilitating a more precise and effective response
- Strengthening the Region's routine dengue surveillance also enhances the capacity to emerging pathogens—chikungunya, Zika, oropouche.

Thank you

Epidemiology of Chikungunya in Colombia

FERNANDO DE LA HOZ RESTREPO. MD MSc PhD

Universidad Nacional de Colombia-School of Medicine

Department of Public Health

Phase IV post-approval studies in the context of vaccines approved through accelerated procedures: Case study, CHIKUNGUNYA vaccines.

Sao Paulo, Marzo 19 y 20 2025

Burden of disease. 2013-2016

- CHKV was first detected in Colombia in 2014.
- Arboviruses cases reported by SIVIGILA: 9,284,326
- 41% Dengue
- 52.1% CHKV
- 6.9% Zika

Mora Salamanca et al. International Journal of Infectious Diseases 97 (2020) 81–89 85

Burden of disease. 2013-2016

- 1439 deaths
- Highest number: 2015 427 deaths
- Lowest number: 2014 310 deaths
- 92.1% (n = 1326) Dengue
- 6.5% (n = 94) Chikungunya
- 1.3% (n = 19) Zika.

Mora Salamanca et al. International Journal of Infectious Diseases 97 (2020) 81–89 85

Burden of disease. 2013-2016

Table 4
Summary of arboviral burden of disease studies.

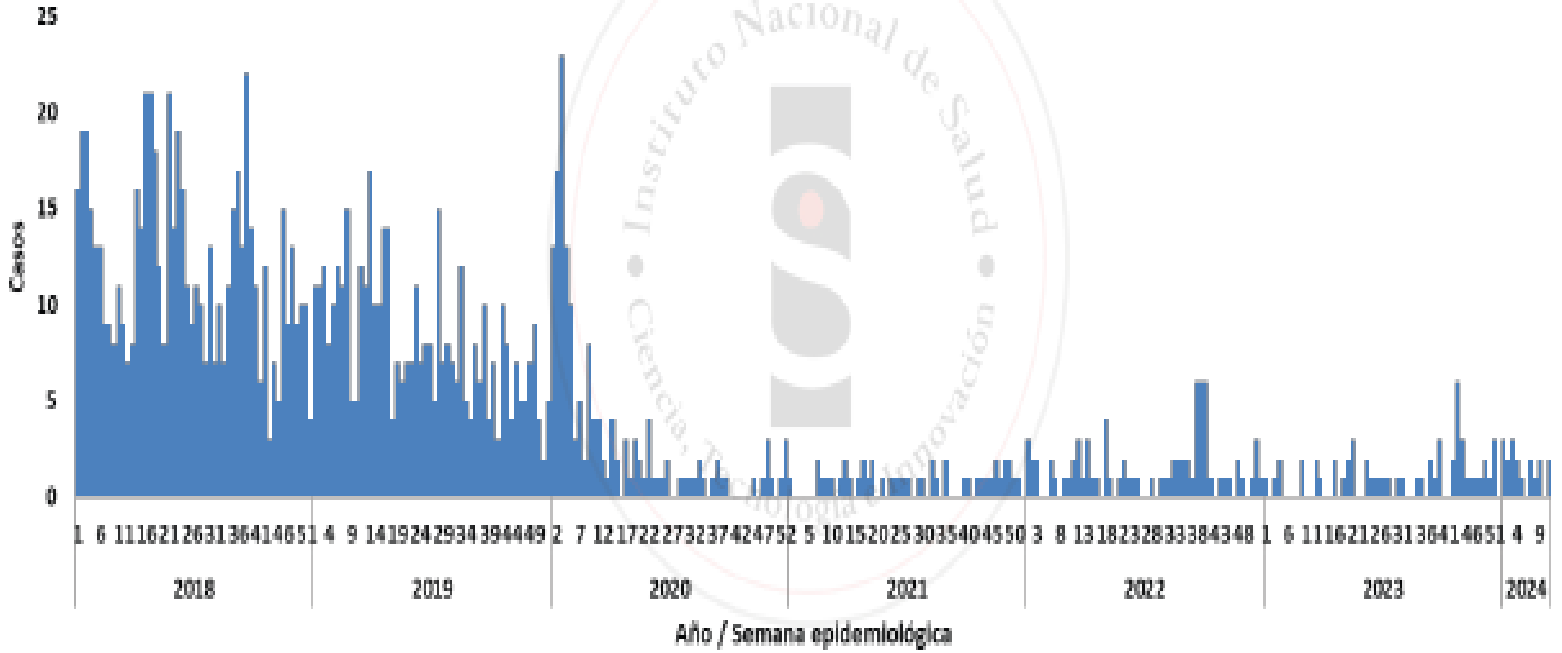
Reference	Arbovirus	Study period; location; total cases estimated	Results	Parameters used for the estimation of disability-adjusted life years (DALYs)
Castro Rodríguez et al. (2016)	Dengue	2010–2012; Colombia; 2010: 153,165, 2011: 32,639, 2012: 57,238	2010: 1.198,73 DALYs per million inhabitants; 2011–2012: 83.88 DALYs per million inhabitants	Disability weight = 0.81 (0.6–0.92); duration: 15 days (10–21)
World Health Organization (WHO), 2018a	Dengue	2000–2016; World and country level; Colombia 2006–2016 Cases: 648,300 (448,100–892,200)	Colombia 2000: 9000 DALYs; 2010: 25,900 DALYs; 2015 and 2016: 25,600 DALYs	Disability weight: Dengue = 0.053; severe dengue = 0.210; moderate post-Dengue chronic fatigue = 0.051, severe = 0.133D uration: dengue = 6 days; severe dengue = 14 days; post-Dengue chronic fatigue = 6 months
Cardona-Ospina et al. (2015b)	Chikungunya	2014; Colombia; 106,592	427.96 DALYs per million inhabitants	Disability weight: acute phase = 0.172; post-Chikungunya chronic arthritis = 0.233; duration: post-Chikungunya chronic arthritis = 20.12 months
Cardona-Ospina et al. (2015a)	Chikungunya	2014; Sucre, Colombia; 14,741	3084.74 DALYs per million inhabitants	Disability weight post-Chikungunya chronic arthritis = 0.233; duration post-

Mora Salamanca et al. International Journal of Infectious Diseases 97 (2020) 81–89 85

Current situation

- 2021: 47 casos
- 2022: 77 casos
- 2023: 49 casos

Figura 3. Casos notificados de chikunguña por semana epidemiológica, Colombia, 2018 a semana epidemiológica 10 de 2024



Fuente: Instituto Nacional de Salud, Sivigila 2024

INS. Protocolo de vigilancia de Chikungunya 2024. https://www.ins.gov.co/buscador-eventos/Lineamientos/Pro_Chikungunya%202024.pdf
INS. Boletin Epidemiologico Semanal. 2024. Semana 12. Arbovirosis en Colombia.

Summary

- Colombia has a passive surveillance system of arboviruses.
- There is some degree of underestimation because there are technical and financial restrictions for a more complete laboratory based surveillance
- CHKV have decreased sharply in Colombia in the last 5 years.
- Cases are detected more in the Andean Region and The Amazon.
- Centinel surveillance of febrile illness in some areas may help to fix the gap on arboviruses disease burden.

Epidemiology of Chikungunya Virus (CHIKV) Infection in India

Chikungunya Meeting

Sao Paulo

March 19-20, 2025

Dr. Nivedita Gupta
Scientist G & Head
Division of Communicable Diseases
Indian Council of Medical Research
New Delhi – 110029; INDIA

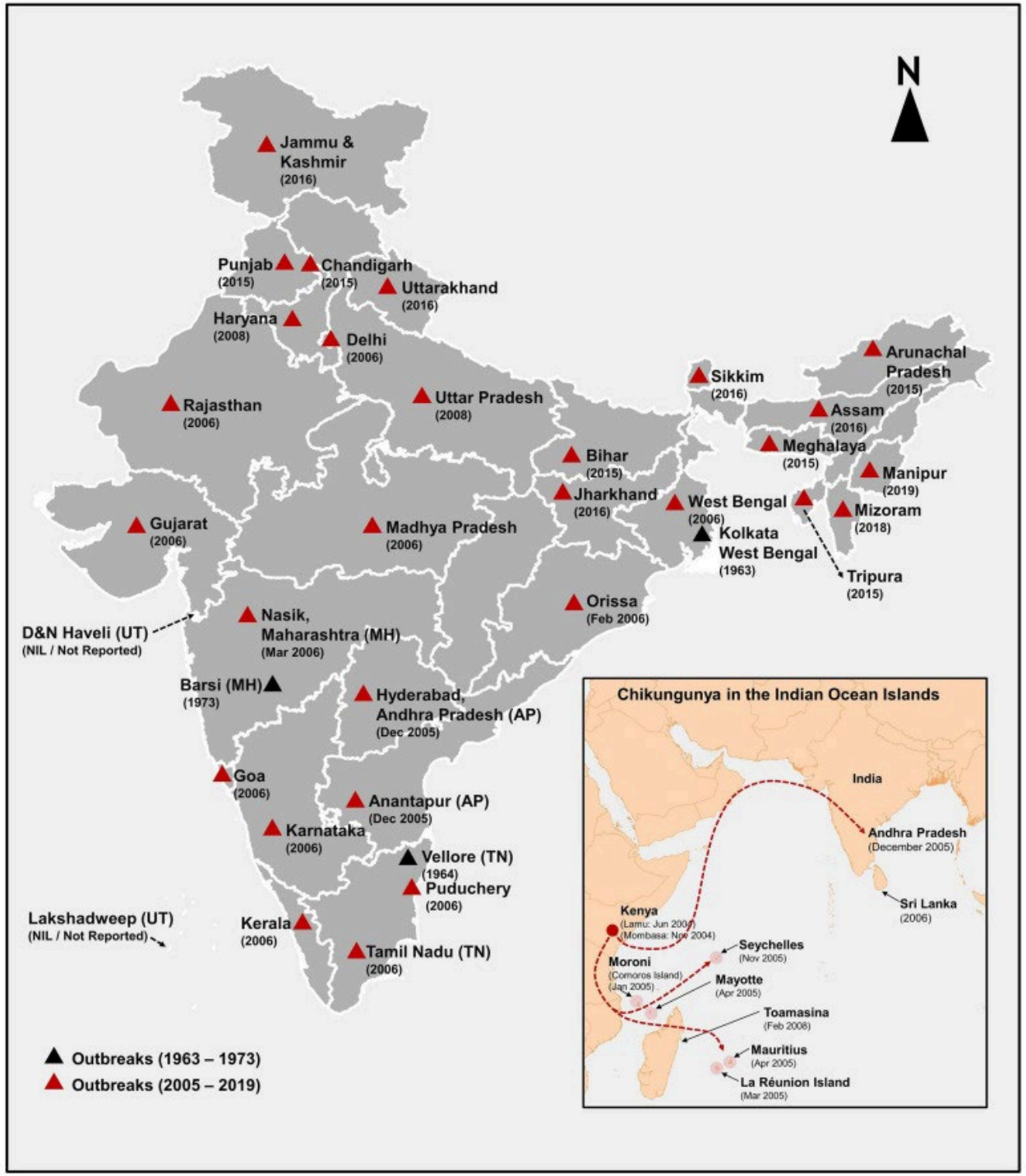
Chikungunya

- Chikungunya first identified in 1952 in Tanzania
- India reported the first outbreak in 1963 and thereafter regular outbreaks till 1973
- In 2004, CHIKV emerged in south-west Indian Ocean
- In January 2005 a major outbreak was reported in Comoros
- March 2005 onwards virus spread to Mayotte, Seychelles, Réunion, and Mauritius.
- India experienced a major outbreak in 2006 wherein 13 states and and ~0.1 million people were affected

Epidemiology of CHIKV in India

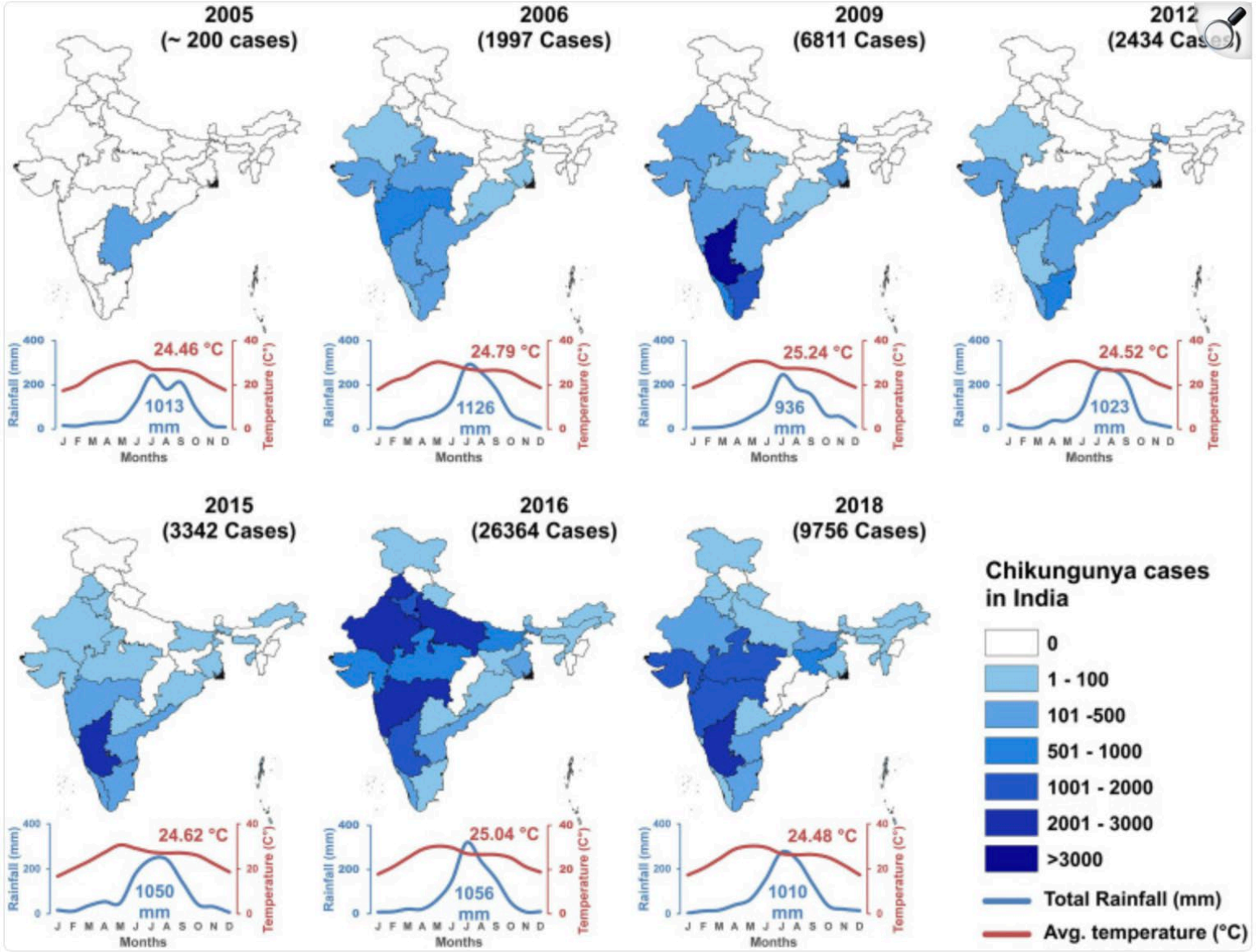
- CHIKV outbreaks from 1963–1973: Asian lineage (black triangles)
- CHIKV outbreaks from 2005–2019: ECSA lineage (red triangles)
- Source of the figure:

Ref: Translational Research Consortia (TRC) for Chikungunya Virus in India. Current Status of Chikungunya in India. Front Microbiol. 2021 Jun 24;12:695173. doi: 10.3389/fmicb.2021.695173.



Year-wise CHIKF Cases in India with Annual Rainfall and Temperature (2005–2018).

- General trend of lower % positivity in summers which increases as rainy season sets in and continues to be high through winter



Ref: Translational Research Consortia (TRC) for Chikungunya Virus in India. Current Status of Chikungunya in India. Front Microbiol. 2021 Jun 24;12:695173. doi: 10.3389/fmicb.2021.695173

Genesis of Virus Research & Diagnostic Laboratory Network (VRDLN): Post 2009 H1N1 Pandemic

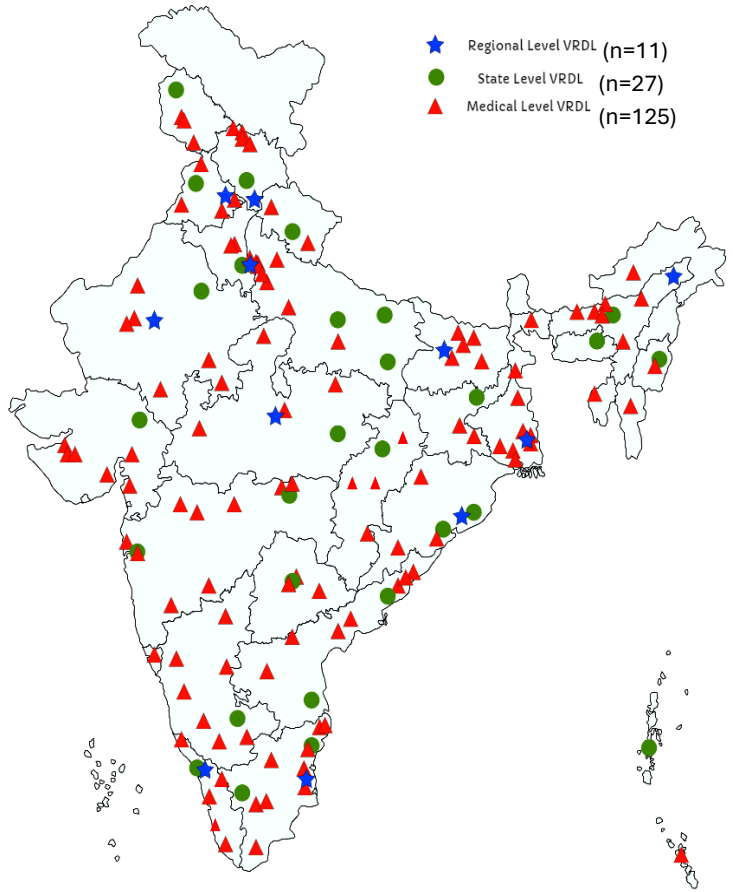
- 2013 - Govt. of India through ICMR/DHR implemented a scheme to establish VRDLs
- 163 VRDLs (27 states & 5 UTs):

- Regional (11):
  Serology, Molecular Tests, Sequencing, Virus Isolation
- State Level (27):
  Serology, Molecular Tests, Sequencing
- Medical College Level (125):
  Serology, Molecular Testing

Mandate:

- Timely detection, diagnosis & outbreak investigation of known/ novel viruses
- Training
- Research

➢ *Upgradation of 30 VRDLs to Infectious Disease Research Labs: detection of bacteria fungi, parasites*



- Capacity to test 20-25 viruses of public health importance
- Resource centers for Training & LQMS and data mining at ICMR-NIV & NIE
- Actively involved in Zika, CCHF, KFD, Dengue, AES, SARI/ILI surveillance

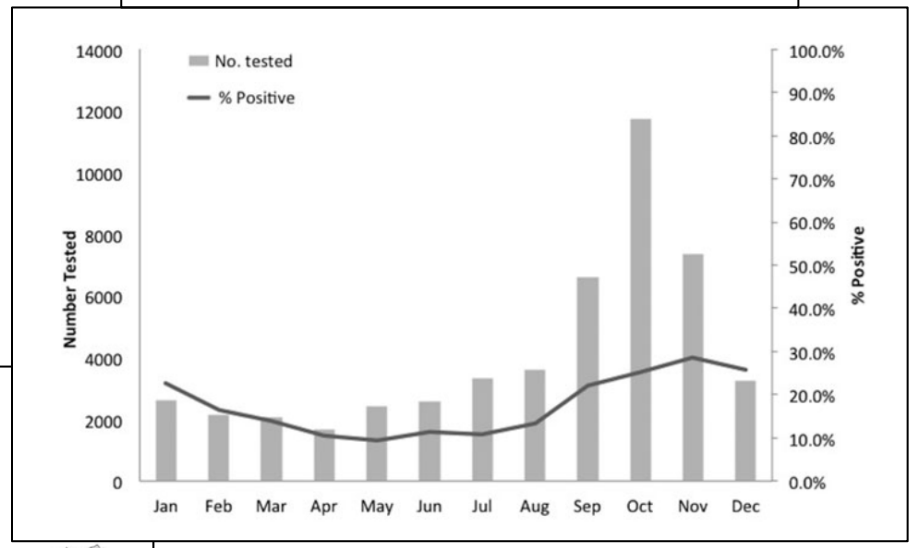
Epidemiology of Chikungunya :

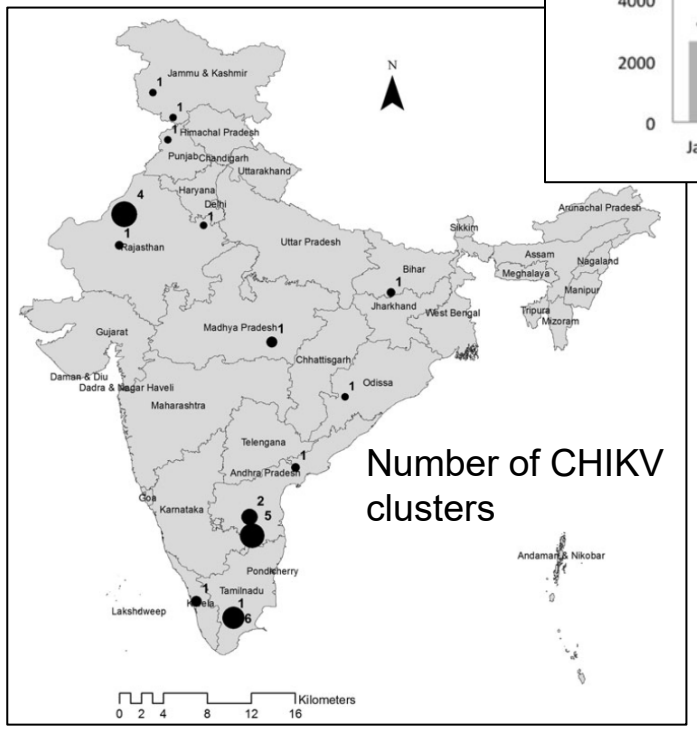
Jan 2016-July18

CHIKV by age group, sex and region

Variable	Patients tested, n	Positive tests, n (%)
Age group (y)		
≤9	4903	678 (13.8)
10–19	7709	1282 (16.6)
20–29	13 111	2610 (19.9)
30–39	8339	1866 (22.4)
40–49	6732	1731 (25.7)
50–59	4231	1007 (23.8)
≥60	3793	858 (22.6)
Not available	562	92 (16.4)
Sex		
Male	27 744	5607 (20.2)
Female	21 607	4508 (20.9)
Not available	29	9 (31.0)
Region		
South	8491	1541 (18.2)
North	20 792	5252 (25.3)
East	5327	1104 (20.7)
Northeast	2259	289 (12.8)
West/central	12 511	1938 (15.5)
Year		
2016	20 791	5256 (25.3)
2017	20 552	3934 (19.1)
2018 (through July)	8037	934 (11.6)
Total	49 380	10 124 (20.5)

Average numbers of patients tested & % positivity by month





Number of CHIKV clusters

Limitations:

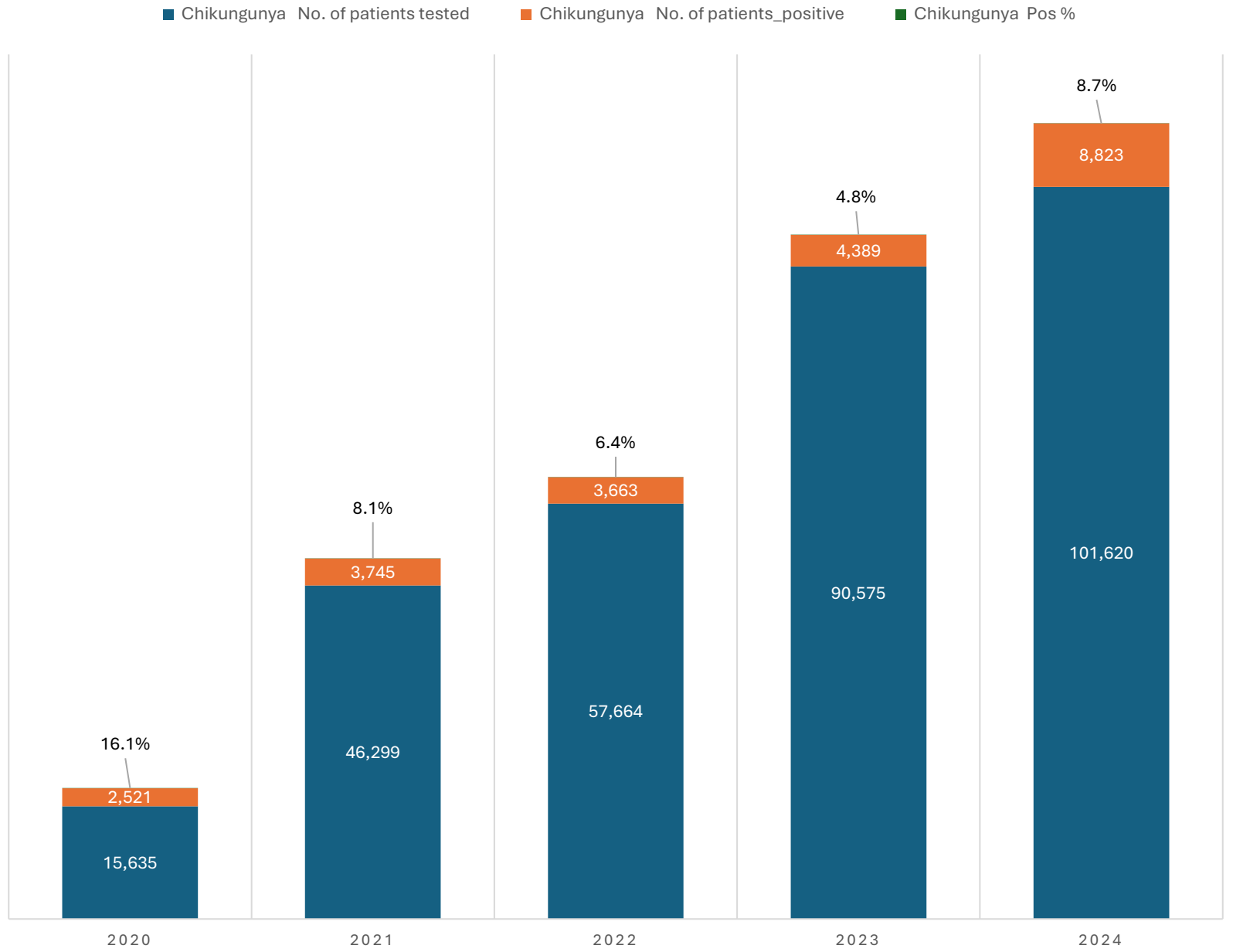
- Prevalence of infection could not be estimated as VRDLs have a large catchment area
- Only patients seeking hospital care were included

Conclusion:

- There is continued CHIKV transmission across India

Ref: Trans R Soc Trop Med Hyg. 2019 May 1;113(5):259-262. doi: 10.1093/trstmh/try141.

TRENDS OF CHIKV POSITIVITY IN INDIA



National Serosurvey:
Dengue & Chikungunya Seroprevalence

- Nationally representative, cross-sectional serosurvey in which 12300 individuals were included in 3 age groups (5–8, 9–17, and 18–45 years)
- From June 2017 to April 2018, individuals randomly selected covering 240 clusters from 60 selected districts of 15 Indian states (north, northeast, east, south, and west)
- IgG antibodies against CHIKV tested and weighted age-group-specific
- seroprevalence of CHIKV infection calculated
- Catalytic models to estimate the FOI and the proportion of the population susceptible to CHIKV in each region.

Ref: Lancet Microbe. 2021 Jan;2(1):e41-e47. doi: 10.1016/S2666-5247(20)30175-0.

CHIKV Seroprevalence in India

- CHIKV transmission was higher in the southern, western, and northern regions of India than in the eastern and northeastern regions.
- A higher proportion of the population susceptible to CHIKV in the eastern and northeastern regions suggests a susceptibility of these regions to outbreaks in the future.
- The survey findings will be useful in identifying appropriate target age groups and sites for setting up surveillance and for future CHIKV vaccine trials

	Northern region	Northeastern region	Eastern region	Southern region	Western region	All regions
Age group, years						
5–8	794; 16·9% (6·9–35·9)	722; 1·3% (0·3–5·2)	815; 3·1% (1·8–5·5)	960; 10·7% (7·3–15·6)	768; 7·0% (4·7–10·3)	4059; 9·2% (5·4–15·1)
9–17	826; 14·0% (3·9–38·9)	805; 0·5% (0·1–1·8)	874; 4·6% (2·7–7·9)	936; 36·4% (28·9–44·7)	824; 16·4% (10·0–25·7)	4265; 14·0% (8·8–21·4)
18–45	782; 19·9% (7·9–41·8)	833; 0·03% (0·005–0·19)	797; 4·5% (2·6–7·7)	820; 50·2% (37·3–63·1)	744; 30% (21·2–40·6)	3976; 21·6% (15·9–28·5)
All, 5–45	2402; 17·9% (9·4–31·5)	2360; 0·3% (0·1–0·8)	2486; 4·4% (3·0–6·3)	2716; 43·1% (34·3–52·3)	2336; 23·3% (17·5–30·3)	12 300; 18·1% (14·2–22·6)
Sex						
Male	1145; 18·0% (10·6–29·0)	1028; 0·6% (0·2–2·1)	1192; 5·9% (3·8–8·9)	1289; 42·1% (32·1–52·9)	1159; 23·8% (16·7–32·6)	5813; 18·8% (15·2–23·0)
Female	1257; 18·0% (8·5–34·2)	1332; 0·1% (0·02–0·21)	1294; 3·3% (1·7–6·2)	1427; 43·9% (34·1–54·1)	1177; 23·0% (17·4–29·8)	6487; 17·6% (13·2–23·1)
Area of residence						
Rural	1117; 3·8% (1·7–8·0)	1196; 0·3% (0·08–0·92)	1280; 4·2% (2·8–6·3)	1415; 38·6% (27·6–50·9)	1229; 20·0% (13·5–28·6)	6237; 11·5% (8·8–15·0)
Urban	1285; 48·1% (33·5–62·9)	1164; 0·6% (0·2–1·6)	1206; 5·3% (2·1–12·8)	1301; 53·2% (44·1–62·0)	1107; 37·2% (26·2–49·8)	6063; 40·2% (31·7–49·3)

Data are number tested; prevalence (95% CI). n=12 300.

Table 1: **Weighted seroprevalence of IgG antibodies against chikungunya virus**

Conclusion

- CHIKV transmission is seen in almost all parts of India
- Seasonal variations are seen with rise in cases in post-monsoon season
- Since different parts of India have variable monsoon timings, the outbreaks happen at different time points
- The number of cases in public health programmes are under-estimated due to asymptomatic infections

Thank You

Chikungunya in Kenya

George Warimwe

Professor of Vaccinology

UNIVERSITY OF OXFORD

KEMRI | Wellcome Trust

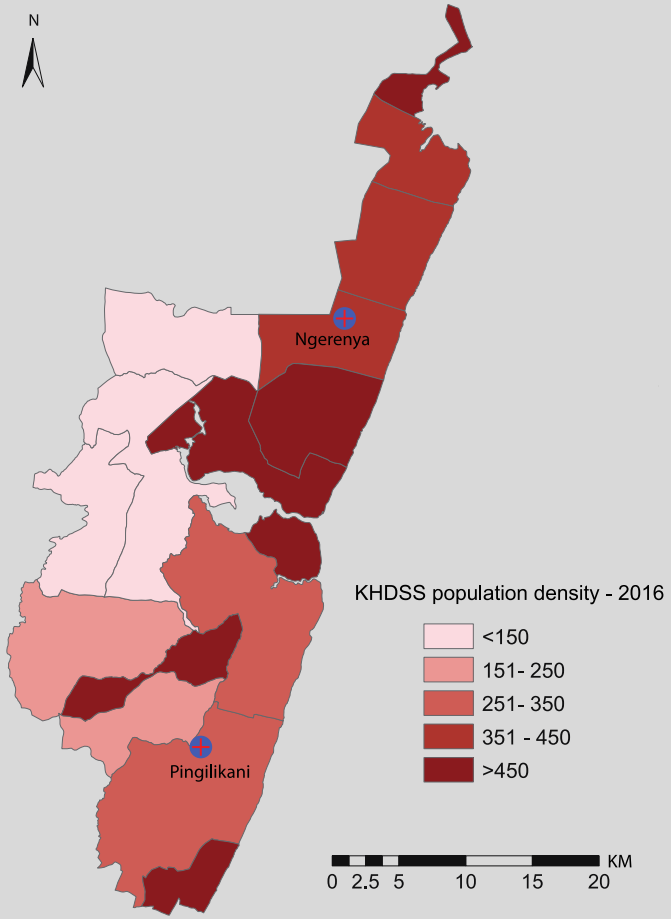
Uncovering a significant Chikungunya burden

- Child (5yrs) admitted 15th May 2018
- Involuntary movements
- Not malaria / bacteremia / meningitis
- Dx: “Undefined neurological problem”
- Discharged 7th June 2018

PLoS Med 19(5): e1003994

Integrated surveillance platform

Demographic surveillance
(since 2002)

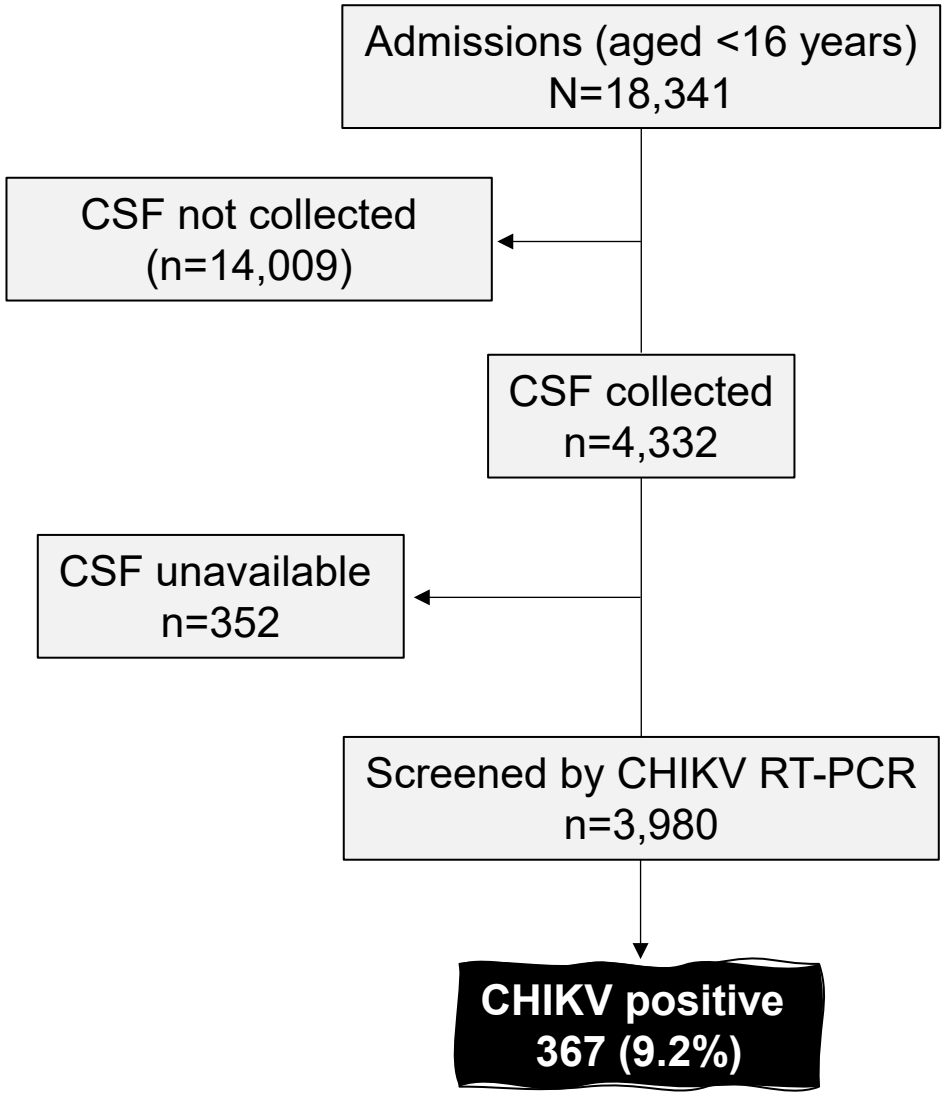


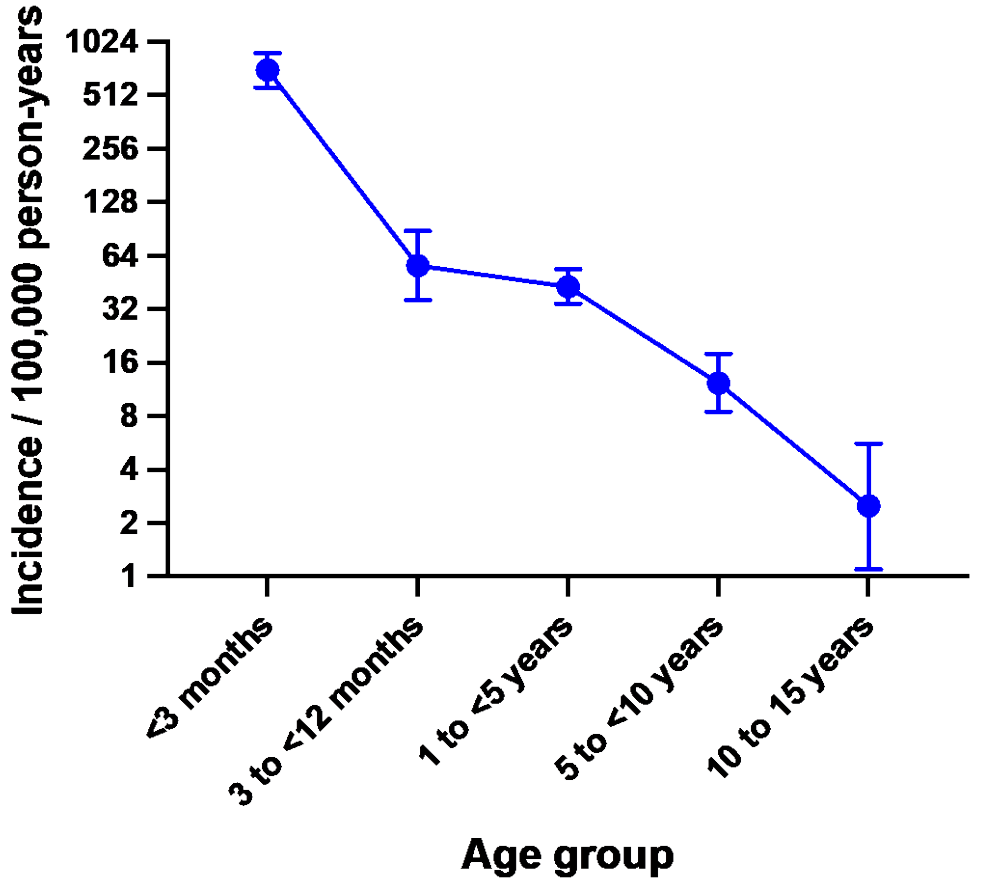
Clinical surveillance
(since 1989)

GCLP-accredited lab

Analysis of stored samples, 2014-2018

Hospital admissions
(Referral hospital)





PLoS Med 19(5): e1003994

Analysis of stored samples, 2014-2018

Community fevers
(Primary healthcare)

Dispensary visits
N=29,819

Exclusions:
Not febrile (n=16,123)

Febrile cases
n=13,696

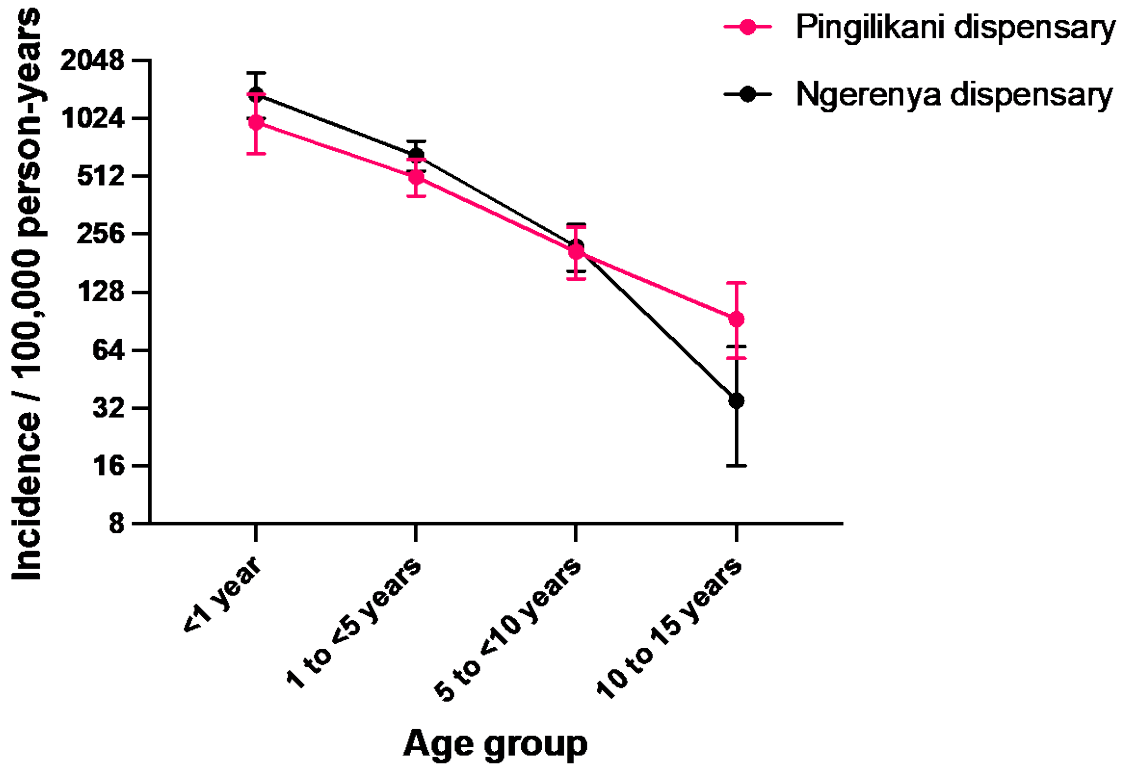
Exclusions:
Missing patient ID (n=1,256)
Unavailable samples (n=732)

Eligible febrile cases
n=11,708
(5,669 unique patients)

Not screened for CHIKV
n=8,208
(2,169 unique patients)

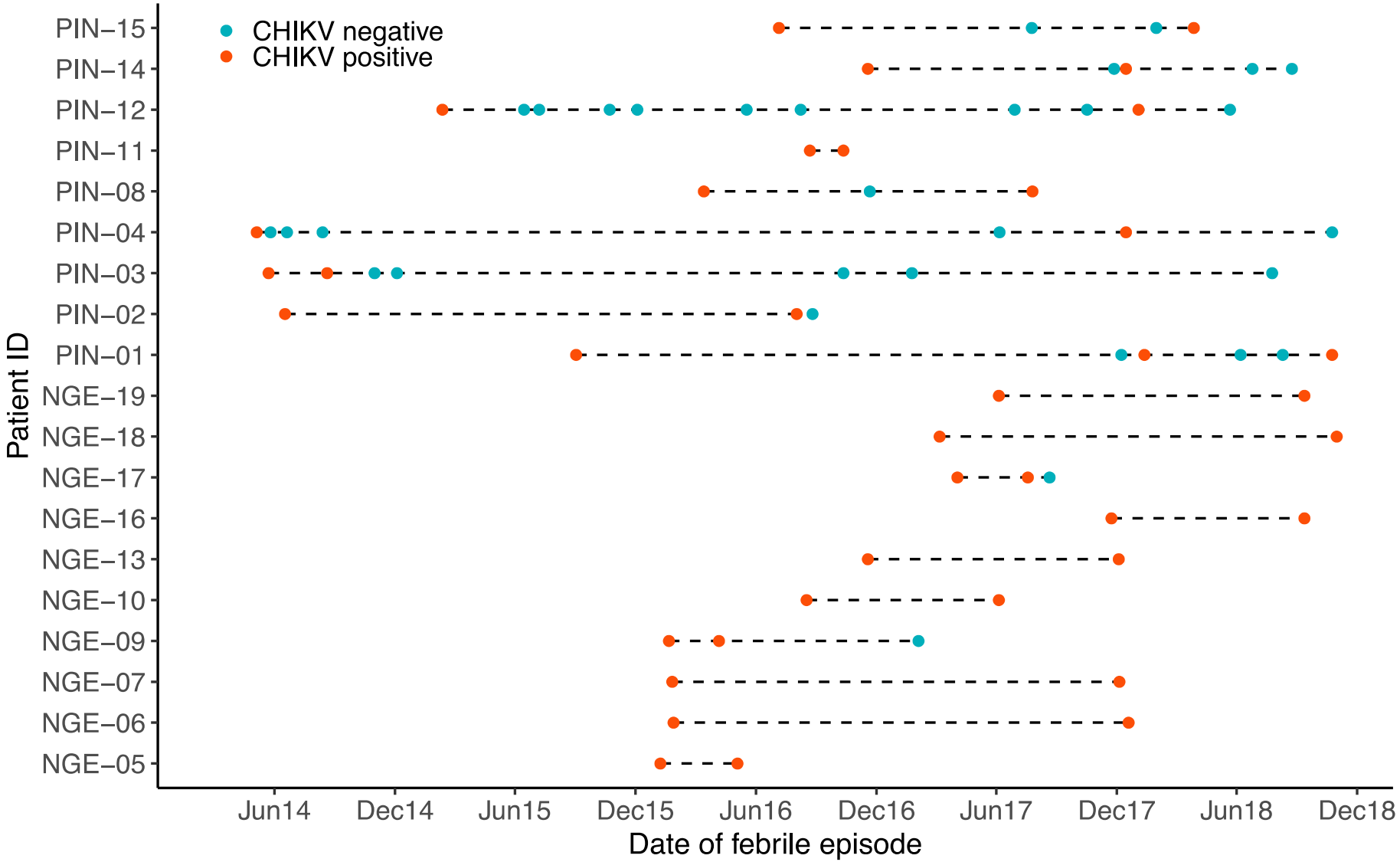
Screened by CHIKV RT-PCR
n=3,500

CHIKV positive
443 (12.7%)



BMC Infect Dis **21**, 186 (2021)

Analysis of stored samples, 2014-2018 (Recurrent infections)



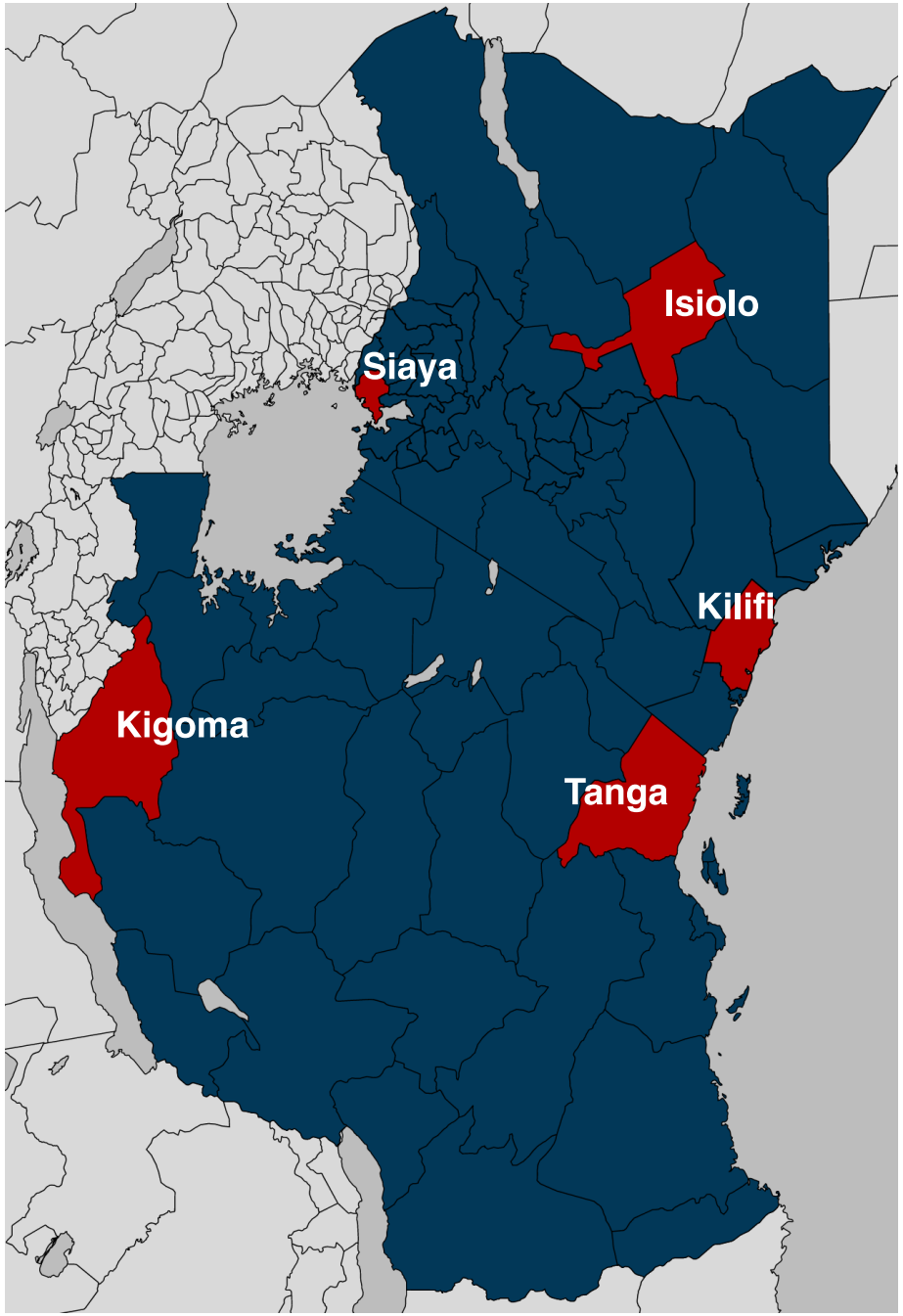
Summary and next steps

~13% of all childhood fevers in the community

Incidence among children <5 years old with neuorological illness

- Chikungunya: **77 per 100,000**
- Cerebral Malaria: 20 per 100,000
- Bacterial Meningitis: 7 per 100,000

Recurrent infections



Accelerating CHIkungunya burden Estimation to inform Vaccine Evaluation (ACHIEVE)

What is the burden of chikungunya among:

1) Patients with fever (N=9,000)

2) Patients hospitalised with neurological illness (N=9,000)

3) Pregnant women at the time of delivery (N=3,000)

CEPI

ACKNOWLEDGEMENTS

KEMRI | Wellcome Trust

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Mainga Hamaluba

Thumbi Mwangi
Ally Olotu
Isabella Oyier
Richard Omore

กรมควบคุมโรค

Department of Disease Control

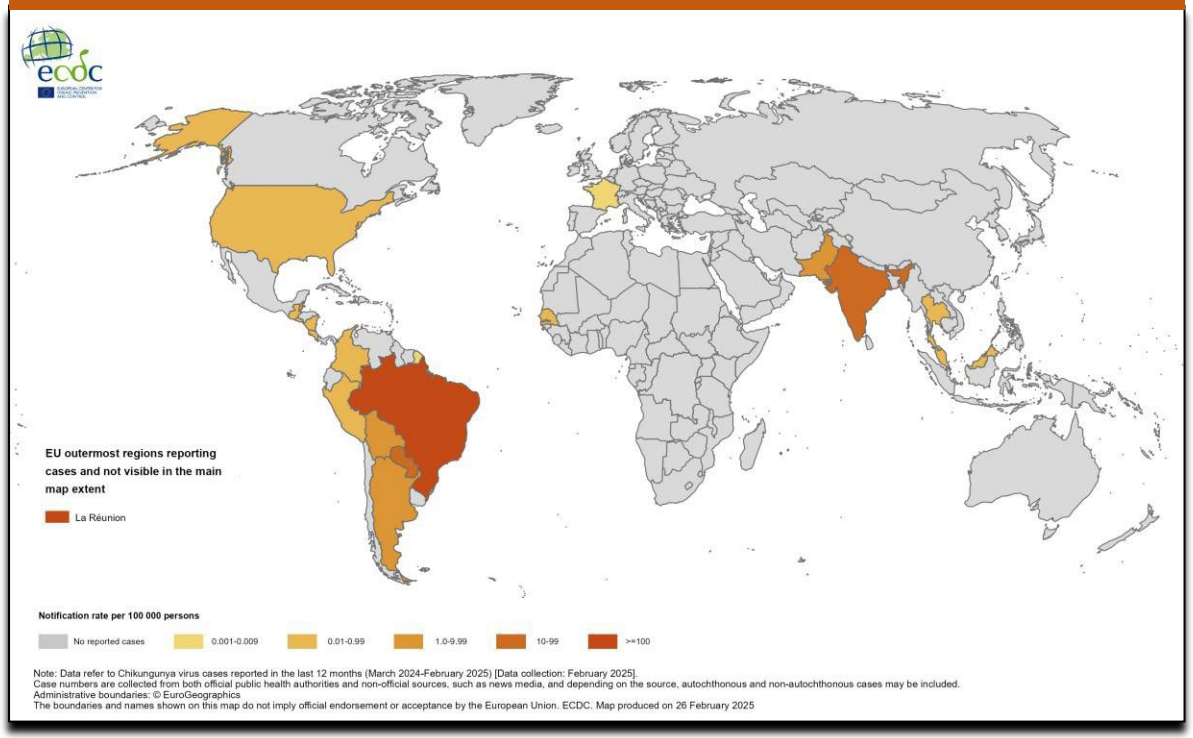
Epidemiology of Chikungunya Disease in Thailand

Department of Disease Control,
Thailand's Ministry of Public Health

กรมควบคุมโรค
Department of Disease Control

Chikungunya Situation in Thailand

Chikungunya virus reported in the last 12 months
(March 2024-February 2025)



In the past...

- The first outbreak in Thailand was in Bangkok in 1958.
- A notable outbreak occurred in southern Thailand between 2008 and 2009.
- A smaller local outbreak occurred in north-eastern Thailand in 2013.
- A major outbreak occurred in 2018, with over 10,000 cases reported by the end of 2020.

Now...

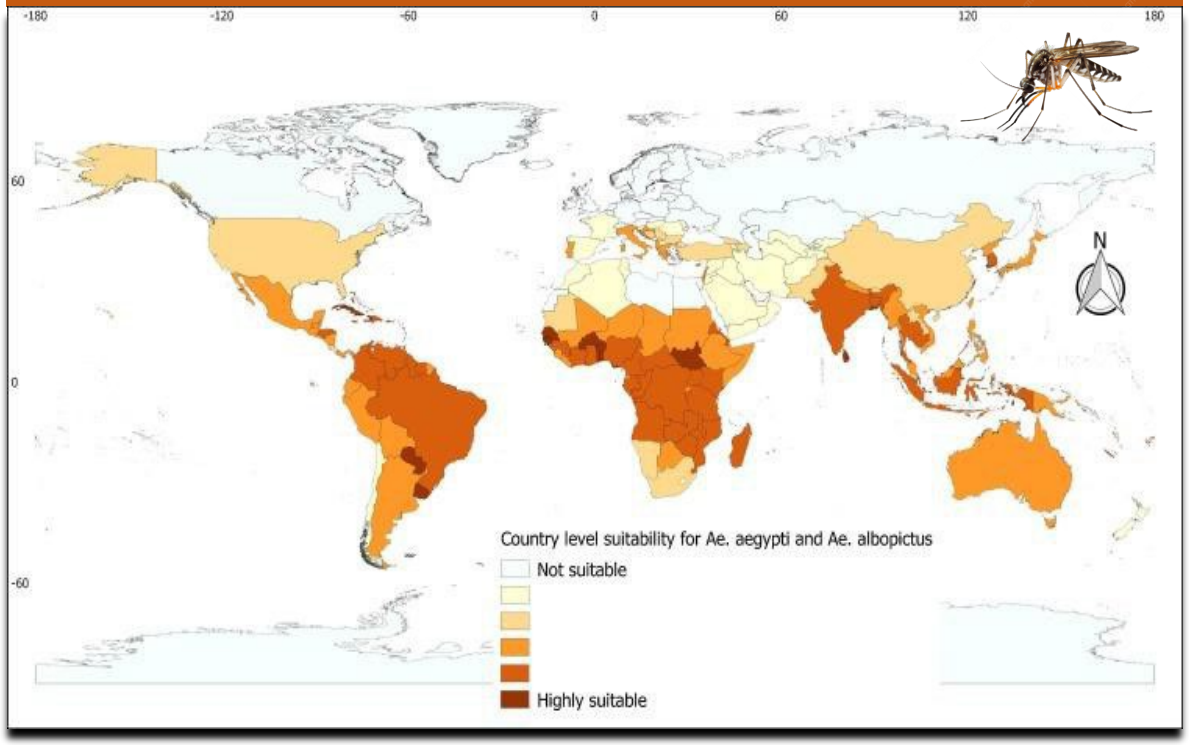
- Smaller outbreaks and sporadic cases now occur year-round

Source: https://www.ecdc.europa.eu/en/chikungunya-monthly

กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH

Chikungunya Situation in Thailand

Country level suitability for Aedes mosquitoes



Aedes mosquitoes, which are the primary vectors, *are widespread across Thailand and Southeast Asia*.

Source: https://www.ecdc.europa.eu/en/chikungunya-monthly

Thailand's Experience in *CHIKV* Outbreak Response

Background

- A major outbreak from 2008–2018 had significant social and economic effects. Smaller outbreaks now occur year-round, mainly in the south and northeast.
- Aedes mosquitoes, the primary vectors, are widespread in Thailand and Southeast Asia.

Key control measures including;

- **Buffer Zone – Vector Control:** Targeted mosquito control by eliminating breeding sites and reducing mosquito density.
- **Managing Infected Individuals:** Isolating cases and promoting mosquito repellent use.
- **Community-Based Surveillance:** Engaging communities in outbreak monitoring and data-driven responses.
- **Triple 3 Strategy (3-3-3):**

  3 Days: Stop transmission from infected individuals**.**

  3 Weeks: Eliminate mosquito breeding sites.

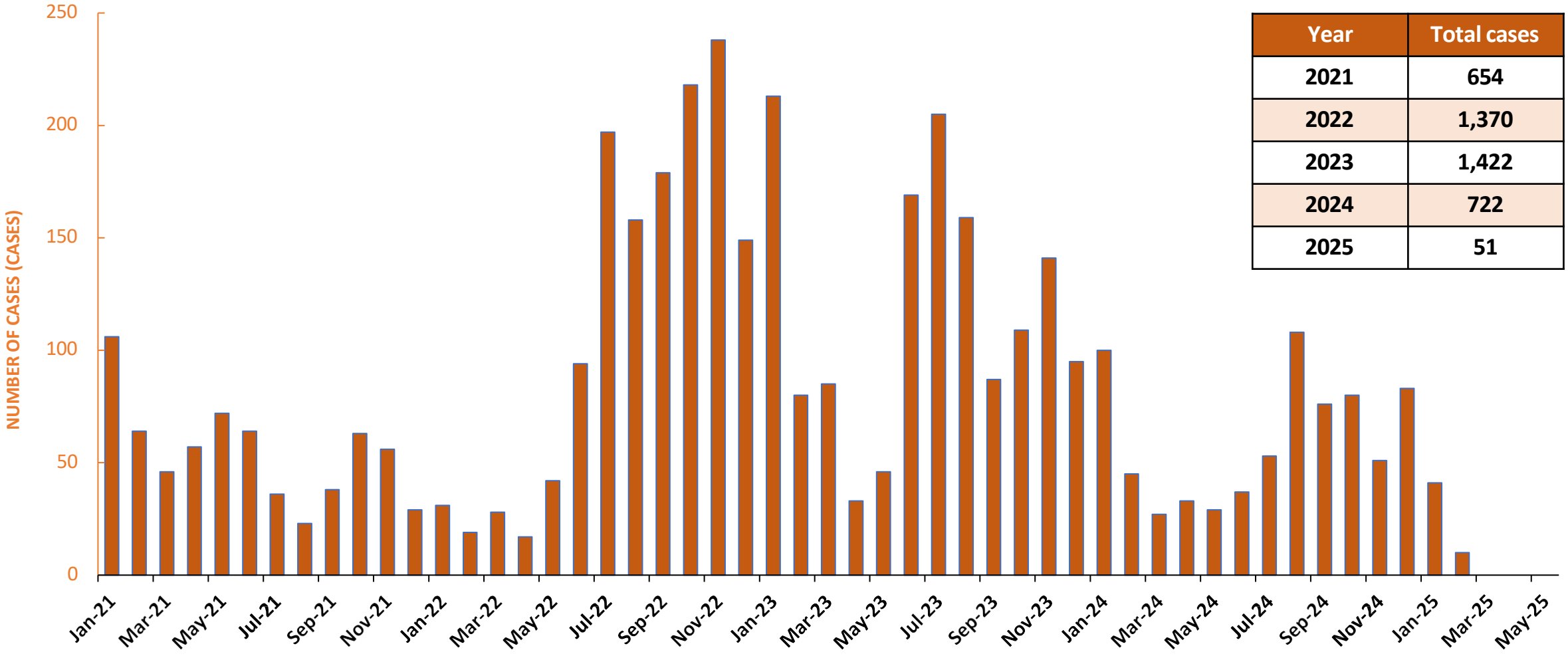
  3 Months: Maintain long-term prevention efforts.

Source: the Division of Epidemiology, the Department of Disease Control, Ministry of Public Health, Thailand

กรมควบคุมโรค
Department of Disease Control

Reported cases of *Chikungunya Situation* in Thailand

By month (2021-2025)



Year	Total cases
2021	654
2022	1,370
2023	1,422
2024	722
2025	51

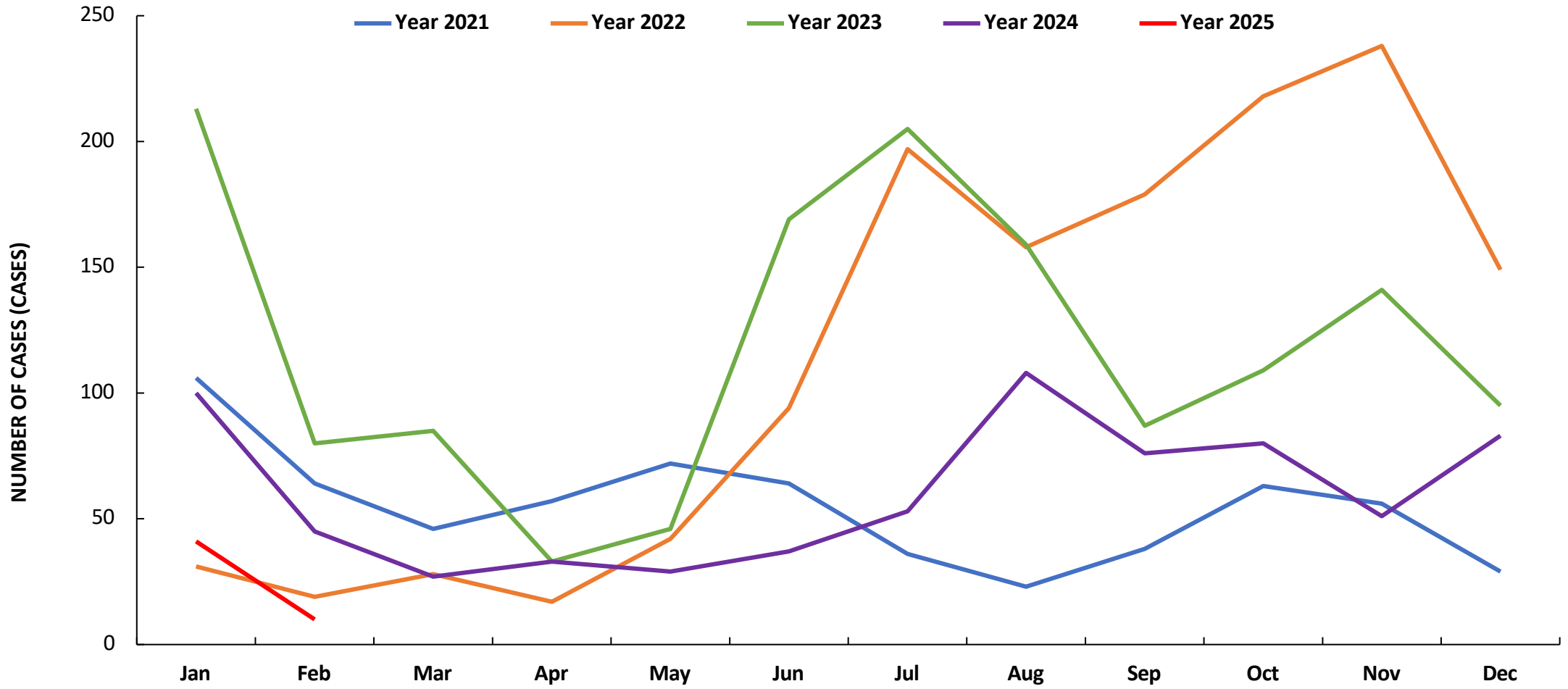
Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH

กรมควบคุมโรค
Department of Disease Control

Reported cases of *Chikungunya Situation* in Thailand

By month (2021-2025)



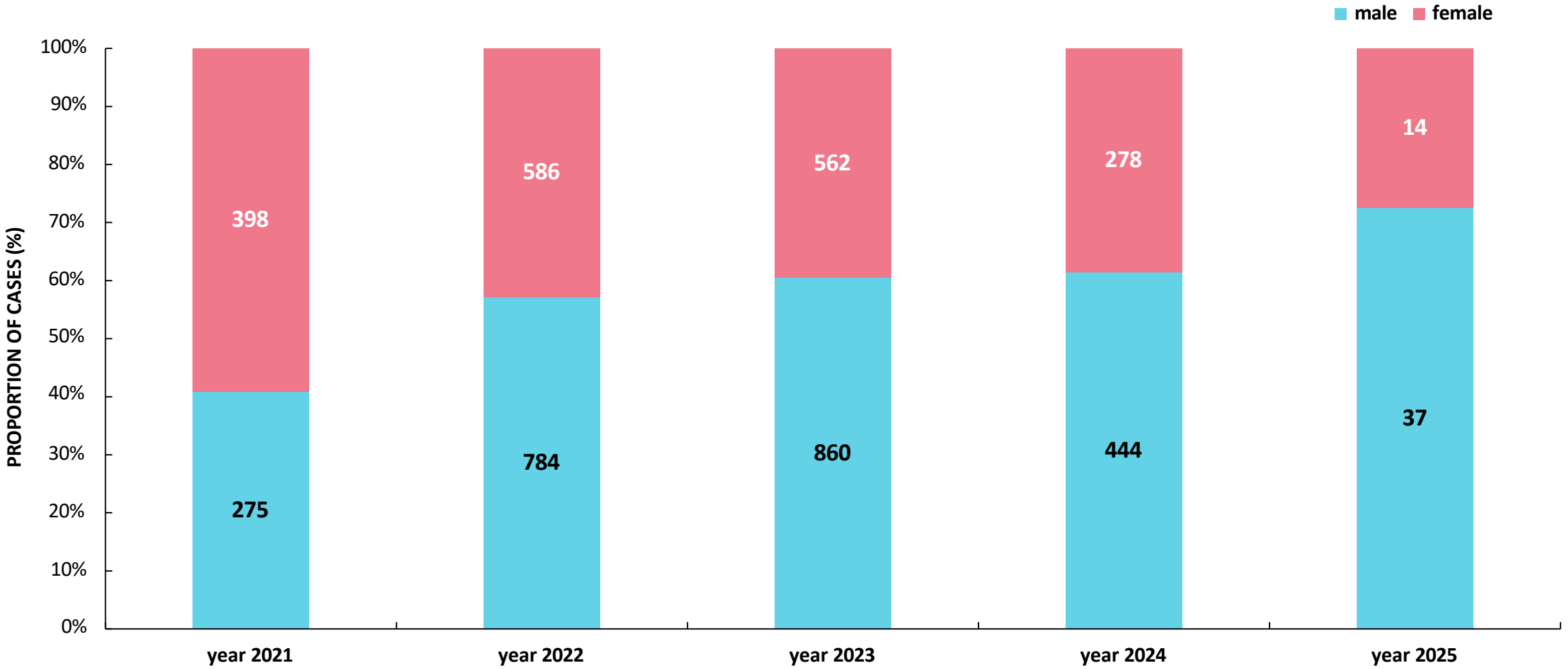
Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH

กรมควบคุมโรค
Department of Disease Control

Reported cases of *Chikungunya Situation* in Thailand

By gender (2021-2025)



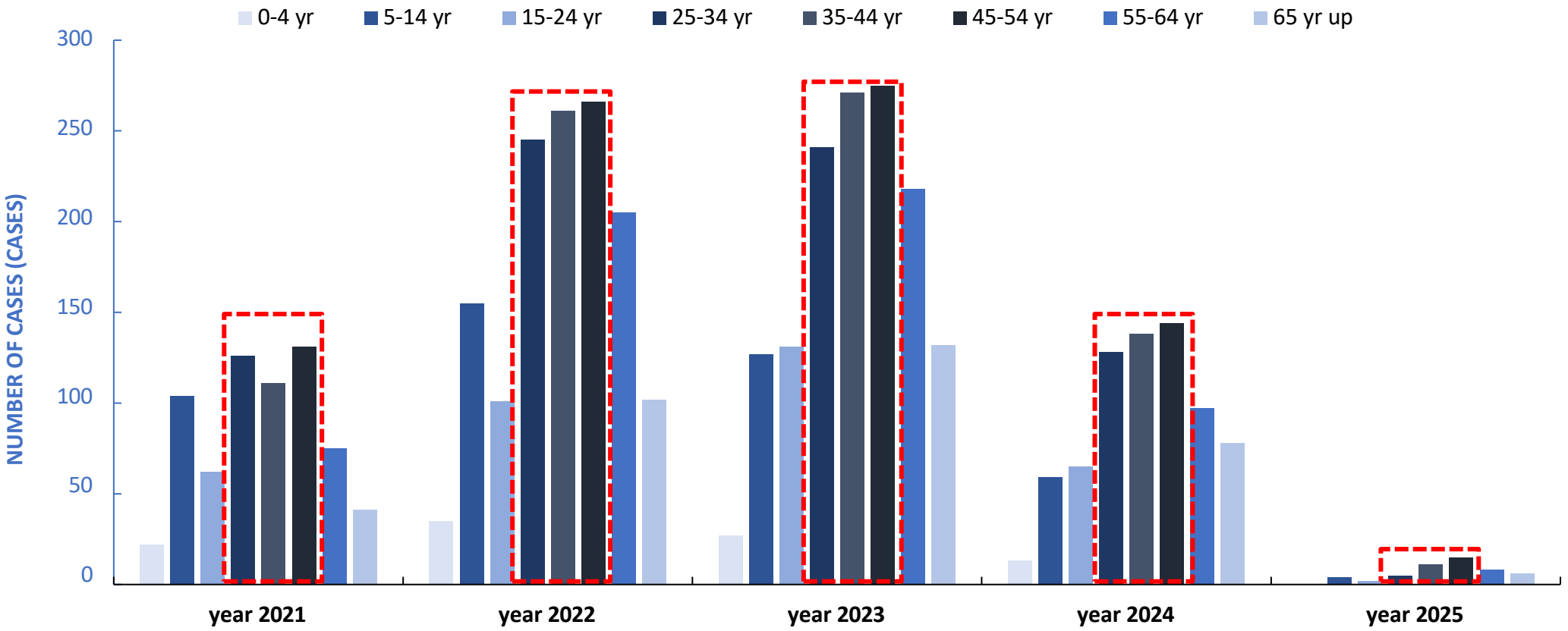
Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH

กรมควบคุมโรค
Department of Disease Control

Reported cases of *Chikungunya Situation* in Thailand

By age group (2021-2025)



It has been found that...

Most people who have suffered from Chikungunya each year have been **between 25 to 54 years old.**

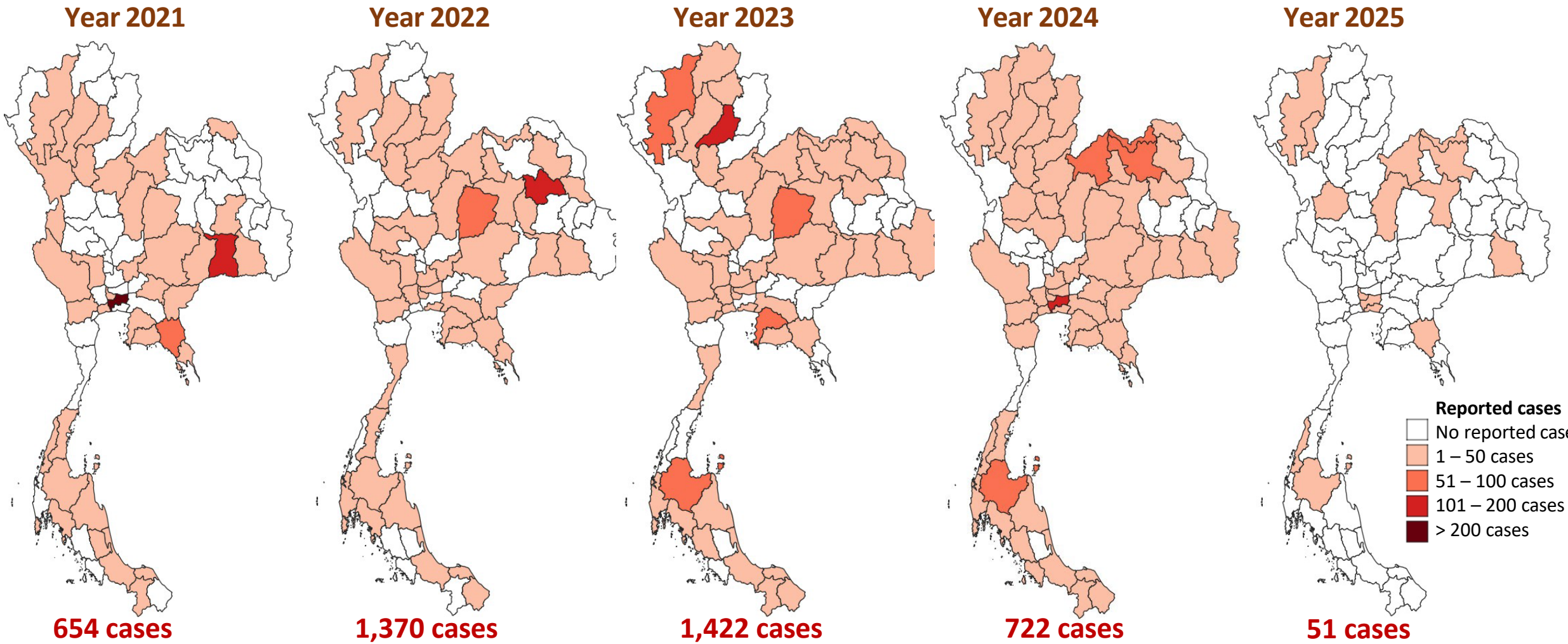
Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH

กรมควบคุมโรค
Department of Disease Control

Reported cases of *Chikungunya Situation* in Thailand

By province (2021-2025)

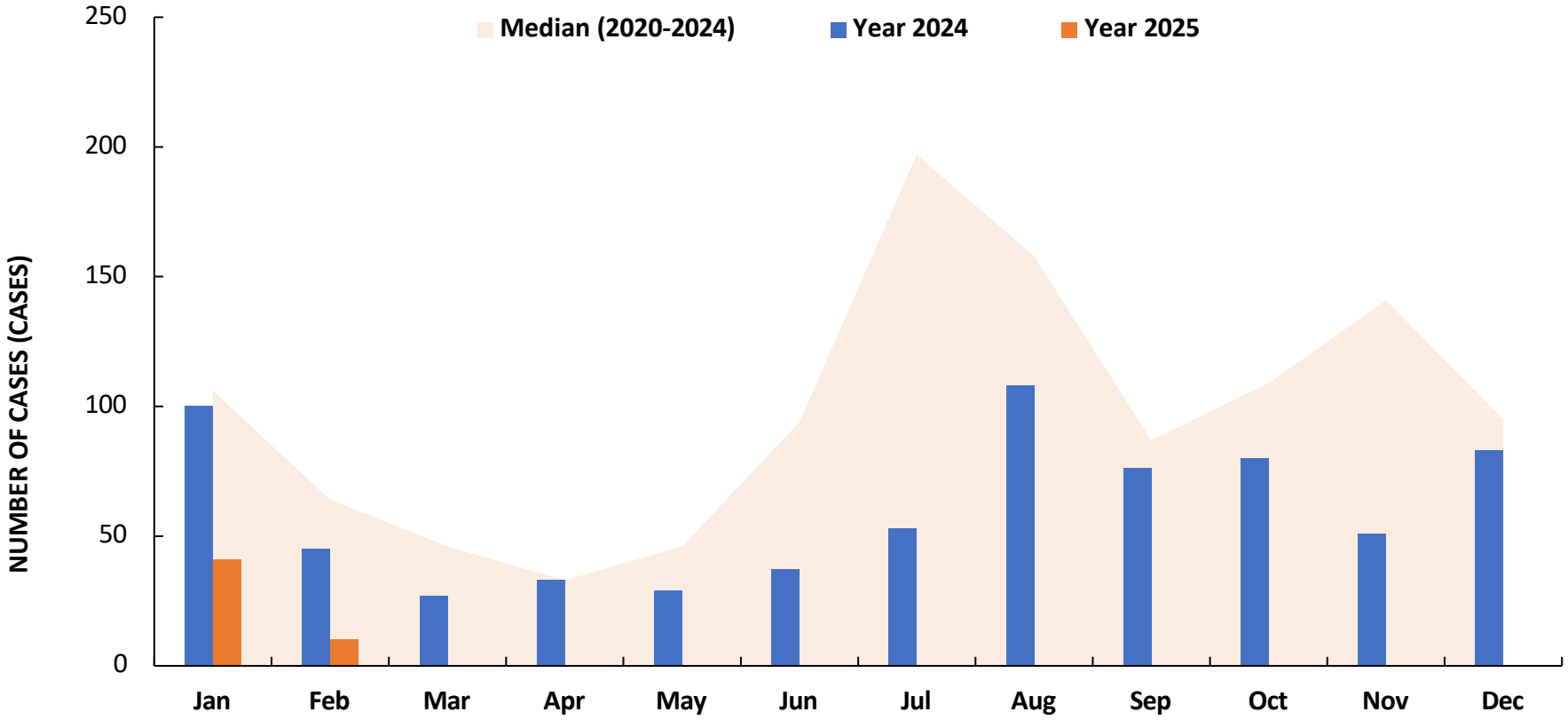


Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

กระทรวงสาธารณสุข
MINISTRY OF PUBLIC HEALTH

Reported cases of *Chikungunya Situation* in Thailand, 2025

In 2025, Thailand reported **51 chikungunya cases** (morbidity rate: 0.08 per 100,000 population), with **the highest cases occurring in the 35–44 age group, followed by the 45–54 age group, respectively**.



Male to female ratio
1 : 2.8

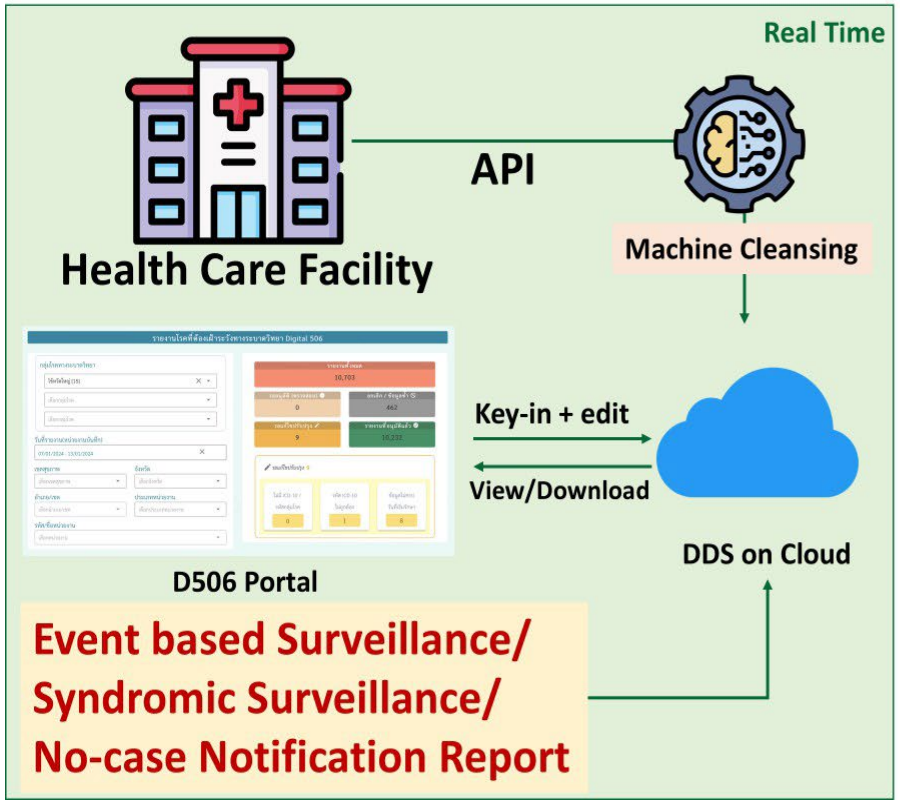
sex	Number (i...	Percentage
female	37	72.55%
man	14	27.45%
Total	**51**	**100%**

Age group	Number of cases	Incidence rate (1:100,000)
0 – 4	0	0
5 – 14	4	0.05
15 – 24	2	0.02
25 – 34	5	0.05
35 – 44	11	0.11
45 – 54	15	0.15
55 – 64	8	0.09
65 and older	6	0.07

Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

Chikungunya Disease Surveillance and Reporting

Digital Disease Surveillance (DDS)



Behavioral and Risk Factor Survey Data

Meteorological Data

Vector Survey

Environmental and Animal Data

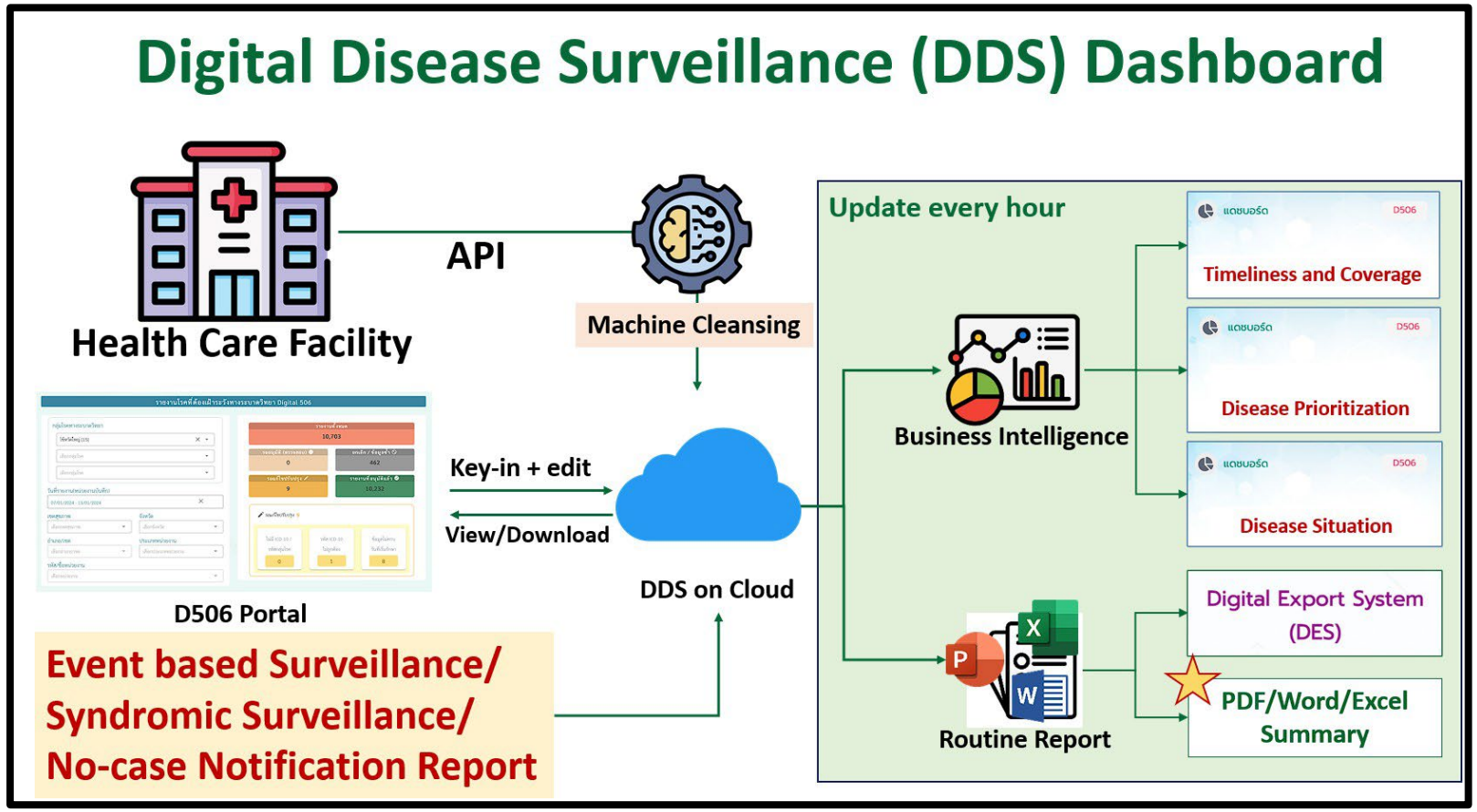
Clinical Data (e.g., Immunization, Underlying data)

- CHIKV is a **notifiable disease** under the Communicable Disease Act.
- All healthcare facilities **must report cases** to DDC via the HIS API.
- **Surveillance data** is **semi-real-time**, requiring verification before submission
- **Event-based surveillance** detects outbreaks and unusual events.

Source: the Division of Epidemiology, the Department of Disease Control, Ministry of Public Health, Thailand

Chikungunya Disease Surveillance and Reporting

Nowadays, the Division of Epidemiology has developed a **digital disease surveillance (DDS) system for semi-real-time control of infectious diseases**.

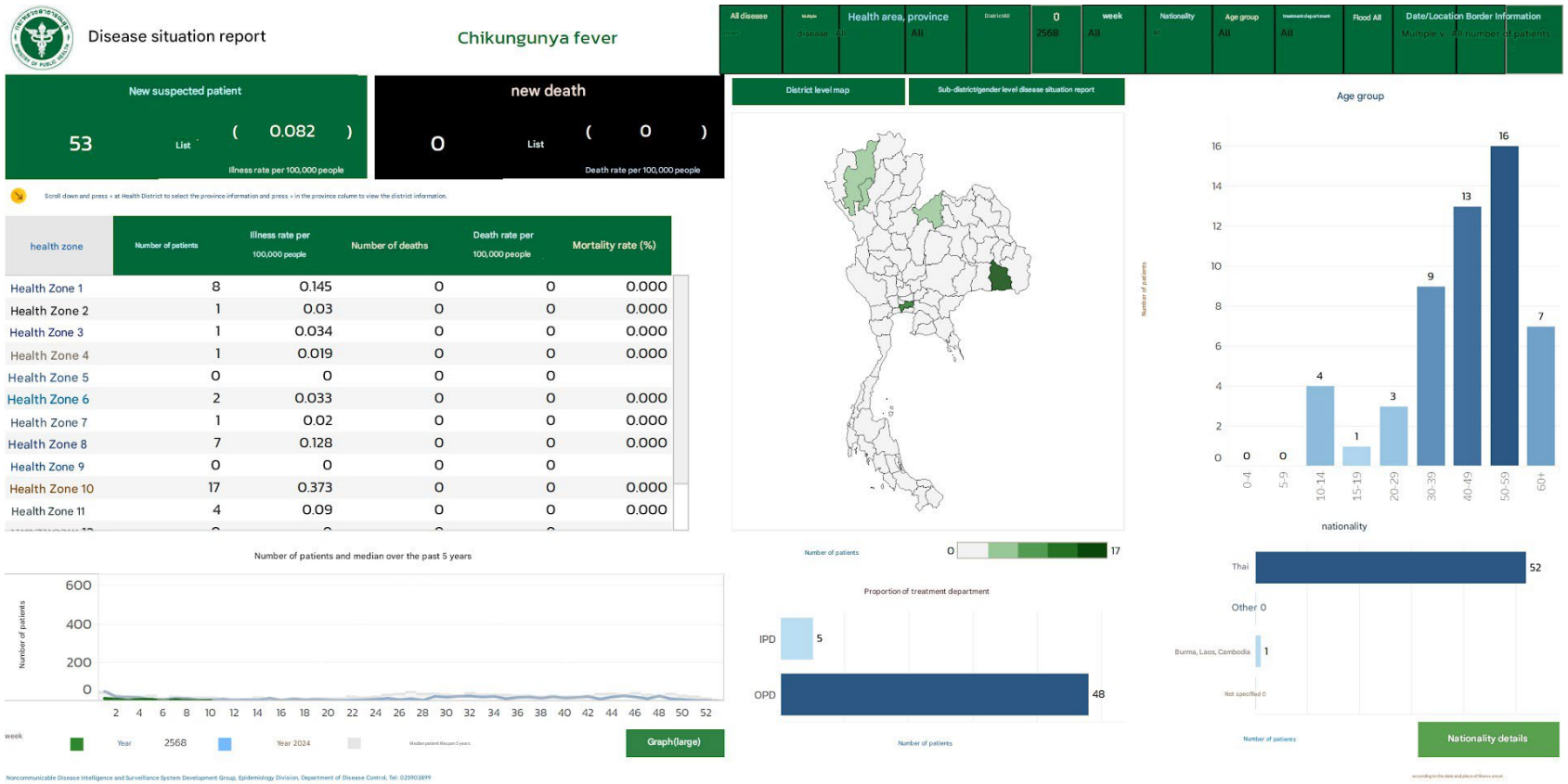


There are 57 infectious diseases for control under Communicable Disease Act B.E. 2558 (A.D. 2015) ***which including Chikungunya Disease***

Source: the Division of Epidemiology, the Department of Disease Control, Ministry of Public Health, Thailand

Chikungunya Disease Surveillance and Reporting

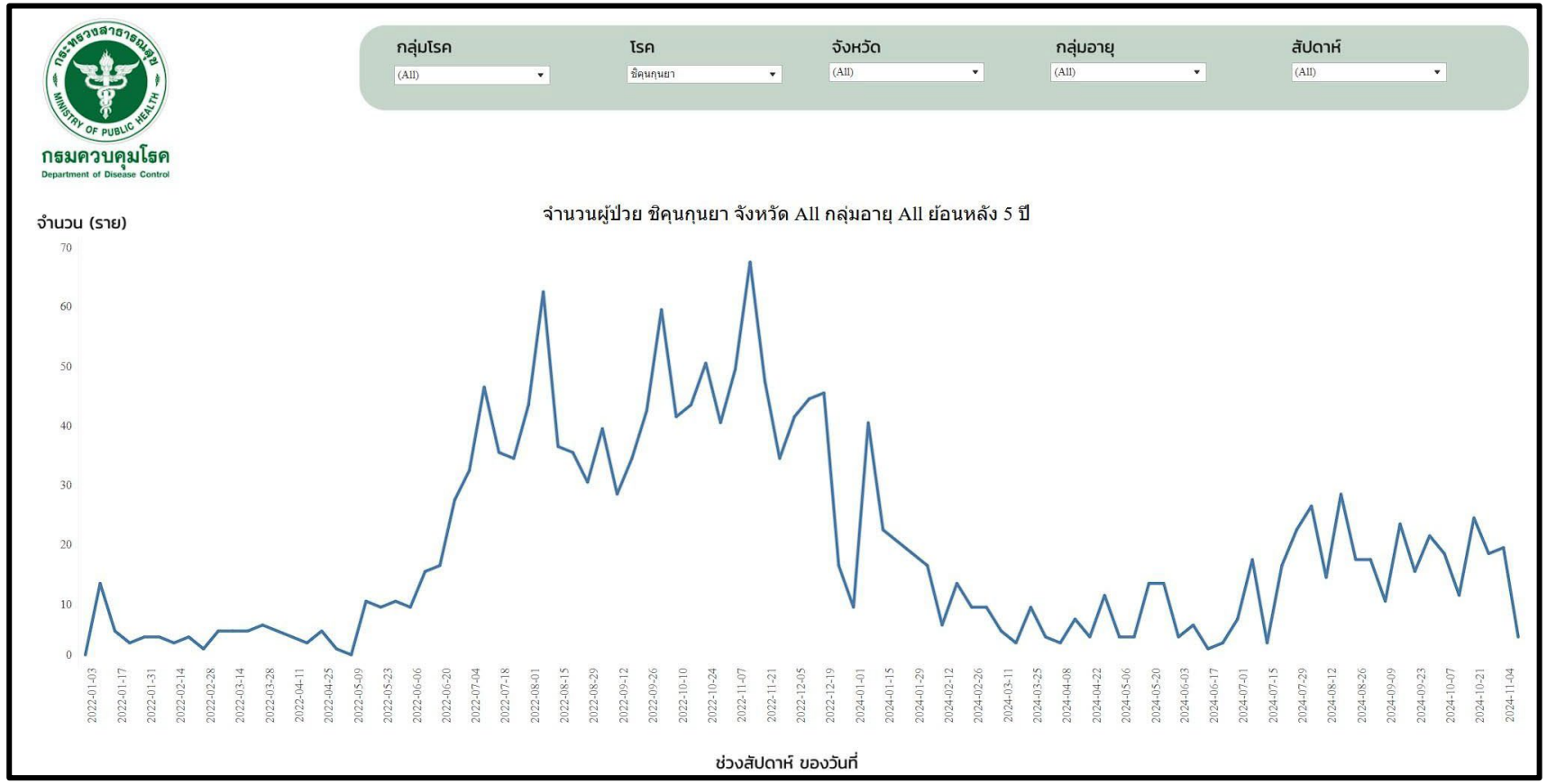
The dashboard illustrates a Chikungunya fever situation in Thailand, which users **can filter by time, place and person**



Source: https://dvis3.ddc.moph.go.th/#/site/DDC_CENTER_DOE/views/DDS2/sheet33?%3Aembed=y&%3AisGuestRedirectFromVizportal=y

Chikungunya Disease Surveillance and Reporting

The dashboard illustrates a line graph depicting the number of Chikungunya fever patients in Thailand over the past 5 years (2022-2024).



From this dashboard, users can filter by

>> Disease group

>> Disease

>> Province

>> Age group

>> Epidemic week.

Source: https://dvis3.ddc.moph.go.th/#/site/DDC_CENTER_DOE/views/DDS2/sheet33?%3Aembed=y&%3AisGuestRedirectFromVizportal=y

Research about AI-Powered Dengue Vector Surveillance::

Utilizing AI and Street View Imagery for Early Prediction of Vector Breeding Sites

Using Google Street View for Analyzing Disease Risk Areas; Leveraging AI and Object Detection for Public Health Surveillance

RESEARCH ARTICLE

Large scale detailed mapping of dengue vector breeding sites using street view images

Peter Haddawy[1,2]*, Poom Wettayakorn[1], Boonpakorn Nonthaleerak[1], Myat Su Yin[1], Anuwat Wiratsudakul[3], Johannes Schöning[4], Yongjua Laosiritaworn[5], Klestia Balla[6], Sirinut Euaungkanakul[1], Papichaya Quengdaeng[1], Kittipop Choknitipakin[1], Siripong Traivijitkhun[1], Benyarut Erawan[1], Thansuda Kraisang[1]

1 Faculty of ICT, Mahidol University, Salaya, Thailand, **2** Bremen Spatial Cognition Center, University of Bremen, Bremen, Germany, **3** Faculty of Veterinary Science, Mahidol University, Salaya, Thailand, **4** University of Bremen, Bremen, Germany, **5** Ministry of Public Health, Bangkok, Thailand, **6** Computer Science Department, School of Science and Technology, University of Camerino, Camerino, Italy

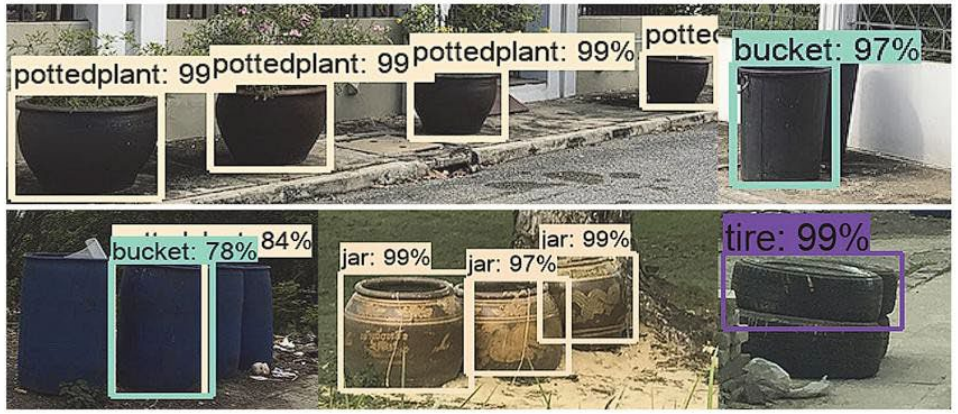


Fig 3. Examples of containers detected by using Faster R-CNN with new transferred categories.

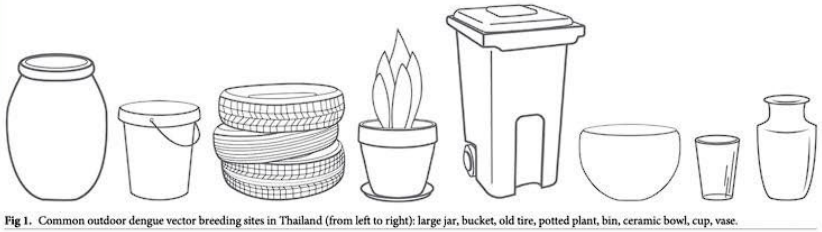
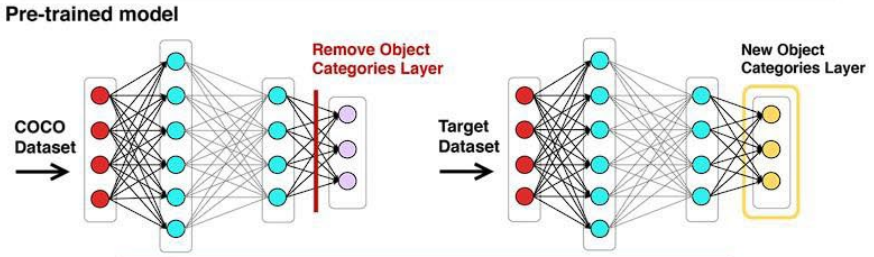
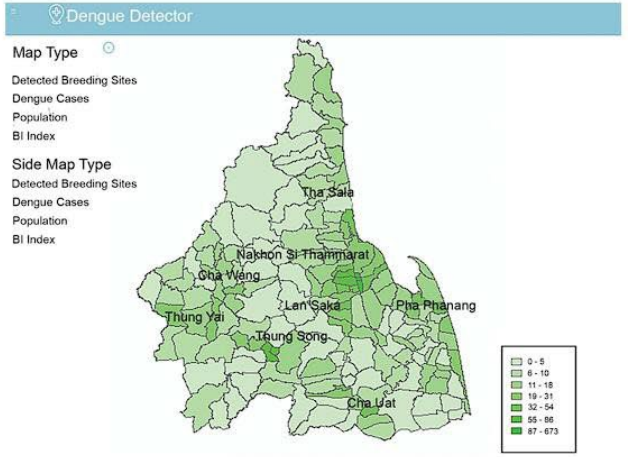


Fig 1. Common outdoor dengue vector breeding sites in Thailand (from left to right): large jar, bucket, old tire, potted plant, bin, ceramic bowl, cup, vase.





Source: https://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0007555&type=printable

THANK YOU!

กรมควบคุมโรค

Department of Disease Control

Modelling of chikungunya

Henrik Salje

Professor, University of Cambridge

UNIVERSITY OF CAMBRIDGE

PathogenDynamicsUnit
UNIVERSITY OF CAMBRIDGE

Declaration of conflicts

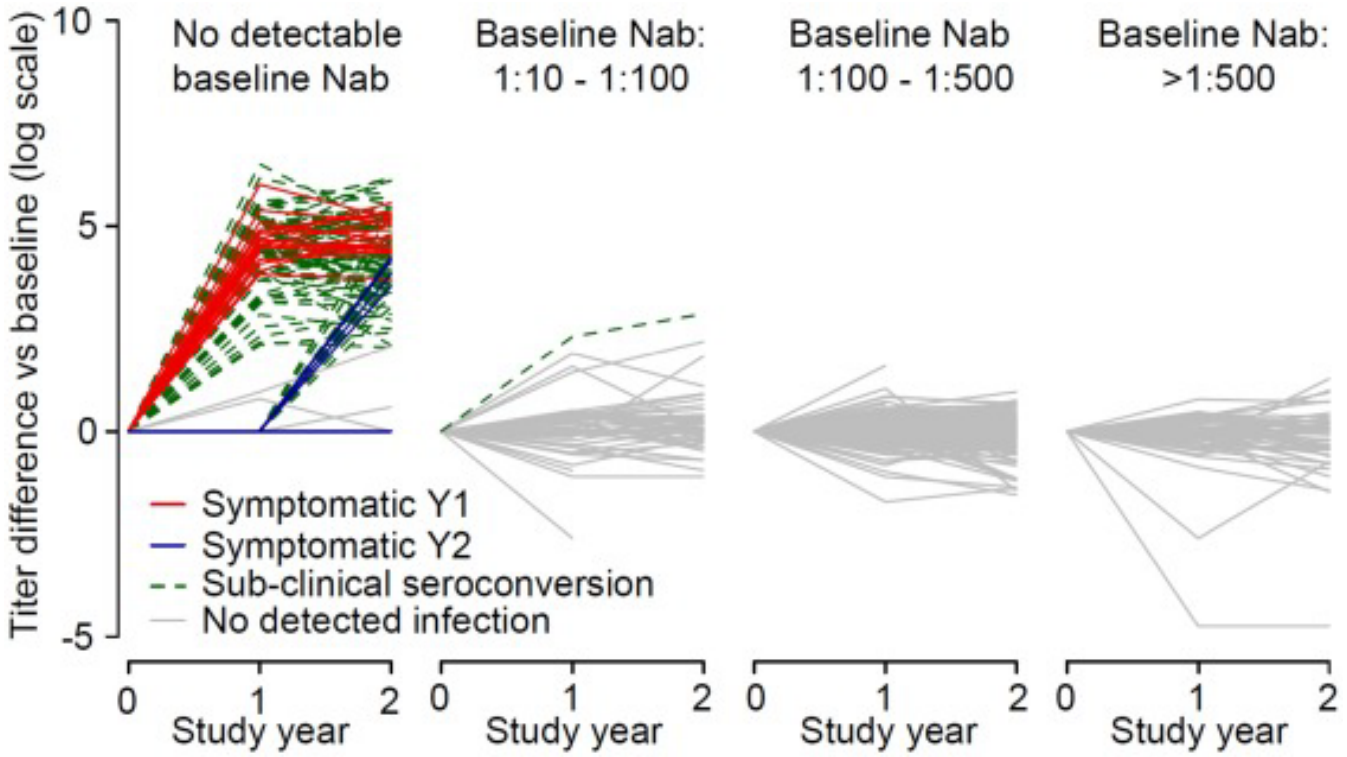
- Paid consultant to Gavi to understand CHIKV burden in eligible countries
- Paid consultant to Valneva to help with phase IV trial design
- Active grants with CEPI/UKRI to understand CHIKV burden and potential of vaccines

Key issues in licensure and use of CHIKV vaccines

- **Epidemiology**
  - Global distribution of infection burden poorly understood
  - Endemic in some places but often epidemic
  - Entire outbreaks can be entirely missed
  - Cannot rely on case data to understand burden (potential exception in parts of Americas/Europe)
  - Risk of disease following infection unclear, and how this differs by age/death

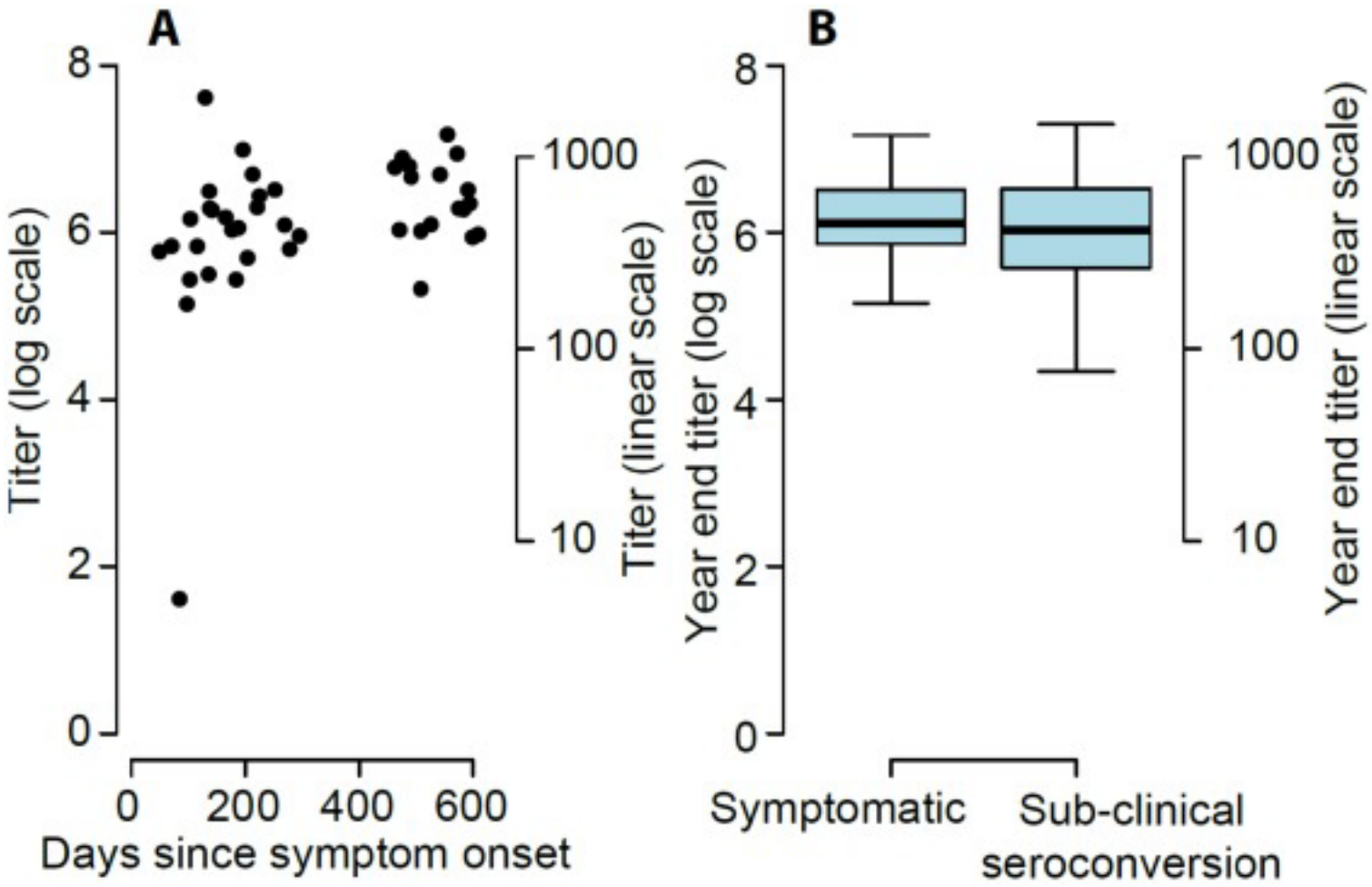
- **Vaccine characteristics**
  - IXCHIQ (and maybe future vaccines) approved via accelerated pathway – means:
    - No direct estimates of vaccine efficacy
    - No direct estimates of duration of protection
    - Infection vs disease blocking?

1. Identifying an immune correlate



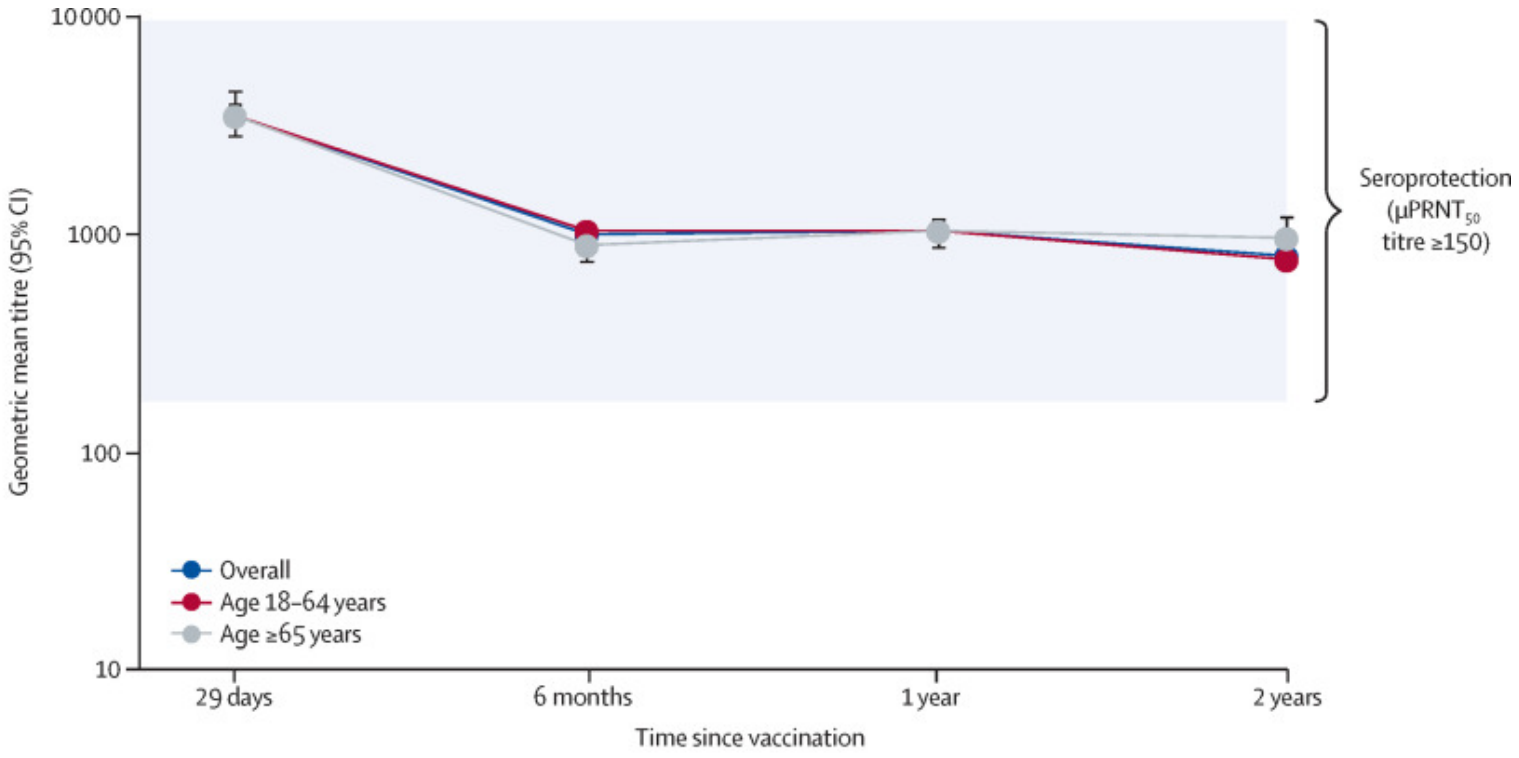
Yoon et al., PLoS NTD 2014; Yoon et al., IJID 2020

CHIKV titers from natural infection are usually high and stay high



Yoon et al., IJID 2020

VLA1553 (IXCHIQ) in US participants



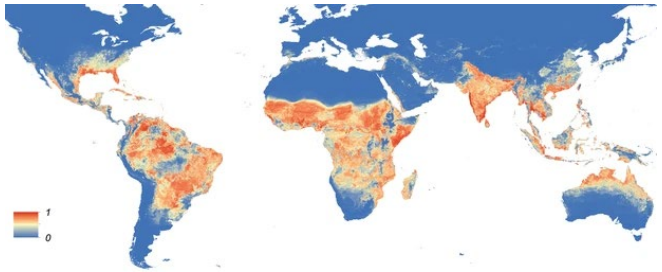
Overall (N=363)	3541·8 (95% CI 3206·0–3912·9; n=348)	1009·1 (95% CI 912·1–1116·5; n=360)	1055·5 (95% CI 959·0–1161·7; n=362)	784·7 (95% CI 701·9–877·4; n=317)
Age 18–64 years (N=310)	3537·4 (95% CI 3170·1–3947·3; n=298)	1030·8 (95% CI 919·9–1155·1; n=307)	1055·6 (95% CI 949·1–1174·1; n=309)	756·7 (95% CI 668·0–857·2; n=266)
Age ≥65 years (N=53)	3568·1 (95% CI 3206·0–3912·9; n=50)	892·2 (95% CI 734·4–1083·9; n=53)	1054·6 (95% CI 847·9–1311·6; n=53)	948·6 (95% CI 743·7–1209·9; n=51)

McMahon et al., Lancet ID 2024

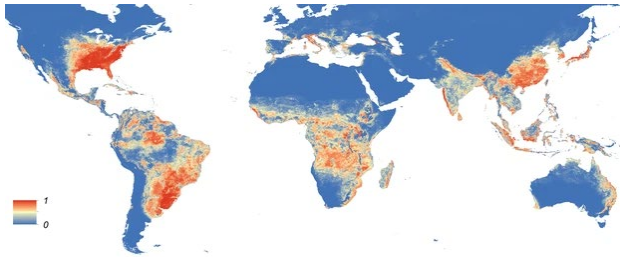
2. Where is there transmission?

- Literature review and link to Aedes distributions

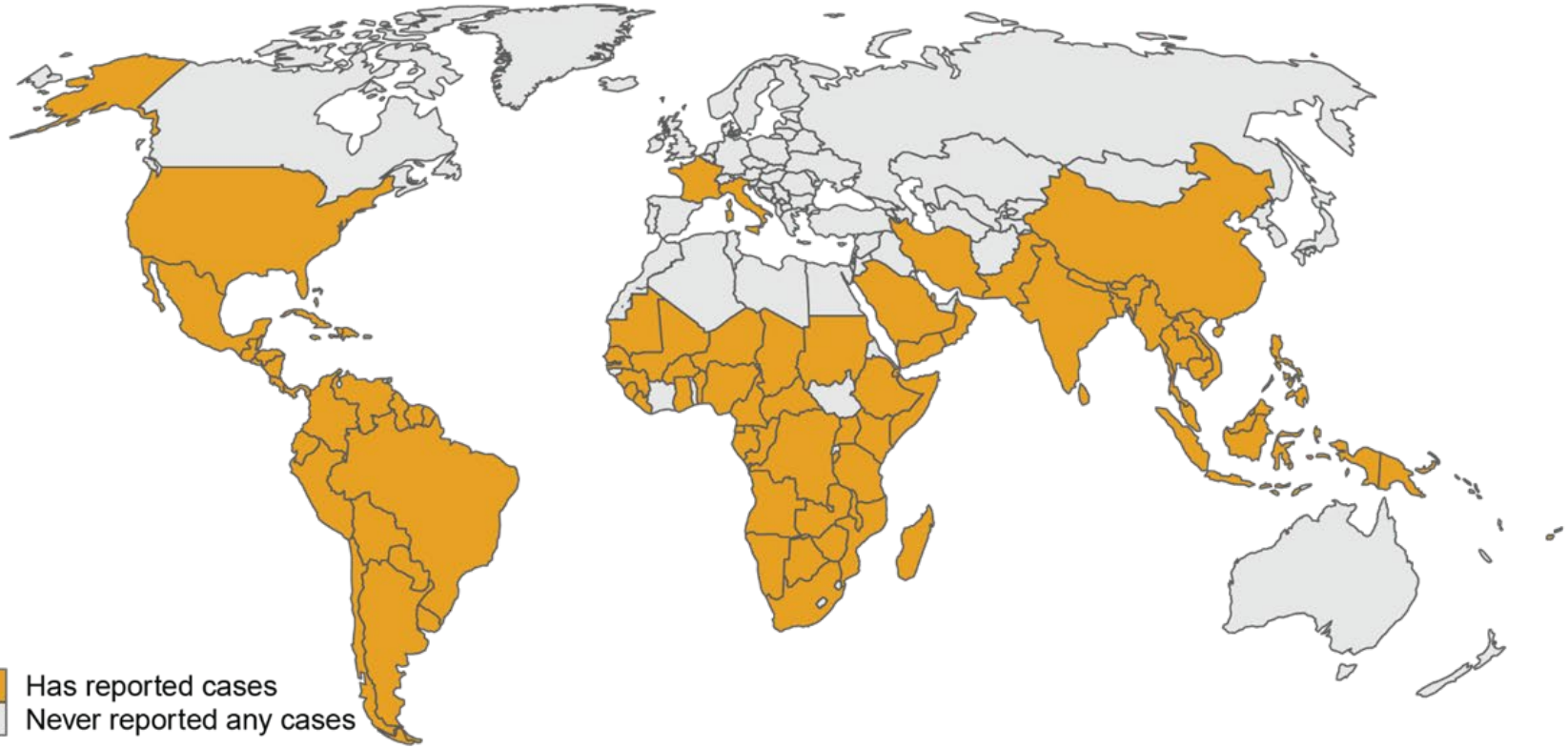
Predicted Ae. Aegypti

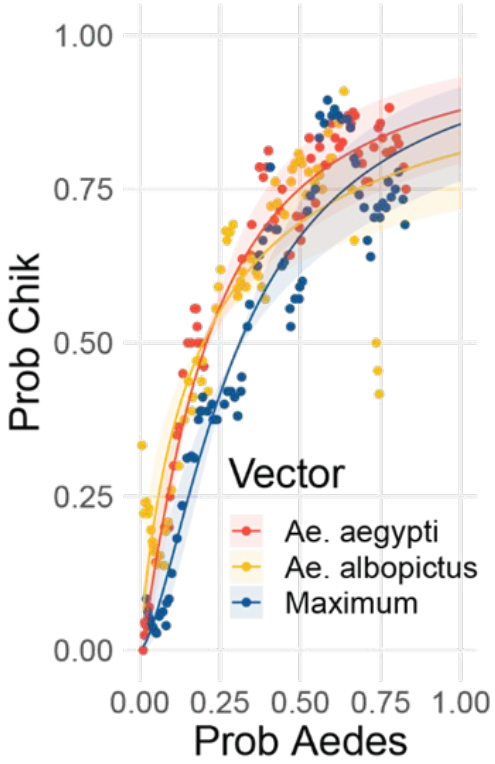


Predicted Ae. Albopictus



From Kraemer et al., eLife 2015

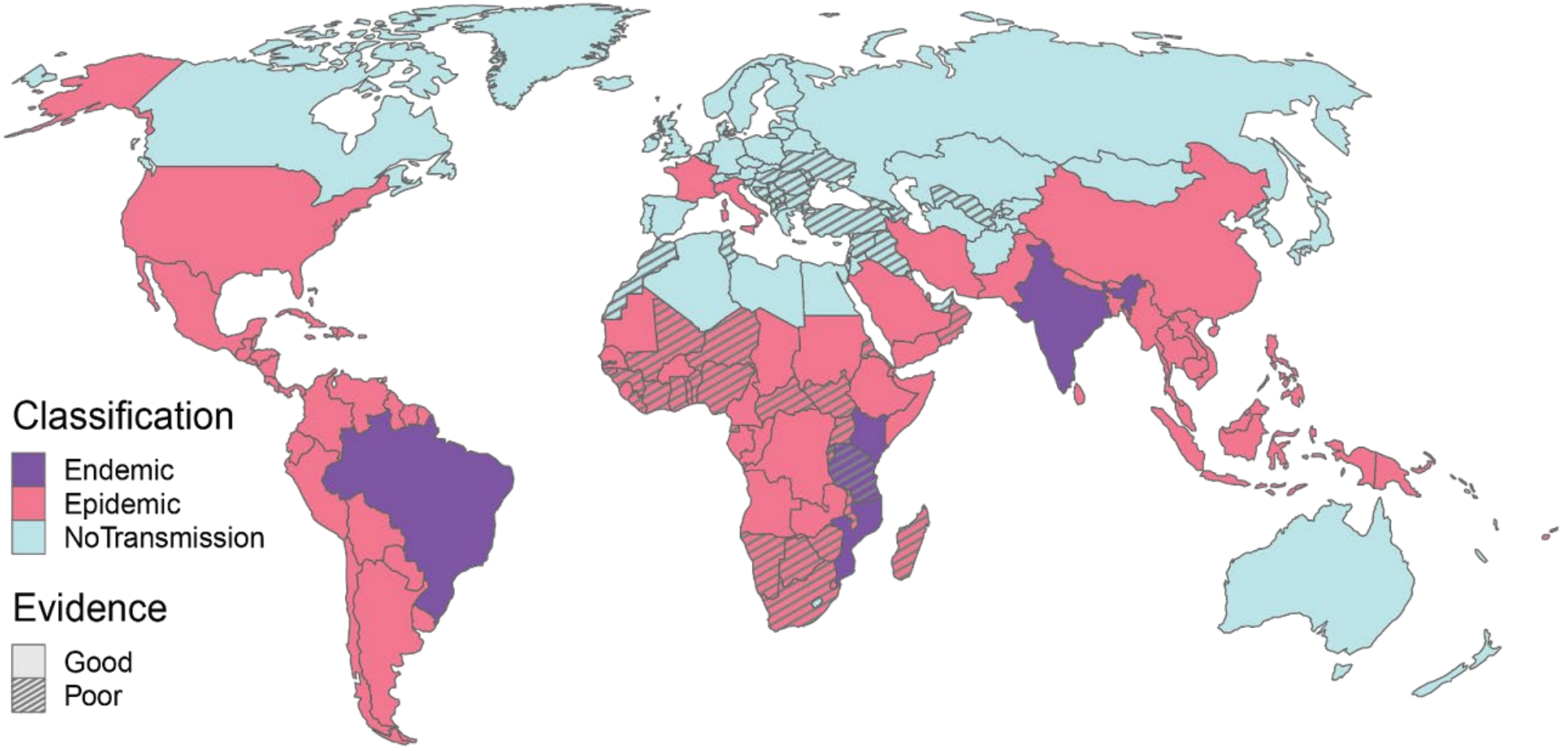




Dos Santos et al., Nature Medicine (in press)

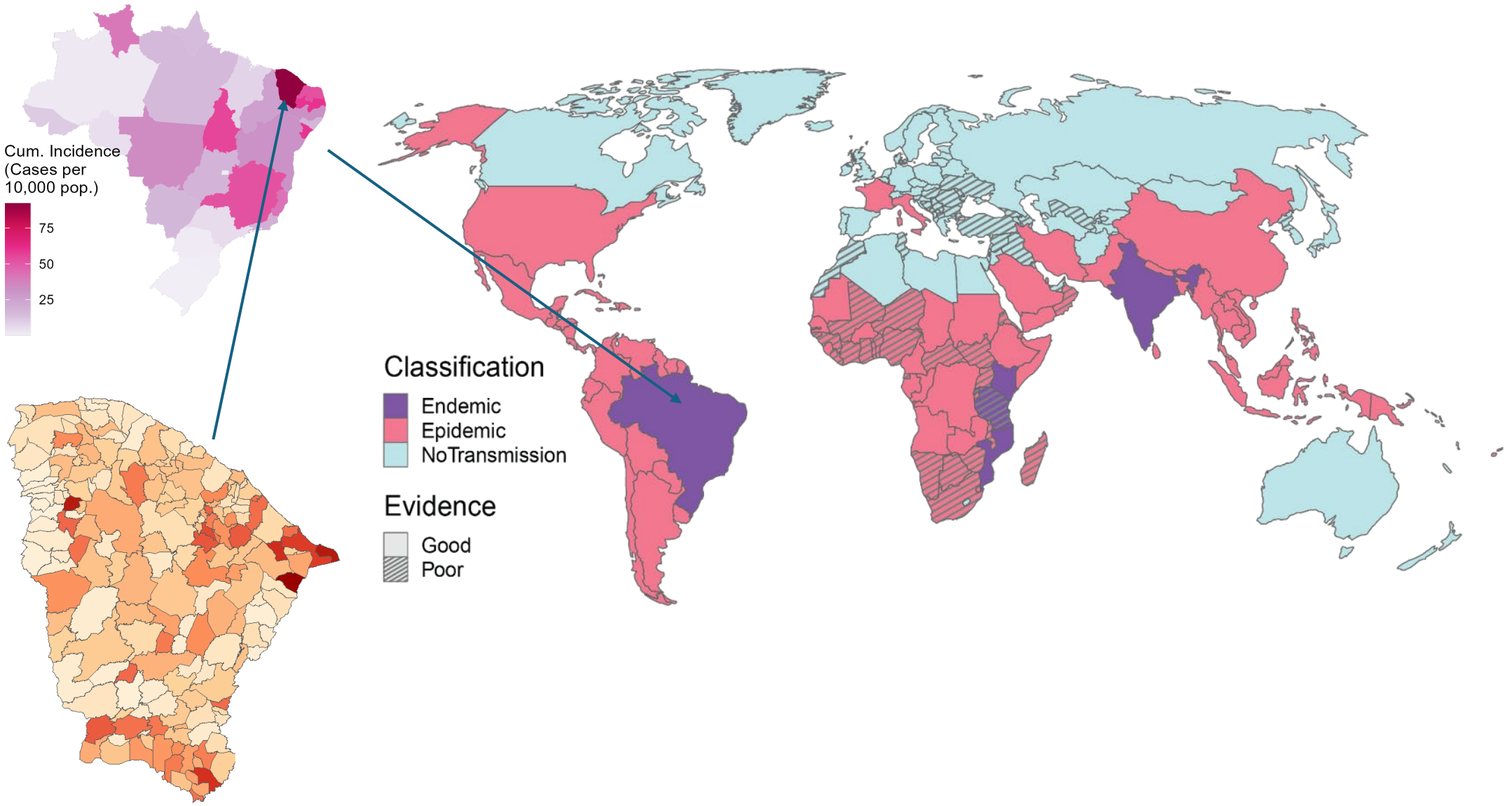
CEPI

Categorisation of countries



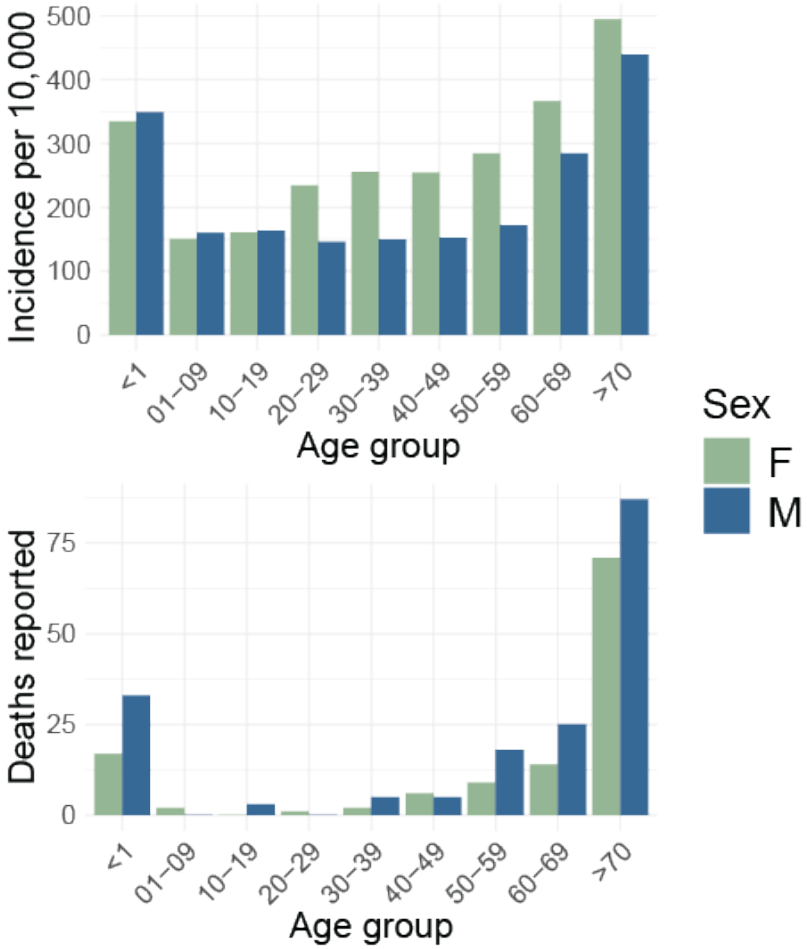
Dos Santos et al., Nature Medicine (in press)

Categorisation of countries



3. Identifying differences in risk of disease/death by age/sex

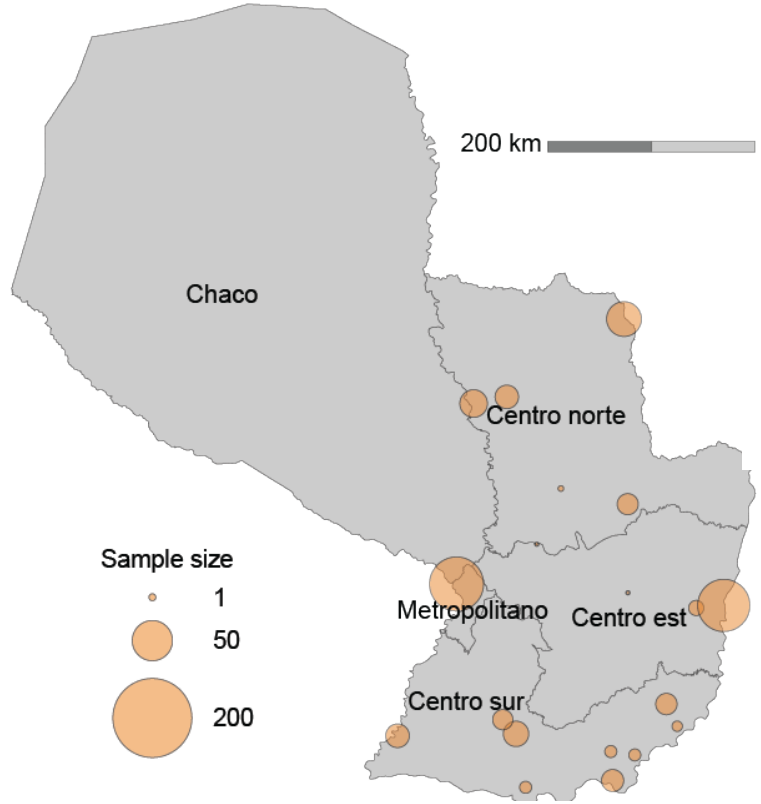
Case data from Paraguay outbreak 2022-23



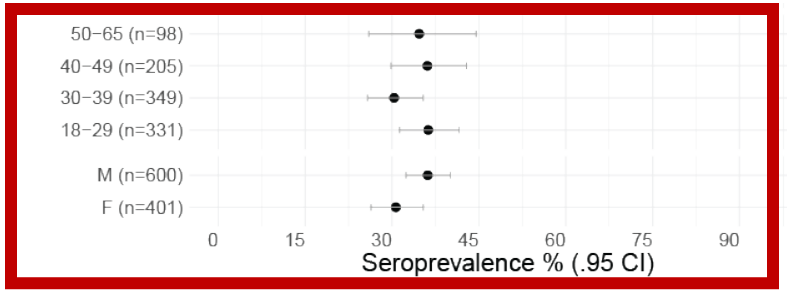
Pérez-Estigarribia et al., Nature Medicine (In Press)

Seroprevalence study following Paraguay outbreak allows us to identify case detection proportion and IFR

Source of samples:



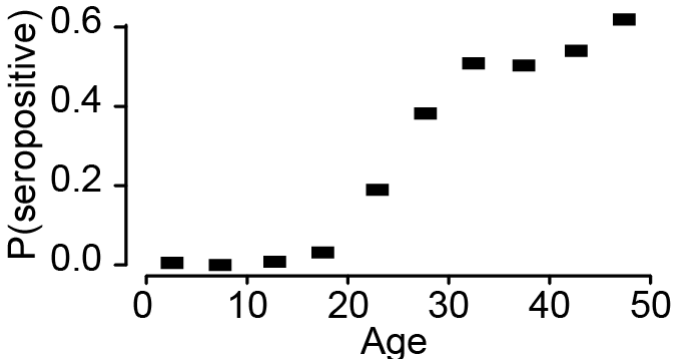
No difference in infection risk by age/sex



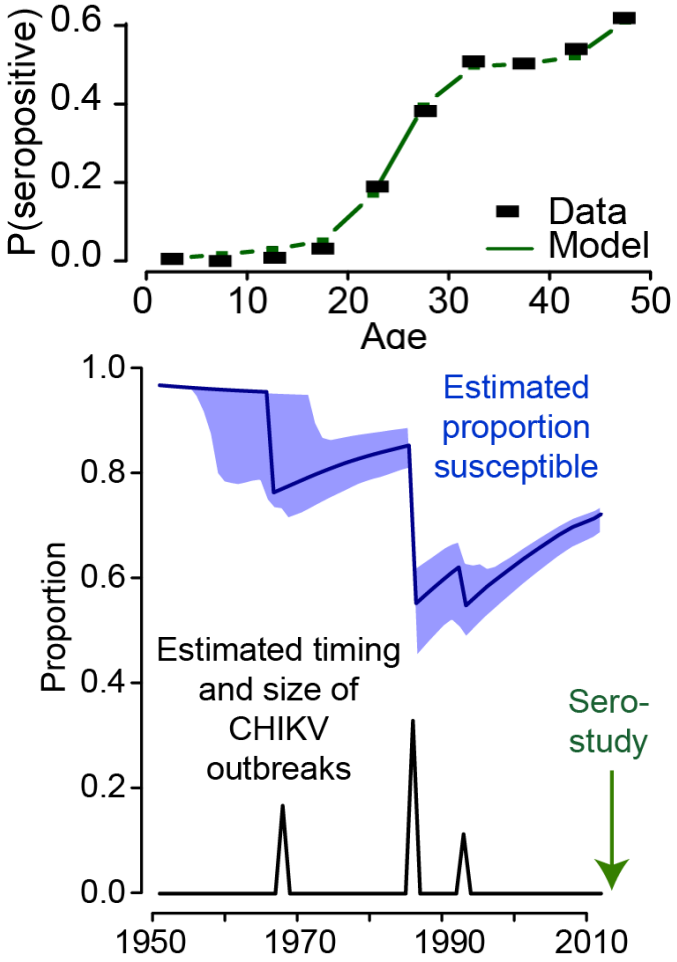
Pérez-Estigarribia et al., Nature Medicine (In Press)

4. Understanding burden in places with poor surveillance

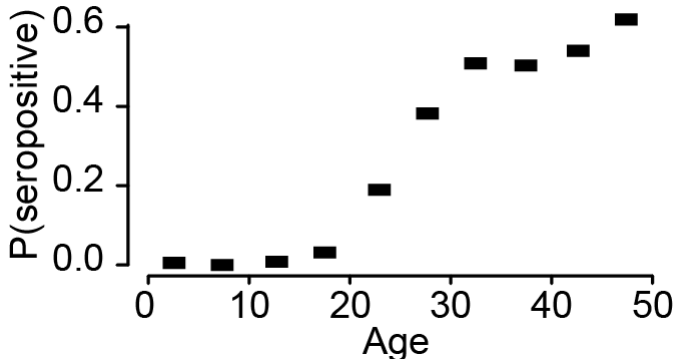
Where unreliable case data, we can use age-specific seroprevalence studies and catalytic models to quantify historic burden



Cebu, Philippines
Seroprevalence study

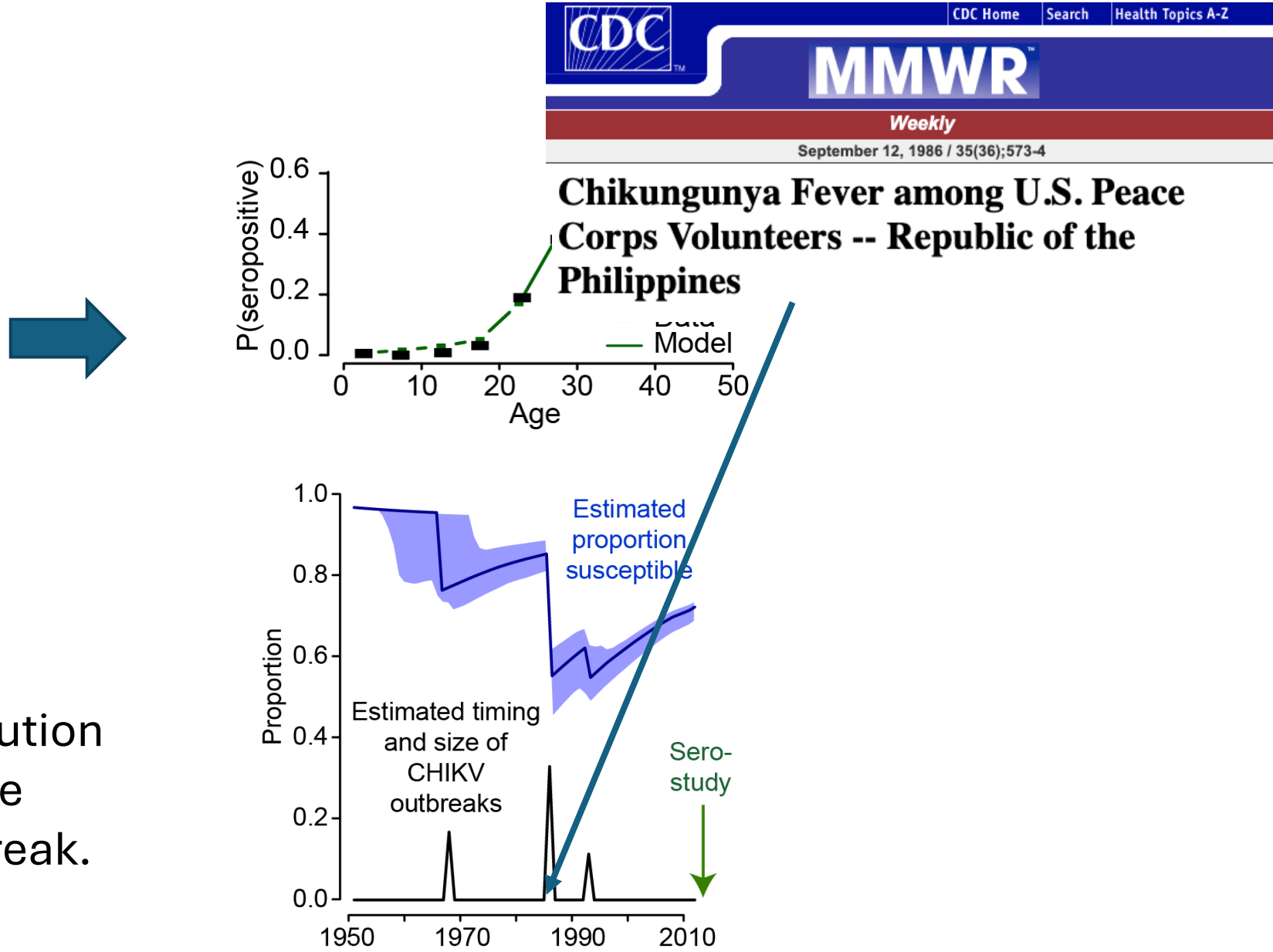


Salje et al., JID, 2015



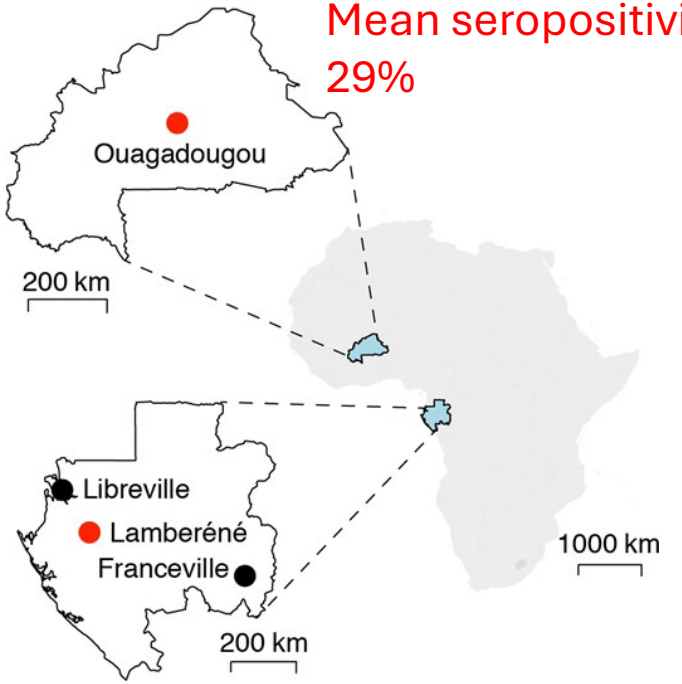
Cebu, Philippines
Seroprevalence study

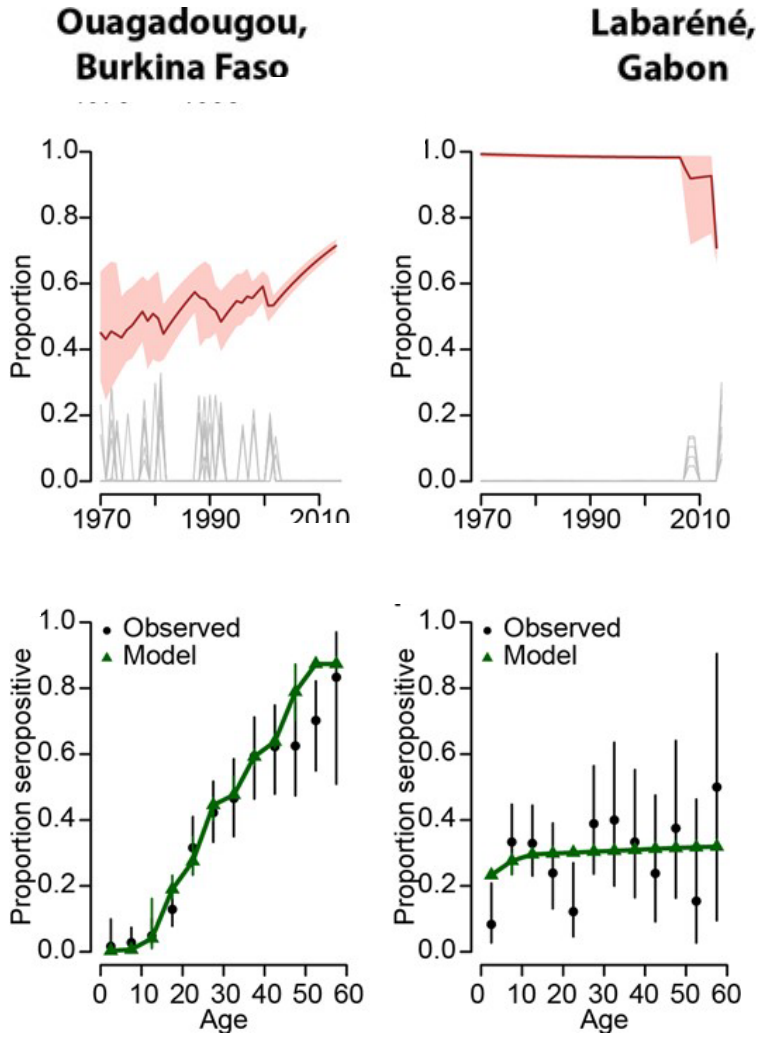
If we know size and age distribution of population, we can calculate number of infections per outbreak. Over 3 outbreaks – 350,000 infections (none reported)



Salje et al., JID, 2015

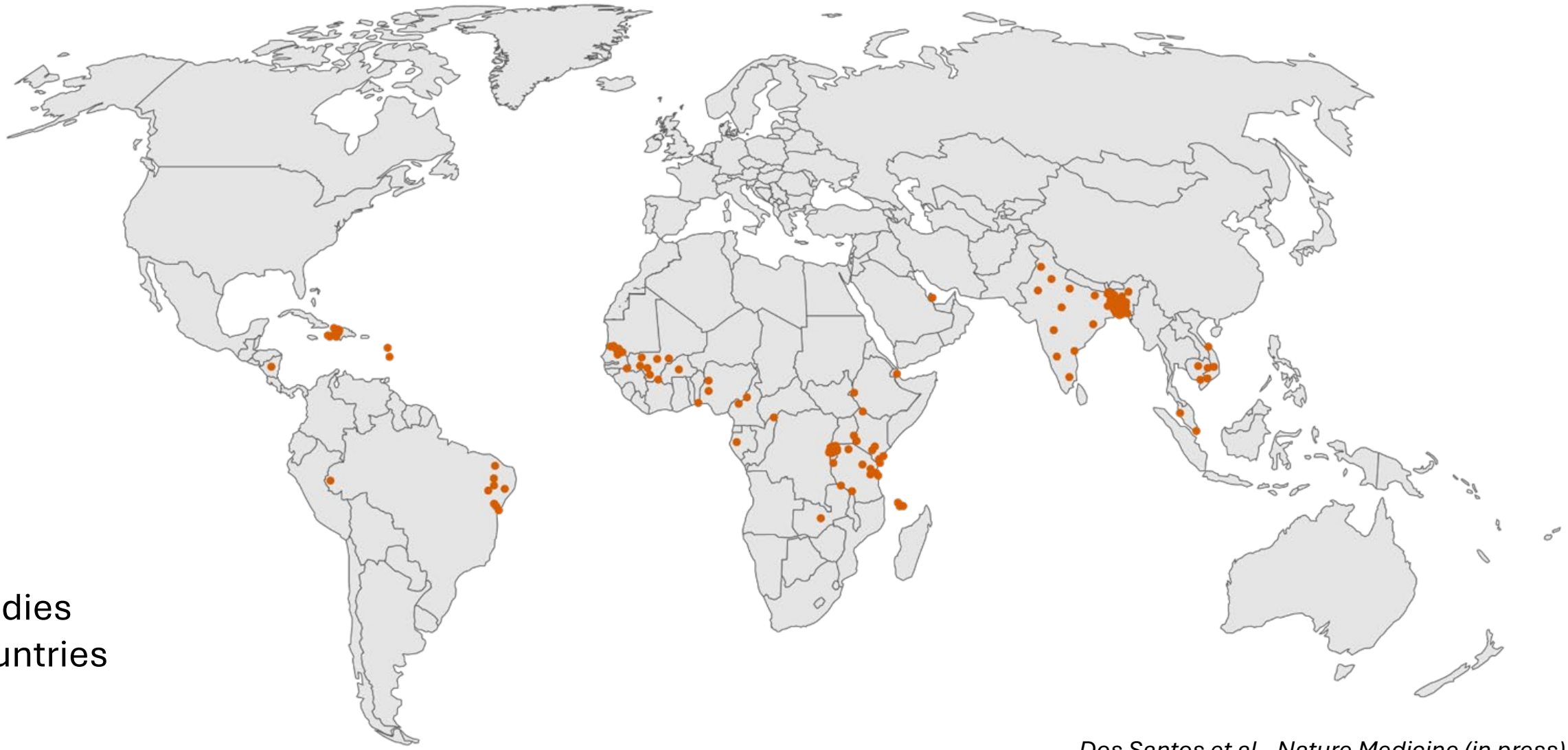
Two places – similar seropositivity but very different CHIKV circulation histories





Lim et al., JID, 2022

Serodatasets



40 studies
26 countries

Dos Santos et al., Nature Medicine (in press)

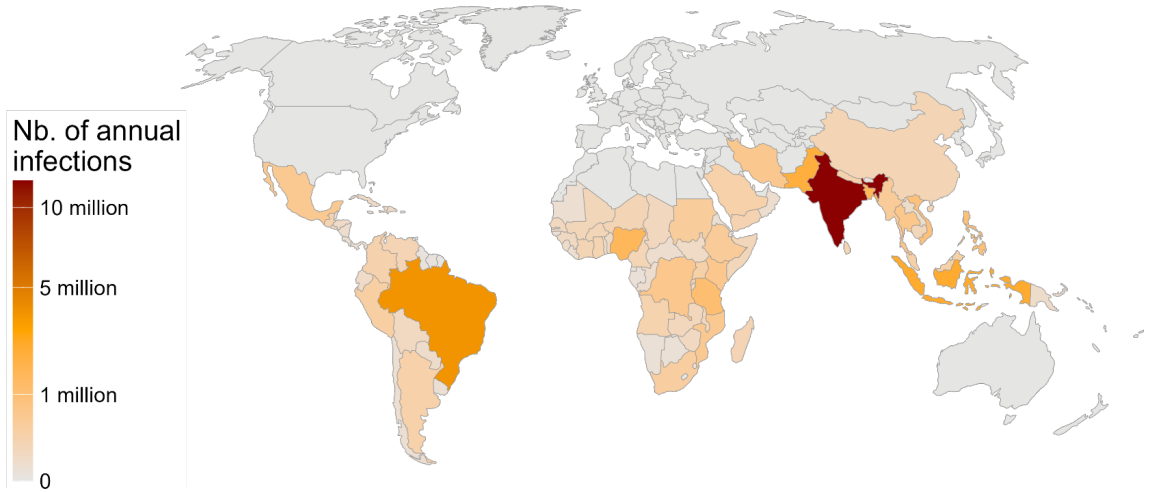
Mathematical models to reconstruct infection risk

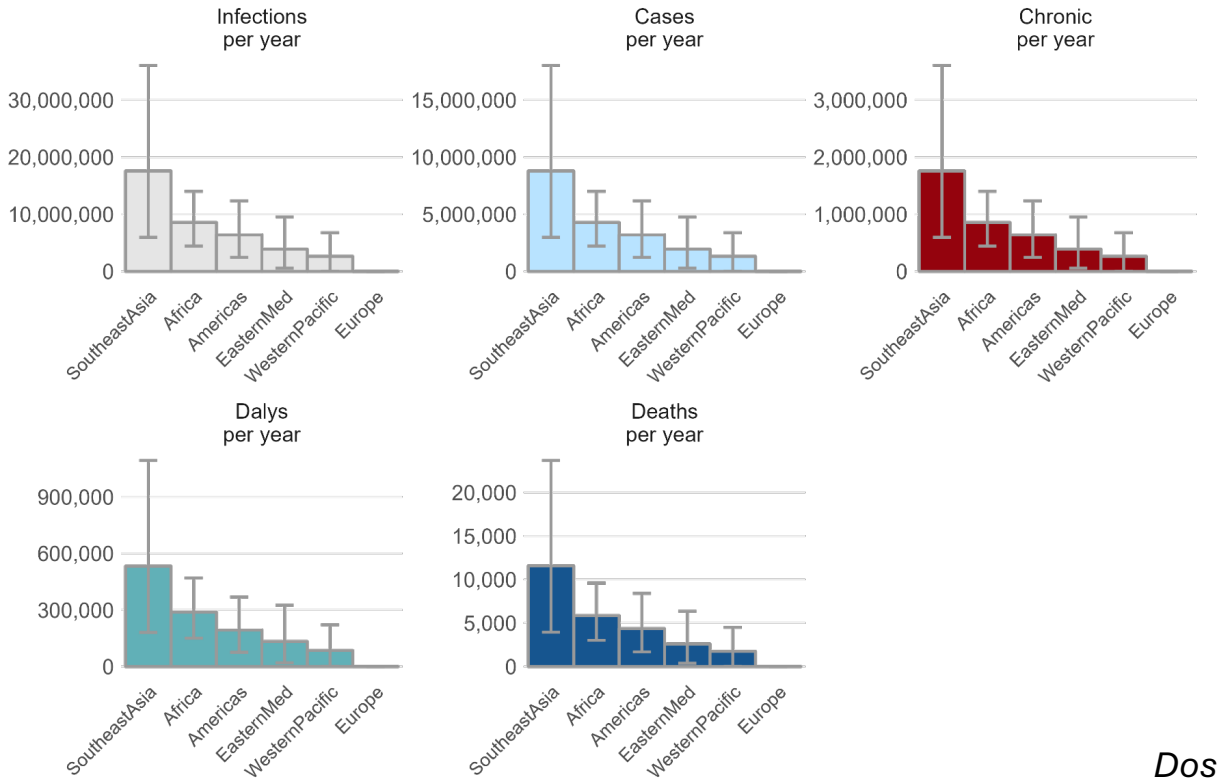
- We can fit a single model to all epidemic countries at the same time (and separately to all endemic countries).

- This gives us an estimate of:
  For epidemic countries:
  - The average duration between outbreaks (~6 years)
  - The size of outbreaks (~8%)

  For endemic countries:
  - The average force of infection per year (~2.6%)

- As we know the population and age distribution of populations, we can translate this to the number of infections, cases, deaths per country.





Overall estimates

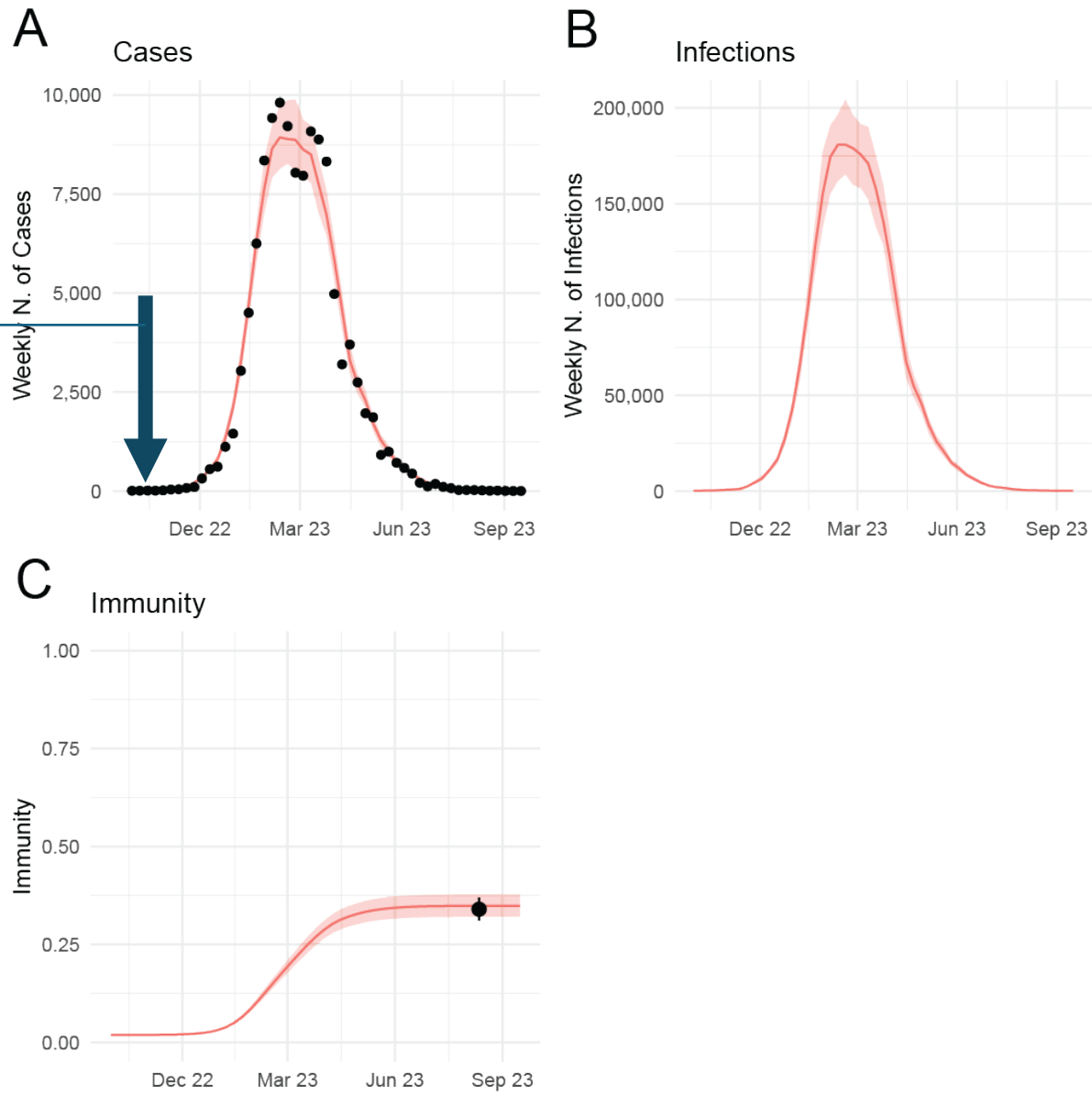
- 34 million infections per year (9 million in India)
- 3 million with chronic sequelae
- 23,000 deaths

Dos Santos et al., Nature Medicine (in press)

5. Quantifying the impact of vaccines – first using Paraguay outbreak as a case study

We can build mathematical models (compartmental models), that can recover but the observed number of cases and the immunity in the population

Outbreak declared by Ministry of Health (Oct 2022)



Pérez-Estigarribia et al., Nature Medicine (In press)

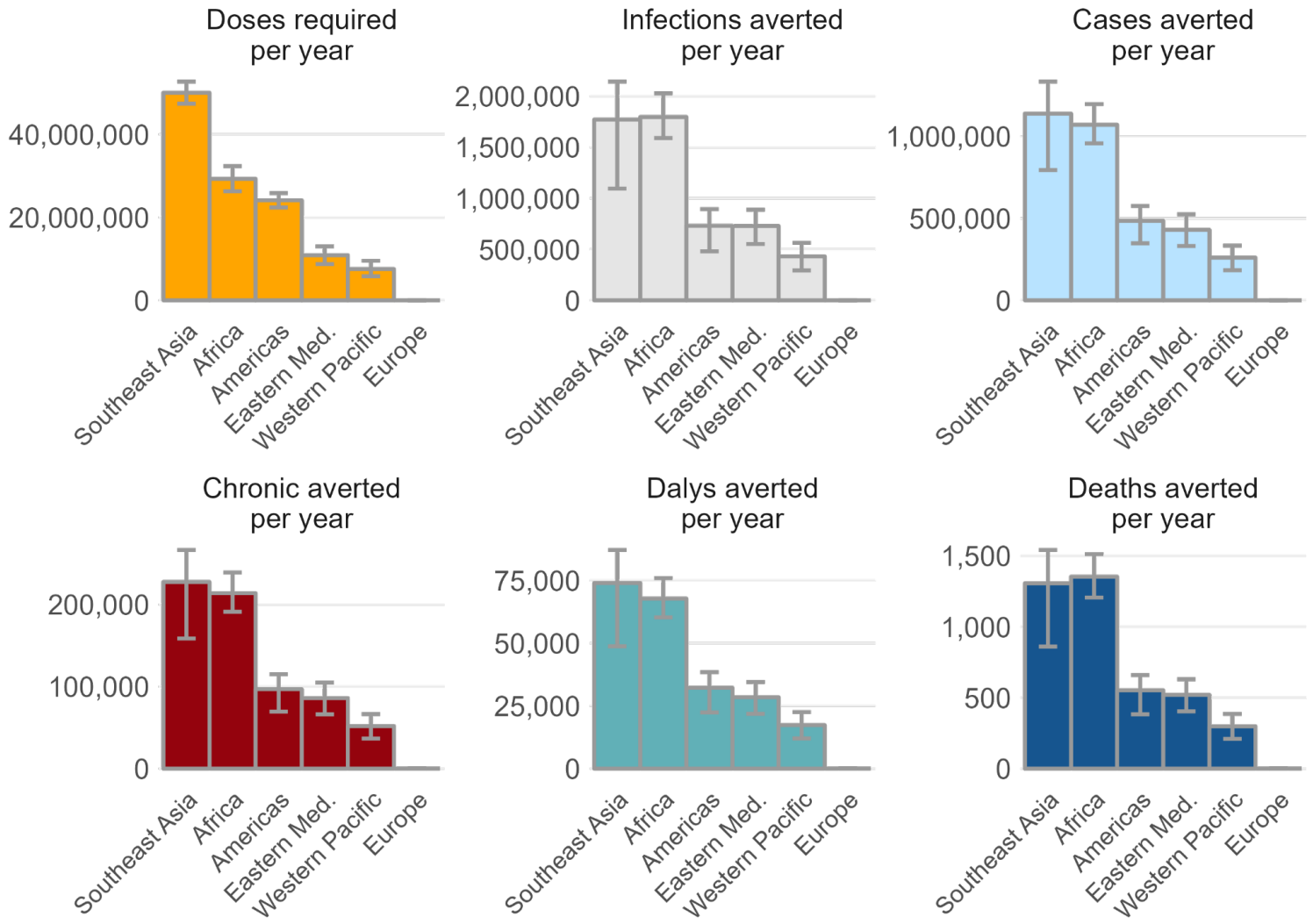
Extension to global potential of vaccines

- At a more general level, we can apply our understanding of global CHIKV epidemiology to
  - Endemic countries: Annual immunization of 12y (plus initial 12y+ campaign)
  - Epidemic countries: Stockpile based approach

Average impact

Epidemic settings: 370 cases, 74 chronic cases and 0.4 deaths averted per year per 10,000 doses

Endemic settings: 172 cases, 34 chronic cases and 0.2 deaths averted per year per 10,000 doses

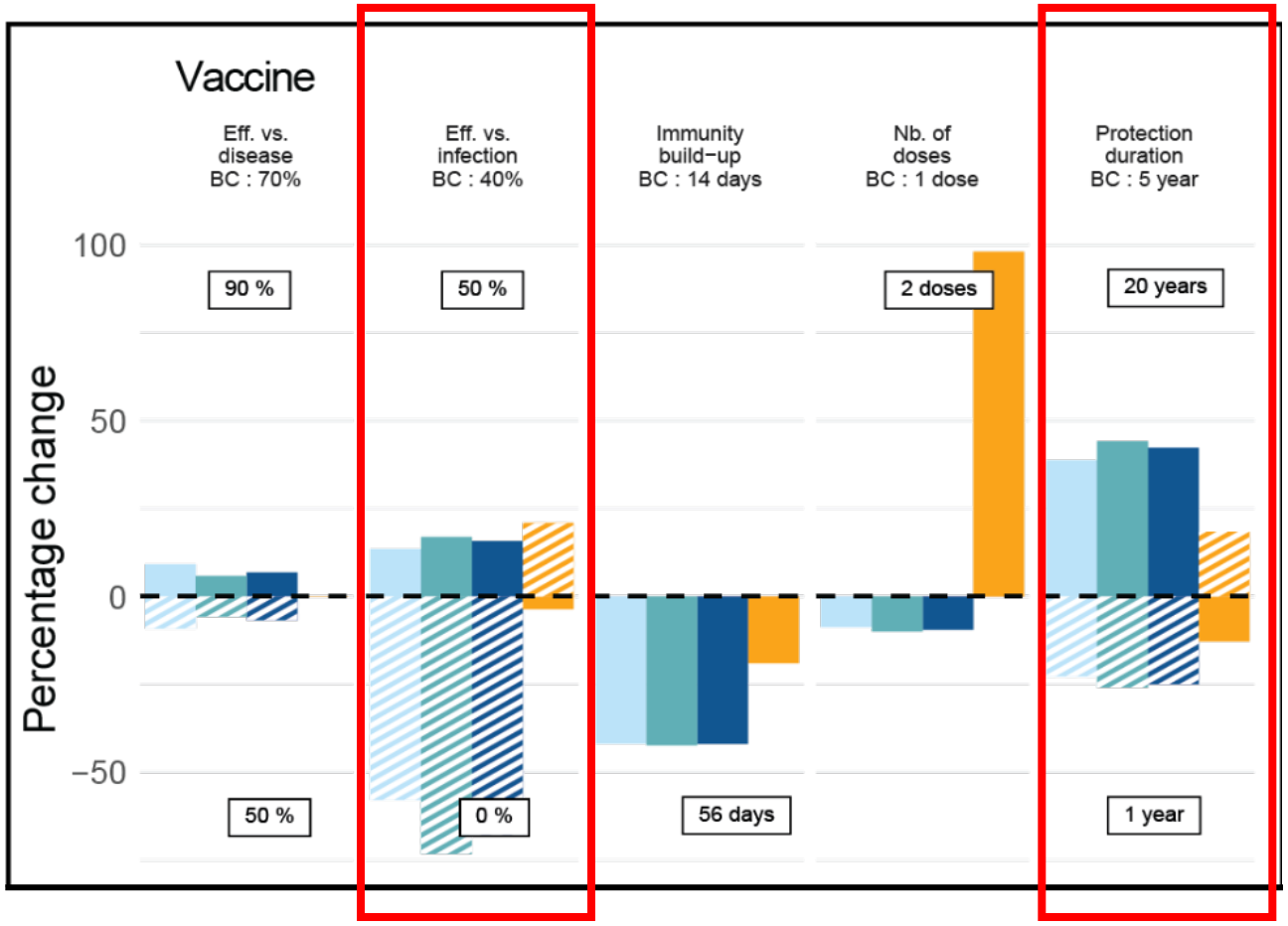


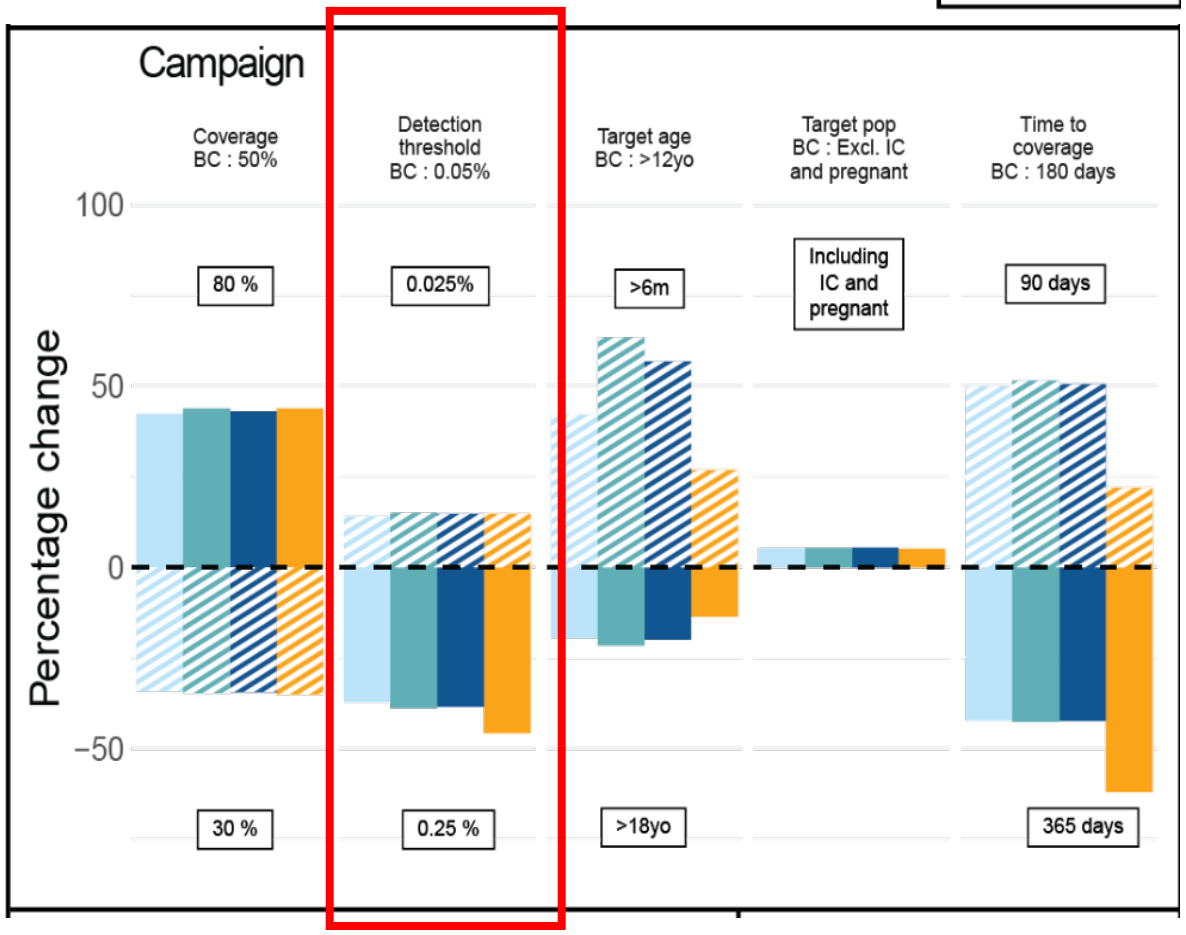
Doses required

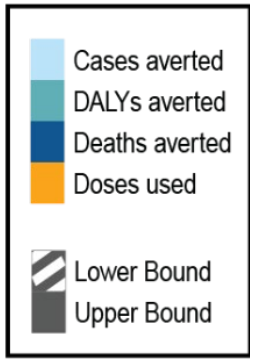
- 50% vaccination coverage would require:
  - 53.9 million in endemic locations
  - 68.5 million in epidemic locations

Dos Santos et al., Nature Medicine (in press)

Strong assumptions necessary







Base case: 0.05% equivalent to 5,000 cases per 10 million. Paraguay was ~20 cases per per 10 million when outbreak declared.

(Some) key unknowns

- Importance of strain/host on:
  a) Long term immunity (natural and from vaccine)
     - Reports of reinfection in Kenya
  b) Symptom risk
     - Wide variability in risk of acute and chronic sequelae
- Are there sufficiently ‘endemic’ settings to allow traditional phase III trials?
  - Maybe in a small number of locations but you also need established clinical infrastructure
  - Unclear if you can get sufficient power – will depend on timing/size of outbreaks – maybe across locations
- Can you run a reactive vaccine trial?
  - Need sufficiently large outbreak (e.g., Paraguay)
  - Need established protocols/approvals/stockpile

Summary

- Case data, seroprevalence studies and models have allowed us to quantify where CHIKV circulates and typical transmission patterns
- Patterns of disease by age and sex also clear with greater disease burden in females and older individuals/infants
- Across range of plausible assumptions, CHIKV vaccines appear to be effective in reducing burden – but will likely require stockpile based approach in most settings.
- Success of a responsive approach reliant on improved surveillance to quickly identify outbreaks.
- Still unclear if traditional Phase III trials or ‘reactive’ trials feasible but likely risky
- If reliant on correlates, Phase IV trials will be important to understand key vaccine characteristics.

Extra slides

Acknowledgements

Pathogen Dynamics Unit (Cambridge)
Emilie Finch
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Christinah Mukandavire

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Ana Karina Ibarrola-Vannucci

Gavi The Vaccine Alliance

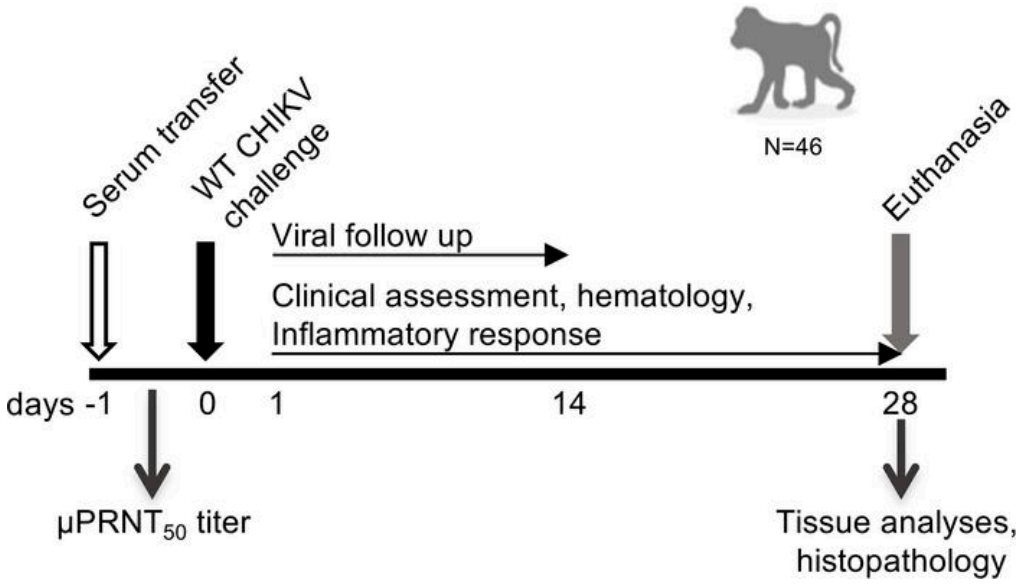
NIH

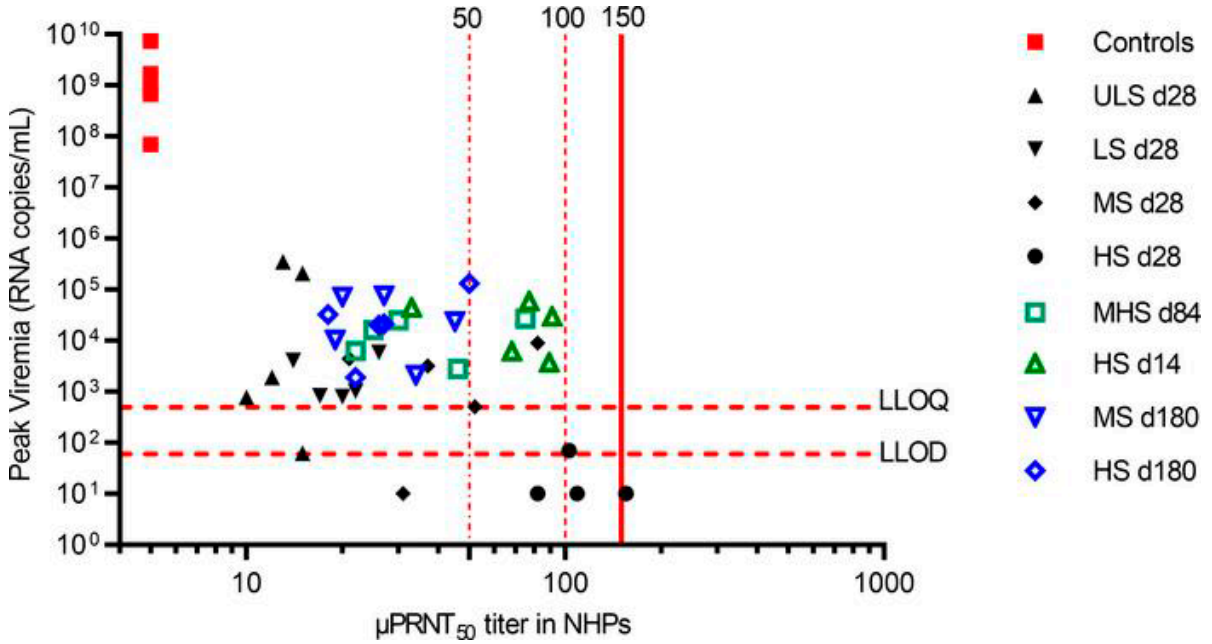
erc

wellcome

CEPI

Identifying a correlate using passive transfer in NHPs





FEASIBILITY OF CLINICAL EFFICACY STUDIES FOR CHIKUNGUNYA VACCINES

André Ricardo Ribas Freitas, MD PhD
Medical Epidemiologist
São Leopoldo Mandic School of Medicine
Dr. Mário Gatti Municipal Hospital

Chikungunya Meeting, March 19-20, 2024, São Paulo, SP/BRA

Declaration of No Conflict of Interest

Professional Affiliations:

- Assistant Physician at the Mário Gatti Municipal Hospital, Campinas
- Professor at São Leopoldo Mandic Medical School, Campinas and Araras (SP/Brazil)
- Member of the Working Group for the evaluation of the efficacy and safety of vaccines for Chikungunya, Dengue, and Zika at the Technical Chamber for the Registration of Medications (CATEME, ANVISA)
- Member of the Technical Advisory Committee on Arboviruses (CTA-Arboviruses), Ministry of Health
- Representative of the National Council of Municipal Health Departments (CONASEMS) at the Public Health Emergency Operations Center for Dengue and other Arboviruses (Centro de Operações de Emergências para Dengue e outras Arboviroses, COE-ARBOVIROSES)
- Volunteer Physician of the National Force of the Unified Health System (Força Nacional do SUS), Ministry of Health

Conflict of Interest Statement:

- I declare that I have no ties to any vaccine manufacturer and affirm that I have no conflicts of interest related to this presentation or research.

Key Considerations for Any Clinical Efficacy Studies

- **Study Design**:
  - Randomized controlled trials (RCTs) as the gold standard.
  - Endpoints: e.g., prevention of infection, reduction in disease severity.
- **Target Population**:
  - Geographic areas with high chikungunya prevalence.
  - Inclusion of diverse populations (e.g., age groups, immune status).
- **Challenges**:
  - Seasonal and sporadic nature of outbreaks.
  - Ethical considerations in placebo-controlled trials.
  - Logistics: site selection, participant recruitment, and follow-up.

Feasibility Assessment

Epidemiological Feasibility:

- Identifying regions with predictable outbreaks.
- Collaboration with local health authorities for surveillance.

Operational Feasibility:

- Infrastructure for large-scale trials (e.g., labs, cold chain).
- Training of healthcare workers and community engagement.

Regulatory and Ethical Feasibility:

- Compliance with international and local regulations.
- Ensuring informed consent and addressing community concerns.

Challenges of Epidemiology

Unpredictable Epidemiology

- CHIKV outbreaks occur sporadically and unpredictably, making it difficult to plan and execute trials.
- Variability in geographic spread and case numbers complicates patient recruitment.
- Differences in viral circulation between endemic and non-endemic areas create additional obstacles.

High Prevalence of Pre-existing Immunity

- Many endemic regions have high seroprevalence, reducing the number of susceptible individuals.
- Herd immunity in previously affected populations limits the ability to observe vaccine efficacy.
- Need for alternative trial locations or strategies to ensure sufficient case accrual.

Ethical and Logistical Constraints

- Conducting placebo-controlled trials may not be ethical in high-risk areas.
- The rapid spread of outbreaks limits the timeframe for recruitment and follow-up.

Immunological Correlates

- Unlike other vaccines, CHIKV lacks a well-established correlate of protection.
- WHO recommends seroneutralizing antibodies as a potential surrogate marker.
- Further research is needed to validate immunogenicity endpoints as reliable measures of efficacy.

Alternative Study Designs

- Real-world effectiveness studies as an alternative to traditional phase III trials.
- Use of observational studies, cohort analyses, and post-marketing surveillance.
- Exploring the feasibility of outbreak response studies with pre-approved protocols.
- Strengthening Surveillance and Data Collection
- Improved epidemiological surveillance is critical for vaccine assessment.
- Strengthening reporting systems to track vaccine impact and long-term immunity.
- Enhancing laboratory capacity for reliable diagnostics and case confirmation.

Regulatory Challenges

- Overcoming these challenges is essential for successful vaccine implementation.
- Innovative trial designs and regulatory adaptations are crucial to accelerating vaccine approval.
- Strengthened global collaboration among researchers, policymakers, and public health institutions.
- Different regulatory agencies have varying requirements for vaccine approval.
- Harmonization of alternative efficacy endpoints is needed for global vaccine deployment.
- Coordination between stakeholders to define acceptable efficacy markers.

THANKS!

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Predicting outbreaks Chikungunya in Colombia

FERNANDO DE LA HOZ RESTREPO. MD MSc PhD

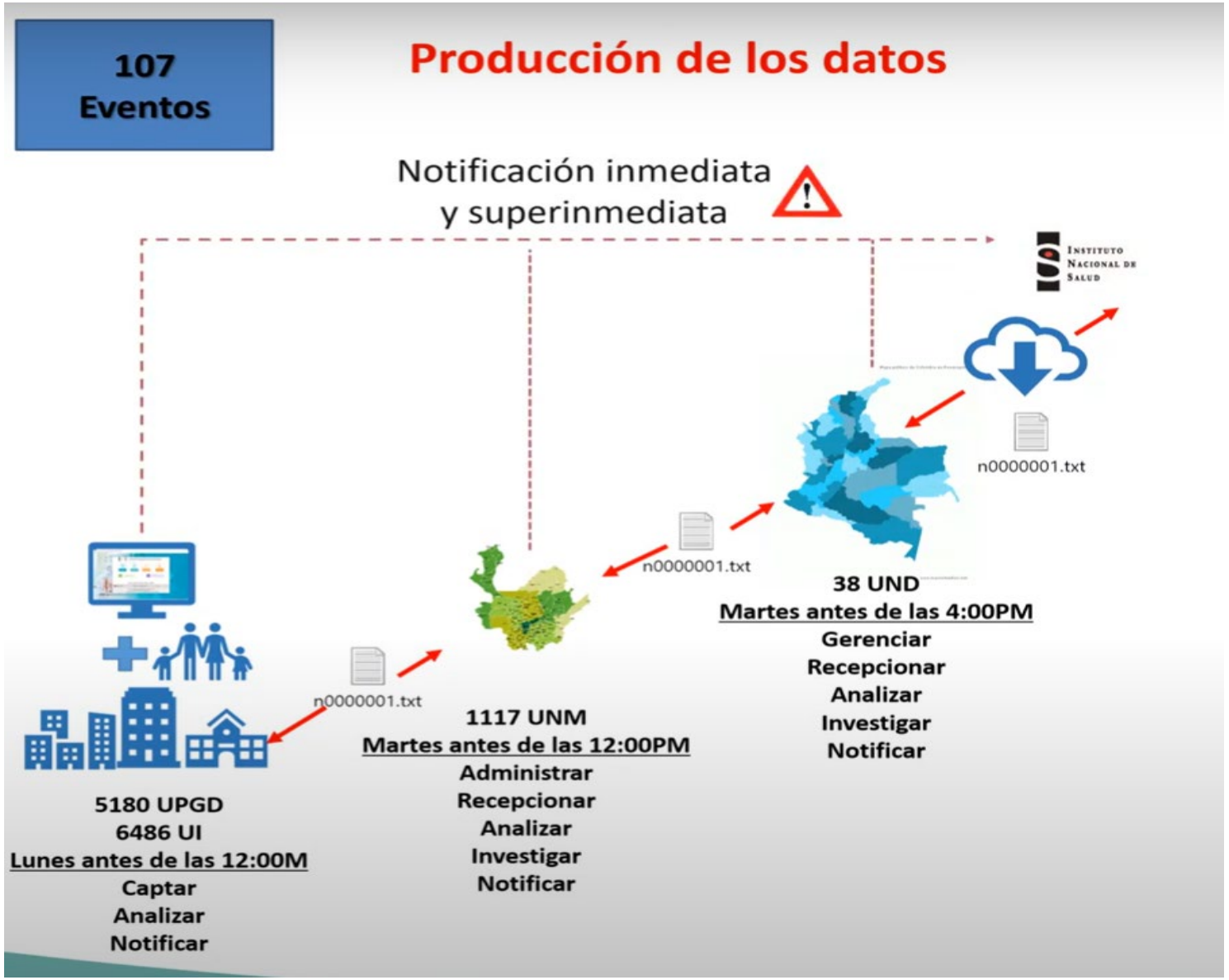
Universidad Nacional de Colombia-School of Medicine

Department of Public Health

Phase IV post-approval studies in the context of vaccines approved through accelerated procedures: Case study, CHIKUNGUNYA vaccines.

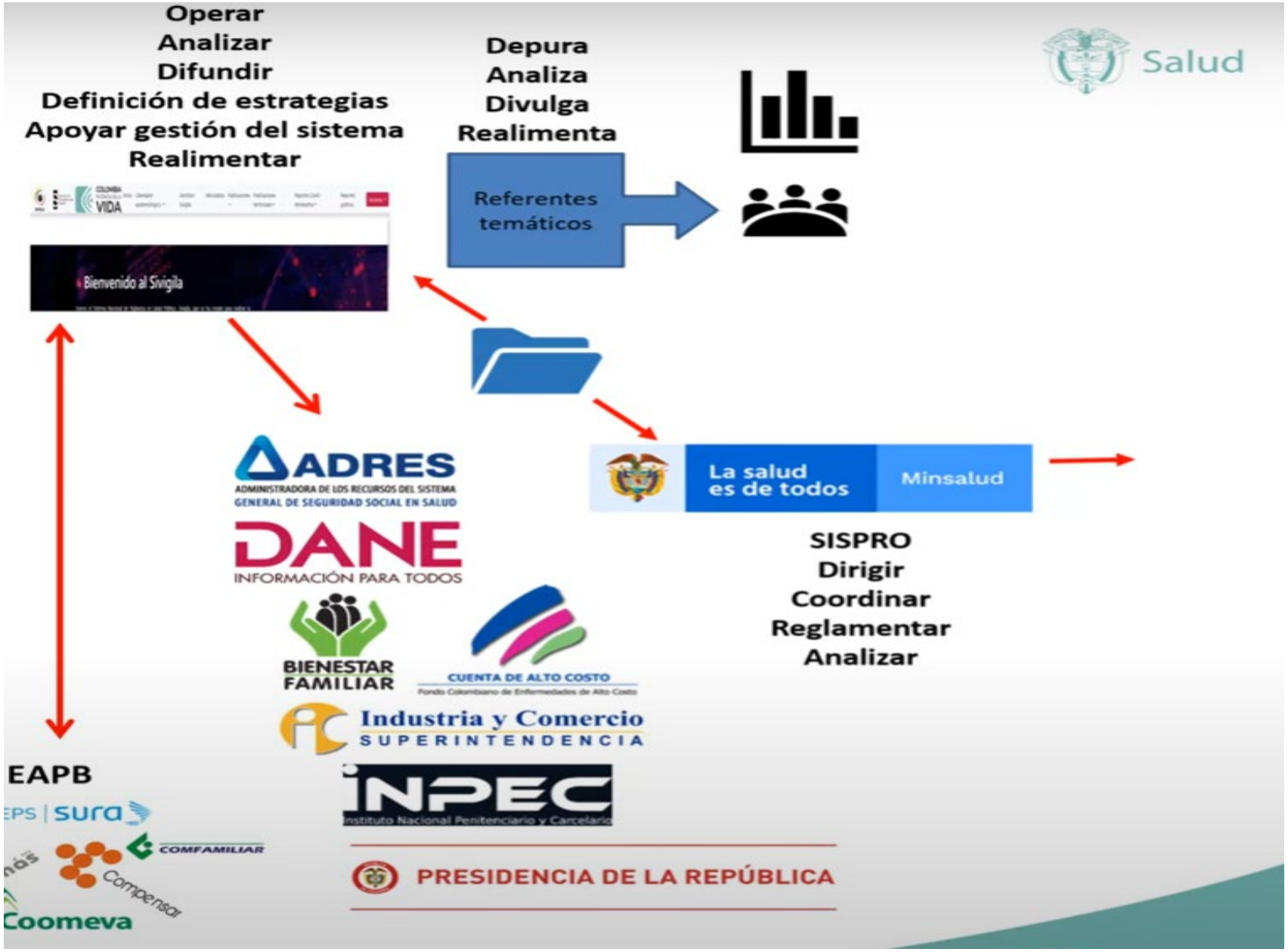
Sao Paulo, Marzo 19 y 20 2025

Estructura del Sistema de Vigilancia



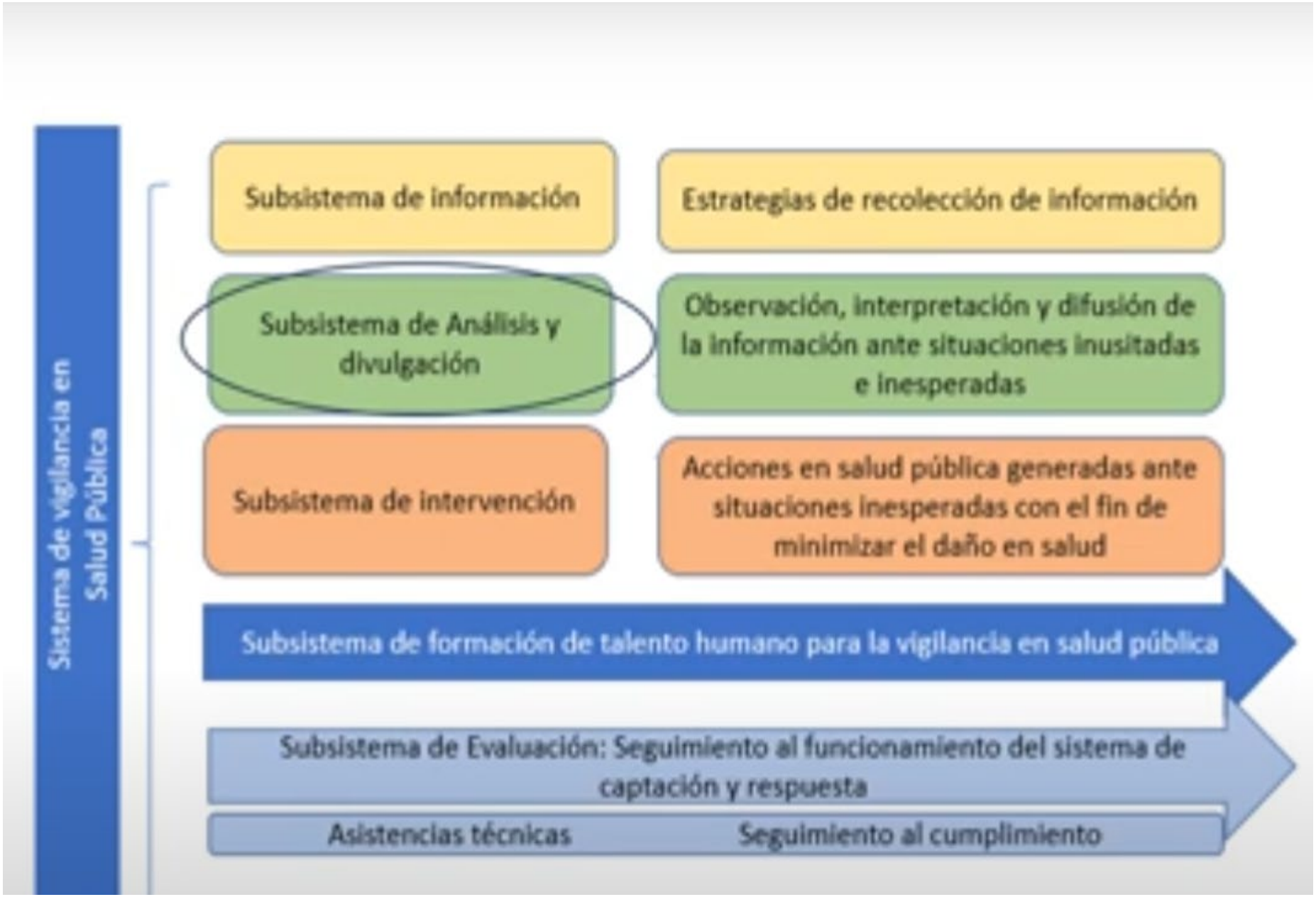
Fuente. Direccion de Vigilancia. Instituto Nacional de Salud.

Estructura del Sistema de Vigilancia



Fuente. Direccion de Vigilancia. Instituto Nacional de Salud.

Estructura del Sistema de Vigilancia



Fuente. Direccion de Vigilancia. Instituto Nacional de Salud.

Definiciones del Sistema de vigilancia

Tabla 2. Definiciones operativas de caso para la enfermedad causada por virus de Chikungunya

Tipo de caso	Características de la clasificación
Caso sospechoso	Paciente que resida o haya visitado de 8 a 15 días antes del inicio de síntomas, un municipio ubicado entre los 0 y los 2 200 m.s.n.m., en donde no se hayan confirmado casos de chikungunya por laboratorio y que presente fiebre mayor a 38°C, artralgia grave o artritis de comienzo agudo, eritema multiforme o síntomas que no se explican por otras condiciones médicas. Paciente de grupo de riesgo (gestantes, menores de 5 años, personas de 65 años o más y/o con comorbilidades) que proceda de zonas ubicadas entre los 0 y los 2 200 m.s.n.m. (sin importar si tiene, o no, circulación viral confirmada), 8 a 15 días antes del inicio de síntomas, que presente fiebre mayor a 38°C, artralgia grave o artritis de comienzo agudo y eritema multiforme o síntomas que no se explican por otras condiciones médicas.
Caso confirmado por clínica	Paciente que presente fiebre mayor a 38°C, artralgia grave o artritis de comienzo agudo, eritema multiforme o síntomas que no se explican por otras condiciones médicas, que resida o haya visitado un municipio en donde se tenga evidencia de la circulación del virus CHIKV, o esté ubicado en un municipio con radio de 30 kilómetros a municipios con circulación viral.
Caso confirmado por laboratorio	Caso sospechoso con alguna de las siguientes pruebas de laboratorio específicas para el virus con resultado positivo: RT-PCR o Elisa IgM, o aumento de cuatro veces en el título de anticuerpos específicos IgG para virus chikungunya en muestras pareadas con diferencia de 15 días entre la toma de estas.
Caso descartado por laboratorio	Caso sospechoso al que se le tomaron muestras de laboratorio, presentó resultados negativos y se confirma otro diagnóstico.

Fuente. Direccion de Vigilancia. Instituto Nacional de Salud.

Definiciones del Sistema de vigilancia

- Notificacion inmediata: Muertes sospechosas CHKV

- Notificacion semanal: Casos sospechosos.

Fuente. Direccion de Vigilancia. Instituto Nacional de Salud.

Estudios CHKV en Colombia

- **Estudios en vectores:**

  - **1. Vigilancia entomo-virológica de arbovirus en el distrito de Santa Marta, Colombia. 2018 – 2019** **https://bibliotecadigital.udea.edu.co/bitstream/10495/32905/4/FrancoJuan_2022_Arboviruses_Flavivirus_Surveillance.pdf**
  - **Se capturaron un total de 3022 mosquitos adultos, de 14 géneros y 22 especies.**
  - **Se encontró positividad a Dengue y Zika pero no a CHKV**

  - **2. Arbovirus infection in Aedes aegypti from different departments of Colombia** **Front. Ecol. Evol. 10:999169.**
  - **30% de espécimenes fueron positivos a arbovirus**
  - **La gran mayoria de muestras fueron positivas a dengue y 1 para CHKV**

Estudios CHKV en Colombia

- **Estudios en humanos:**

  - **1.Unexpected arboviruses found in an epidemiological surveillance of acute tropical febrile syndrome in the department of Meta, Eastern Colombia** Journal of Infection and Public Health 17 (2024) 102510
  - **100 pacientes con enfermedad febril aguda.**
  - **Seroprevalence for CHKV was 42%**
  - **1 patient seroconverted for CHKV**

  - **2. Caracterización clínica de pacientes menores de 18 años con diagnóstico de Dengue y coinfecciones con zika y/o Chikungunya por pruebas moleculares en el Hospital Infantil Napoleón Franco pareja, durante 2018-2019.** https:// repositorio.unicartagena.edu.co/server/api/core/bitstreams/5af4ce65-d4f0-4800-983a-d0d677f3d539/content
  - **Se diagnosticaron 78 pacientes con infección única por virus Dengue y 24 con co-infección (18 con dengue Chikungunya, 3 con dengue Zika y 3 con triple infección)**

Estudios CHKV en Colombia

- **Estudios en humanos:**

  - **3. Dengue-chikungunya coinfection outbreak in children from Cali, Colombia in 2018–2019.** **International Journal of Infectious Diseases Volume 102, January 2021, Pages 97-102**
  - **345 febrile children for 12 months in a pediatric clinic**
  - **Molecular detection and serology tests.**
  - **143 CHIKV-positive (41.4%).**
  - **20 DENV-positive (5.8%).**
  - **123 DENV-CHIKV coinfection patients (35.7%).**

Debilidades del Sistema de vigilancia

- No tiene la misma cobertura en todos los municipios.
- Hay limitaciones para hacer diagnosticos diferenciales de enfermedades febriles.
- El diagnostico de CHKV descansa mas en muestras pareadas que son dificiles de conseguir.
- La notificacion semanal de casos hace mas dificil la confirmacion.
-

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Department of Disease Control

The Feasibility of Predicting Outbreaks

Department of Disease Control,
Thailand's Ministry of Public Health

กรมควบคุมโรค
Department of Disease Control

Statistical Modeling Research::

Identifying High-Risk Areas of Chikungunya Disease Outbreak in Southernmost Thailand

Article | Open access | Published: 03 November 2023

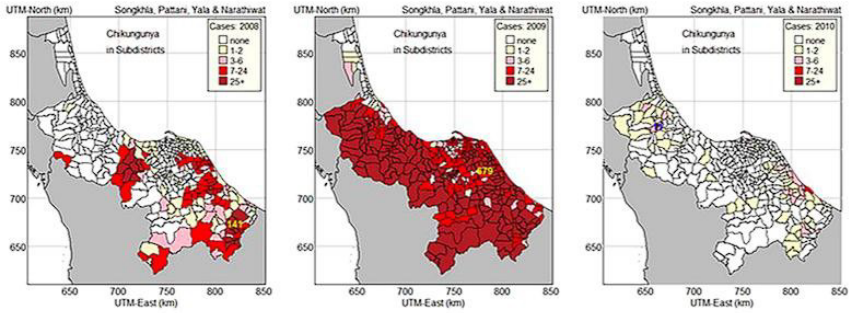
Statistical modeling for identifying chikungunya high-risk areas of two large-scale outbreaks in Thailand's southernmost provinces

Lumpoo Ammatawiyanon, Phattrawan Tongkumchum, Don McNeil & Apiradee Lim

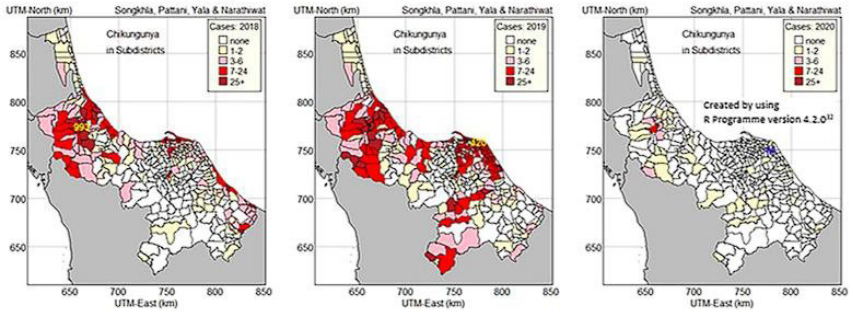
nature
international weekly journal of science

The study analyzed chikungunya fever (CHIKF) outbreaks in Thailand's southernmost provinces using statistical modeling to identify high-risk areas and transmission patterns.

Chikungunya cases in the first outbreak between 2008 and 2010



Chikungunya cases in the second outbreak between 2018 and 2020



Determinates	First outbreak		Second outbreak	
	Occurrence	Incidence	Occurrence	Incidence
Year				
2008	15.49	6.57	–	–
2009	67.09	16.63	–	–
2010	2.70	1.66	–	–
2018	–	–	16.88	2.84
2019	–	–	27.54	4.64
2020	–	–	2.015	2.01
Gender–age group				
Male				
0–9 years	26.04	6.91	12.38	2.93
10–19 years	31.00	9.66	17.70	3.50
20–29 years	33.14	8.82	17.81	3.02
30–39 years	31.49	10.75	17.60	2.79
40–49 years	31.20	13.70	13.90	2.98
50–59 years	26.24	16.32	9.99	3.64
60–69 years	19.34	22.51	8.69	5.97
70 + years	14.97	19.81	5.86	7.21
Female				
0–9 years	26.92	5.98	9.99	2.75
10–19 years	32.36	9.50	16.94	3.65
20–29 years	35.96	12.52	26.72	4.38
30–39 years	36.15	16.63	27.58	4.35
40–49 years	31.20	19.86	22.26	3.87
50–59 years	23.52	22.10	19.22	3.58
60–69 years	19.34	24.36	13.14	5.38
70 + years	26.92	16.65	7.93	4.32
Province				
Yala	22.92	10.19	9.45	2.47
Pattani	21.54	15.04	16.58	6.44
Narathiwat	42.15	15.26	10.20	2.06
Songkhla	28.89	14.51	18.49	2.61

Objective

To determine the geographic epidemic patterns and high-risk locations

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC10624817/

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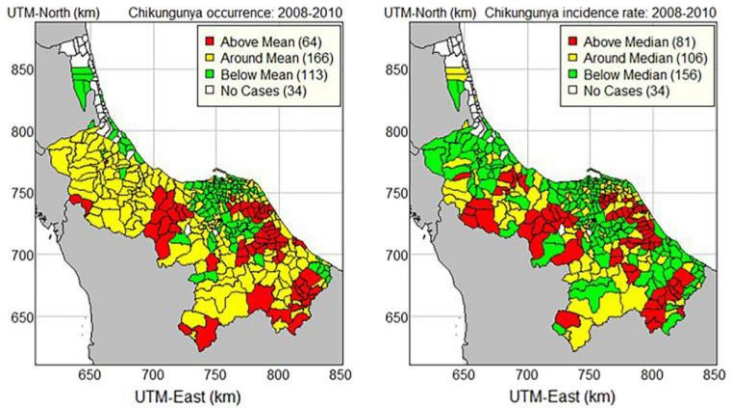
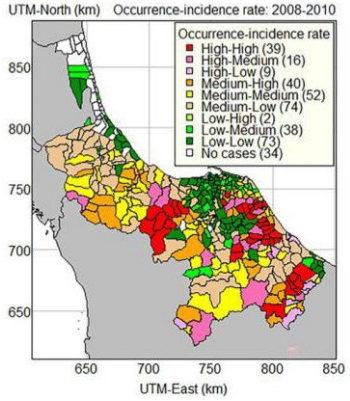
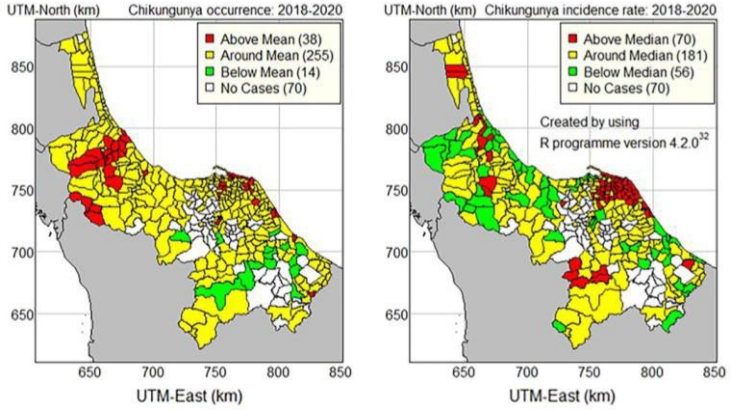
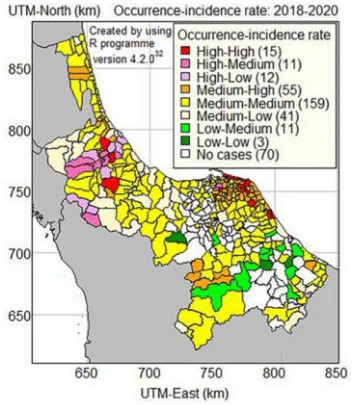
Statistical Modeling Research::

Identifying High-Risk Areas of Chikungunya Disease Outbreak in Southernmost Thailand

Compared year	Thematic maps of CHIKF occurrence and incidence rate	Occurrence-incidence rate map of CHIKF
2008-2010		
2018-2020		

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC10624817/

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Statistical Modeling Research::

Identifying High-Risk Areas of Chikungunya Disease Outbreak in Southernmost Thailand

Conclusions

- **CHIKF outbreaks occurred in 2008-2010 and 2018-2020**, following a 10-year cycle.
- **The occurrence of CHIKF decreased after 50 years of age and older in the first outbreak** and 10 years earlier in the second outbreak, at age 40 and older. *Except for those aged 70 and older in the first outbreak and females in the second outbreak, the incidence of CHIKF outbreaks increased with age.*
- Occurrence and incidence for the regions affected by the first outbreak tended to disappear or have fewer problems in the second outbreak, **suggesting acquired immunity**.
- Identifying issue regions **can be approached through a combination of occurrence and incidence rate.**

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC10624817/

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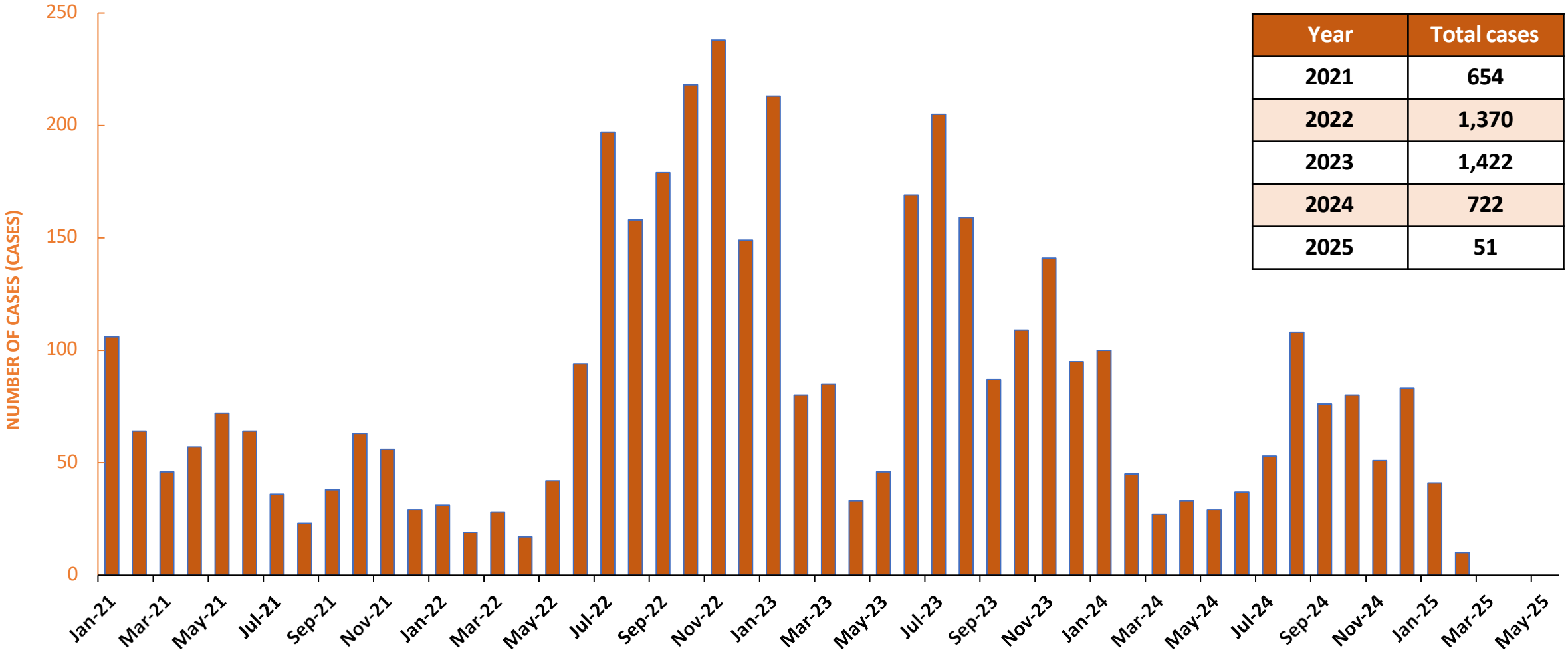
Department of Disease Control

Reported cases of *Chikungunya Situation* in Thailand

By month (2021-2025)



Year	Total cases
2021	654
2022	1,370
2023	1,422
2024	722
2025	51

Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

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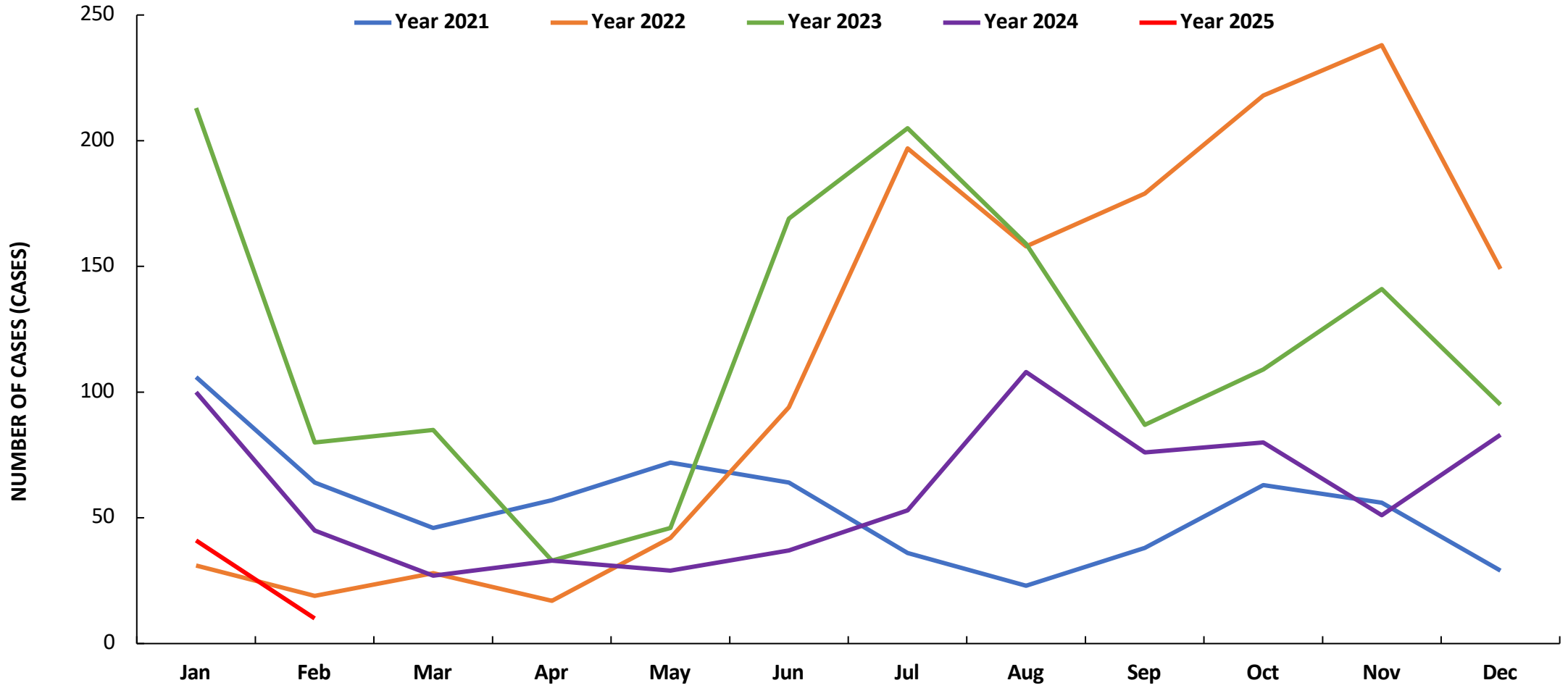
MINISTRY OF PUBLIC HEALTH

Reported cases of *Chikungunya Situation* in Thailand

By month (2021-2025)



Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

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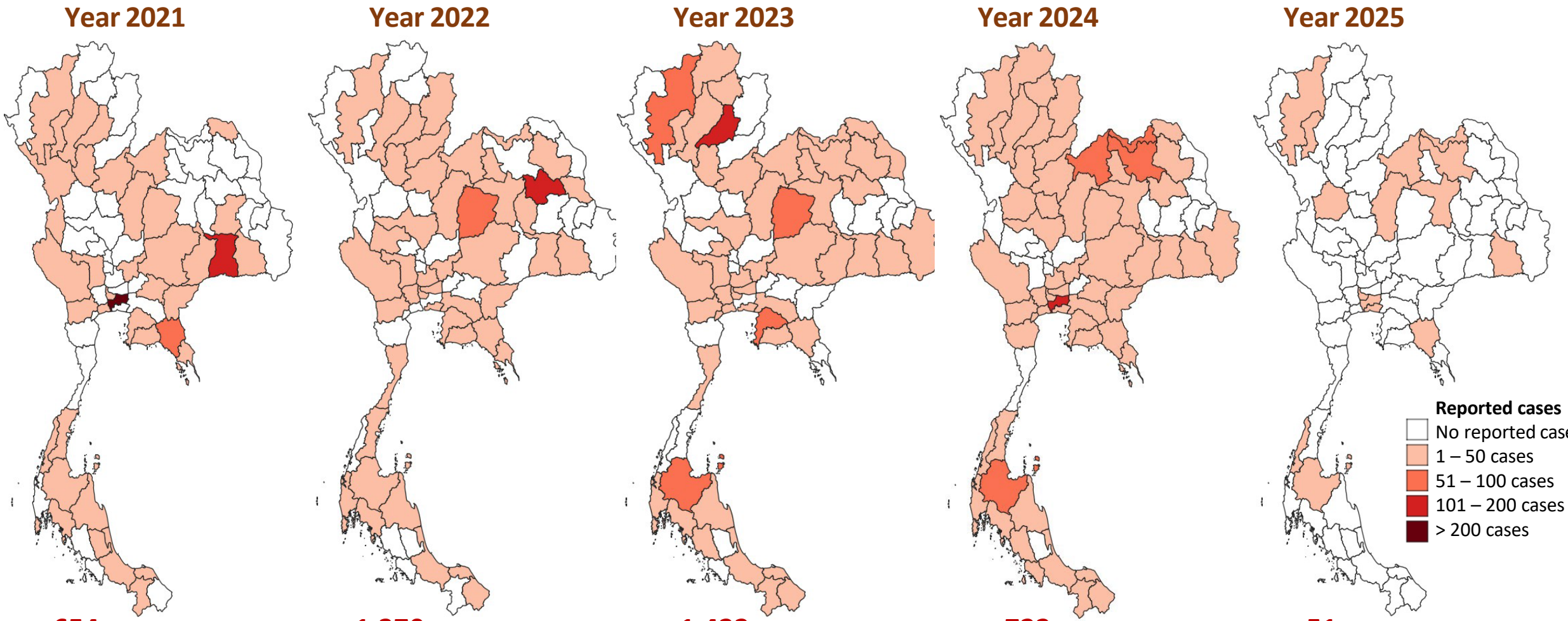
Department of Disease Control

Reported cases of *Chikungunya Situation* in Thailand

By province (2021-2025)



Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

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MINISTRY OF PUBLIC HEALTH

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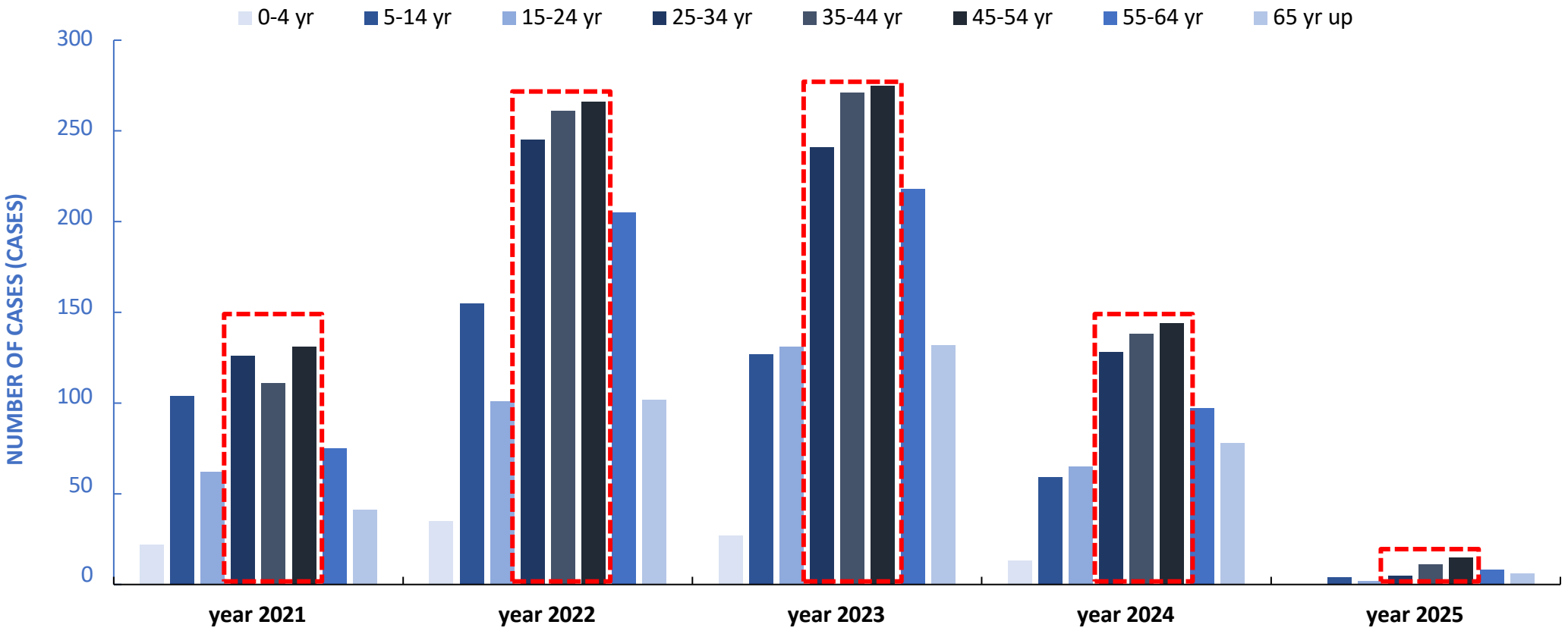
Reported cases of *Chikungunya Situation* in Thailand

By age group (2021-2025)



It has been found that...

Most people who have suffered from Chikungunya each year have been **between 25 to 54 years old.**

Source: Digital Disease Surveillance (DDS), the Division of Epidemiology, the Department of Disease Control, Thailand as of March 5, 2025

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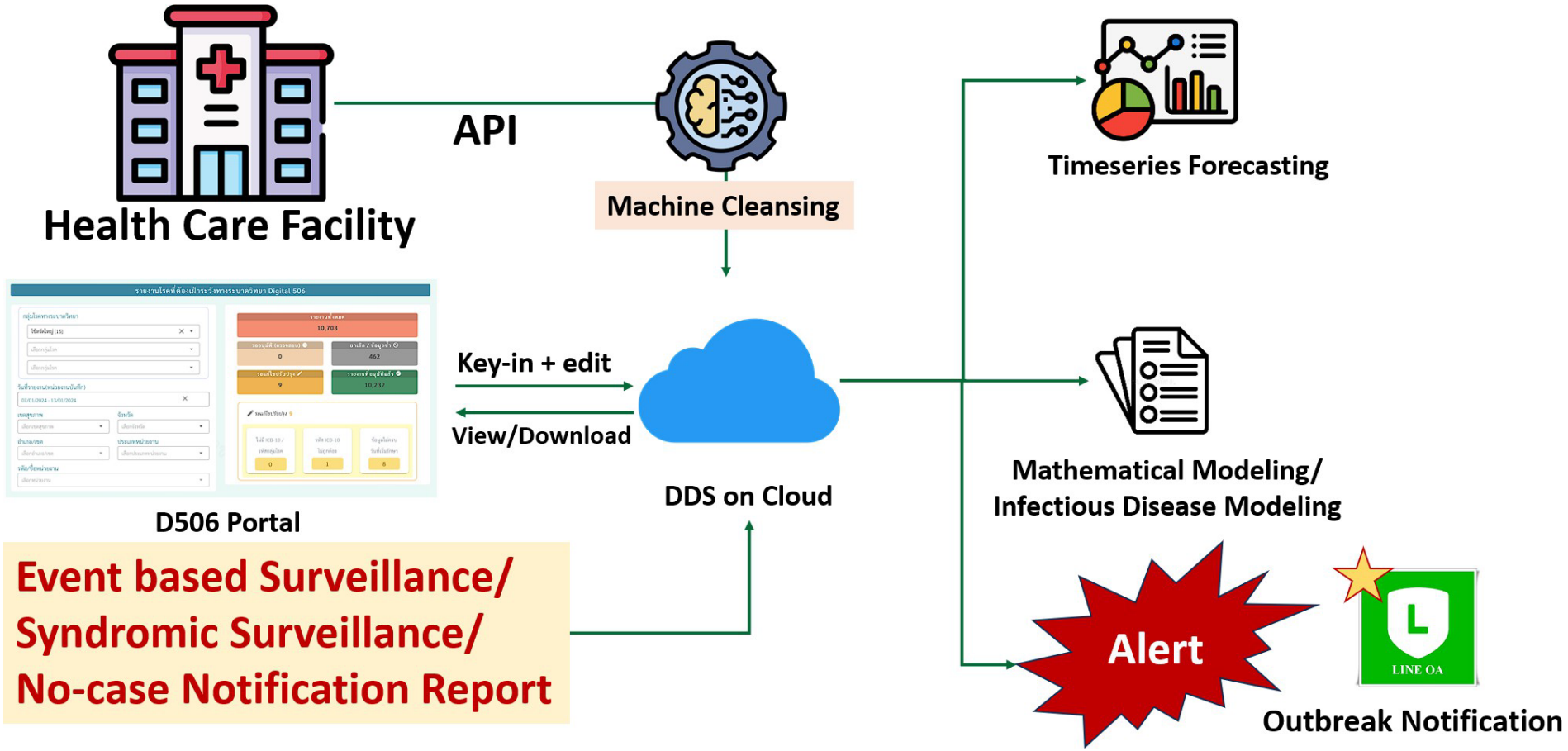
The Application of AI in a DDS *for Predicting Outbreaks* through Mathematical or Infectious Disease Modeling



Source: the Division of Epidemiology, the Department of Disease Control, Ministry of Public Health, Thailand

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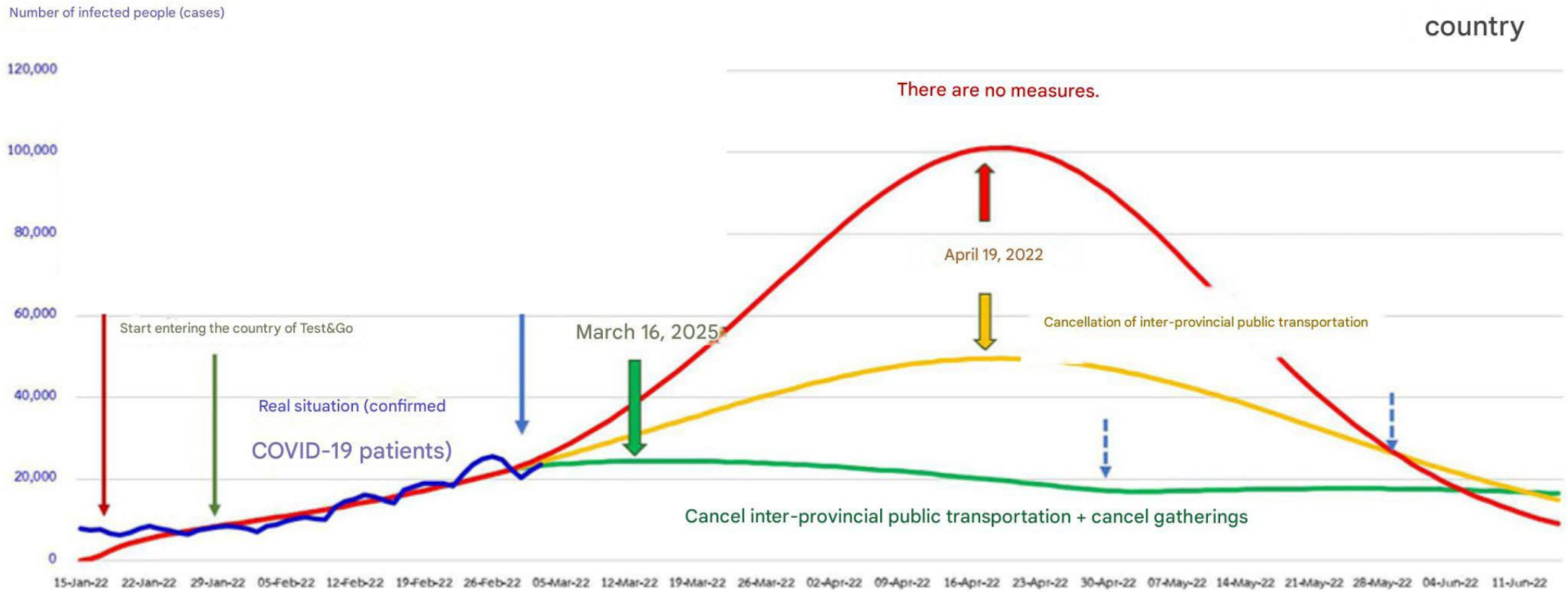
MINISTRY OF PUBLIC HEALTH

The Usefulness of the Model *for Policy Decision-Making*

Example: COVID-19 Modeling



Source: the Division of Epidemiology, the Department of Disease Control, Ministry of Public Health, Thailand

Disease and Outbreak Predcition Platform

Influenza ในประเทศไทย

ข้อมูล ณ วันที่ February 2, 2025
กองระบาดวิทยา กรมควบคุมโรค
ddsdoe.ddc.moph.go.th/dds
02 590 3899

Year	Week	Province	Disease	Timeframe		Time Series Component.		
(All)	(All)	(All)	ไข้หวัดใหญ่	รายเดือน	รายสัปดาห์	Trend	Season	TrendและSeason

จำนวนผู้ป่วย จากข้อมูลปี 2563 ถึง 2568

สะสมถึงปัจจุบัน **1,438,543** ราย

ค่าพยากรณ์ **1,328,494** ราย

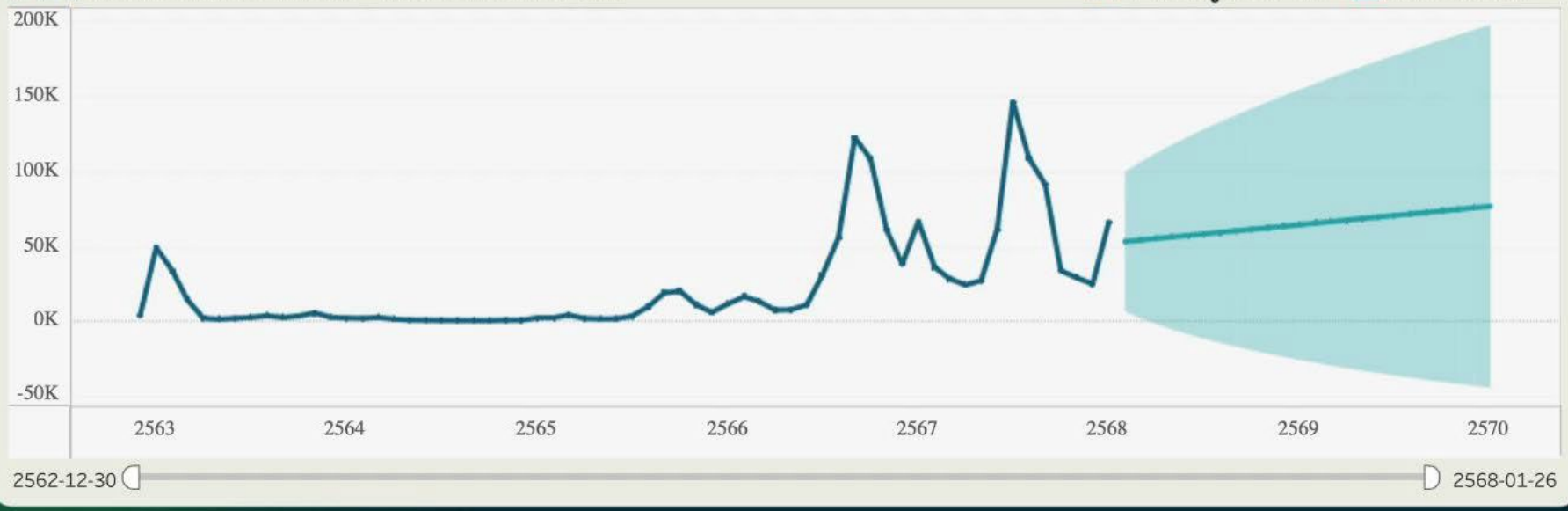
ผลการพยากรณ์

- ช่วงเวลา: กุมภาพันธ์ 2568 – มกราคม 2570 (2ปี)
- จำนวนผู้ป่วยเฉลี่ยในเดือนกุมภาพันธ์ 2568 : 43,695 ราย (±45,924)
- การเปลี่ยนแปลงจากจุดเริ่มต้น : เพิ่มขึ้น 16,995 ราย
- ผลกระทบตามฤดูกาล : ไม่มีรูปแบบตามฤดูกาล
- แนวโน้ม: แนวโน้ม 100%, ฤดูกาล 0%

การประเมินคุณภาพ

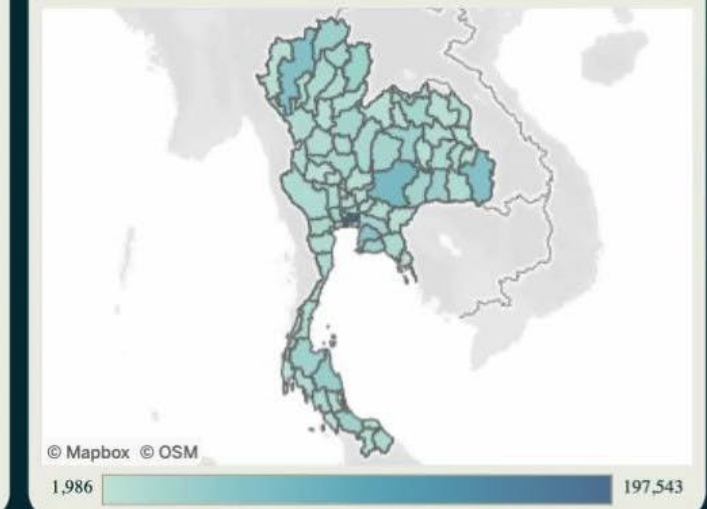
- โมเดลที่ใช้: Exponential Smoothing (Additive Level & Trend)
- ค่าความคลาดเคลื่อน: RMSE:23,431, MAE:13,336, MAPE:162.3%, MASE:1.16, AIC:1,258
- พารามิเตอร์: Alpha:0.500, Beta:0.000, Gamma:0.000
- คุณภาพการพยากรณ์โดยรวม: ประสิทธิภาพอยู่ในระดับต่ำ

กราฟการพยากรณ์ ที่ค่าความเชื่อมั่น 95%

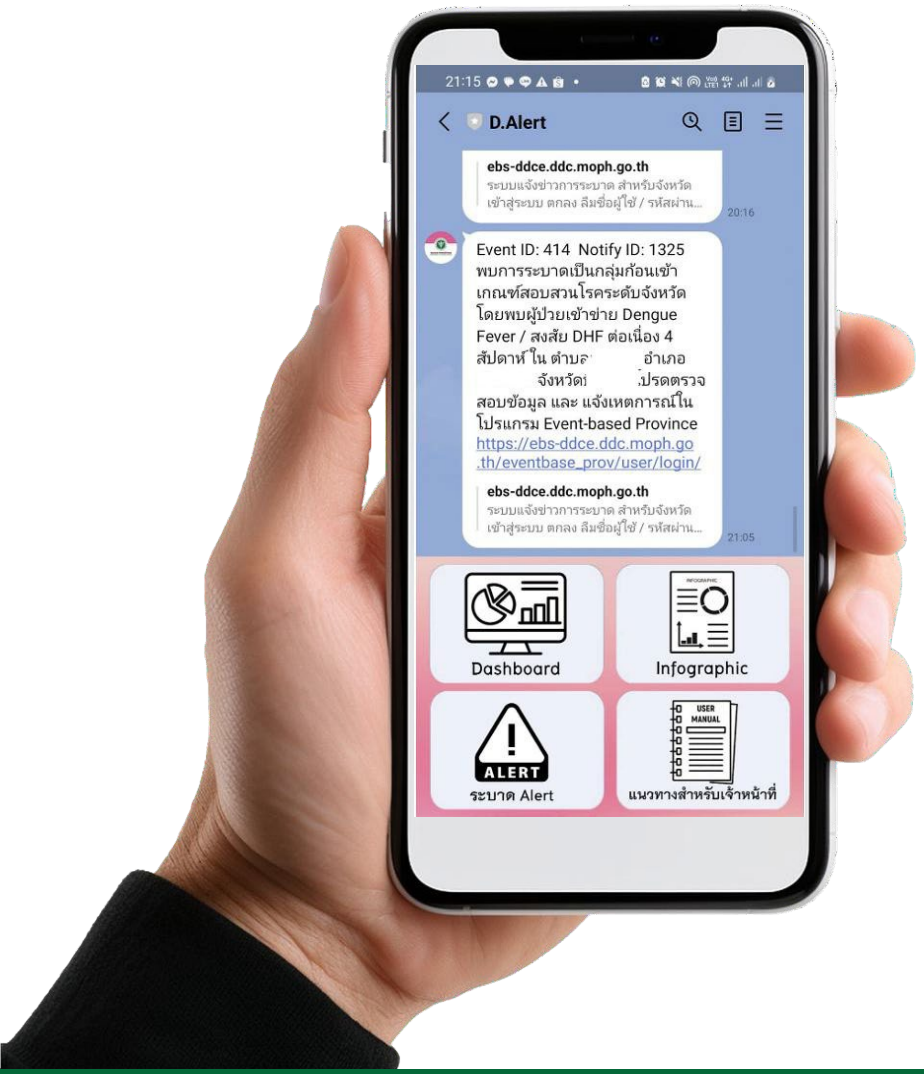


แผนที่ค่าความคลาดเคลื่อนการพยากรณ์เชิงพื้นที่

เปรียบเทียบการกระจายตัวของโรคและค่าพยากรณ์



The Application of AI in a DDS *for Case/Cluster Notification* through Mathematical or Infectious Disease Modeling



Example: Dengue Fever

Message Translation: *"Event ID: 414 Notify ID: 1325*

Found a cluster of outbreaks that meet the criteria for a provincial outbreak verification. There were patients with ***Dengue Fever / suspected Dengue Hemorrhagic Fever*** *for 4 consecutive weeks in Subdistrict xxx, District xxx, Province xxx. Please check information and report events in the Event-based Province program*

https://ebs-ddce.ddc.moph.go.th/eventbase_prov/user/login/"

Source: the Division of Epidemiology, the Department of Disease Control, Ministry of Public Health, Thailand

THANK YOU!

กรมควบคุมโรค

Department of Disease Control

Update on vaccine development

Purpose: Developers will present a brief description of the vaccine developments and the planned or ongoing regulatory processes.

Phase IV post-approval studies in the context of vaccines approved through accelerated procedures: Case study, CHIKUNGUNYA vaccines

Sao Paolo, March 19-20, 2025

Dr. Shailesh Dewasthaly

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Agenda

- Introduction & Regulatory status update
- Pediatric studies update
- Post Marketing studies

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Valneva's Augmented Commercial and R&D Portfolio

Further extending a unique, differentiated portfolio

1 ETEC indication in some markets only; 2 Controlled human infection model

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IXCHIQ License Status

Country	Date of Approval *(18 & above indication)*	Variations / Supplement *(12 & above indication)*
USA	9-Nov-2023	Under review
Canada	20-Jun-2024	Under review
European Union	28-Jun-2024	Received positive CHMP opinion
UK	04-Feb-2025	To be submitted
Brazil	Under review	To be submitted

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Regulatory Status - Brazil

Live-attenuated, single-dose chikungunya virus vaccine

Done → **Planned/Expected**

Vaccine full manufactured by Valneva

- Submission: December/2023
- First LOQ: February/2024
- Second LOQ: December/2024
- *Approval: ?
- *CMED Price: Apr-Jun/2025

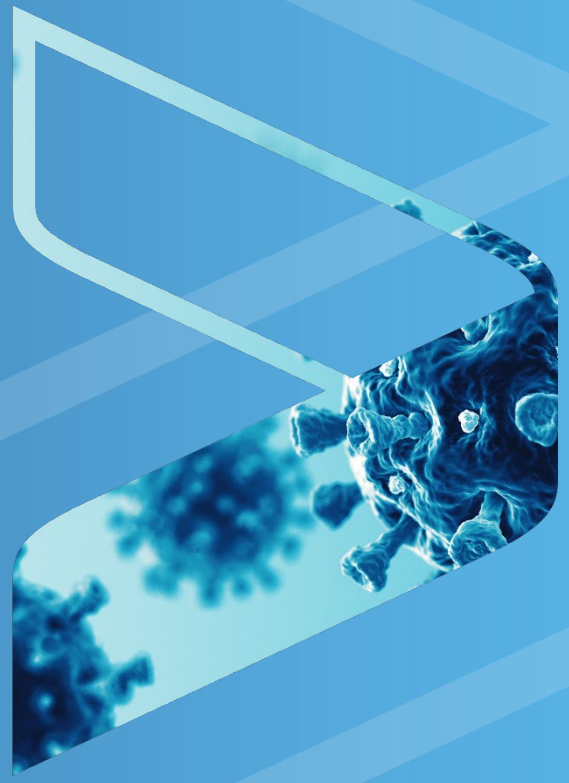
Vaccine form&fill at Butantan

- Submission (CMC): December/2024
- *MA Approval: May/2025
- *CMED Price: Jun-Aug/2025
- *CONITEC: Sept - Dec/2025

- *Assuming MA Approval in May/2025*
- *CMED and CONITEC starts after MA approval*

VLA1553-221

A Randomized, Observer-blinded, Dose Response Phase 2 Study To Assess The Safety And Immunogenicity Of Two Different Dose Levels Of A Live-attenuated Chikungunya Virus Vaccine (VLA1553) In Healthy Children Aged 1 To 11 Years.



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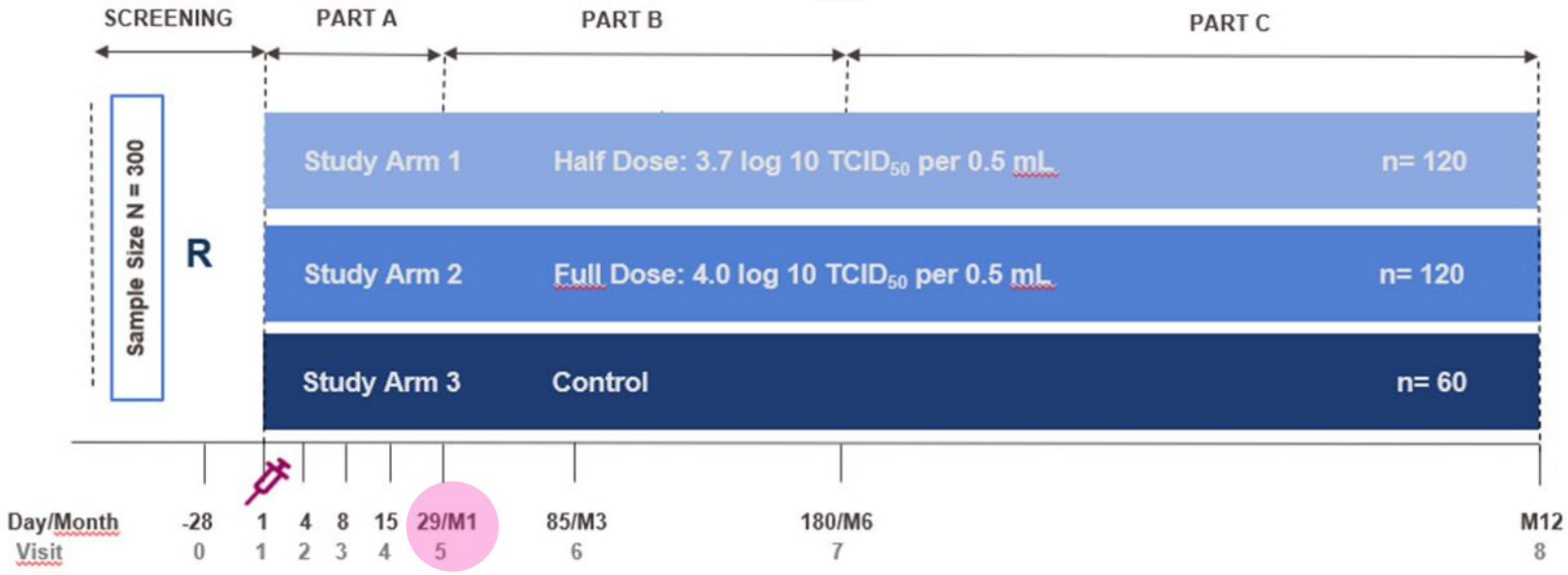
VLA1553-221 Trial Design

A Randomized, Observer-blinded, Dose Response Phase 2 Study To Assess The Safety And Immunogenicity Of Two Different Dose Levels Of A Live-attenuated Chikungunya Virus Vaccine (VLA1553) In Healthy Children Aged 1 To 11 Years.



Within each treatment arm participants were stratified into **three age strata:**

Stratum A: 7 to 11 years
Stratum B: 3 to 6 years
Stratum C: 1 to 2 years

Study Design

- At least 300 healthy children, randomized 2:2:1 to VLA1553 or Control
- Health CHIKV naive and pre-exposed children aged 1-11 years;
- Dominican Republic, Honduras (endemic countries)

Administration

- Intramuscular vaccination (on Day 1)
- Full dose or Half Dose
- Control: Nimenrix (meningococcal tetravalent vaccine)

Duration: 12 months post-vaccination

VLA1553-221 – Day 29 Part A Analysis

Results for Dose Selection:

- Safety and tolerability (reactogenicity) profile was highly similar for both dose levels (Full and Half Dose) of VLA1553 when administered as a single dose to children aged 1 to 11 years.

- Robust immune response of the Full Dose (compared to Half Dose) in all age groups in children aged 1 to 11 years, supports to move forward with this dose to pediatric Phase 3.

- The comparability of the VLA1553 Full and Half Dose in post-vaccination safety and tolerability, along with the more pronounced immune response of the Full Dose observed for all age groups tested in children, confirm the suitability of the Full Dose for this population and led to the selection of the **Full Dose** to proceed to pivotal Phase 3 evaluation in participants aged 1 to 11 years.

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VLA1553-221 – Day 29 Part A Analysis

Overall Conclusions :

- Trial VLA1553-221 met its primary endpoint demonstrating that VLA1553 was well tolerated across all age groups in children aged 1-11 years regardless of the dose (Half Dose vs Full Dose), or previous CHIKV infection and to a similar extent as Nimenrix (active control).
- Overall, the safety profile is consistent with the profile observed in Valneva's pivotal phase 3 trials in adults and adolescents. [1][2][3] [4]
- An independent DSMB rigorously monitored safety data throughout the trial and confirmed the absence of any safety concerns.
- Valneva's vaccine VLA1553 in children aged 1-11 years was highly immunogenic in both dose groups (Full and Half Dose).
- A Full Dose (licensed IXCHIQ® formulation and presentation) of VLA1553 (compared to Half Dose) exhibited a more robust immune response in children aged 1-11 years by providing protective antibody titers already at Day 15 and Day 29 post-vaccination, confirming the excellent immunogenicity previously observed in adults and adolescents. [1][2][3][5][6]
- The comparability of the VLA1553 Full and Half Dose in post-vaccination safety and tolerability, along with the more pronounced immune response of the Full Dose observed for all age groups tested in children, confirm the suitability of the Full Dose for this population and led to the selection of the **Full Dose** to proceed to pivotal Phase 3 evaluation in participants aged 1 to 11 years.

[1] Valneva Press release: *Valneva Announces Positive Phase 3 Pivotal Results for its Single-Shot Chikungunya Vaccine Candidate*
[2] Valneva Press release: *Valneva Successfully Completes Pivotal Phase 3 Trial of Single-Shot Chikungunya Vaccine Candidate*
[3] Lancet Paper: *https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00641-4/fulltext*
[4] Valneva Press release: *Valneva Reports Positive Initial Phase 3 Safety Data in Adolescents for its Single-Shot Chikungunya Vaccine Candidate*
[5] Valneva Press release: *Valneva Reports Positive Pivotal Phase 3 Immunogenicity Data in Adolescents for its Single-Shot Chikungunya Vaccine Candidate*
[6] Lancet Paper: *https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(24)00458-4/abstract*

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VLA1553-321
Part C Analysis
SAFETY and IMMUNOGENICITY

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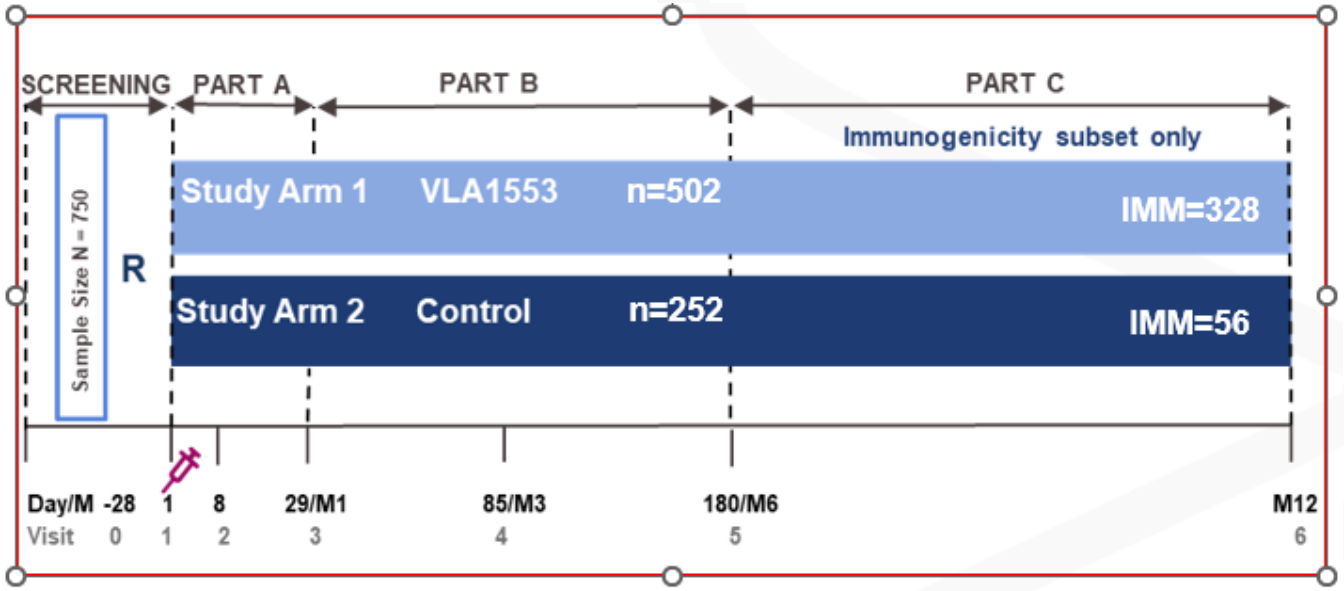
VLA1553-321

A multicenter, randomized, controlled, double-blinded pivotal study to evaluate safety and immunogenicity of a live-attenuated chikungunya virus vaccine candidate (VLA1553) in adolescents aged 12 years to <18 years



The presented **Part C Analysis** provides the full set of safety and immunogenicity data of VLA1553-321 up to study end.

It is important to note that **only the immunogenicity subset** (comprising 384 participants) was **followed up to Month 12 for immunogenicity, SAEs and AESI.**

Update since Month 6 data presentation:

- **Complete trial analyses** (SAEs, AESI and Immunogenicity data up to Month 12),
- **Comparison of age groups**
- **Comparison of serostatus strata**
- **final Chikungunya cases ascertainment**
- Analysis of **CHIK-Like-Adverse-Reactions** according to FDA/EMA

VLA1553-321 Part C Analysis
Overall Summary and Conclusions

- Trial VLA1553-321 met its primary endpoint, with **98.8%** (248/251) of participants developing protective levels of antibodies 28 days after a single vaccination with VLA1553.
  - Seroresponse, defined as μPRNT$_{50}$ antibody titer ≥150 agreed with the FDA as surrogate of protection to support accelerated approval, was reached in 98.8% (95% CI: 96.5, 99.8; 248 of 251 baseline seronegative participants from the per-protocol population)
  - Seroresponse rate significantly exceeded FDA's requirement for licensure of >70%

- The immunogenicity results observed up to one year after vaccination with VLA1553 indicate sustained high seroresponse rates with **99.2%** (239 of 241 participants) on Day 85, **98.8%** (242 of 254 participants) on Day 180 and notable **98.3%** (232 of 236 participants) on Day 365, in adolescents seronegative at baseline.

- Geometric mean antibody titers (GMTs) in baseline seronegative participants consistently surpassed the seroresponse threshold (μPRNT$_{50}$ antibody titer ≥150 agreed with FDA as surrogate of protection) and remained stable from Month 6 up to Month 12.

- A single-dose vaccination with VLA1553 induced a robust immune response in adolescents aged 12 to <18 years up to Month 12, affirming the outstanding immunogenicity previously observed in adults. [1][2][3]

- Month 12 data confirm that VLA1553 administered as a single-dose was generally safe and well tolerated in adolescents aged 12 to <18 years, irrespective of previous CHIKV infections. [4][5]

- An independent DSMB continuously evaluated safety data during the trial and had not identified any safety concerns.

[1] Valneva Press release: Valneva Announces Positive Phase 3 Pivotal Results for its Single-Shot Chikungunya Vaccine Candidate

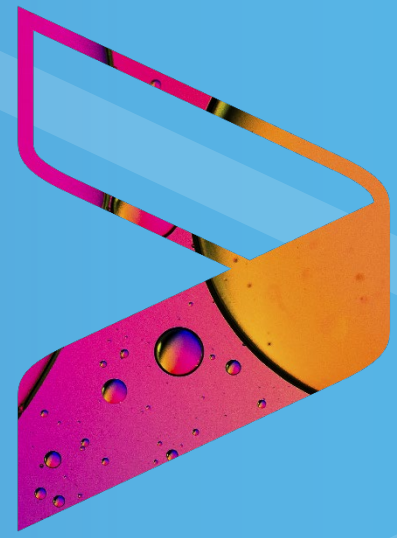
[2] Valneva Press release: Valneva Successfully Completes Pivotal Phase 3 Trial of Single-Shot Chikungunya Vaccine Candidate

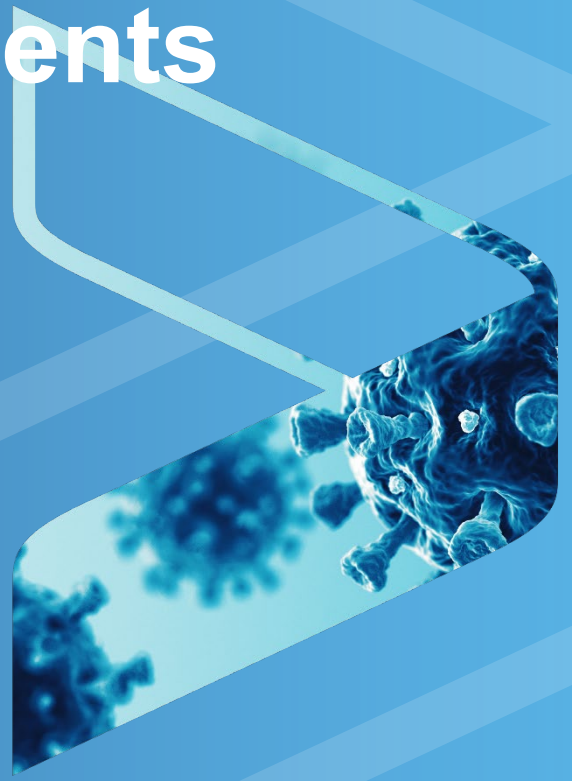
[3] Lancet Paper: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00641-4/fulltext

[4] Valneva Press release: Valneva Reports Positive Initial Phase 3 Safety Data in Adolescents for its Single-Shot Chikungunya Vaccine Candidate

[5] Valneva Press release: Valneva Reports Positive Pivotal Phase 3 Immunogenicity Data in Adolescents for its Single-Shot Chikungunya Vaccine Candidate

Ixchiq – post-marketing commitments & requirements





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Post-authorization Studies (1/2)

	VLA1553-401 Post-authorization safety study (PASS)	VLA1553-402 Post-authorization effectiveness study (PAES)	VLA1553-403 Observational study	VLA1553-404 Pragmatic, interventional trial
Effectiveness		✓		✓
Safety	✓		✓	✓
Estimated start	**Q2 2025**	**Q4 2025** *After Brazilian licensure* *During/ After Pilot Vaccination Program*	**Q4 2025** *After Brazilian licensure* *During Pilot Vaccination Program*	**Q4 2025**
Location	**US**	**Brazil**	**Brazil**	**Endemic countries**
Details	• **Design:** prospective, observational, descriptive cohort study • ~5,000 adults aged 18 years and above planning to travel to endemic areas • **Primary objective:** estimate the incidence of medically-attended AESIs, including Chikungunya-like adverse reactions including vaccine-associated arthralgia, and cardiac events, leukopenia (especially neutropenia), after a single vaccination with IXCHIQ®/VLA1553 vaccine candidate – including infection with CHIKV	• **Design:** test negative, case-control, observational study • ~1,200 cases in (adolescents and) adults in endemic areas • **Primary objective:** estimate the VE of VLA1553 in the prevention of symptomatic laboratory-confirmed CHIKV cases after a single vaccination with IXCHIQ® • Prerequisite: Pilot Vaccination Program in selected Brazilian municipalities • **Separate Serosurvey Protocol (VLA1553-407):** study to be done *before* pilot vaccination program; includes vaccinees and non-vaccinees; supports estimation of VE	• **Design:** prospective active surveillance study • **Primary objective:** assess the incidence of pregnancy and infant outcomes in women of childbearing potential vaccinated with IXCHIQ® up to 30 days before their last menstrual period or at any point during pregnancy • Follow-up until end of pregnancy and, if applicable, 12 weeks after delivery • Target to include ~90 pregnant women • The study protocol includes a comparator group of routinely vaccinated pregnant women not exposed to VLA1553.	• **Design:** pragmatic randomized (1:1), blinded, controlled trial in ~20,000 adults and adolescents • **Primary objective**: assess the effectiveness of VLA1553 in preventing acute symptomatic virologically-confirmed CHIKV infection with onset ≥14 days after vaccination • **Secondary safety objectives:** evaluate the effectiveness of VLA1553 in preventing chronic chikungunya symptoms at 12 weeks after an acute symptomatic virologically positive CHIKV infection with onset ≥14 days after vaccination; evaluate the safety of VLA1553

AESI = adverse event of special interest; CHIKV = chikungunya virus; SAE = serious adverse event.

Post-authorization Studies (2/2)

	VLA1553-405 US pregnancy registry	VLA1553-406 Prospective Safety Cohort Study
Effectiveness		
Safety	✓	✓
Estimated start	**Q1 2025**	**Q4 2025** *After Brazilian licensure* *During Pilot Vaccination Program*
Location	**US**	**Brazil**
Details	• **Design:** Non-interventional, web-based pregnancy registry in women in the US who receive IXCHIQ from 30 days before their last menstrual period (LMP) up to 12-weeks post expected delivery date. • **Primary objective**: to monitor and evaluate the outcomes of pregnancy and infant health up to 12 weeks among women in the United States who received IXCHIQ® while pregnant, utilizing a web-based pregnancy registry.	• **Design:** prospective safety cohort study • ~5,000 (adolescents and) adults participating in the pilot vaccination program • **Primary objective:** estimate the incidence rates of a predefined set of adverse events (AEs) which constitute safety concerns according to the VLA1553 Risk Management Plan (RMP) following the administration of the live-attenuated VLA1553 vaccine in individuals that are targeted in the pilot vaccination program, within a defined risk window following vaccination • Participants will be followed for 6 months post-vaccination

AESI = adverse event of special interest; CHIKV = chikungunya virus; SAE = serious adverse event.

Thank you

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Update on vaccine development Bavarian Nordic

CEPI/ANVISA, Sao Paulo, Brazil 19-20 March 2025

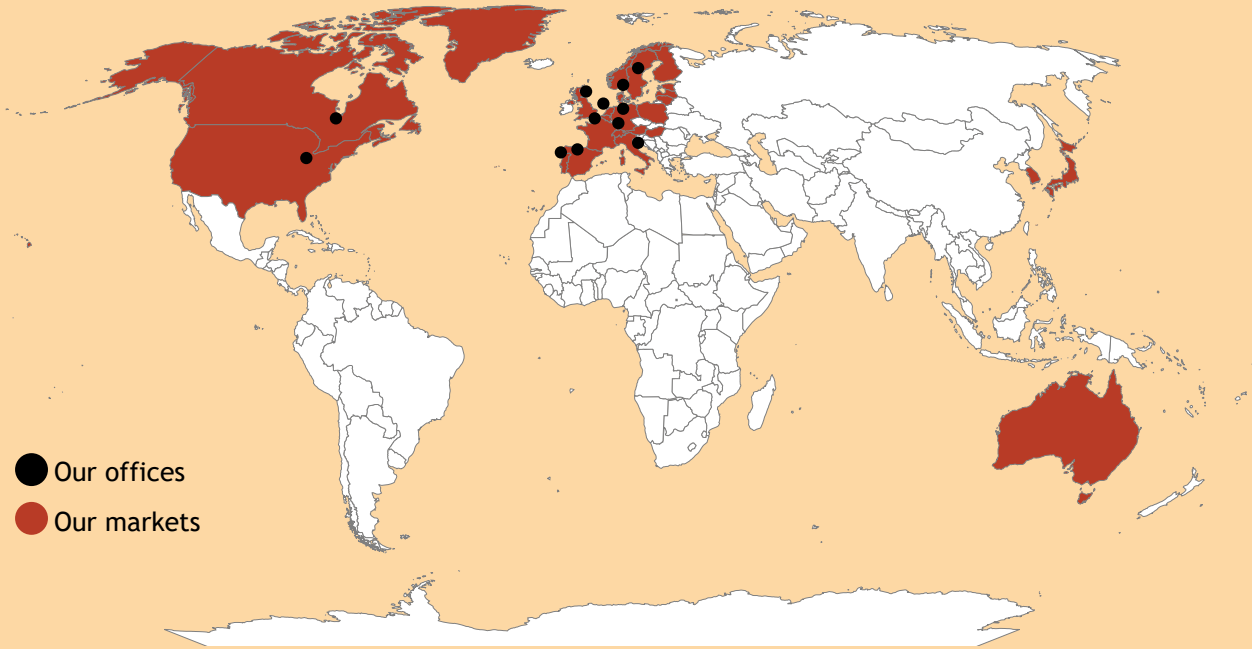
Ben Simone, MD FFPH, Global Medical Affairs Director, Travel Vaccines, Bavarian Nordic

Bavarian Nordic **at a glance**

*A preferred partner to governments on vaccines for **public preparedness***

*Leading commercialized portfolio of **travel vaccines***

Since 2020, we have successfully transformed Bavarian Nordic into one of the largest pure-play vaccine companies with global presence and more than 1,600 employees.



USA
Clinical Development, Regulatory and commercial functions

Switzerland
Manufacturing, global marketing and sales functions

Germany
Research and development, sales and commercial functions

Denmark
Headquarters
Manufacturing

Other countries
Commercial and administrative functions: Belgium, Canada, France, Italy, Portugal, Spain, Sweden and United Kingdom

BAVARIAN NORDIC

Products and pipeline

Commercial products

Public preparedness

Developed and commercialized our proprietary **MVA platform:**

- Mpox
- Smallpox
- JYNNEOS™

Travel Health

Created a leading travel health business via acquisitions and in-licensing:

- Chikungunya — Vimkunya®
- Rabies — Rabipur® RabAvert®
- Tick-borne encephalitis (TBE) — Encepur®
- Cholera — Vaxchora®
- Typhoid — Vivotif®

Pipeline

	Phase 1	*Phase 2*	*Phase 3*
MVA-BN WEV *Equine encephalitis*	✓	2025	
Epstein-Barr virus	2026		
Lyme disease	2026		

VIMKUNYA®

Chikungunya vaccine (recombinant, absorbed)

- Virus-like particle (VLP) technology
- Pre-filled syringe
- 3-year shelf life

- **Indication:** prevention of disease caused by chikungunya virus in individuals 12 years of age and older

- **Contraindications:** hypersensitivity to the vaccine components

- *PRIME Designation (2019), Fast Track (2018) and Breakthrough Therapy Designation (2020) granted*
- *Rolling BLA submission and EU MAA submission (June 2024); both reviewed under accelerated pathways*

14 February
FDA Approval, United States

28 February
EC Approval, European Union

19 February
MHRA submission, United Kingdom

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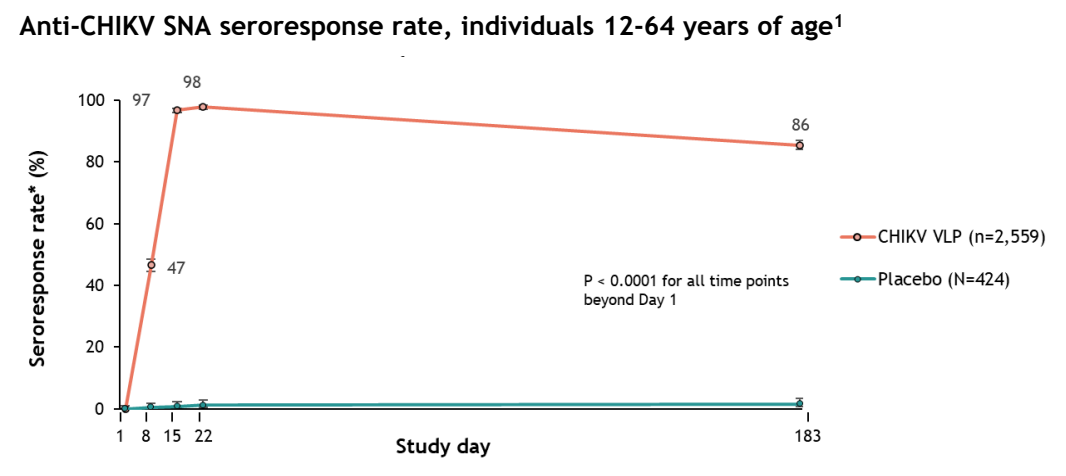
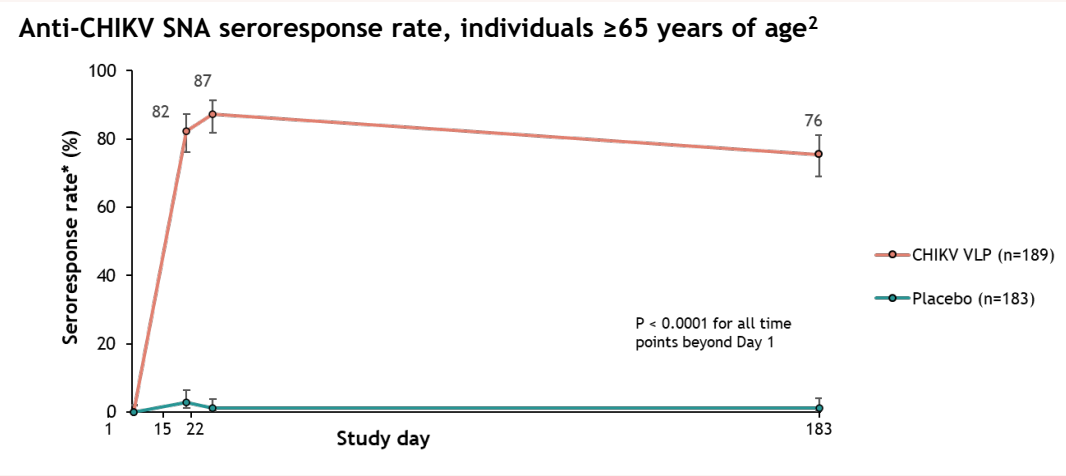
FDA: U.S. Food and Drug Administration; EC: European Commission: MAA: Marketing Authorisation Application
VIMKUNYA, US Prescribing Information. Available at: Link. Accessed March 2025

Rapid induction of robust seroresponse

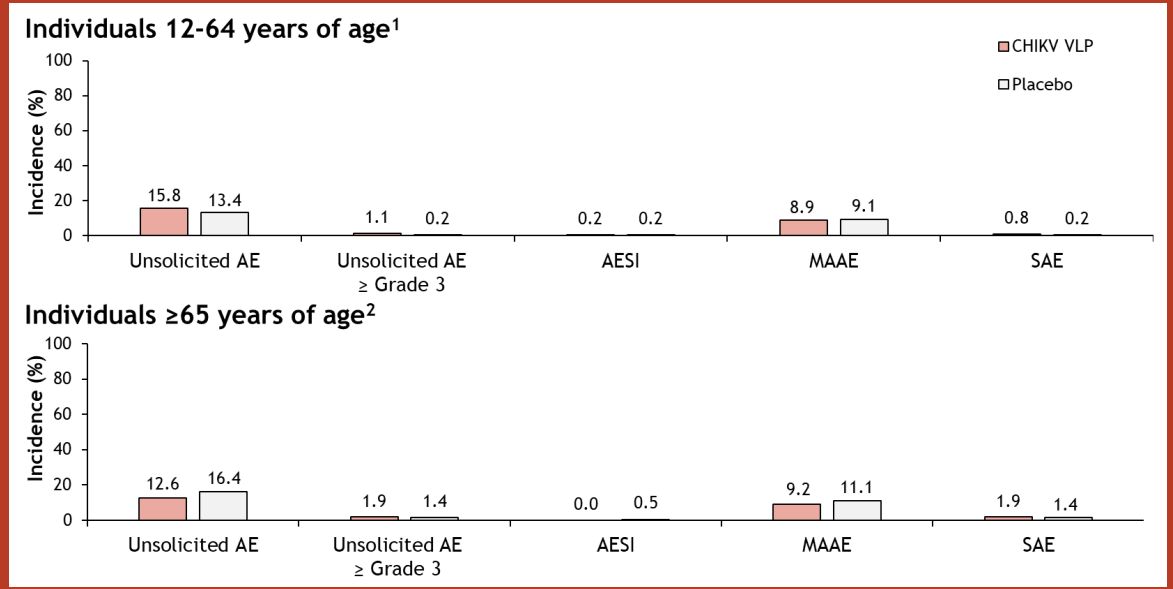




BAVARIAN NORDIC

1. Richardson *et al*. doi: https://doi.org/10.1101/2024.10.11.24315179. 2. Tindale et al. doi: https://doi.org/10.1101/2024.10.10.24315205

Mostly mild/moderate Adverse Events



- Incidence of Adverse Events of Special Interest (AESI) and Medically-Attended Adverse Events (MAAEs) did not differ between the vaccine group and the placebo group
- No treatment-related Serious Adverse Events, including medically-attended arthralgia

AESI = adverse event of special interest: defined as new onset or worsening arthralgia that was medically attended; AE = adverse event; MAAE = medically attended adverse event; SAE = serious adverse event

How did we get here?

Nov 2019 ➔ VRBPAC meeting on CHIKV:

- CHIKV recognised as a global threat
- Epidemiology of CHIKV acknowledged as unpredictable and sporadic
- Due to challenge of conducting efficacy study, agreement to surrogate marker of protection for initial licensure
- Passive transfer study in non-human primates to establish threshold based on protection against infection (not disease)

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Advisory Commission on Childhood Vaccines (ACCV) - Food and Drug Administration Update December 5, 2019. Available at: Link. Accessed March 2025.

Key considerations

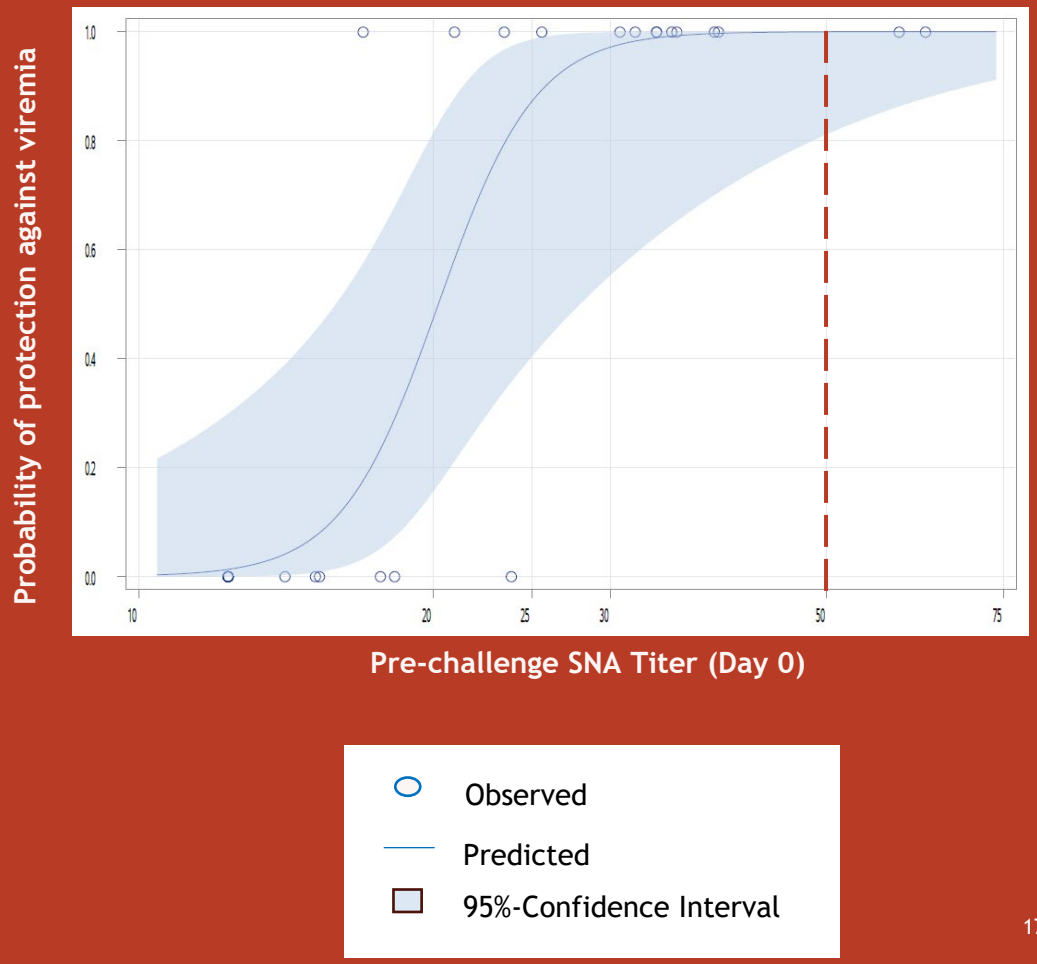
The most complex items to discuss were:

- Definition of anti-CHIKV serum neutralising antibodies threshold
- Post-authorisation commitments

Serum Neutralising Antibody threshold for Phase 3 endpoints

Serum passive transfer and challenge study in NHP

- NHPs received pooled sera from human participants vaccinated with CHIKV VLP at various dilutions intravenously and were challenged with CHIKV 24 hours later
- Logistic regression model: SNA titre of 50 results in 99.97% [81-100] probability of protection against viremia
- FDA/EMA agreed on a more conservative SNA titre threshold of 100 to be an acceptable surrogate endpoint



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NHPs, nonhuman primate; SNA, serum neutralizing antibodies; CI, confidence interval
Data presented at ESCMID Global 2024 (publication in development)

Post-authorisation activities

Pregnancy Registry

Efficacy Study

Paediatric trials

Long-term Follow Up

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Pregnancy Registry

An Observational Prospective Study of the Safety of VIMKUNYA Vaccine Exposure in Pregnant Women and their Offspring

- Exposure to VIMKUNYA (received in a healthcare setting) up to 28 days before conception or during pregnancy
- Enrolment will be determined by passive reporting of pregnancy exposures to VIMKUNYA and consent to the collection of follow-up data
- No limit to participation during the 3-year enrolment period
- European Union and United States

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Efficacy Study

A Phase 3b Randomised, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of an Adjuvanted Chikungunya Virus Virus-like Particle (CHIKV VLP) Vaccine for the Prevention of Chikungunya Disease in Adolescents (12 to <18 Years) and Adults (≥18 Years)

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Objectives

Efficacy: To evaluate the vaccine efficacy of VIMKUNYA compared to placebo in the prevention of laboratory confirmed acute CHIKV disease in adolescents and adults (12 years of age and older)

Safety: To evaluate the safety of VIMKUNYA in adolescents and adults (12 years of age and older)

Efficacy Study

Up to 6,144 participants, randomised 1:1 to VIMKUNYA or placebo

6-month to 3-year follow up

Event-driven study enrolment, with a target of 64 acute CHIKV cases

Initiation planned from Q3 2025 dependent on the declaration of a CHIKV outbreak

Final study report tentatively planned for submission by August 2030

BAVARIAN NORDIC

Efficacy Study

Up to 6,144 participants, randomised 1:1 to VIMKUNYA or placebo

6-month to 3-year follow up

Event-driven study enrolment, with a target of 64 acute CHIKV cases

Initiation planned from Q3 2025 dependent on the declaration of a CHIKV outbreak

Final study report tentatively planned fur submission by August 2030

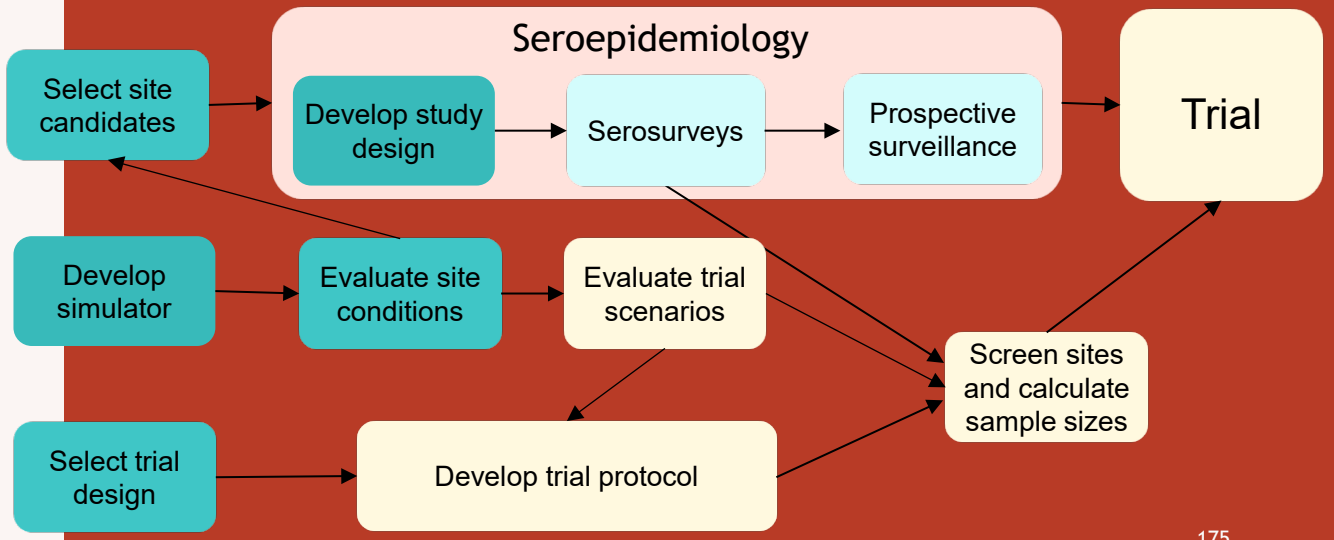
Multiple sites engagement across several countries

Sero-epidemiological studies, sites assessment and simulation modelling

Adoption of a design responsive to CHIKV surveillance and focus on communities with the highest transmission potential

Elucidate epidemiology
- Transmission criteria:
  - Identify ideal/likely scenarios
  - Assess historical data
  - Develop simulation model

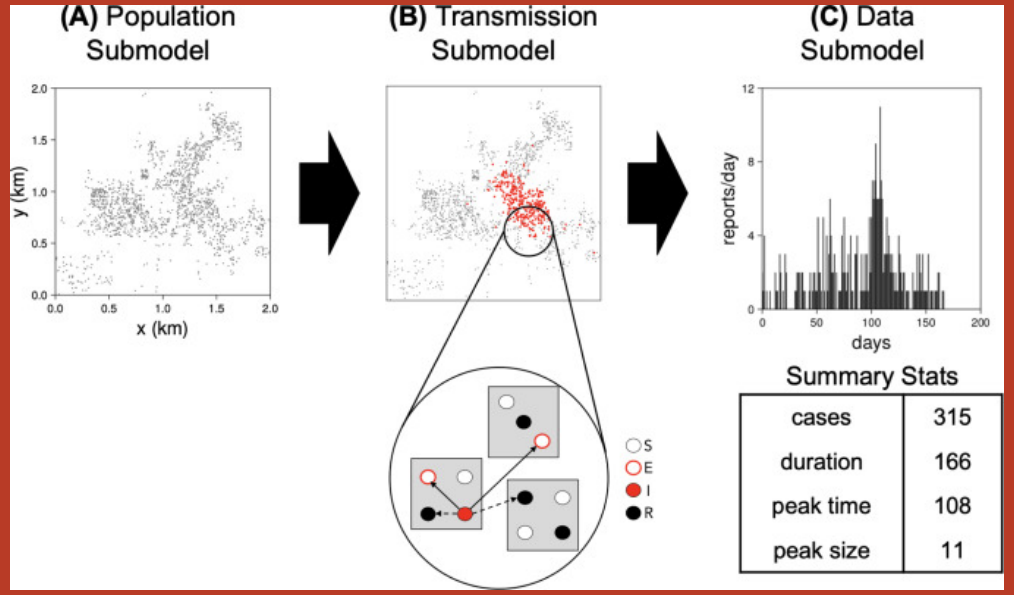
Assess feasibility
- Feasibility criteria
  - Identify constraints
  - Profile eligible sites
  - Rank sites



BAVARIAN NORDIC

Efficacy study: Simulation Modelling

- Challenges in comparing outbreak severity
- Bayesian inference method to enable direct comparison of outbreaks based on epidemiological parameters
- Application to CHIKV outbreaks in different countries, considering differences like pre-existing immunity and mosquito activity
- Model showed utility to understand outbreak dynamics



BAVARIAN NORDIC

Meyer AD, et al. Epidemics. 2023 Dec;45:100721. doi: 10.1016/j.epidem.2023.100721. Epub 2023 Oct 18. PMID: 37890441.

Paediatric studies

Study	Design
Phase 4 safety and immunogenicity Paediatric Study: 2 to less than 12 years of age Due to start 2025	Randomised, controlled, double-blind
Phase 4 safety and immunogenicity Paediatric Study: 0 to less than 2 years of age Due to start 2029	Randomised, controlled, double-blind

Long-term Follow Up

Study	Design
Phase 3 long-term follow up to evaluate immunogenicity through 5 years, with and without a booster dose 3 to 5 years postvaccination Started 2023	Rollover from BN's phase 3 studies, randomised, double-blind

BAVARIAN NORDIC

Additional developments…

- Co-administration studies under evaluation

… and strategic partnerships

- Agreement with Biological E. Limited (BE), India, to expand access to BN's CHIKV vaccine in LMICs
- Contract manufacturing agreement to enable future supply to endemic LMICs
- Technology transfer of the manufacturing process. Option to transfer the drug substance process at a later stage.

- **BN continues to explore opportunities to provide global access to its CHIKV vaccine through license- and distribution partners**

BAVARIAN NORDIC

LMICs: Low- and Middle-Income Countries

Bavarian Nordic Press Release, 25 February 2025. Available at: Link. Accessed March 2025

Lessons learned

- Preparation and submission of a global dossier and adequate planning for overlapping review period allowed to achieve parallel accelerated approval in major regions (US and EU)

- Engagement and dialogue with regulatory authorities was key from the early stages to define and roll out our clinical plan

- It is critical, especially for a small company, to rely on a harmonised approach to licensure and post-marketing requirements

BAVARIAN NORDIC

FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency

Thank you!

Manufacturing: Thörishaus, Switzerland

R&D: **Martinsried, Germany**

Immune correlates/surrogates and update on regulatory status of chikungunya vaccines

Purpose: Conducting Phase 3 randomized clinical trials with disease outcomes is challenging with some vaccines, either because trials require very large sample sizes, or because of the unpredictability of outbreaks. This session will discuss generalities of the use of correlates of protection in the assessment of vaccine efficacy, and NRAs where vaccine has been licensed will present a brief description of the use of correlates and other criteria and regulatory elements used for the licensing of the CHIKV vaccine.
Two panels will follow, one panel of NRAs will discuss if correlates of protection can be or are considered in their current regulations, and a second panel will discuss feasibility of licensing vaccine with current data.

Medicines & Healthcare products Regulatory Agency

Use of Correlate/Surrogate of Protection to Assess Vaccines

Dr Debbie Ferguson

19th March 2025

MHRA Science Campus

We are the Medicines and Healthcare products Regulatory Agency (MHRA). We are the regulator of medicines, medical devices and blood components for transfusion in the UK. We are responsible for making sure these products meet set standards for safety, quality and efficacy (effectiveness).

We are the UK's Official Medicines Control Laboratory	• Independent batch release of biological medicines (eg vaccines, blood products)
We are a World Health Organization international laboratory for biological standardisation	• Prepare, Curate and Distribute >90% of WHO International Standards (1° Calibrants; Int'l Unit) • Supply secondary standards and run controls • Research reagent repository
We perform applied research that assures the quality of biological medicines	• Quality = Both Potency and Safety

The MHRA science campus. Home of our **NIBSC standards** which are available globally to set the quality of biological medicines. We develop and produce over 90% of the WHO International Standards in use around the world. We also offer NIBSC contract and control testing services. nibsc.org

Established programme working with WHO to develop International Reference Materials for Escalating Diseases

- Serological reference materials prepared from pooled convalescent serum
- CEPI support facilitates programme that underpins vaccine evaluation esp multi-centre trials
- Molecular diagnostic reference materials harmonises measurement of innovative diagnostics
- Programme focus mirrored WHO Blueprint for Emerging Diseases including Disease(s) X

Parallel Programme to establish Correlates of Protection (funded by Innovate UK and CEPI)

- Using high containment facilities at Science Campus
- Collaborating with UK Health Security Agency and UK Defence Science and Technology Laboratories to access specialist facilities
- Focus on serological correlates in relationship with WHO International Standards
- Designed to inform and accelerate vaccine development and licensing

The Role of Correlates of Protection in Assessment of Vaccines

Why are these of value:

- Human challenge trials not possible where pathogens are lethal
- Human field trials not possible where outbreaks are infrequent and/or unpredictable
- Potential to provide a scientific framework for vaccine development, regulatory approval and ongoing post market assessments

Correlates of Protection

- Broadly defined as an immunological marker that can be predictive of protection against a defined disease endpoint

- What that endpoint is can vary depending upon disease and the level of ‘protection’ required
    - sterilising immunity with no pathogen infection or replication
    - infection with limited replication and prevention / reduction of associated detrimental pathology

- The correlate and endpoint can vary depending upon pathogen
    - knowledge of disease pathology and associated host immune responses or tissue specific damage

Correlates of Protection

- Confidence in a correlate is based on a depth of knowledge gained from studies including those looking at responses to natural infections, clinical trials, animal model passive transfer studies

- Animal model used must be able to assess the required clinical endpoint

- In vitro assays must be well calibrated and comparable
    - international standards included in assays and levels reported in international units/ml harmonise results and enable direct comparison

Correlates and Animal Models

- A suitable animal model replicates relevant human immune responses and disease pathology
- A suitable animal model allows the use of the same vaccine strategy and challenge virus
- The model enables identification of a correlate predictive of the desired clinical study end point
- A correlate should be usable across models/species including humans
    - correlate may differ between natural infection and vaccine induced responses
    - correlates do not need to identify or be related to the mechanism of protection
- Suitability of correlate must be traceable back to the desired end point

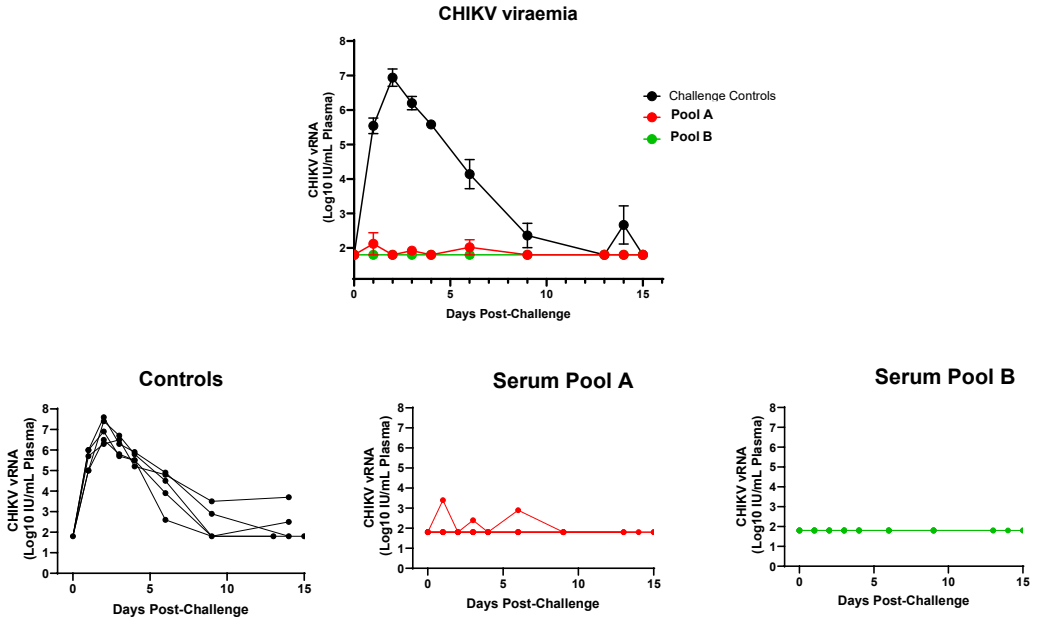
Comparing *in vitro* Assays

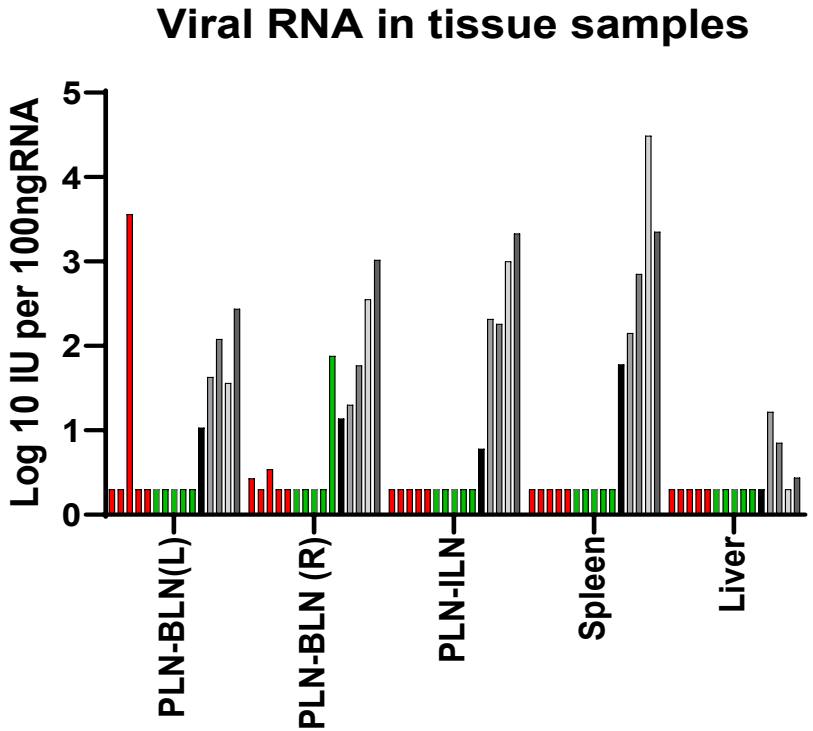
- *In vitro* assays must be well calibrated and comparable
- Results are generated from a range of different sources (groups, experiments, assay types/platforms, cell types, time frames……..) and reported in absolute values/titres
- International Standard Reference Reagents included in assays and levels reported in international units/ml enable direct comparison of results
- The International Standard Reference Reagent used must be appropriate for the assay – serological or nucleic acid based testing
- A standard reagent rather than a standard protocol

Selection of an Animal Model

Non-human Primates: Macaque model of Chikungunya

- Suitable animal model that replicates relevant human immune responses and disease pathology
    - Used to assess level of ‘protection’ required: Infected or not infected



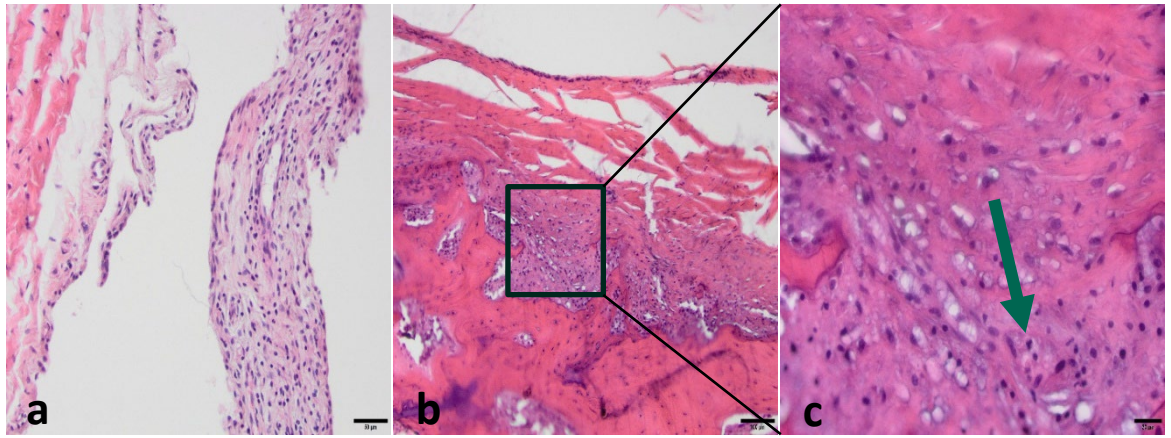


Detection of Chikungunya virus RNA by RT-qPCR in plasma or selected tissues of macaques that had been administered pooled serum A, pooled serum B or control (anti-Chikungunya virus negative) human serum 1 day prior to challenge with virus intra-dermally on day 0 (assay LOD has been established to be 50 IU/mL).

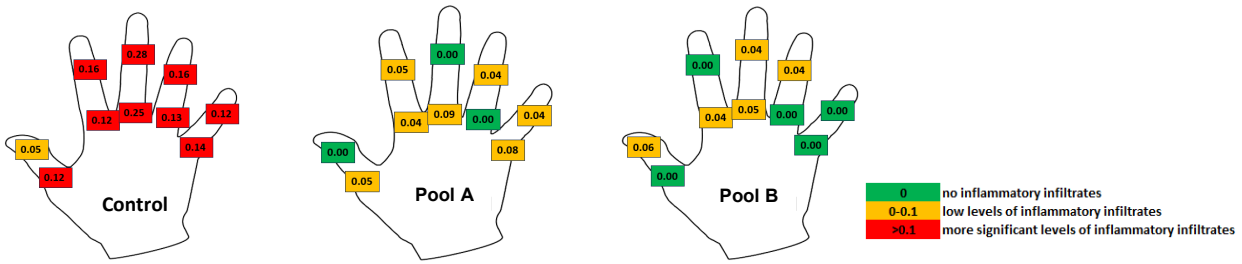
Selection of an Animal Model

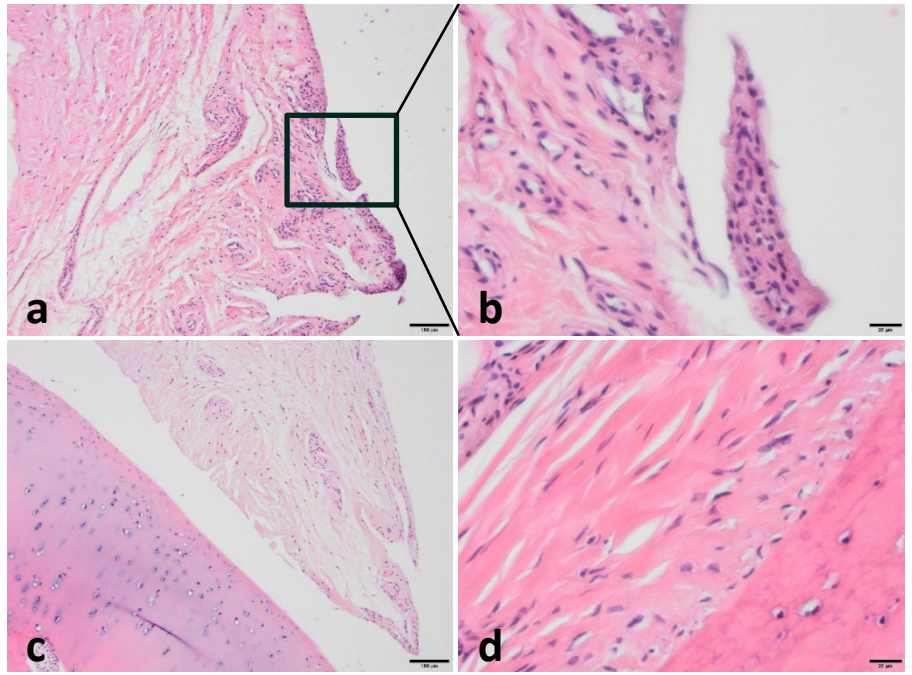
Non-human Primates: Macaque model of Chikungunya

- Suitable animal model that replicates relevant human immune responses and disease pathology
  - Used to assess level of ‘protection’ required: protection against disease pathology - polyarthralgia



Representative images (13-15dpc) of synovium (panel a) and periosteum (panel b and c) of macaques that had received control sera prior to challenge with CHIKV. Arrow indicates additional presence of neutrophils within the periosteum.



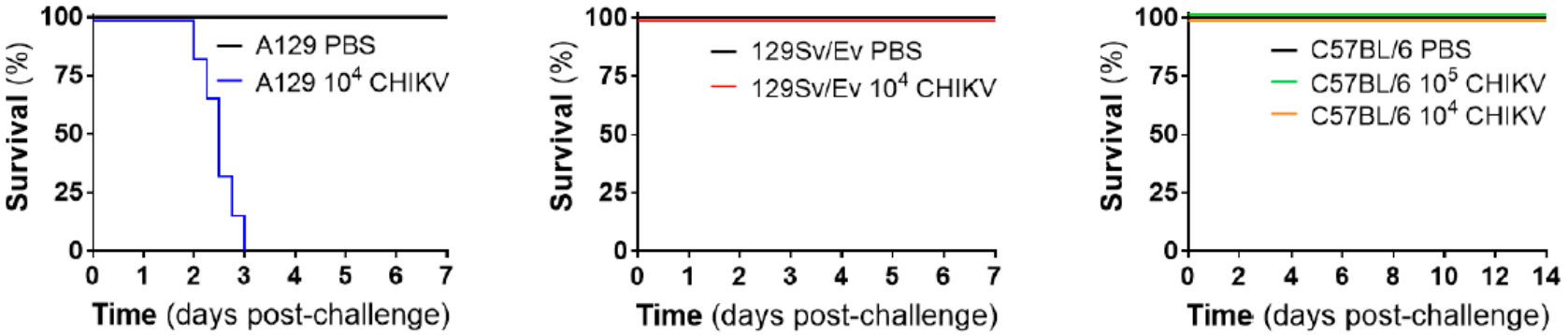


Representative images (13-15dpc) of synovium lymphocytic infiltrates in macaques that received sera pool A (panels a and b) or sera pool B (panel c normal synovium and panel d normal periosteum) prior to challenge with CHIKV

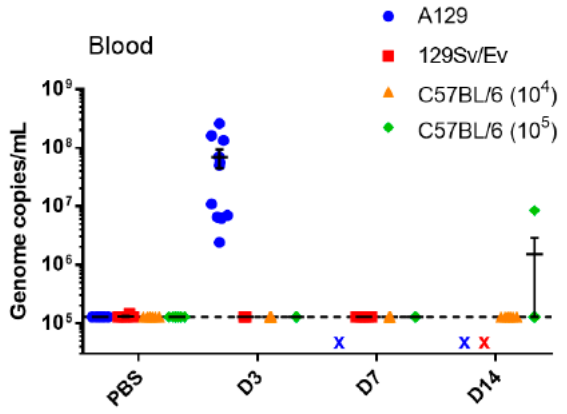
Selection of an Animal Model

Mouse Models: Comparison of Immunodeficient and Wild Type Mouse Strain Models of Chikungunya

- **Type-I Interferon Receptor deficient strain A129**
- Wild type 129Sv/Ev and C57BL/6



Clinical outcomes of mice challenged with CHIKV. Kaplan–Meier survival plots,



Viral RNA levels in blood and tissues from CHIKV-challenged mice measured by RT-PCR

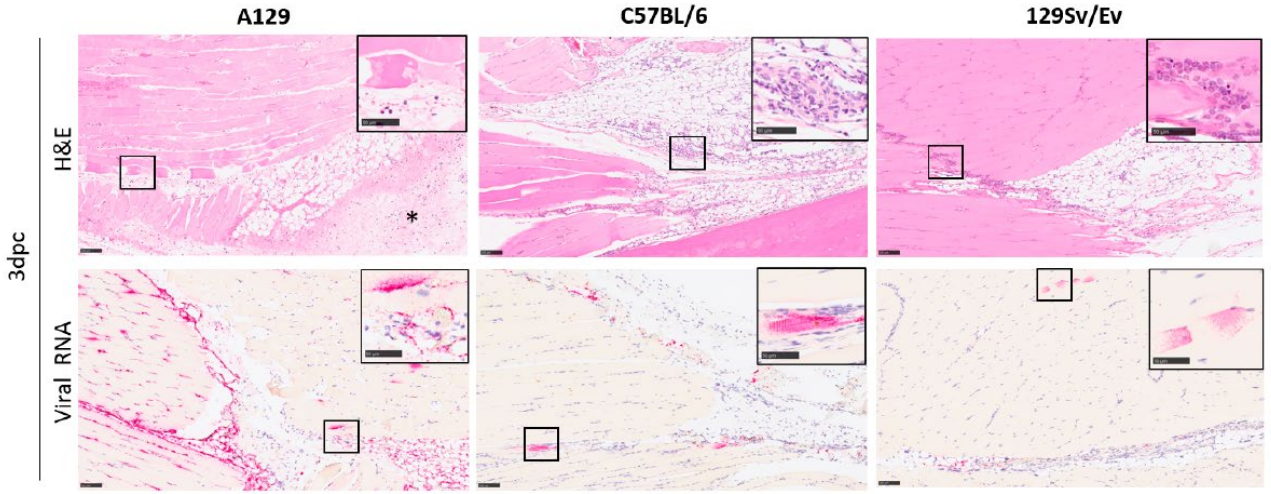
- The A129 mouse model, for which CHIKV produces a uniformly lethal disease, allows survival readouts as a relevant endpoint for a success criteria of infected or not infected.

Viruses **2024**, 16, 1534. https://doi.org/10.3390/v16101534

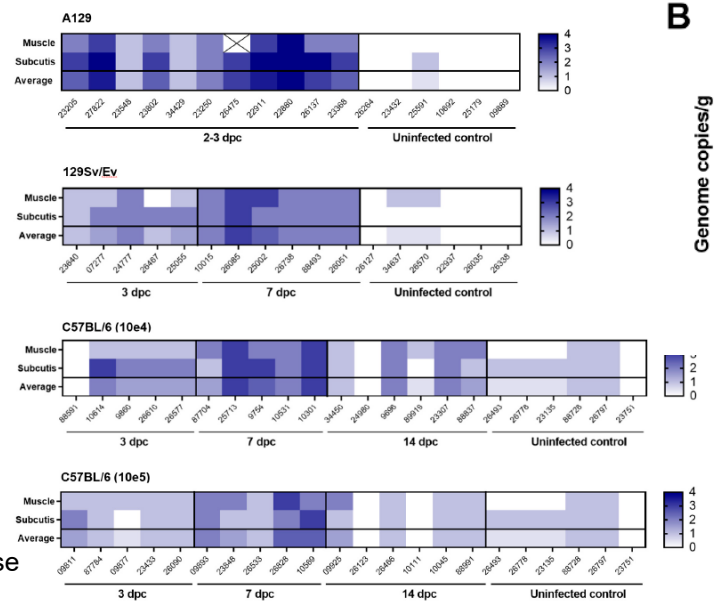
Selection of an Animal Model

Mouse Models: Comparison of Immunodeficient and Wild Type Mouse Strain Models of Chikungunya

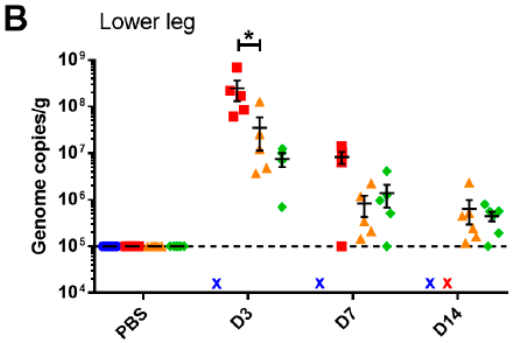
- Type-I Interferon Receptor deficient strain A129
- **Wild type 129Sv/Ev and C57BL/6**



Representative images illustrating the type and severity of microscopic changes, and the presence of viral RNA staining, in the skeletal muscle and subcutis of the hindlimb from A129, C57BL/6 and 129Sv/Ev mouse



Heatmap illustrating the severity of microscopic changes in muscle and subcutaneous tissue of hindlimbs in individual animals.



Viral RNA levels in blood and tissues from CHIKV-challenged mice measured by RT-PCR

Of the wild-type mice strains tested, in the absence of clinical disease, viral loads and histological changes could be appropriate readouts for changes to disease pathology where the pathology observed in the mouse model has been bridged back to polyarthralgia observed in the macaque model

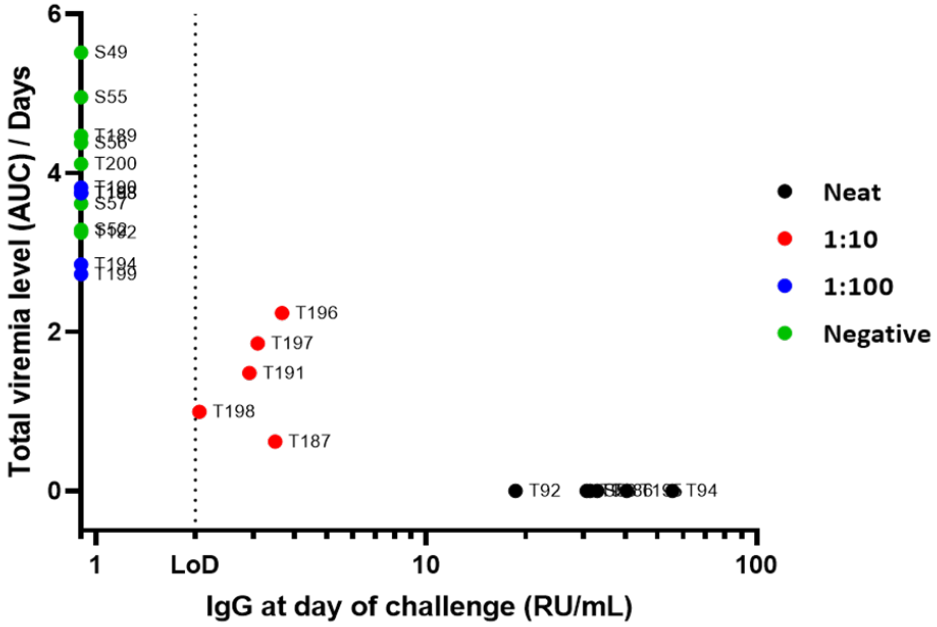
Viruses **2024**, 16, 1534. https://doi.org/10.3390/v16101534

Comparing *in vitro* Assays

Harmonising *in vitro* serological assays reported using different assays and to different criteria.

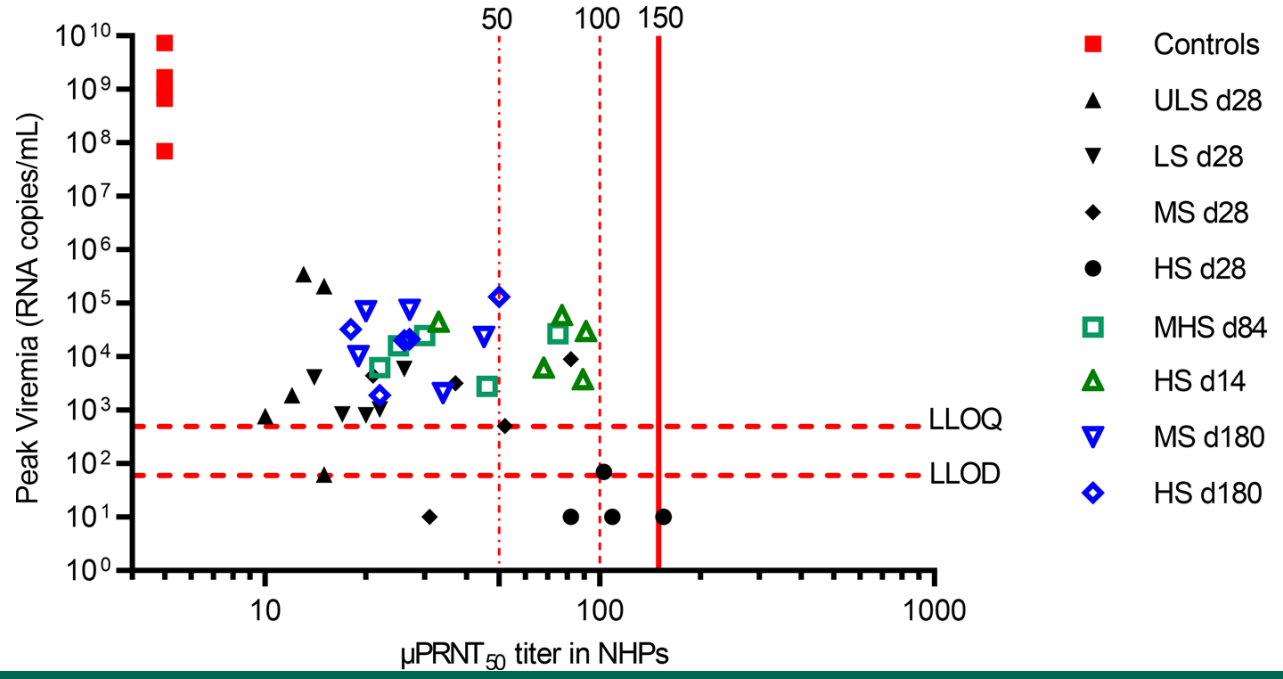
- Including international reference standards in the assays and reporting in International Units enables direct comparison across data

ELISA Antibody Binding Assay: colourmetric



Micro Virus Neutralisation Assay:

- 80% virus neutralisation via luciferase fluorescence
  - BioDrugs (2024) 38:727–742https://doi.org/10.1007/s40259-024-00677-y
- 50% virus neutralisation via plaque reduction counting
  - *JCI Insight.* 2022;7(14):e160173. https://doi.org/10.1172/jci.insight.160173.



Conclusions

- Correlates of protection can be a useful tool to support the development and licencing of vaccines.
  - development decisions – prioritising candidates
  - licensing where classic trials pathway is not possible
- Defining the clinical endpoint is essential to enable correct choice of model system
  - absolute immunity or disease pathology prevention/reduction
- An understanding of the disease pathology and host immune responses enables these choices to be made
  - basic research into natural infection and pathology
- Standardisation through the use of standard reference reagents will enable cross comparisons of vaccine technologies and immune responses
  - standard reference reagent not standard protocols
- Correlates must always be traceable back to the desired clinical output
  - bridging studies back through model species / *in vitro* assays

Thank you

Medicines & Healthcare products Regulatory Agency

MHRA - Diagnostics

- Sarah Kempster
- Adrian Jenkins
- Debbie Ferguson
- Claire Ham
- Jo Hall
- Neil Berry
- Neil Almond

MHRA - BSD

- Elaine Giles
- James Melton
- Paul Daniels

Paul-Ehrlich-Institut

- Sally A. Baylis

CEA

- Pierre Roques
- Roger LeGrand

IVI

- Raphaël Zellweger
- Sushant Sahastrabuddhe

IVI

- Raphaël Zellweger
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International Vaccine Institute

Innovate UK

BHARAT BIOTECH

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Produced by the Medicines and Healthcare products Regulatory Agency.

Copyright information

Health Canada and Chikungunya Vaccine Licensure

Richard Siggers, PhD

Vaccine Quality Division (VQD)
Biologics and Radiopharmaceutical
Drugs Directorate (BRDD)

CEPI – Sao Paulo, Brazil
March 19 – 20, 2025

DISCLAIMER

The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the official position of Health Canada.

DISCUSSION TOPICS

- Unique considerations for Chikungunya vaccine licensure
- Regulatory Pathways
- Animal models, surrogates/correlates, and clinical assays
- Foreign agencies
- Regulatory modernization
- Regulatory Elements for Chikungunya Vaccine Licensure

CHIKUNGUNYA VACCINE – Unique Considerations

No clinical efficacy study

Establishment of a clinically meaningful surrogate marker threshold

Safety considerations for live attenuated (replication-competent) vaccines

Clinical assays for immunogenicity – sero-response rates, neutralizing antibodies

- $PRNT_{80}$ (Phase 1; Yoon et al., 2015) and $\mu PRNT_{50}$ (Phase 3; Roques et al., 2022)

Passive transfer non-clinical model – NHP challenge after receiving human sera

Target population – traveller's vaccine in Canada

- Risk/benefit assessment considers epidemiology

REGULATORY PATHWAYS

New Drug Submission (NDS) Pathways

- Standard
- Extraordinary Use
- Public Health Emergency

STANDARD – NEW DRUG SUBMISSION (NDS)

FDR C.08.002

(2) A new drug submission ***shall contain sufficient information*** and material to enable the Minister to ***assess the safety and effectiveness*** of the new drug, including the following:

(a) a description of the new drug.. (b) (c) (d) (e) (f)…

(g) detailed reports of the tests made to ***establish the safety of the new drug*** for the purpose and under the conditions of use recommended;

(h) ***substantial evidence of the clinical effectiveness*** of the new drug for the purpose and under the conditions of use recommended;

Clinical effectiveness may be demonstrated by clinical efficacy trials, challenge studies, immunogenicity, animal models etc.

EXTRAORDINIARY USE (EUNDS)

FDR C.08.002.01

(1) A manufacturer of a new drug may file an extraordinary use new drug submission for the new drug if

(a) the new drug is intended for

(i) ***emergency use in situations where persons have been exposed*** to a chemical, biological, radiological or nuclear substance and action is required to treat, mitigate or prevent a life-threatening or other serious disease, disorder or abnormal physical state, or its symptoms, that results, or is likely to result, from that exposure, or

(ii) ***preventative use in persons who are at risk of exposure*** to a chemical, biological, radiological or nuclear substance that is potentially lethal or permanently disabling; and

(b) the requirements set out in paragraphs ***C.08.002(2)(g) and (h) cannot be met*** because

(i) exposing human volunteers to the substance referred to in paragraph (a) would be potentially lethal or permanently disabling, and

(ii) the circumstances in which exposure to the substance occurs are sporadic and infrequent.

VACCINE LICENSURE WITHOUT CLINICAL EFFICACY

STANDARD PATHWAY (NDS)

Pneumococcal

Meningococcal

Yellow fever

Japanese encephalitis

Chikungunya

EXTRAORDINARY USE (EUNDS)

Anthrax

Smallpox / M-pox

ANIMAL MODELS AND CLINICAL ASSAYS

Relevance (closeness) of model to humans

- Comparison of immunological response
- Disease progress and symptoms in model → similarity to humans
- Comparison of clinical endpoints

Experimental design

- representative of clinical program

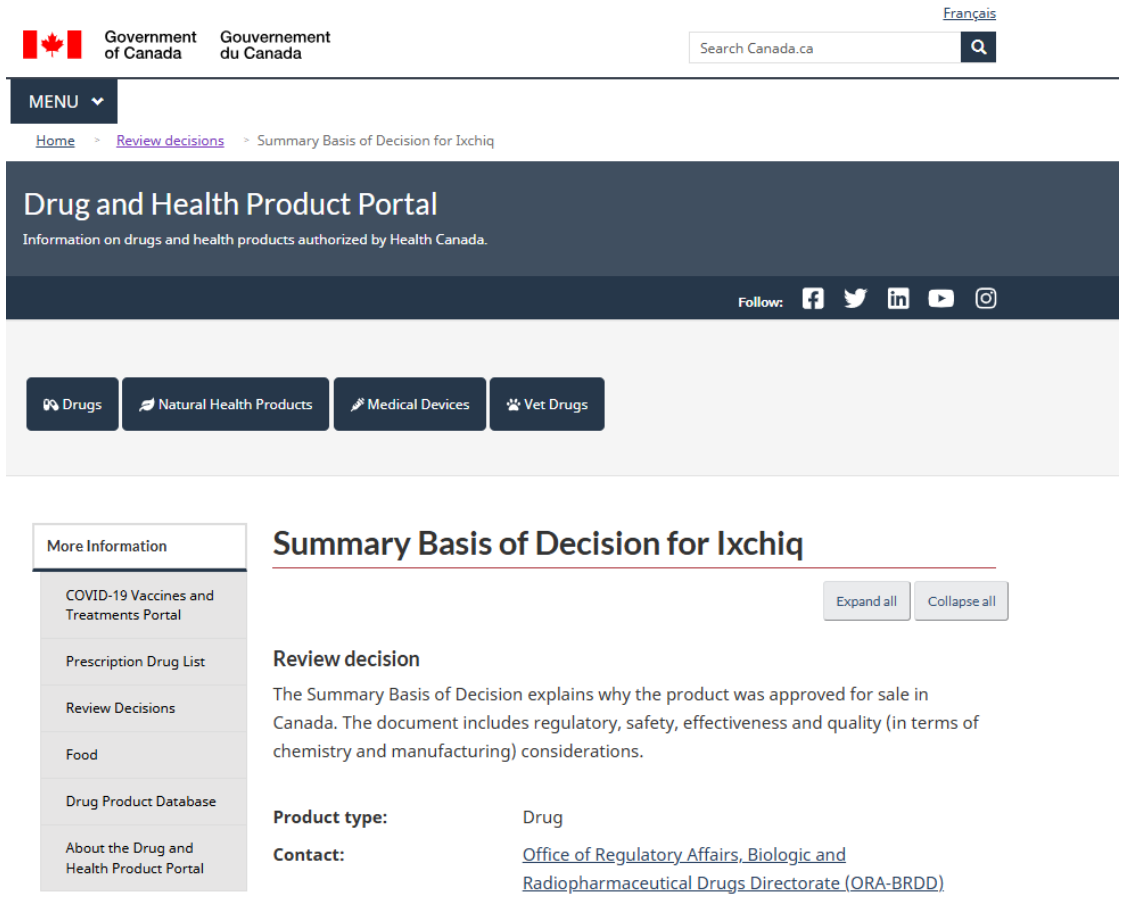
Relevance of analytical assay

- Immunological endpoints scientifically justified
- Quality of clinical assay

⚠ Animals are not humans – caution must be exercised when interpreting data. ⚠

SUMMARY BASIS OF DECISION (SBD)

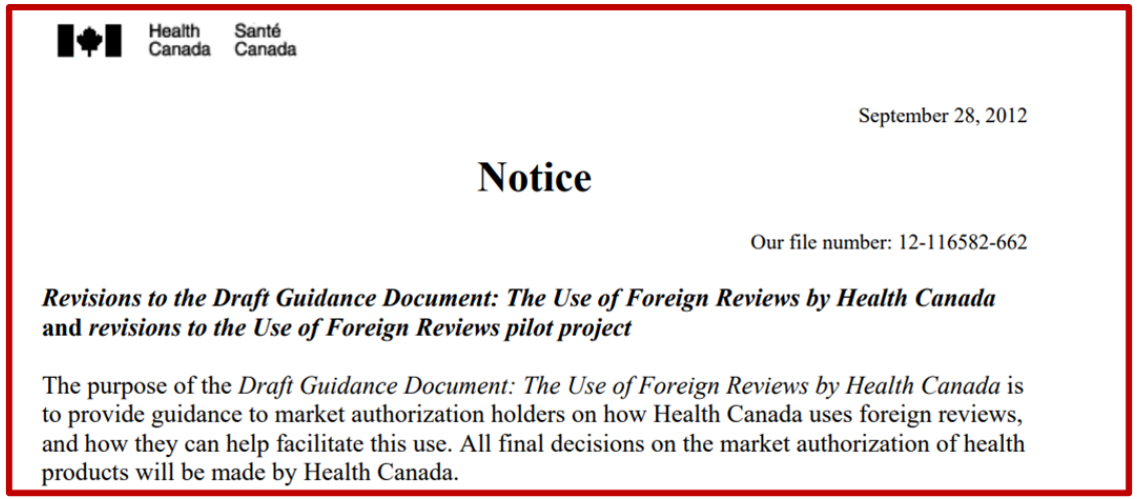
Safety, Effectiveness, Quality considerations



https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/summary-basis-decision.html

FOREIGN AGENCIES

The review of the quality and clinical components of the New Drug Submission (NDS) for Ixchiq was based on a critical assessment of the data package submitted to Health Canada. The reviews and correspondence completed by the United States Food and Drug Administration were used as added references, as per Method 3 described in the Draft Guidance Document: The Use of Foreign Reviews by Health Canada. The Canadian regulatory decision on the Ixchiq NDS was made independently based on the Canadian review.



Health Canada Santé Canada

September 28, 2012

Notice

Our file number: 12-116582-662

Revisions to the Draft Guidance Document: The Use of Foreign Reviews by Health Canada* and *revisions to the Use of Foreign Reviews pilot project

The purpose of the *Draft Guidance Document: The Use of Foreign Reviews by Health Canada* is to provide guidance to market authorization holders on how Health Canada uses foreign reviews, and how they can help facilitate this use. All final decisions on the market authorization of health products will be made by Health Canada.

https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/use-foreign-reviews/draft-use-foreign-reviews-health-canada-revisions-use-foreign-reviews-pilot-project.html

HEALTH CANADA REGULATORY MODERNIZATION

HEALTH CANADA REGULATORY MODERNIZATION

“Outcome-based” sets out the “what” or the desired end goal, instead of the “how” to achieve that end goal.

DIV 2, 8 updates in force 12-2024, and Div 4 coming into force 07-2025

https://www.canada.ca/en/health-canada/programs/consultation-proposed-agile-regulations-guidance-licensing-drugs-medical-devices/biologic-drugs-schedule-d-division-4-proposed-regulatory-amendments-notice.html

HEALTH CANADA REGULATORY MODERNIZATION

Old C.08.003.1

- C.08.003.1 In examining a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission, an abbreviated extraordinary use new drug submission or a supplement to any of those submissions, the Minister may examine any information or material filed with the Minister by any person pursuant to Division 5 or section C.08.002, C.08.002.01, C.08.002.1, C.08.003, C.08.005 or C.08.005.1 to establish the safety and effectiveness of the new drug for which the submission or supplement has been filed.

Revised C.08.003.1

- In examining a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission, an abbreviated extraordinary use new drug submission or a supplement to any of those submissions, the Minister may, for the purpose of assessing the safety and effectiveness of the new drug for which the submission or supplement has been filed, examine
- (a) information or material provided by any person under the Act;
- (b) information or material obtained from sites at which the new drug or any active ingredient, as defined in subsection C.01A.001(1), of the new drug is or is proposed to be fabricated or packaged/labelled within the meaning of those terms in that subsection, or tested; and
- (c) information or material obtained, directly or indirectly, from a foreign regulatory authority, as defined in subsection C.10.001(1).

Regulatory Elements for Chikungunya Vaccine Licensure

Submission Milestone	Date
Pre-submission meeting	2023-01-19
New Drug Submission filed	2023-05-29
Screening	
Screening Deficiency Notice issued	2023-07-06
Response to Screening Deficiency Notice filed	2023-08-02
Screening Acceptance Letter issued	2023-08-25
Review	
Quality evaluation completed	2024-06-17
Non-clinical evaluation completed	2024-06-18
Biostatistics evaluation completed	2024-06-18
Review of Risk Management Plan completed	2024-06-19
Labelling review completed	2024-06-19
Clinical/medical evaluation completed	2024-06-20
Notice of Compliance issued by Director General, Biologic and Radiopharmaceutical Drugs Directorate	2024-06-20

Pre-submission :~ 4 months

Screening:~ 1.5 months

Review:~ 8 months

Post approval commitments (1/2)

- As part of the marketing authorization for Ixchiq, Health Canada requested, and the sponsor agreed to several commitments to be addressed post-market. In addition to requirements outlined in the Food and Drugs Act and Food and Drug Regulations, commitments include (but are not limited to):
- Presenting a separate section on the potential vertical transmission of the vaccine virus within the safety review of safety in pregnancy in the Periodic Safety Update Reports (PSURs).

Post approval commitments (2/2)

- Monitoring the risk of brand name confusion between Ixchiq and Ixiaro (Japanese encephalitis vaccine) given a heightened risk of confusion due to the many orthographic and phonetic similarities and overlapping product profile characteristics. The sponsor is requested to include a cumulative review of all cases suggestive of brand name confusion through ‘medication errors and other product use errors and issues’ involving Ixchiq in the PSURs. The review should also include cases without clinical consequences, such as complaints, reports of concern and near misses.
- Including relevant safety findings from the different studies identified as additional pharmacovigilance activities in the PSURs, once the studies are completed.

SUMMARY

- Chikungunya approved via Standard Pathway.
- Scientific knowledge supports regulatory flexibility.
- Regulatory framework modernization provides flexibility to allow for changing landscape in drug regulation.
- Regulatory decisions remain sovereign, but supporting information may be broadly sourced.

ACKNOWLEDGEMENTS

BRDD colleagues for their contributions and discussions.

Licensing of *Chikungunya vaccine* in Brazil – Anvisa's Assessment

March 2025

ANVISA
Agência Nacional de Vigilância Sanitária

Licensing of CHIKV vaccine - Anvisa

Evaluation of the IXCHIQ vaccine

Anvisa's evaluation

IXCHIQ - Chikungunya vaccine (recombinant and attenuated)

Valneva/Butantan Institute

ANVISA
Agência Nacional de Vigilância Sanitária

Licensing of CHIKV vaccine - Anvisa

Evaluation of the IXCHIQ vaccine

Marketing Authorization requested by the Butantan Institute

IXCHIQ vaccine had already been approved by the FDA

ANVISA
Agência Nacional de Vigilância Sanitária

Licensing of CHIKV vaccine - Anvisa

Biologic Products Regulation – Anvisa
Marketing Authorization

Law 6.360/1976
Decree 8.077/2013

RDC 55/2010
Marketing Authorization

RDC 412/2020
Stability

RDC 948/2024
sanitary regularization

Demonstration of quality, efficacy, and safety
Requirements aligned with ICH definitions
Harmonized requirements with various health authorities and WHO

ANVISA
Agência Nacional de Vigilância Sanitária

Licensing of CHIKV vaccine - Anvisa

Priority Review

Priority review was granted as it is a vaccine for an emerging disease

Resolution RDC nº 204,

December 2017

Defines criteria for prioritization of registration and post-registration analysis of medicines

Pediatric population; neglected diseases; ***Emerging or reemerging diseases; Public Health Emergencies;*** Serious debilitating conditions; and Vaccines to be incorporated in the National Immunization Programme (PNI)

Timeline

120 days for the final decision marketing authorization submissions

ANVISA
Agência Nacional de Vigilância Sanitária

Licensing of CHIKV vaccine - Anvisa

Parallel Evaluation - EMA's OPEN Project

Opening procedures at EMA to non-EU authorities

Meetings and discussions with the EMA evaluation team

Contribution to Anvisa's analyses and conclusions

Better understanding of the rationale for EMA approval and uncertainties

Limitations with the timeline

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Licensing of CHIKV vaccine - Anvisa

Additional Evaluation -
Independent consulting technical group

CATEME Arboviruses Group
Scientific Advisory Committee

Evaluation of clinical development data
Report with conclusions on benefit-risk
Advice

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Agência Nacional de Vigilância Sanitária

Licensing of CHIKV vaccine - Anvisa

Clinical development: efficacy and safety evaluation

Efficacy

No evaluation of efficacy outcomes

Use of surrogate proposed by the developer

Safety

Main data from the evaluation of a non-endemic population

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Uncertainties

Magnitude and duration of protection - Surrogate to infer efficacy

Safety Profile in endemic population

Rare adverse reactions

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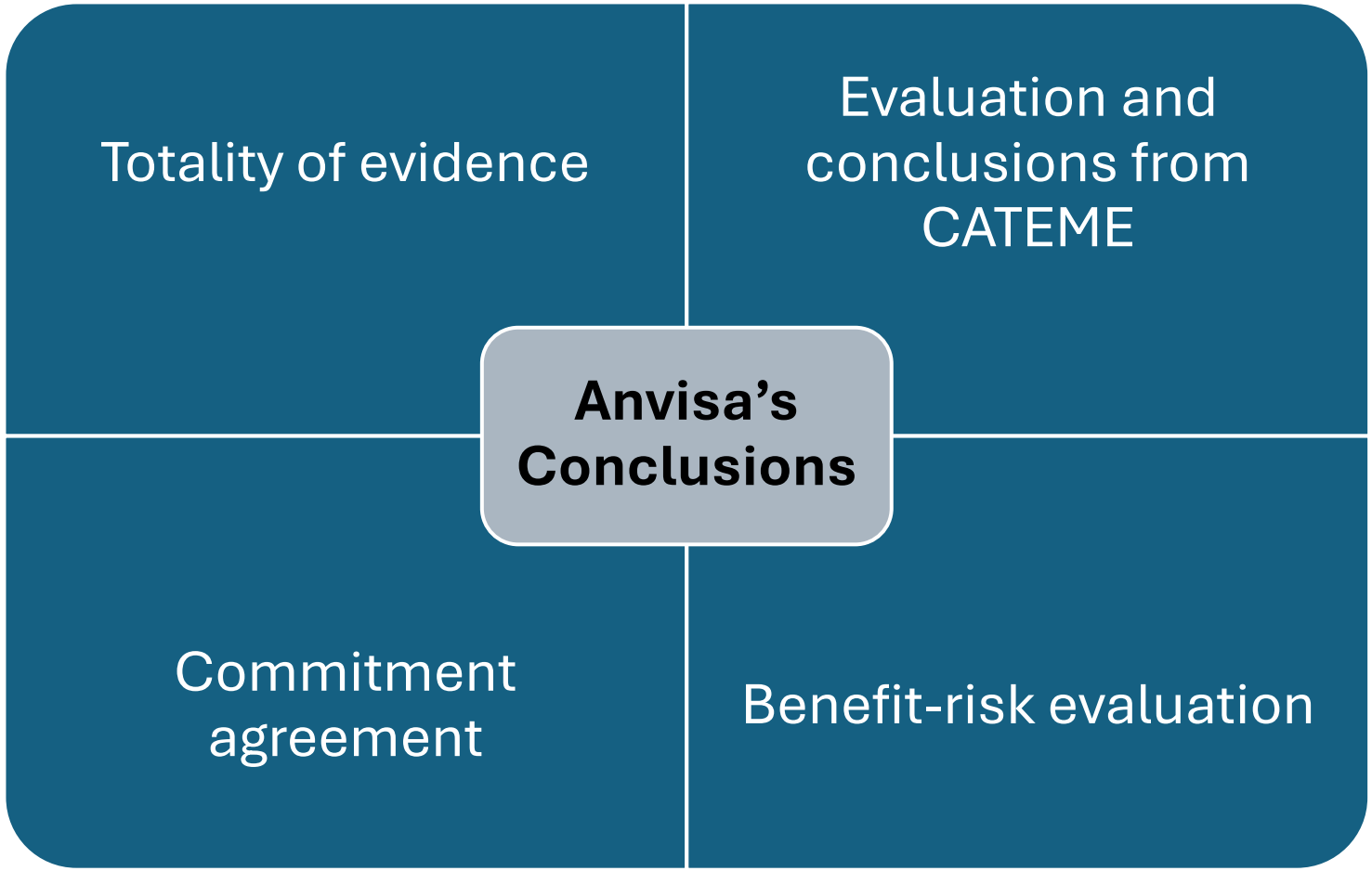
Licensing of CHIKV vaccine - Anvisa

Marketing Authorization



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Licensing of CHIKV vaccine - Anvisa

Commitment Agreement

Post-approval studies

Effectiveness

Understanding the magnitude of protection offered by the vaccine

Safety

Robust data on safety in endemic population

Information on rare adverse reactions

Importance of active surveillance in monitoring adverse reactions

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Licensing of CHIKV vaccine - Anvisa

Benefit-risk evaluation

Uncertainties and the impact of the disease in Brazil – morbidity and mortality

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Licensing of CHIKV vaccine - Anvisa

Thank you!

ANVISA
Agência Nacional de Vigilância Sanitária

Update on regulatory status of Chikungunya vaccines

Dr. Rubina Bose

Deputy Drugs Controller (India)
Central Drugs Standard Control Organization
www.cdsco.gov.in

Chikungunya Vaccines Meeting, 19th - 20th March, 2025 Sao Paulo, Brazil

Evolution of Indian Regulatory System

- The regulatory system in India for the new drug/vaccine development {Rule 2(w)} and approval has evolved significantly in recent years.
- The change has been gradual but steady; Some of the key changes are;
  - Implementation of e-submission platforms
    - SUGAM online platform for;
      - ✓ Clinical Trial Application
      - ✓ Marketing Authorization modules
      - ✓ Post Approval Changes – Quality
      - ✓ Post Approval Changes – Clinical Trial
      - ✓ Registration and import of Drug Substance and Drug Product
    - ONDLS online platform for submission and approval / endorsement of Mfg. license (Form-28D)
    - NSWS online platform for Form CT-10 (test & analysis and/or CT) and Form CT-16 (import)
  - Revision of Regulatory Guidance Documents for Industry i.e. NDCT Rules, 2019; PAC Guidance, GMP, PV, GDP guidelines……

SUGAM: System for Unmanned Gateways Approval for Manufacturers; ONDLS: On-line National Drug Licensing System; NSWS: National Single Window System

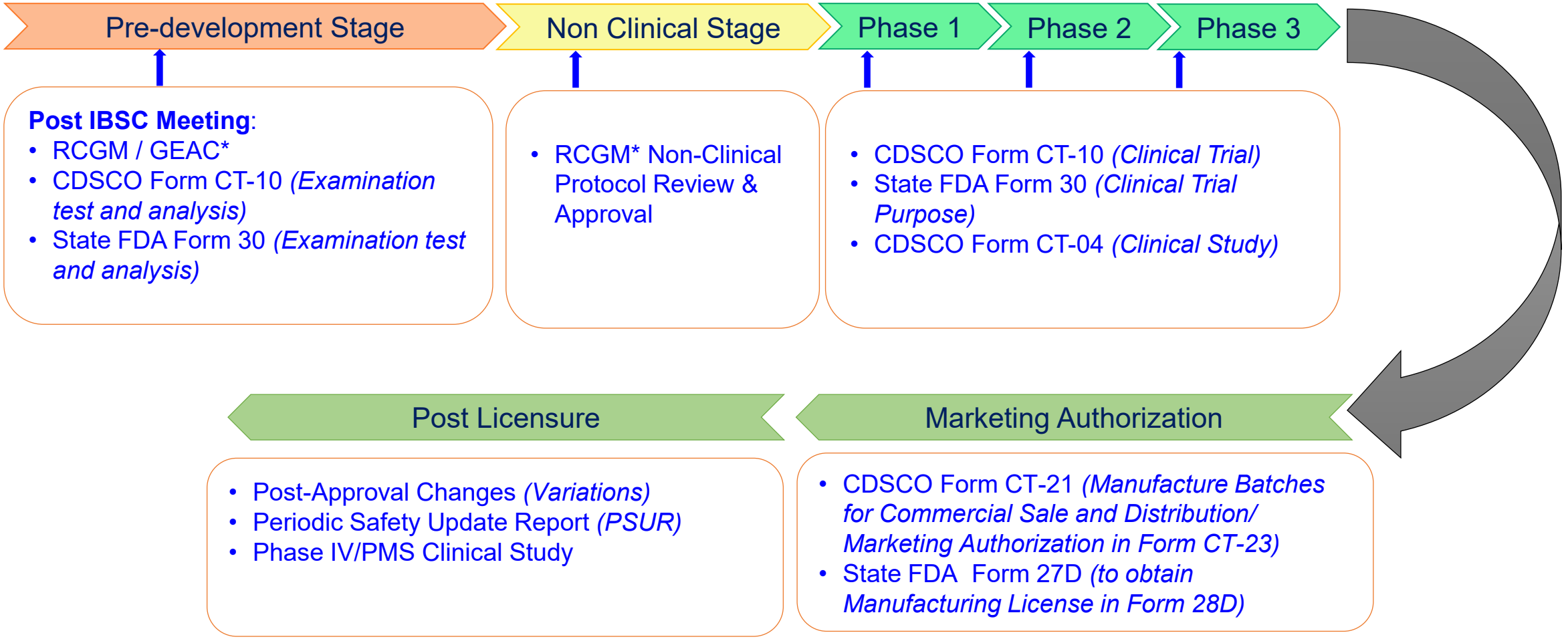
Indian Rules & Regulation and Agencies involved in Human Vaccines Approval

Agencies	Role
Central Drugs Standard Control Organisation (CDSCO) CLA **State Licensing Authority (SLA)**	• Permission to manufacture for examination, test and analysis and clinical trials, Grant of Form-29, New Drug permission to manufacture or import, Joint Inspection of manufacturing facilities, Grant or renewal of Form-28D • Registration and Import License. • PSUR, Pharmacovigilance monitoring (Post Market Surveillance).
Review Committee on Genetic Manipulation (RCGM)	• Research & Development and preclinical evaluation of recombinant vaccines
Genetic Engineering Appraisal Committee (GEAC)	• Release of genetically engineered (GE) organisms and products into the environment including experimental field trials
Central Drugs Laboratory (CDL), Kasauli	• Quality Testing & Lot release of each batch along with review of Chemistry, Manufacturing and Control (CMC) data. • Joint Inspection for grant or renewal of Form-28D
Advisory committee Subject Expert Committee (SEC) of vaccines	• To advise and give recommendation on the clinical trial protocol, report and marketing authorisation

Rules & Regulation
Drugs and Cosmetics Act,1940 and Rules there under.
New Drugs and Clinical Trial Rules, 2019.
Draft Regulatory Guidelines For Development Of Vaccines With Special Consideration For Covid-19 Vaccine
CDSCO guidance for Industry.
PAC in Biological Products: Quality Safety and Efficacy Documents
GMP specific regulation Schedule M,(G.S.R. 922(E), 28.12.2023) GSR 1337 dated 27.10.2017
Guidance for Industry on Pharmacovigilance requirements for Biological Products
Guidelines on Recall and Rapid Alert System for drugs (including Biologics & Vaccines)

Regulatory Approval Pathway: India *(for Vaccines)*

INDIA NRA (CDSCO HQ/DCG(I) Office)



* *For Recombinant, Living Modified Organism (LMO), Genetically Modified Organism (LMO) Vaccine only*

Marketing and Post-Marketing Requirements

Submission & Review Process of Application

- Applications for clinical trials, manufacturing, import, and marketing are submitted to CDSCO.
- Adequate data on quality, safety, immunogenicity and efficacy are to be generated before approval of any vaccine to ensure the safety and effectiveness of the vaccine
- SEC (Subject Expert Committee) review the clinical trial protocol / data before approval.
- GMP compliance inspections jointly conducted by CDSCO, State Authorities & CDL, Kasauli.

- Final approvals are granted based on:
  - ✓ Adequately controlled manufacturing & GMP compliance
  - ✓ Clinical trial results & CTD dossier evaluation
  - ✓ Joint inspections outcome
  - ✓ Lot release by CDL, Kasauli

❑ Post-Marketing Requirements

- Periodic Safety Update Reports (PSUR)
- Every 6 months for the first 2 years, then annually throughout product lifecycle.

❑ Phase IV Clinical Trial

- Conducted under approved protocol to assess long-term safety & efficacy.
- Post-Marketing Surveillance (PMS)
- Includes observational/non-interventional studies for real-world data.

Fast-Track & Expedited/Accelerated Review Pathways

- **Accelerated Approvals for {second schedule, clause 2 (A)of NDCT Rules 2019}:**
  - Serious/life-threatening diseases.
  - Unmet medical needs.
  - Diseases of special relevance to Indian population.

- **Expedited Reviews {second schedule, clause 2 (B) of NDCT Rules 2019} :**
  - Allowed when clinical safety & efficacy are established early.
  - Requires significant advantage over existing treatments.

- **Ease of Doing Business:**
  - SUGAM Portal for transparency
  - Regulatory reliance for faster approvals.
  - Streamlining global regulatory processes.

Indian Manufacturers Developing Chikungunya Vaccines

1. **Bharat Biotech, India**
   - ❑ **Inactivated Chikungunya vaccine.**
   - ❑ **Phase I clinical trial – *Completed***
   - ❑ **Currently, in Phase II/III Clinical Trial *(12 to 65 years of age, Placebo Controlled)***

2. **Indian Immunologicals Limited, India**
   - ❑ **Inactivated Chikungunya vaccine.**
   - ❑ **Currently, in Phase I Clinical Trial *(18 to 49 years of age, Placebo Controlled)***

3. **Serum Institute of India Pvt. Ltd., India (in partnership with Valneva)**
   - ❑ **Currently, in the early tech transfer stage**


Thank You

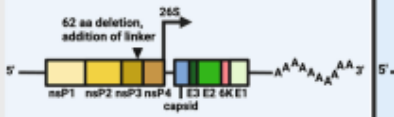
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Approval of Chikungunya vaccines

Chikungunya vaccines workshop, Sao Paulo, 19-20 March 2025

- Dr. Marco Cavaleri
- Head of Health Threats and Vaccines Strategy
- Chair of EMA Emergency Task Force

Chikungunya vaccines received EMA PRIME status

	IXCHIQ (VLA1553)	PXVX0317
PHYSICAL STRUCTURE		
GENETIC STRUCTURE		
PLATFORM	Live-attenuated (LAV)	Virus-like particle (VLP)
CHIKV STRAIN	LR2006-OPY1 (ECSA)	37997 (West African)
DOSE STORAGE	10^4 $TCID_{50}$ x 1 injection 2-8°C	20µg VLP x 2 injections 40µg VLP x 1 injection* not published
APPROVAL STATUS	U.S. FDA ✓ Health Canada ✓ European Medicines Agency ✓ Pending: Brazil	Expected 2025
ONGOING TRIALS	Phase III: Adolescents in Brazil Phase III: long-term safety / immunity in U.S.	Phase III: elderly adults in U.S. Phase III: adolescents + adults in U.S. Phase III: long-term safety / immunity in U.S.
ANTIBODY POTENCY	10^2-10^3 GMT (1 year)	10^2-10^3 GMT (1 year)
DURABILITY	2+ years	2+ years
BREADTH	CHIKV genotypes, ONNV, MAYV, RRV	CHIKV genotypes, ONNV, MAYV, UNAV, RRV
SYMPTOMS/ SIDE EFFECTS	fever 13-24% joint pain 1-18% headache 24-40% muscle pain 15-25% chills 1.5% fatigue 17-39% serious adverse events 1.2-3.7%	fever 2-4% joint pain 10-12% headache 21-27% muscle pain 21-22% chills 6-7% fatigue 16% nausea 4-14% serious adverse events 0.5-4%
VACCINE VIREMIA	Yes	No

[Chikungunya Virus Vaccines: A Review of IXCHIQ and PXVX0317 from Pre-Clinical Evaluation to Licensure | BioDrugs]

Pre-existing chikungunya virus neutralizing antibodies correlate with risk of symptomatic infection and subclinical seroconversion in a Philippine cohort | Elsevier Enhanced Reader

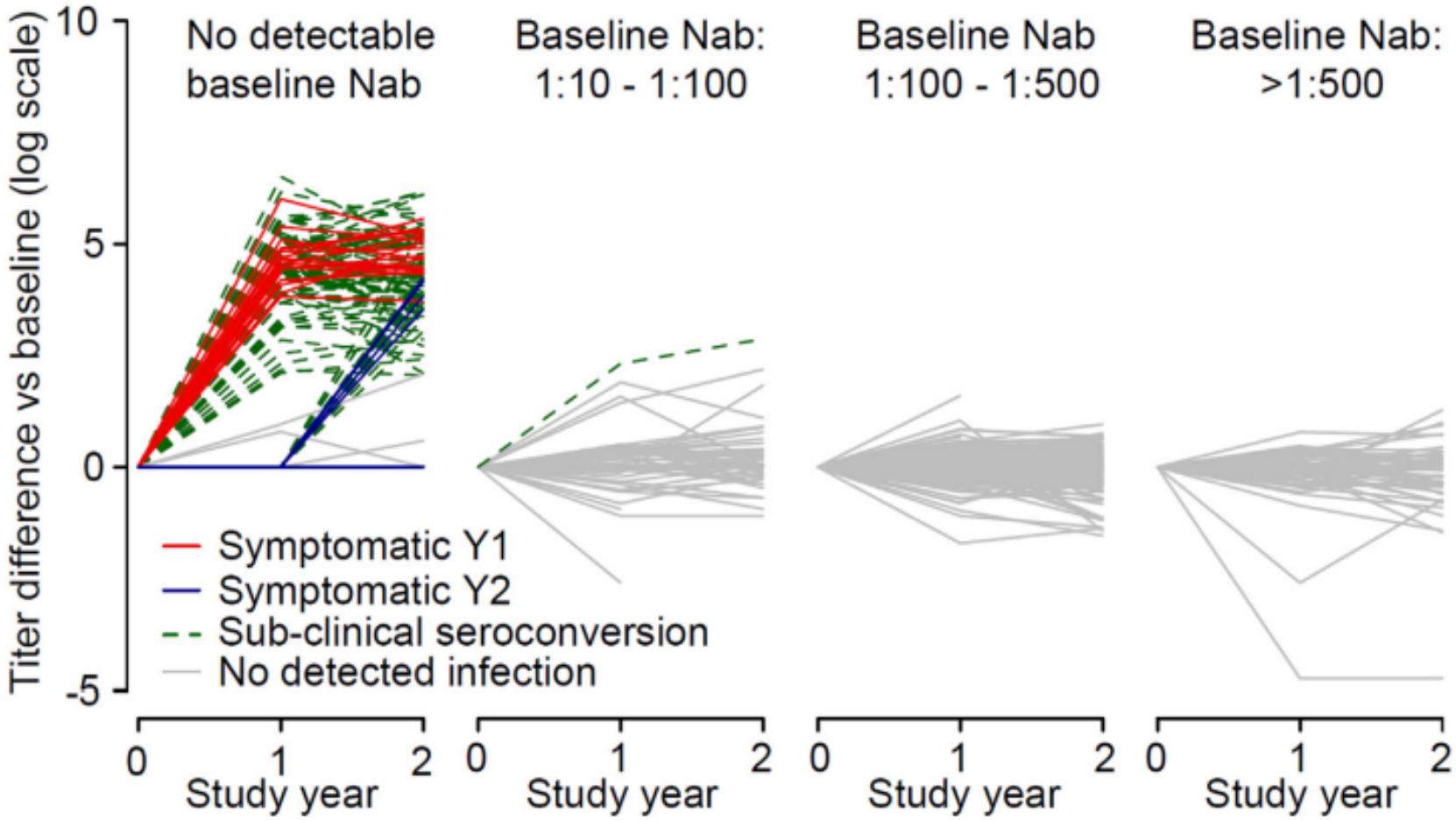
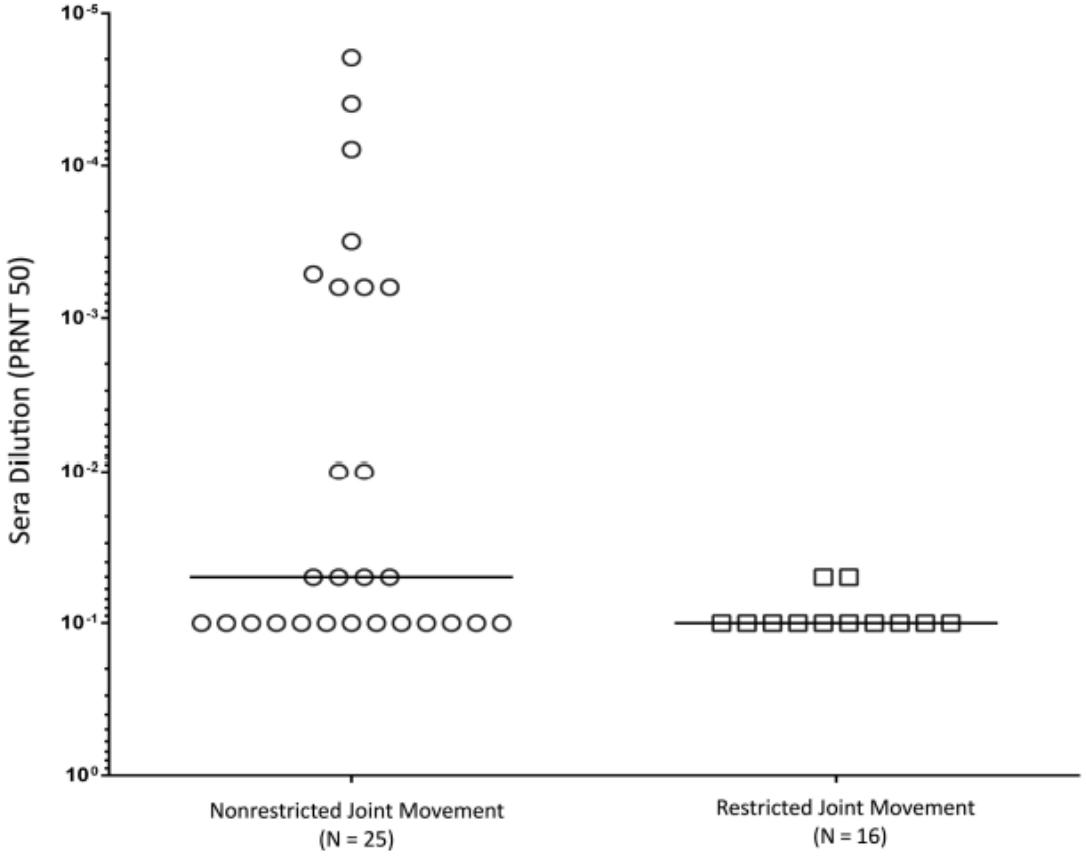


Figure 2. Changes in CHIKV PRNT80 titer (log scale) from baseline to 12 months (study year 1) and 24 months (study year 2) for each cohort participant according to baseline CHIKV PRNT80 titer group: no detectable NAb (<1:10), low titer (1:10 to <1:100), medium titer (1:100–1:500), high titer (>1:500). Red and blue solid lines indicate symptomatic infections, green dotted lines indicate subclinical seroconversions, and gray solid lines indicate no infections/seroconversions. CHIKV, chikungunya virus; PRNT80, 80% plaque reduction neutralization test; NAb, neutralizing antibody.

Clinical, Serological, and Virological Analysis of 572 Chikungunya Patients From 2010 to 2013 in India

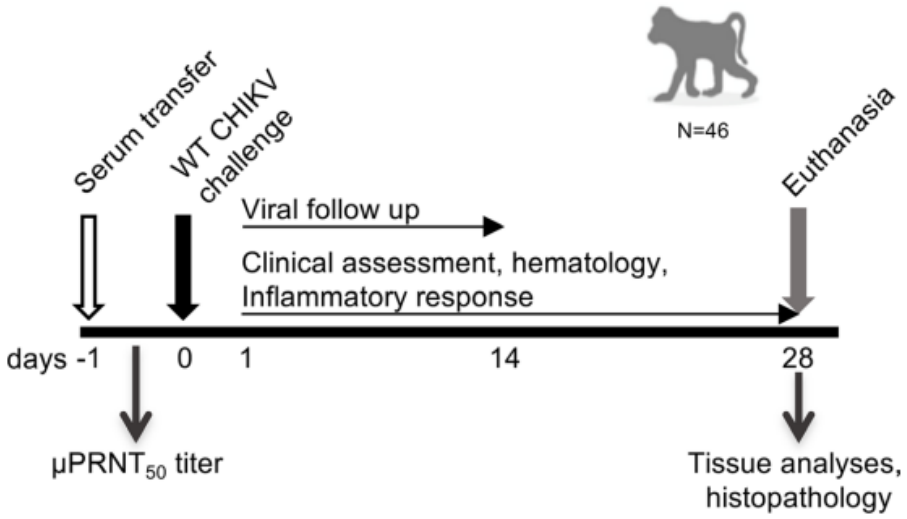
Jaspreet Jain,[1] Kaustuv Nayak,[2] Neha Tanwar,[3] Rajni Gaind,[3] Bhupendra Gupta,[4] J. S. Shastri,[5] Raj K. Bhatnagar,[6] Murali Krishna Kaja,[2,7] Anmol Chandele,[2] and Sujatha Sunil[1]

[1]Vector Borne Diseases Group and [2]ICGEB-Emory Vaccine Center, International Center for Genetic Engineering and Biotechnology, Departments of [3]Microbiology and [4]Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, [5]Department of Microbiology, BYL Nair Ch. Hospital & T. N. Medical College, Mumbai, and [6]International Center for Genetic Engineering and Biotechnology, New Delhi, India; and [7]Emory Vaccine Center, Emory University School of Medicine, Atlanta, Georgia



[cix283.pdf (silverchair.com)]

Figure 4. Neutralization status (plaque reduction neutralization test 50) of patient samples without and with joint movement restriction. Data points are plotted as open circles and open squares, respectively. n = 25 and 16 sample points, respectively. Abbreviation: PRNT, plaque reduction neutralization test.



Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera

Pierre Roques,[1] Andrea Fritzer,[2] Nathalie Dereuddre-Bosquet,[1] Nina Wressnigg,[2] Romana Hochreiter,[2] Laetitia Bossevot,[1] Quentin Pascal,[1] Fabienne Guehenneux,[3] Annegret Bitzer,[2] Irena Corbic Ramljak,[2] Roger Le Grand,[1] Urban Lundberg,[2] and Andreas Meinke[2]

[1]Université Paris-Saclay, INSERM, CEA, Center for Immunology of Viral, Auto-Immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), Fontenay-aux-Roses, France. [2]Valneva Austria GmbH, Campus Vienna Biocenter 3, Vienna, Austria. [3]Valneva SE, Saint Herblain, France.

Table 2. Peak viremia for animals with different $\mu PRNT_{50}$ titer thresholds.

		$\mu PRNT_{50} \geq 50$ ($n = 13$)	$\mu PRNT_{50} \geq 100$ ($n=4$)	$\mu PRNT_{50} \geq 150$ ($n = 2$)
Peak viremia (copies/mL) Day 2–6	Geometric mean	941.1	16.3	10
	[95% CI]	[100, 8846]	[4, 77]	[10, 10]
Number of NHPs with detected CHIKV RNA	Not detected	4 (30.8%)	3 (75.0%)	2 (100%)
	Detected	9 (69.2%)	1 (25.0%)	0 (0.0%)

The geometric mean for the peak viremia (copies/mL) is shown for each group of animals assigned to the 3 $\mu PRNT_{50}$ thresholds. Numbers of animals with or without detectable CHIKV RNA were calculated for the 3 $\mu PRNT_{50}$ thresholds. Therefore, animals with an $\mu PRNT \geq 150$ are included in the $\mu PRNT_{50} \geq 100$ and $\mu PRNT_{50} \geq 50$ columns, and animals with an $\mu PRNT \geq 100$ are included in the $\mu PRNT_{50} \geq 50$ column. Peak copies/mL values reported as 0 were set to 10 for this summary.

jciinsight-7-160173.pdf (nih.gov)

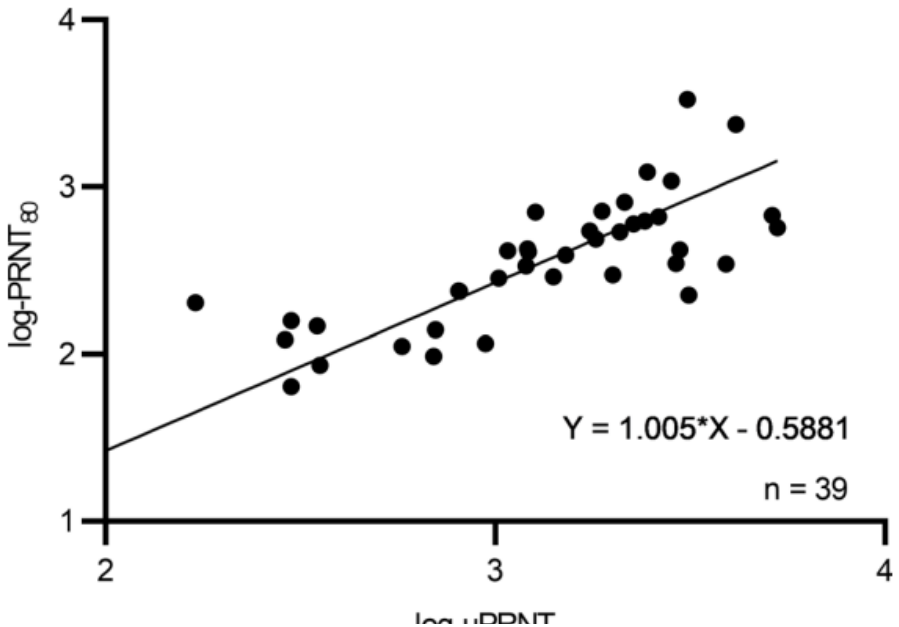


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Figure 5. Linear regression of neutralization antibody titer using Deming regression analysis. Log transformed data of $\mu PRNT_{50}$ versus $PRNT_{80}$ shown.

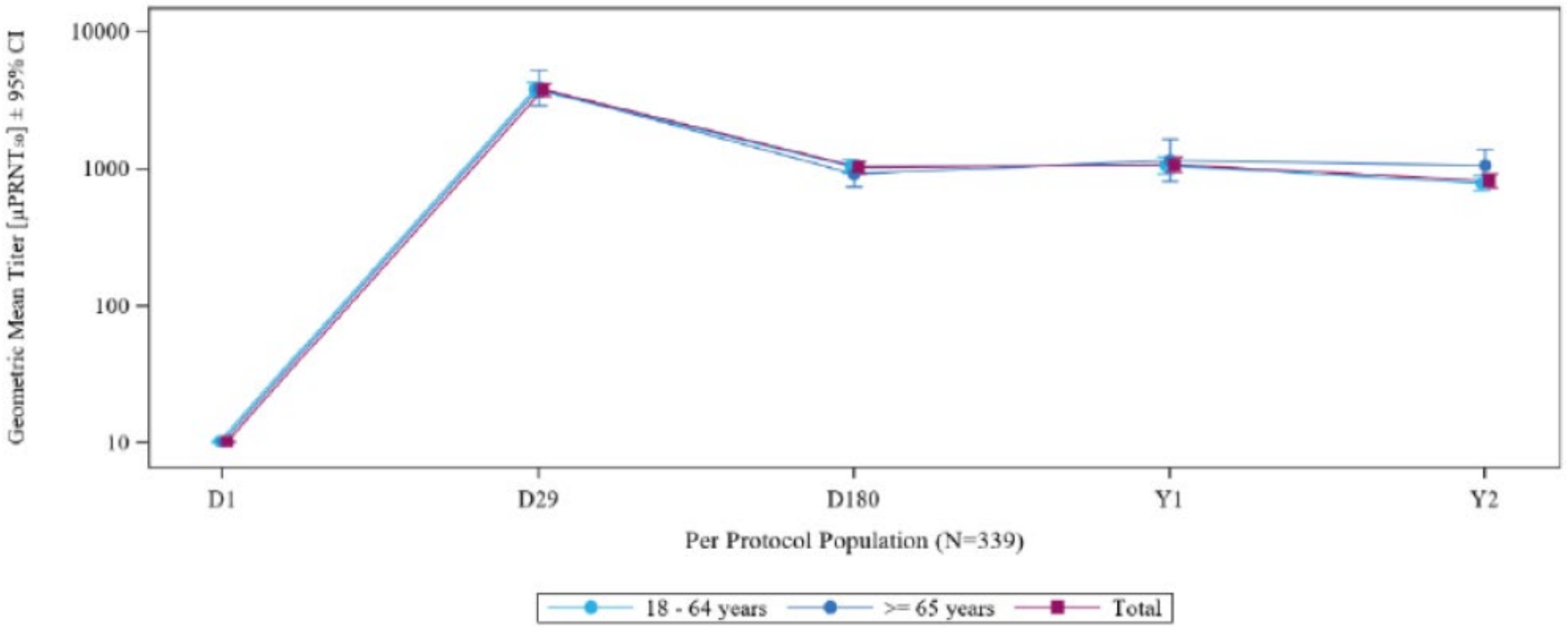
Table 3. Comparison of neutralization antibody titer results measured by the validated assay as $\mu PRNT_{50}$ titer or reported by AFRIMS ($PRNT_{80}$ titer).

	$\mu PRNT_{50}$	$PRNT_{80}$	Ratio $\mu PRNT_{50}/PRNT_{80}$
No. of nAb positive samples	39	39	39
Minimum	170	64	0.84
Maximum	5297	3347	13.93
Geometric mean	1341	360	3.73
Lower 99% CI of geometric mean	920	246	2.86
Upper 99% CI of geometric mean	1957	526	4.87

nAb, neutralizing antibodies; PRNT, plaque reduction neutralization test; $\mu PRNT_{50}$, neutralization titer determined in a microneutralization assay (96 well format) using a 50% plaque reduction; $PRNT_{80}$, neutralization titer using a 80% plaque reduction.

jciinsight-7-160173.pdf (nih.gov)

Persistence of antibodies over time- Ixchiq



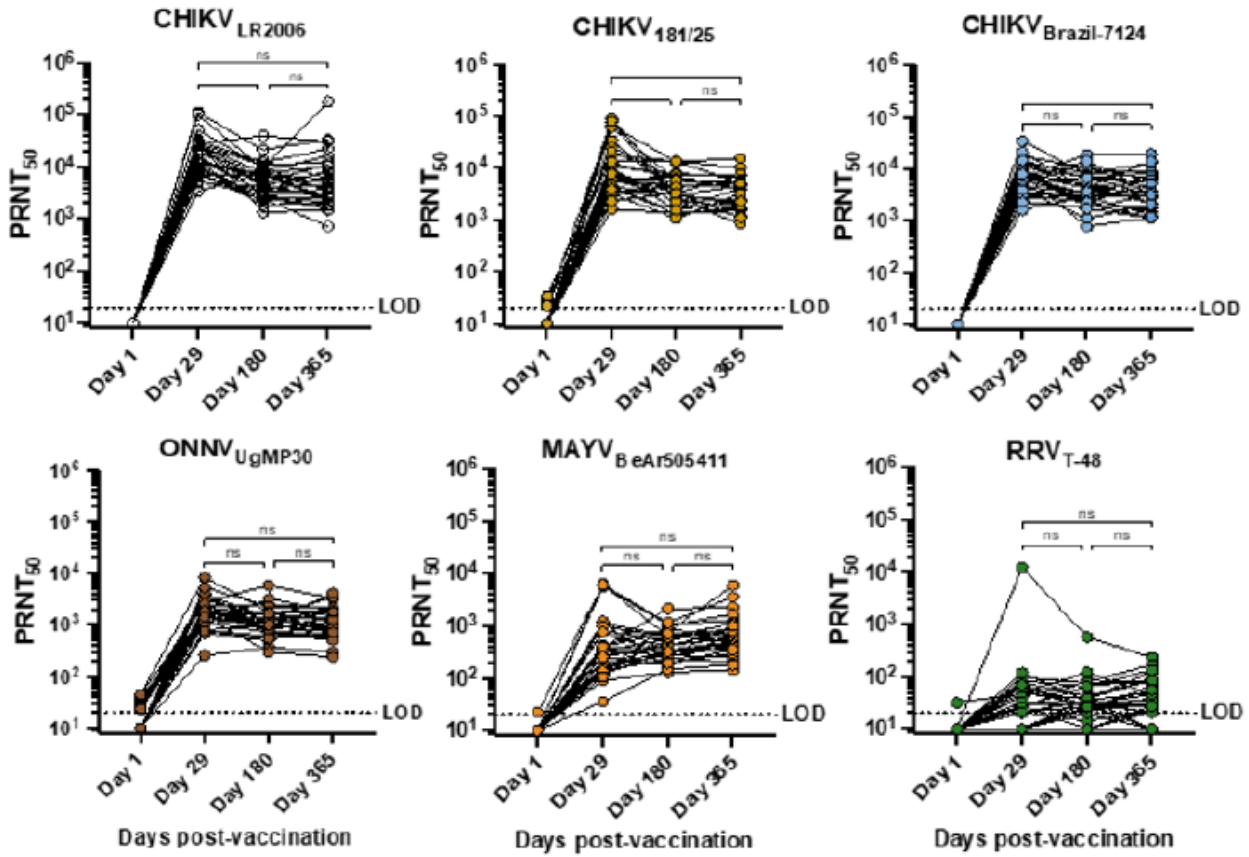
Age Strata	D1	D29	D180	Y1	Y2
18 - 64 years	290	240	279	157	234
>= 65 years	49	39	48	27	42
Total	339	279	327	184	276

CHIKV=chikungunya virus; CI=confidence interval; D1=VLA1553-301 Visit 1 - Day 1; D29=VLA1553-301 Visit 3 - Day 29; D180=VLA1553-301 Visit 5 - Day 180; GMT=geometric mean titers; SAP=statistical analysis plan; Y1=VLA1553-303 Visit 1 - Year 1; Y2=VLA1553-303 Visit 2 - Year 2.

Ixchiq; active substance: Chikungunya virus (CHIKV) Δ5nsP3 strain (live, attenuated)

Cross-immunity alphaviruses - Ixchiq

*Figure 19. : Antibodies in VLA1553 human immune sera cross-neutralize different CHIKV strains and related arthritogenic alphaviruses. Individual data per participant over time is displayed by virus strain. Neutralizing antibody titres are compared by one-way ANOVA with multiple comparisons (Friedman test) where * $p < 0.05$, ** $p < 0.01$. The LOD is shown with a dotted line and refers to the minimum dilution of 1:20 tested (source figure 26 of AtQ 150)*

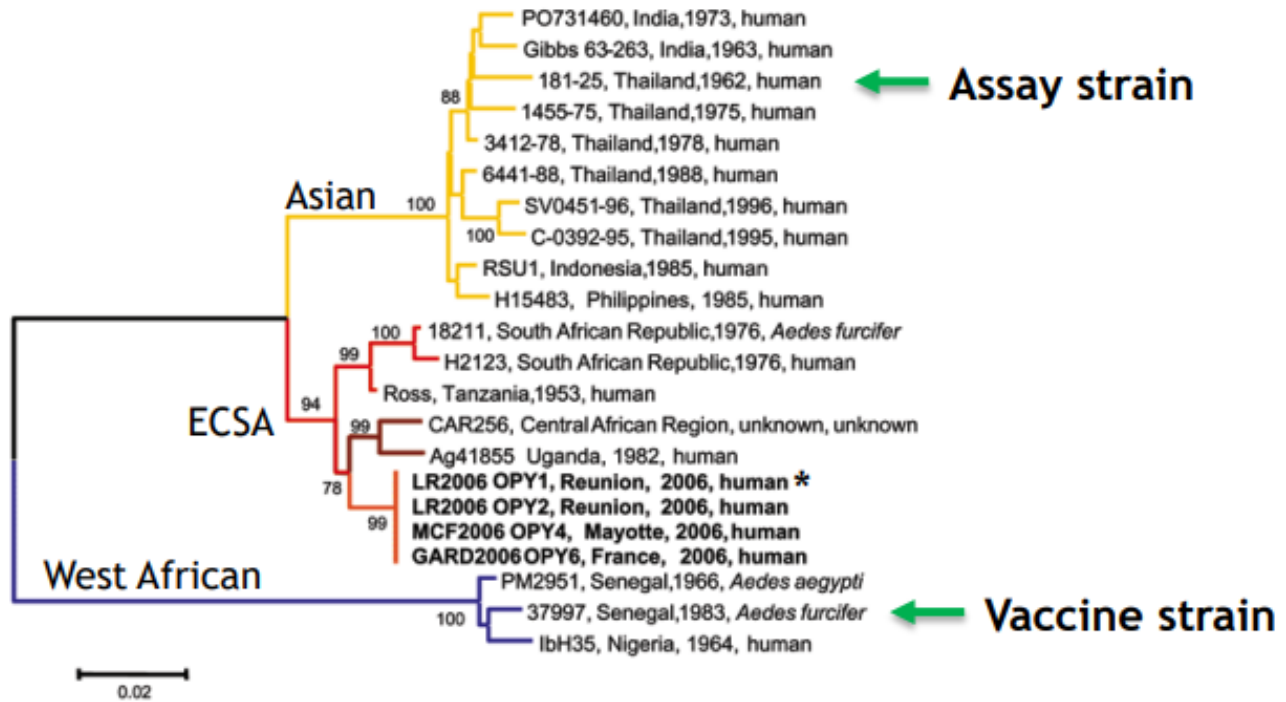


Ixchiq; active substance: Chikungunya virus (CHIKV) Δ5nsP3 strain (live, attenuated)

CHIKV-luciferase assay developed to evaluate vaccine efficacy measures cross-neutralization

- CHIK181/25 live-attenuated virus (Asian lineage AF15561) engineered to express luciferase transgene (CHIKV-luc assay reporter)
- Neutralization assay based on 80% (NT_{80}) reduction of luciferase activity following Vero cell infection with CHIKV-luc
- CHIKV-luc virus used in the assay is heterologous to the CHIKV VLP (Asian vs West African)

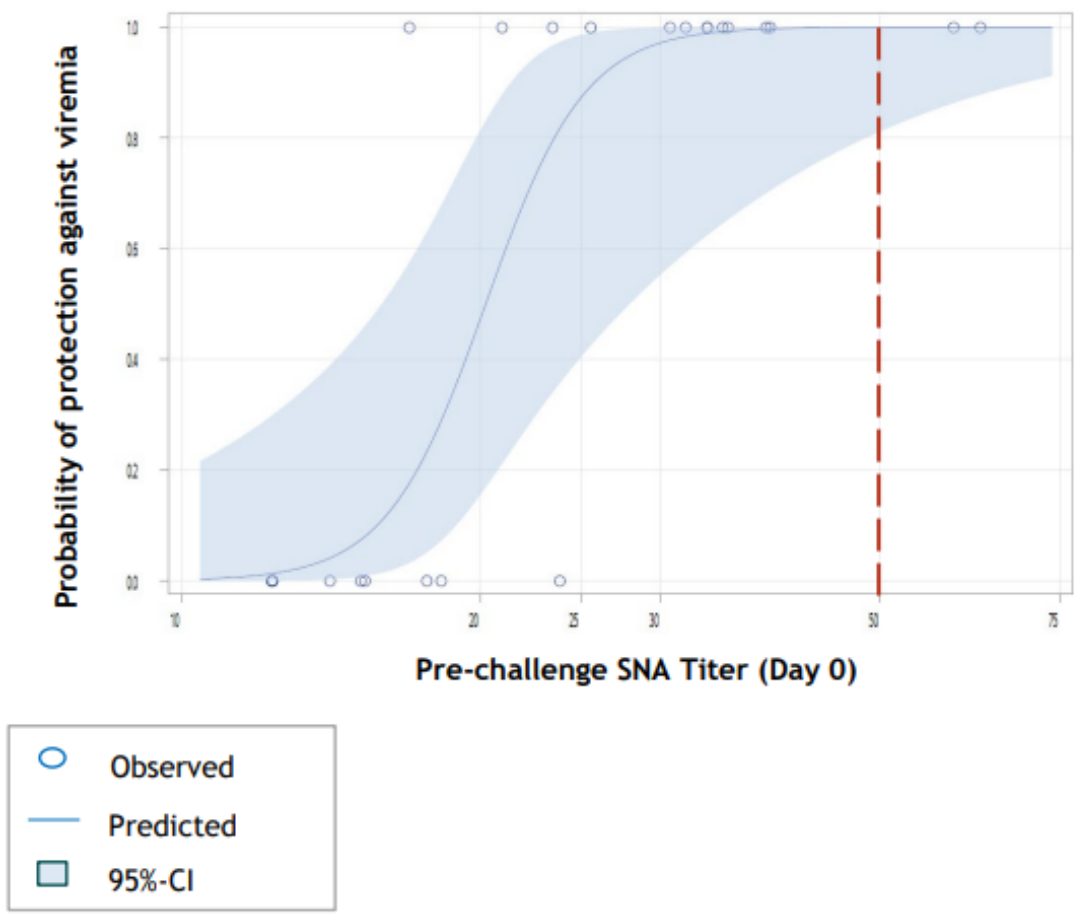
Phylogenetic analysis of CHIKV isolates based on a 1kb fragment in the E1 gene[1]



1. Parola P, de Lamballerie X, Jourdan J, Rovery C, Vaillant V, Minodier P, *et al*. Emerg Infect Dis. 2006;12(10):1493-1499.

ECSA, East-Central-South-African * CHIKV strain that was used as a challenge in nonhuman primate serum transfer study (next slide)

Conservative serum neutralizing antibody (SNA) threshold chosen for phase 3 study immunogenicity endpoints based on NHP data & regulatory agency recommendations

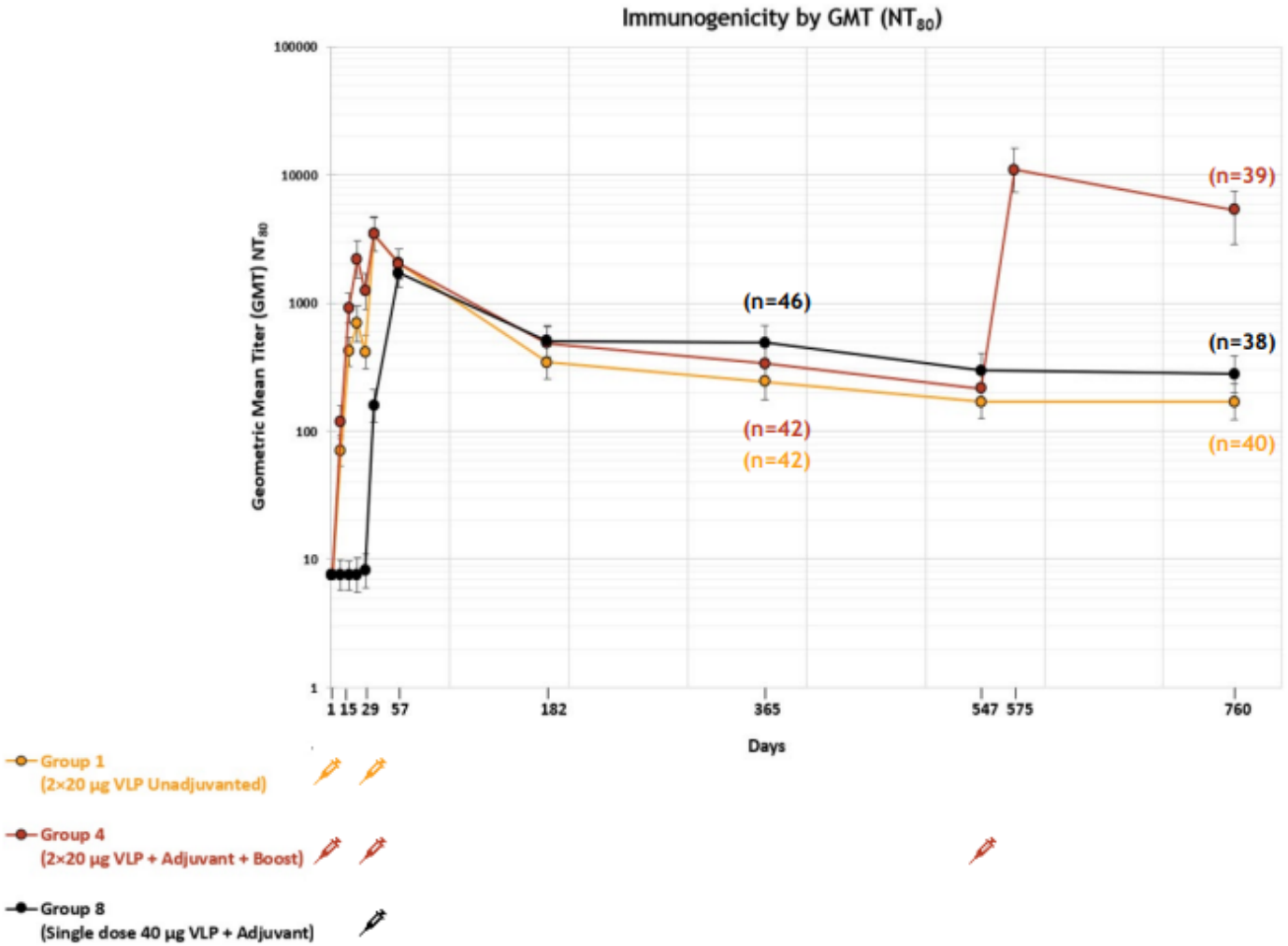


Serum passive transfer and challenge study in NHP

- NHPs received pooled sera from human participants vaccinated with CHIKV VLP at various dilutions intravenously and were challenged with CHIKV 24 hours later
- Logistic regression model:
  - SNA titer of 50 results in 99.97% [81-100] probability of protection against viremia
- Regulatory agencies* proposed and agreed a more conservative SNA titer threshold of 100 to be an acceptable surrogate endpoint

CHIKV, chikungunya virus; NHPs, nonhuman primate; SNA, serum neutralizing antibodies; CI, confidence interval
Data presented at ESCMID Global 2024 (not yet published in a peer-reviewed article)
*FDA and EMA

Single 40 µg CHIKV VLP adjuvanted dose had superior immunogenicity after first vaccination, showed a rapid and durable response, and was well-tolerated



- At year 1, Group 8 had significantly higher GMTs vs Group 1 (491.7 vs 243.4; p-value=0.0019); this was maintained at year 2 (279.7 vs 169.8; p-value=0.0369)
- AEs mostly mild to moderate; no serious treatment-related unsolicited AEs
- Local AEs more frequent in 40 ug adjuvanted CHIKV VLP group (40%) than in unadjuvanted group (23%)

Primary Endpoint: GMT of anti-CHIKV SNA level on Day 57 (28 days after last vaccination); adjuvant = aluminum hydroxide
Vertical bars denote 95% confidence interval. GMT = geometric mean titer; NT_{80} = Neutralization Titer showing 80% neutralization
Bennett *et al.* Lancet Infect Dis. 2022;22(9):1343-55.

BAVARIAN NORDIC

Vimkunya clinical immunogenicity - SmPC

Table 2: Anti-CHIKV SNA seroresponse rate (SRR) at visit days 8, 15, 22 and 183 for phase 3 Study 1 (12 to < 65 years of age) (immunogenicity evaluable population)

Study day	SRR VIMKUNYA (N=2 559) n/N (%)[a] [95% CI][b]	SRR placebo (N=424) n/N (%)[a] [95% CI][b]	SRR difference [95% CI][c]	p-value[d]
Day 8	1 169/2 510 (46.6%) [44.6%, 48.5%]	2/419 (0.5%) [0.1%, 1.7%]	46.1% [43.8%, 48.1%]	< 0.0001
Day 15	2 355/2 434 (96.8%) [96.0%, 97.4%]	3/395 (0.8%) [0.3%, 2.2%]	96.0% [94.3%, 96.8%]	< 0.0001
Day 22	2 503/2 559 (97.8%) [97.2%, 98.3%]	5/424 (1.2%) [0.5%, 2.7%]	96.6% [95.0%, 97.5%]	< 0.0001
Day 183	1 967/2 301 (85.5%) [84.0%, 86.9%]	6/401 (1.5%) [0.7%, 3.2%]	84.0% [81.7%, 85.6%]	< 0.0001

CI = confidence interval; SNA = serum neutralising antibody, SRR = seroresponse rate

[a] n is the number of participants with seroresponse ≥ titre 100, divided by N, the total number of participants in the group.

[b] 95% CIs of seroresponse rates are based on the Wilson method.

[c] Seroresponse rate difference is (VIMKUNYA minus placebo); 95% CIs are based on the Newcombe hybrid score method. Statistical superiority to placebo and lower bound of the 2-sided 95% CI on the difference in seroresponse rates between VIMKUNYA group and placebo group ≥ 70% (considered clinically significant).

[d] p-value is from a 2-sided chi-square test of equality of seroresponse percentages between groups.

Vimkunya Safety – EMA assessment report

Effect	Short Description	Unit	CHIKV VLP	Placebo	Uncertainties/ Strength of evidence	References
Solicited AEs (Reactogenicity)	Solicited administration site effects [a]	% of individuals	23.4	8.0	Transient effect, majority mild to moderate in severity	pooled data from ISS (mainly from study -004)
	Solicited systemic effects [b]	% of individuals	30.7	21.6		
Unsolicited AEs	all	% of individuals	15.7	14.4		
	related [c]	% of individuals	2.4	1.9		
SAEs	all	% of individuals	1.0	0.6		
	related	% of individuals	0	0		

Ixchiq clinical immunogenicity - SmPC

Table 2. Seroresponse rates over time, as determined by µPRNT$_{50}$ assay, in study VLA1553-301 (PP population)

Study	**VLA1553-301**	
Treatment	Placebo	IXCHIQ
	N=96	N=266
	(n [95%CI])	(n (%) [95%CI])
28 days post-vaccination	0 [0.0, 3.8]	263 (98.9) [96.7, 99.8]
6 months post-vaccination	0 [0.0, 4.0]	233 (96.3) [93.1, 98.3]

Abbreviations: CI=confidence interval; µPRNT$_{50}$=50% micro plaque reduction neutralization test; PP=per-protocol (population)

Effect	Short Description	Unit	VLA1553	Placebo	Uncertainties / Strength of evidence	References
Liver function test increased	Alanine aminotransferase (ALT)	%	16.9 14.9 (15.5)*	9.9	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.2.2 302 T14.3.3.2.2
	Aspartate aminotransferase (AST)	%	13.0 10.9 (11.7)*	7.4	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.2.2 302 T14.3.3.2.2
Chikungunya-like adverse reactions (broad definition)	Combinations of fever with headache, fatigue, myalgia, arthralgia, or other symptoms also reported for acute-stage chikungunya illness	%	12.1	0.6	Total of 4,643 vaccinated participants	Post Hoc analysis
Solicited systemic AEs	Headache	%	32.0	14.6	Total of 4,643 vaccinated participants	P3.10
	Fatigue	%	29.4	12.6	Idem	P.3.10
	Myalgia	%	23.7	7.4	Idem	P.3.10
	Arthralgia	%	16.6	4.8	Idem	P.3.10
	Fever	%	13.8	0.8	Idem	P.3.10
	Nausea	%	11.4	5.6	Idem	P.3.10
	Rash	%	2.4	0.5	Idem	P.3.10
	Vomiting	%	2.0	1.0	Idem	P.3.10
Solicited local AEs	Tenderness	%	10.8	8.1	Idem	P3.8.
	Vaccination site pain	%	6.1	3.7	Idem	P3.8.
	Erythema	%	1.6	1.5	Idem	P3.8.

Effect	Short Description	Unit	VLA1553	Placebo	Uncertainties / Strength of evidence	References
White blood cell count decreased	Neutropenia (neutrophile decreased)	%	42.3 42.7 (41.8)*	12.4	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.1.2 302 T14.3.3.1.2
	Leukopenia (leukocyte decreased)	%	32.0 31.4 (31.2)*	5.8	301: 497 vac. part. 302: 408 vac. part.	301 T14.3.3.1.2 302 T14.3.3.1.2
	Lymphopenia (lymphocyte decreased)	%	23.5 22.0 (22.3)*	7.4	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.1.2 302 T14.3.3.1.2

Ixchiq Safety –EMA assessment

4.3 Contraindications

Immunodeficient or immunosuppressed individuals due to disease or medical therapy (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised)

Additional evidence

- Immunogenicity and safety data in seropositive
- Data in adolescents and children
- Use in pregnant and lactating women
- Cross-reactivity and impact of immunity to other alphaviruses has been explored
- cross-neutralisation against a broad range of heterologous CHIKV strains including the major lineages Asian Urban (AUL), Indian Ocean (IOL), East Central and South African (ECSA) and West African (WA)
- Long term immunogenicity (and possible boosters) need to be investigated post-approval

Conclusions

- Neutralising antibodies titres can be used for inferring protection for CHIKV vaccines
- A threshold needs to be defined taking into account sero-epidemiological studies and NHP passive transfer data – such threshold might differ from one vaccine to the other
- Seroresponse in seronegative subjects should be primary outcome for immunogenicity
- Adolescents can be studied with adults in the pivotal studies – children in endemic settings may have higher baseline seropositivity
- Plans for effectiveness measurement post-approval to be discussed early with regulators to gain good understanding of what can be achieved post-approval

Discussion of NRA's – Panel 1

Danielle Craig – CEPI – Moderator
ANMAT - Argentina, Gabriela Beatriz Bravo
CDSCO - India, Rubina Bose
PPB - Kenya, Mikal Ayiro
Ghana-FDA, Ernest Agyei-Kwame
AVAREF, Kwasi Nyarko (virtual)

Discussion of NRA's – Panel 2

Danielle Craig – CEPI – Moderator
Rwanda-FDA, Jean Pierre Nsanzimfura
SRS-El Salvador, Rosa María Morales Rivas
DINAVISA-Paraguay, Marlene Esquivel
Badan POM-Indonesia, Diah Puspitasari
PPB-Kenya, Mikal Ayiro

Phase IV post-approval studies: CHIKUNGUNYA vaccines.

Feasibility of licensing vaccine with current data.

By;
Name: NSANZIMFURA Jean Pierre
Title: Vaccines and Biosimilar Registration Specialist
Date: 19th March 2025, São Paulo/Brazil

Rwanda Food and Drugs Authority

Was established by the law Nº 003/2018 of 09/02/2018

- **Vision**

A world class regulatory Authority effectively protecting and promoting public health

- **Mandate**

To protect public health through regulation of regulated products

Including **vaccines** and other biological products

ML3 Country!

2021 to 2024

WHO-GBT

Registration process of Vaccines in Rwanda

Normal process

Assessment of all Data of Quality and Safety.

Risk based approach

- Recognition (MoU with ML3Cs)
- Reliance:
  WHO-PQ,
  SRAs Countries
- WHO-CRP,
- EAC Joint Assessment
- Emergency use for Endemic outbreaks

Feasibility of licensing vaccine with current data

- Could a CHIKV vaccine be licensed in your country with the presented clinical development? Yes √

- Can you suggest a way of licensing these vaccines in your country and in the region? Yes √

Feasibility of licensing vaccine with current data

- Would a collaborative/joint procedure for the licensing of the vaccine be possible based on your current regulations? Yes √

- The NRAs where vaccine has been licensed and information presented are most probably included in the list of authorities that your agency relies on. Could you use an accelerated (faster) approval procedure or you must go through the regular procedure? Yes √

RWANDA FDA
Rwanda Food and Drugs Authority

CHIKUNGUNYA
Phase IV

São Paulo, Brazil March 2025

CEPI

ANVISA
Agência Nacional de Vigilância Sanitária