24.11.2025

AMSTERDAM

EMA workshop

CHIKUNGUNYA VACCINES: THE ROAD TO REGULATORY APPROVAL IN THE EU

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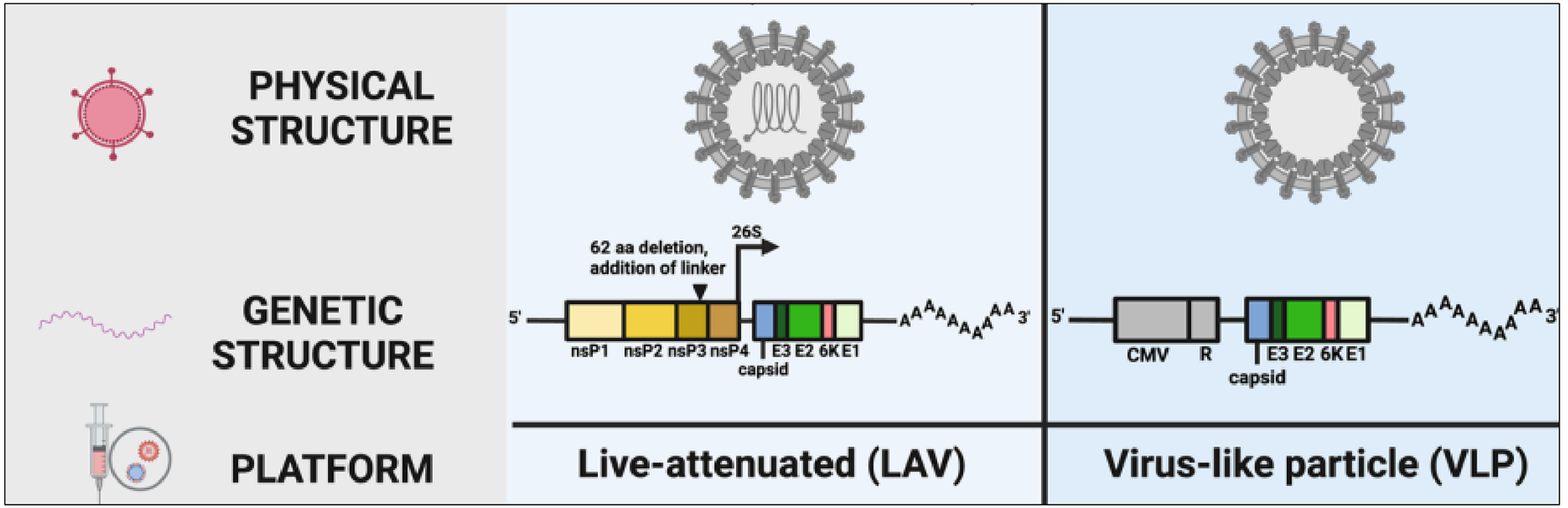
famhp

.be

IXCHIQ - VIMKUNYA

Valneva — Bavarian Nordic

Marketing authorisation — June ’24 — Feb ‘25



Indication — **active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years and older**

From Weber et al., BioDrugs (2024) 38: 727–742

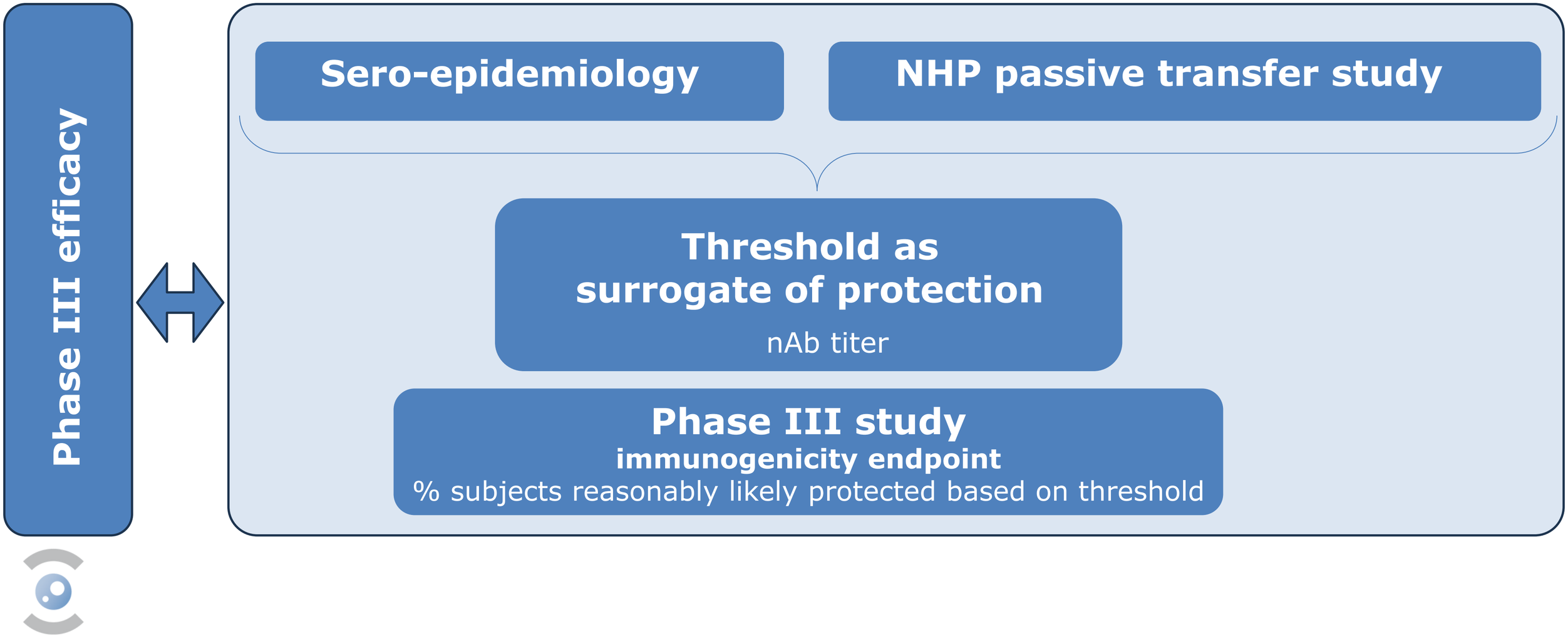
ROAD TO REGULATORY APPROVAL

How to demonstrate protection?

- Efficacy trials are not feasible pre-authorization due to unpredictable and short-lived outbreaks.
- There is no established immune correlate of protection (ICP) for Chikungunya.
- Exact mechanisms of protection unknown, but neutralizing antibodies have a major role in protecting against CHIKV infection and/or disease.
- Approach agreed through several Scientific Advices

ROAD TO REGULATORY APPROVAL

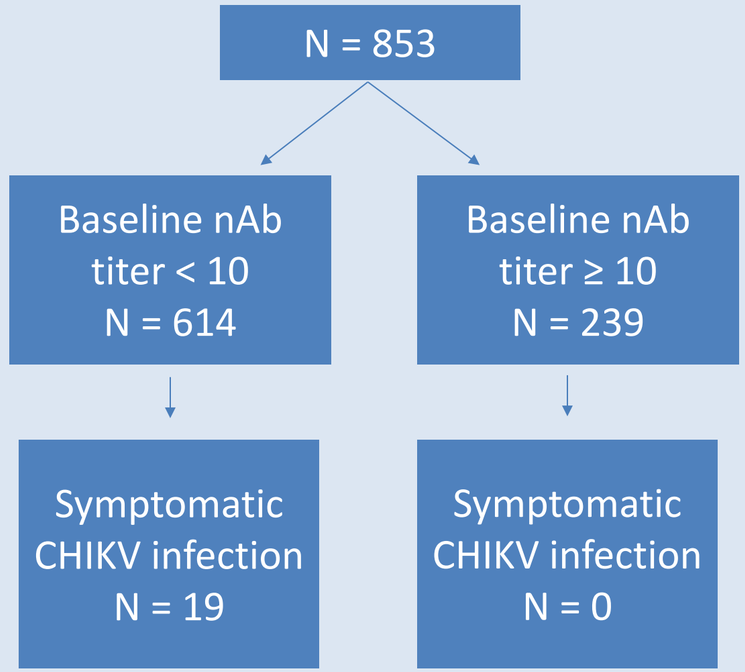
How to demonstrate protection?



How to demonstrate protection?

Sero-epidemiology

- Prospective sero-epidemiologic study Philippines 2012-2014
- Initial publication 1st year Yoon et al. 2015
- Presence of baseline nAb strongly correlates with protection against symptomatic infection
- Assay used: PRNT80
- Longitudinal cohort: protection lasts at least 2 years (Yoon et al. 2020)



From Yoon et al, PLoS Negl Trop Dis (2015) 9(5) : e0003764; Yoon et al, IJID (2020) 95: 167–173

How to demonstrate protection?

Sero-epidemiology

PRNT80 > 10

NHP passive transfer study

Threshold as surrogate of protection

nAb titer

Phase III study

immunogenicity endpoint

% subjects reasonably likely protected based on threshold

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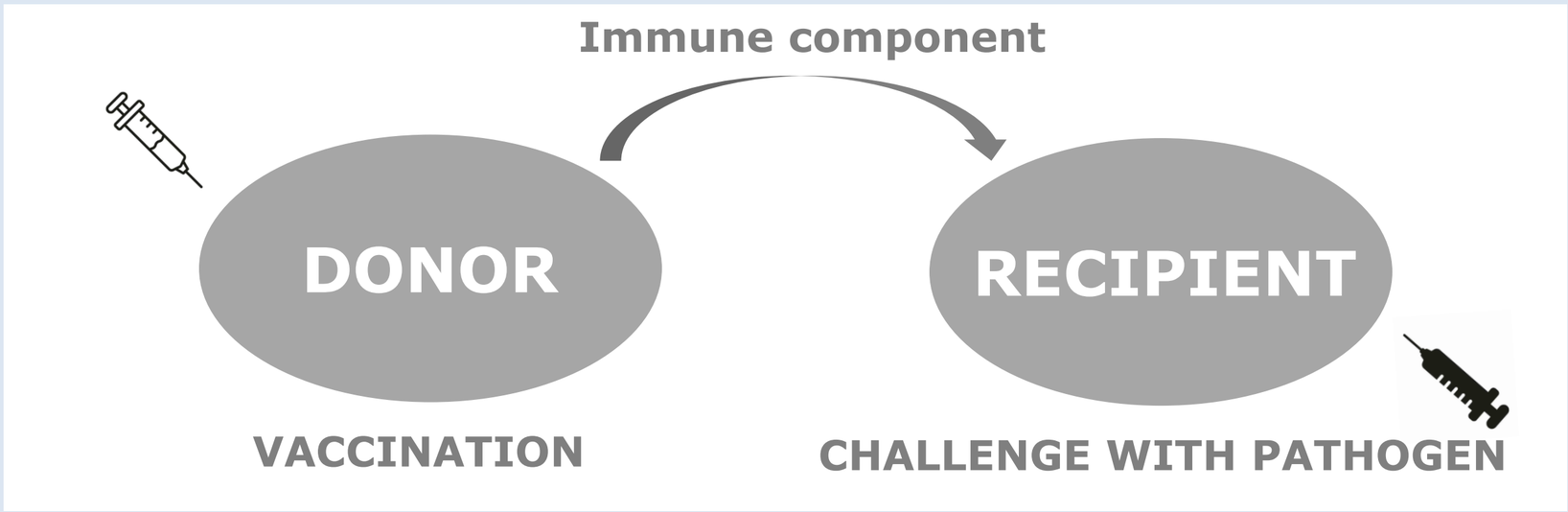


How to demonstrate protection?

NHP passive transfer study

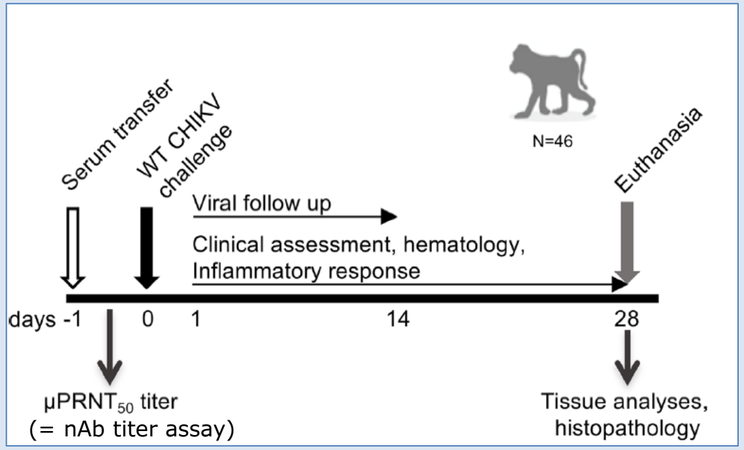
DONORS

Phase I

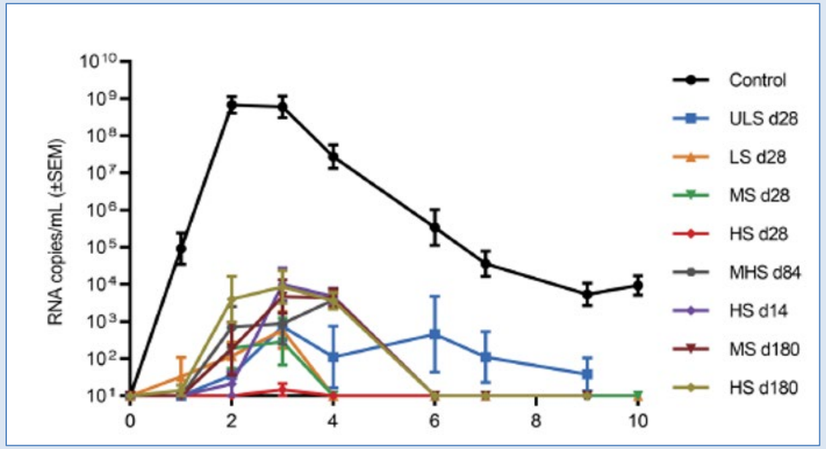
Serum obtained at different timepoints post-vaccination

Generation of serum Pools with different neutralizing antibody titers

RECIPIENTS



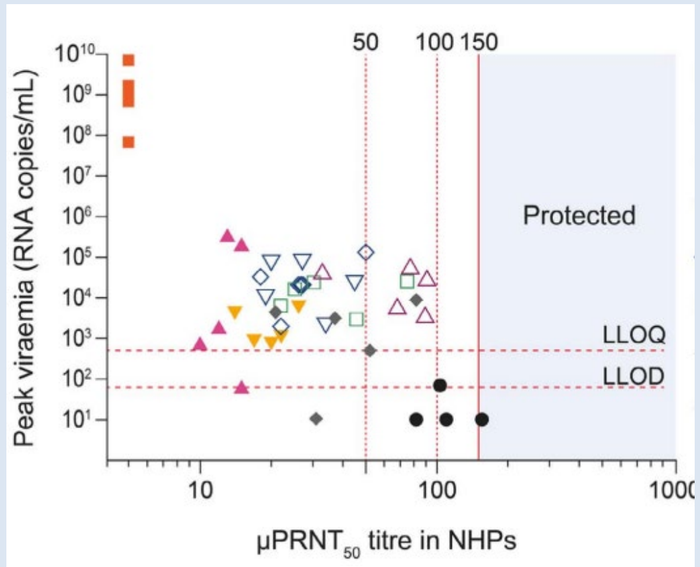
OUTCOME POST-CHALLENGE



Neutralizing antibody titer before challenge ⇒ protection from viremia post-challenge

How to demonstrate protection?

NHP passive transfer study



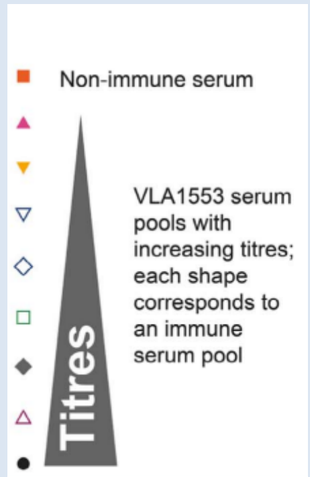


Table 2. Peak viremia for animals with different µPRNT$_{50}$ titer thresholds.

		µPRNT$_{50}$ ≥ 50 (*n* = 13)	µPRNT$_{50}$ ≥ 100 (*n*=4)	µPRNT$_{50}$ ≥ 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%)

From Lin et al. JTM (2024) https://doi.org/10.1093/jtm/taae123, and Roques et al., JCI Insight (2022) 7(14):e160173

How to demonstrate protection?

Sero-epidemiology

PRNT80 > 10

NHP passive transfer study

µPRNT50 > 150

Threshold as surrogate of protection

nAb titer

Phase III study

immunogenicity endpoint

% subjects reasonably likely protected based on threshold

How to demonstrate protection?

Sero-epidemiology

PRNT80 > 10

B

	$\mu PRNT_{50}/PRNT_{80}$	$\mu PRNT_{50}$ equivalent value
Geometric mean ratio	3.73	37.3
99% CI	2.86–4.87	28.6–48.7
Range	0.84–13.93	8.4–139.3

NHP passive transfer study

µPRNT50 > 150

nAb titer threshold as surrogate of protection

µPRNT50 > 150

From Lin et al. JTM (2024) https://doi.org/10.1093/jtm/taae123

How to demonstrate protection?

nAb titer threshold as surrogate of protection

µPRNT50 > 150

Phase III study

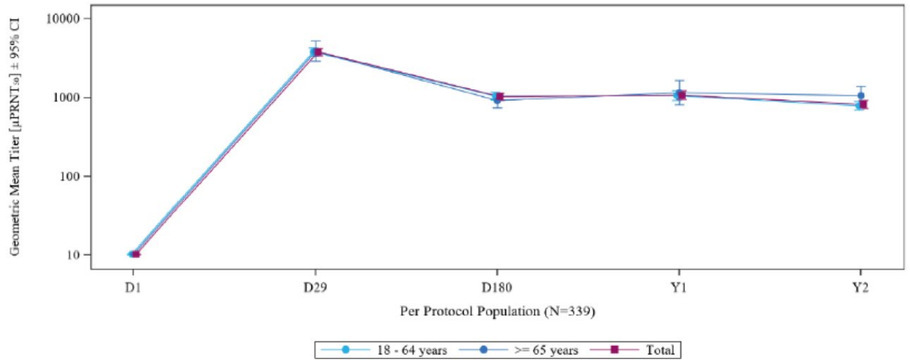
% subjects reasonably likely protected based on threshold

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

Study	VLA1553-301	
Treatment	Placebo	IXCHIQ
	N=96	N=266
	(n [95%CI])	(n (%) [95%CI])
Baseline day 1	0 (0)	0 (0)
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 reductio
PP=per-protocol (population)

Line plot of CHIKV-specific neutralizing antibody titres (GMT) by visit and age strata, using logarithmic scale (PP population)



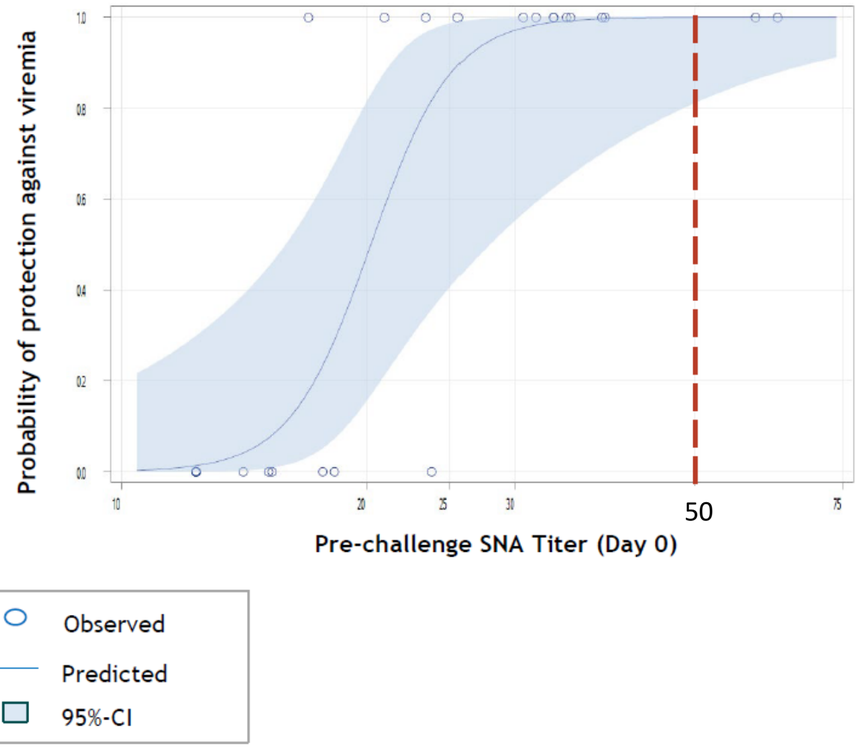
Age Strata	D1	D29	D180	Y1	Y2
18 - 64 years	290	240	279	157	234
>= 65 years	49	39	48	27	42
Total	339	279	327	184	276

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.

From Ixchiq SmPC and EPAR, www.ema.europa.eu

How to demonstrate protection?

NHP passive transfer study



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)

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

How to demonstrate protection?

VIM KUN YA

Sero-epidemiology

PRNT80 > 10

VRC 311 phase 1 clinical trial side-by-side NT80 >15-80

NHP passive transfer study

NT80 > 50

nAb titer threshold as surrogate of protection

NT80 > 100

How to demonstrate protection?

VIM KUN YA

nAb titer threshold as surrogate of protection

PRNT80 > 100

Phase III study

% subjects reasonably likely protected based on threshold

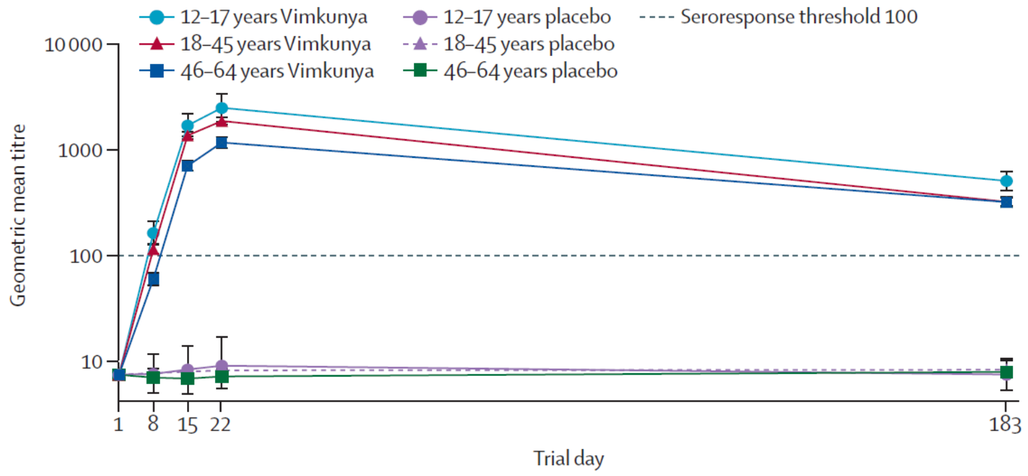
Table 2: Anti-CHIKV SNA seroresponse rate (SRR) at visit days 8, 15, 22 and 183 for phase 3 Study 1 (12 to < 65 years of age) (immunogenicity evaluable population)

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.

geometric mean titres for chikungunya virus serum neutralising antibodies by visit and by age strata (immunogenicity evaluable population)



From Richardson et al., Lancet 2025; 405: 1343–52, and Vimkunya SmPC, www.ema.europa.eu

CHIKUNGUNYA VACCINE LICENSURE

Recap and lessons learned

- Weight of evidence approach

  integration of complimentary data from different sources

- Decision for approval based on strong evidence (Strategy + Outcome phase III)
- Consequence of choice animal model

  How well model replicates human disease

  uncertainties translate in conservative approach in threshold identification

- Power of passive transfer study: mechanistic insight

  IR induced by infection $\stackrel{?}{=}$ IR induced by vaccination

  human antibodies induced by vaccination with specific vaccines, are sufficient to protect

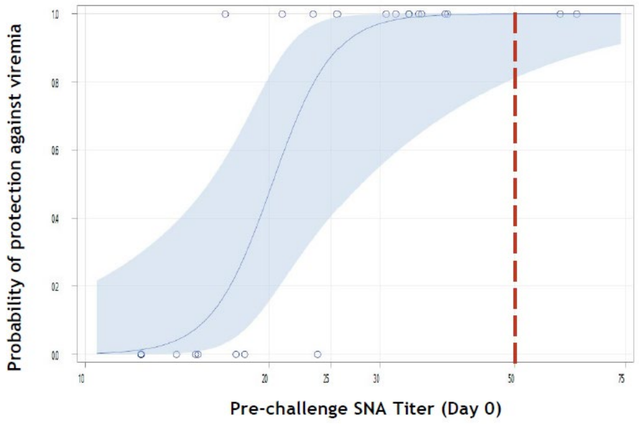
CHIKUNGUNYA VACCINE LICENSURE

Recap and lessons learned

- Different translation approaches possible

Chikungunya vaccine experience vs **Ebola vaccine experience**

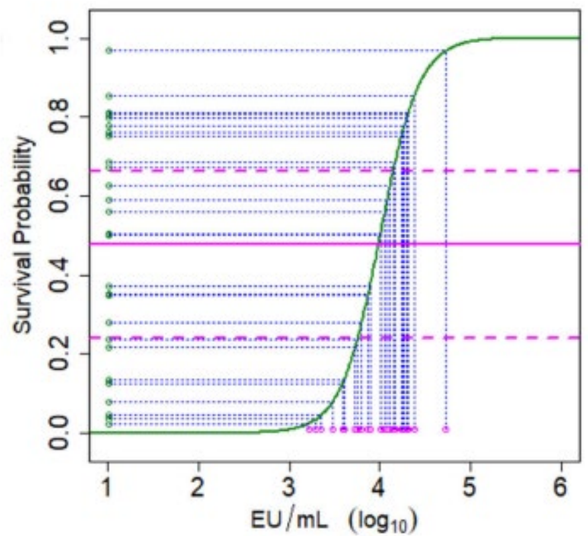
threshold-based **model-based**



Sero-epidemiology **NHP passive transfer study**

nAb titer **Threshold**

Phase III study
% subjects reasonably likely protected based on threshold



Roozendaal et al. 2020 Vaccines

Import human immune response in logistic regr model

Individual probability of protection

Derive mean probability of protection

CHIKUNGUNYA VACCINE LICENSURE

Recap and lessons learned

- Different translation approaches possible

  Chikungunya vaccine experience vs **Ebola vaccine experience**

  threshold-based **model-based**

- Threshold is different for the chikungunya vaccines

  µPRNT50>150 , NT80>100

  Specific for the assay used! development and validation

  Specific for the vaccine

- Post approval effectiveness data requested

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