Prospects and challenges for development of vaccines against dengue and Chikungunya

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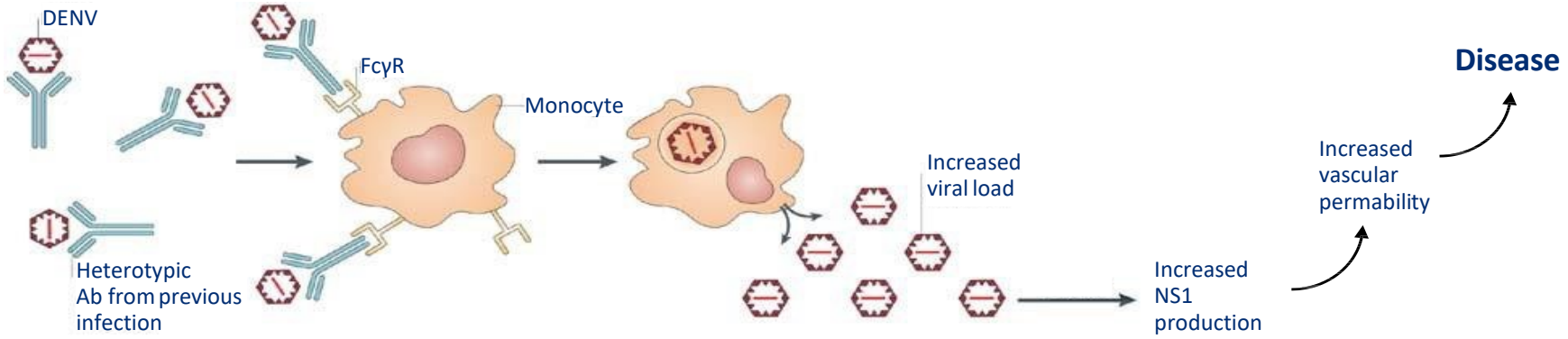
Objectives

- Discuss the challenges for the development of vaccines against dengue, chikungunya, and Zika
- Discuss landscape of dengue vaccines and implications for use
- Discuss the role of alternative pathways for licensure of chikungunya and Zika vaccines

Dengue: critical issues for vaccine development

- Four serotypes of DENV all capable of causing the full spectrum of disease (need for a tetravalent dengue vaccine)
- **Life-long homotypic** protection afforded after infection, but only short term (few months) heterotypic protection is afforded
- ***Secondary infection with a different serotype is strongly associated with severe disease***
  - Enhanced risk starts to occur ~ 2 years post 1° infection
  - Antibody-mediated enhancement of infection
  - Partial immunity to dengue is **BAD**

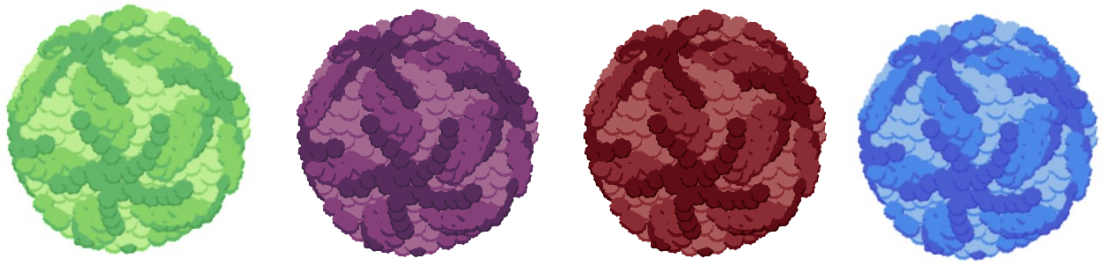


Whitehead Nat Rev Microbiology 2007 Nature Reviews | Microbiology

Beatty *et al*, *Science Trans Med* 2015

Important considerations for dengue vaccines

- ***A dengue vaccine is really 4 vaccines***: must be effective against all 4 DENV serotypes
- **Dengue vaccine must protect against all four DENV serotypes**
- Neutralizing antibody is the standard measure of immunogencity but is not predictive of efficacy (not a correlate of protection)
- Long-term safety follow-up required (~ 5 years)
- 80-90% of CD8 epitopes are located in the NS proteins



DENV-1 DENV-2 DENV-3 DENV-4

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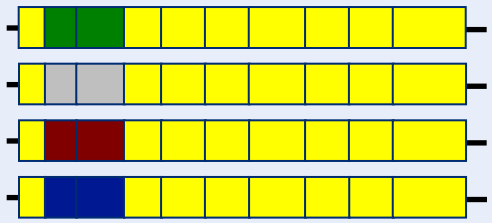
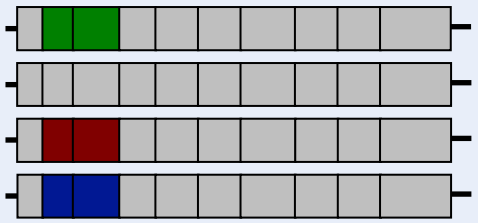
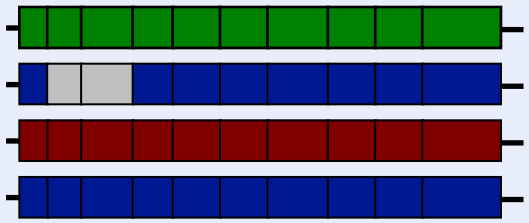
Dengue vaccines

- All licensed & advanced candidate dengue vaccines are live attenuated viruses
  - ***Live attenuated vaccines must infect and replicate within the host to induce a protective immune response***
- 2 vaccines are licensed in several different countries and have received recommendations from SAGE for use
  - Dengvaxia is restricted to those who have had a previous dengue infection
  - QDenga is recommended for those ≥ 6 years of age living in highly dengue regions as defined by a dengue seroprevalence of ≥ 60% by age 9

Live attenuated dengue vaccines

	Dengvaxia™ (Sanofi Pasteur)	QDenga (TAK-003 - Takeda)	TV003 (multiple manufacturers)
Status	Licensed	Licensed	Phase 3 (Instituto Butantan)
# Doses	**3 doses** over 12 months (0, 6, 12)	**2 doses** (0, 3 months)	**Single dose**
Indicated age	6 – 16 (US), 9-45 (WHO)	Phase 3 (age 4 – 16)	Phase 3 age 2 - 59
Other	**Documented previous DENV infection**	≥ 6 in areas of high DENV endemicity	?
Construct			
Dengue proteins	8	16	32

Dengvaxia

- First licensed dengue vaccine
- Comprised of 4 chimeric viruses with the prM and E of DENV-1, -2, -3, or -4 replacing those of YF17D on the YF17D vaccine background
- Had variable efficacy by serotype, serostatus, age
- A safety signal was observed in year 3 of the trial (2 years after the last dose)
  - Children 2 – 5 years of age at the time of vaccination had a 7.45 RR of hospitalized dengue in year 3 if they had received vaccine compared with placebo

Efficacy[1] of CYD-TDV (Dengvaxia™) against VCD

Trial	Region	Vaccine recipients enrolled	Age	Overall Efficacy (95% CI)	Efficacy, hospitalization	Efficacy, severe disease
CYD23[2]	Thailand	2,669	4-11	**30.2 (-13.4-56.6)**	Not reported	Not reported
CYD14[3]	SE Asia	6,851	2-14	56.5 (43.8-66.4)	**67%**	**80%**
CYD15[4]	Latin America	13,920	9-16	60.8 (52.0-68.0)	**80%**	**91.7%**

1. Per protocol analysis. Period of primary efficacy evaluation was > 28 days after the third dose to month 25 (12-month period)
2. Sabchareon, The Lancet, 2012
3. Capeding et al, The Lancet, 2014
4. Villar et al, NEJM, 2014

Efficacy[1] of CYD-TDV against VCD by serotype

Study	Overall Efficacy	DENV-1	DENV-2	DENV-3	DENV-4
CYD23[2]	30.2 (-13.4-56.6)	**55.6% (-21.6 - 84)**	**9.2% (-75 – 51.3)**	**75.3% (-37.5 – 99.6)**	100% (24.8 – 100)
CYD14[3]	56.5 (43.8-66.4)	50.0% (24.6 – 61.0)	**35.0% (-9.2 – 61.0)**	78.4% (52.9 – 90.8)	75.3% (54.5 – 87.0)
CYD15[4]	60.8 (52.0-68.0)	50.3% (29.1 – 65.2)	42.3% (14.0 – 61.1)	74.0% (61.9 – 82.4)	77.7% (60.2 – 88.0)

1. Per Protocol analysis
2. Sabchareon, The Lancet, 2012
3. Capeding et al, The Lancet, 2014
4. Villar et al, NEJM, 2014

Efficacy[1] of CYD-TDV (Dengvaxia™) against VCD by serostatus

Trial	Region	Vaccine recipients enrolled	Age	Efficacy in seropositive at baseline	Efficacy in seronegative at baseline
CYD23[2]	Thailand	2,669	4-11	Not reported	Not reported
CYD14[3]	SE Asia	6,851	2-14	**74.3 (53.2-86.3)**	**35.5 (-26.8-66.7)**
CYD15[4]	Latin America	13,920	9-16	**83.7 (62.2-93.7)**	**43.2 (-61.5-80)**

1. Per protocol analysis. Period of primary efficacy evaluation was > 28 days after the third dose to month 25 (12-month period)
2. Sabchareon, The Lancet, 2012
3. Capeding et al, The Lancet, 2014
4. Villar et al, NEJM, 2014

Hospitalized VCD CYD14

	Vaccine Group			Control Group			
	VCD	Total subjects	Annual Incidence	VCD	Total subjects	Annual Incidence	Relative Risk
All	27	6,778	0.4	13	3387	0.4	1.04 (0.52-2.19)
2 - 5	15	1,636	0.3	1	813	0.1	7.45 (1.15-313.8)
6 - 11	10	3,598	0.3	4	1806	0.5	0.63 (0.22-1.83)
12 - 14	2	1,544	0.1	4	768	0.6	0.25 (0.02-1.74)

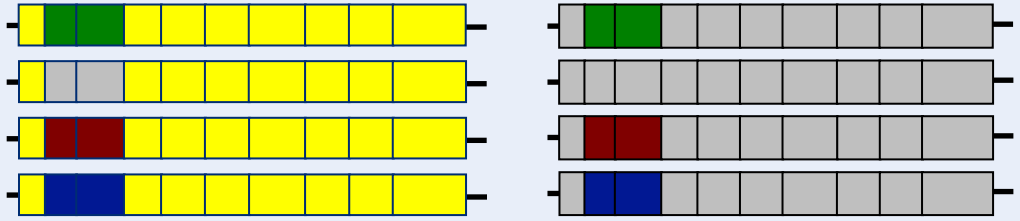
- Post-hoc analysis of CYD14 & CYD15 determined there was not an increased risk of hospitalization in those ≥ 9 years of age
- Additional studies determined increased risk was due to serostatus at vaccination (seronaive)

Hadinegoro NEJM 2015

SAGE recommendations

- Initially recommended for children ≥ 9 in areas of high endemicity
- Further studies identified seronegative at baseline as risk for more severe DENV disease 2 years following vaccination
- Recommendations changed to vaccinate only those ≥ 9 who have already had documented dengue
  - There is no point of care diagnostic
  - Uptake of vaccine has been very low and the company is discontinuing production

Qdenga (TAK-003)

	Dengvaxia™ (Sanofi Pasteur)	TAK-003 (Takeda)
Status	Licensed	Licensed
# Doses	**3 doses** over 12 months (0, 6, 12)	**2 doses** (0, 3 months)
Indicated age	6 – 16 (US), 9-45 (WHO)	Phase 3 (age 4 – 16)
Other	**Documented previous DENV infection**	≥ 6 in areas of high DENV endemicity (> 60% by age 9)
Construct		
Dengue proteins	8 (no NS proteins)	16 (8 DENV-2 NS proteins)

- Phase 3 clinical trial conducted in children 4 – 16 years of age in 8 countries
- Enrolled 20,071
- Randomized 2:1 vaccine:placebo
- **27.6% were dengue-naïve** at time of enrollment

TAK-003 Phase 3 results during each time period & through year 3 (36 months)

	Efficacy against VCD		Efficacy against hospitalized dengue	
	Seropositive	Seronegative	Seropositive	Seronegative
Year 1[1]	**82.2%** (74.5; 87.6)	**74.9%** (57.0;85.4)	**94.4%** (84.3; 98.0)	**97.2%** (79.1; 99.6)
Year 2[2]	60.3% (44.7; 71.5)	45.3% (9.9; 66.8)	90.0% (81.9; 94.5)	87.0 (70.1; 94.3)[2]
Year 3[3]	48.3% (34.2; 59.3)	35.5% (7.3;55.1)	78.4% (57.1; 89.1)	45.0% (**-42.6**; 78.8)
36 mo[3]	65% (58.9; 70.1)	54.3% (41.9; 64.1)	86% (78.4; 91)	77.1% (58.6; 87.3)

1. Biswal, S et al NEJM 2019
2. Lopez-Medina et al JID 2020. Hospitalized cases in year 1 43/58 were DENV-2; year 2 7/33 were DENV-2
3. Rivera, L et al CID 2021

Vaccine efficacy against VCD over time

	DENV-1		DENV-2		DENV-3		DENV-4	
	Seropos	Seroneg	Seropos	Seroneg	Seropos	Seroneg	Seropos	Seroneg
Year 1[1]	79.8% (51.3;91.6)	67.2% (23.2;86.0)	**96.5% (88.7;98.8)**	**100%**	71.4% (54.3;82.1)	**-38.7% (-335;55.8)**	**63.8% (-61.8;91.9)**	n/a
Year 2[2]	59.1% (31.1;75.7)	60.7% (22.1;80.2	**75.5% (49.5;88.1)**	**70.5% (23.4;93.0)**	44.9% (1.6;69.1)	**-18.5% (-236.2;58.3)**	**69.0% (-85.8;94.8)**	**-47.6% (-1319;84.6)**
Year 3[3]	45.4% (24.5;60.6)	**17.2% (-31.8;47.9)**	**72.1% (51.6;84.0)**	**84.9 (58.7;94.5)**	**15.2% (-46.1;50.8)**	**9.5% (-144.7;66.5)**	**61.9% (-24.9;88.4)**	**-99.0% (-1681;77.8)**

1. Biswal, S et al NEJM 2019
2. Lopez-Medina et al JID 2020.
3. Rivera, L et al CID 2021

Vaccine efficacy against VCD by serostatus through 57 months after first dose

	Placebo n=6687	TAK-003 n=13,380	VE (95% CI)
VCD (per 100 person-yrs)			
Seropositive			
DENV-1	151 (0.7)	133 (0.3)	**56.1 (44.6, 65.2)**
DENV-2	135 (0.6)	54 (0.1)	**80.4 (73.1, 86.7)**
DENV-3	97 (0.4)	96 (0.2)	**52.3 (36.6, 64.0)**
DENV-4	20 (<0.1)	12 (<0.1)	**70.6 (39.9, 85.6)**
Seronegative			
DENV-1	79 (1.0	89 (0.5)	**45.4 (26.1, 59.7)**
DENV-2	58 (0.7)	14 (<0.1)	**88.1 (78.6, 93.3)**
DENV-3	16 (0.2)	36 (0.2)	**-15.5 (-108.2, 35.9)**
DENV-4	3 (<0.1)	12 (0.1)	**-105.6 (-628.7, 42.0)**

SAGE, Tricou 2024

Vaccine efficacy against hospitalized VCD by serostatus through 57 months after first dose

	Placebo n=6687	TAK-003 n=13,380	VE (95% CI)
VCD (per 100 person-yrs)			
Seropositive			
DENV-1	24 (0.1)	16 (<0.1)	**66.8 (37.4, 82.3)**
DENV-2	59 (0.3)	5 (<0.1)	**95.8 (89.6, 98.3)**
DENV-3	15 (<0.1)	8 (<0.1)	**74.0(38.6, 89.0)**
DENV-4	3 (<0.1)	0 (<0.1)	**100 (NE)**
Seronegative			
DENV-1	14 (0.2)	6 (<0.1)	**78.4 (43.9, 91.7)**
DENV-2	23 (0.3)	0 (0.0)	**100 (NE, NE)**
DENV-3	**3 (<0.1)**	**11 (<0.1)**	**-87.9 (-573, 47.6)**
DENV-4	1 (<0.1)	0 (0.0)	**100 (NE, NE)**

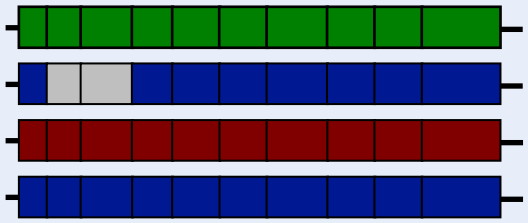
SAGE, Tricou 2024

TAK-003: SAGE Guidance

- SAGE met September 23, 2023
  - Recommend introduction to children aged 6 to 16 in settings with a dengue seroprevalence of ≥ 60% by age of 9
    - 2-dose schedule
  - Does not recommend use in children 4 – 5 years of age as the vaccine performance in this age group in seropositive and seronegative is lower
  - Recommend post-licensure studies to provide more precise estimates of effectiveness/risk profile against DENV-3 and DENV-4 in seronegative persons

Clinical development of the NIH LATV vaccine

- Components of tetravalent vaccine first evaluated as monovalent vaccines in flavivirus-naïve volunteers
  - Several tetravalent admixtures evaluated for infectivity, safety, and immunogenicity
- **Single dose vaccine**
- Phase 3 trial conducted by Instituto Butantan in Brazil
  - **47% vaccine recipients were seronaive**
- Interim results through 2 years post vaccination published

	TV003 (multiple manufacturers)
Status	Phase 3 (Instituto Butantan)
# Doses	**Single dose**
Indicated age	Phase 3 age 2 - 59
Other	?
Construct	
Dengue proteins	32 (NS proteins of DENV-1, DENV-3, & DENV-4)

Efficacy of DEN-03 through 2 years post-vaccination

	Overall efficacy	DENV-1	DENV-2
Overall	**79.6** (70.0-86.3)	**89.5** (78.7-95.0)	**69.6** (50.8-81.5)
Seropositive	**89.2** (77.6-95.6)	**96.8** (81.0-99.8)	**83.7** (63.1-93.5)
Sero-naive	**73.6** (57.6-83.7)	**85.5** (61.1-94.0)	**57.9** (20.8-78.1)

1. **There were not any cases of severe dengue in the 2 years post-vaccination.**
2. **There were not any cases of DENV-3 or DENV-4 detected in the first 2 years of the trial**

Kallas E, et al, NEJM 2024

Efficacy against severe dengue/dengue with warning signs through the cut-off (average follow-up of 3.7 years) was 88.2% (50.8-98.2)

Efficacy by age group & serostatus through 2 years post- vaccination

	2 – 6 years	7 – 17 years	18 – 59 years
Overall	**80.1** (66.0-88.4)	**77.8** (55.6-89.6)	**90.0** (68.2-97.5)
Seropositive	**96.6** (79.6-99.8)	**82.1** (53.7-93.1)	**94.8** (68.5-99.8)
Sero-naive	**73.4** (53.1-85.6)	**75.4** (29.6-91.8)	**81.1** (5.7-97.1)
% sero-naive	**82%**	**37%**	**28%**

Viremia following single dose of TV003 by PCR or (culture – infectious viremia)

The percentage of subjects with detectable viremia by PCR after a single dose in flavivirus-naïve subjects				
	DENV-1	**DENV-2**	**DENV-3**	**DENV-4**
CYD (n=95)[1]	7.4	0	12.6	**44.2**
TAK (n=74)[2]	0	**68.9**	0	0
TV003 (n=19)[3]	**58.0**	**63.2**	**78.9**	**78.9**
TV003 (n=40)[4]	**(23)**	**(5)**	**(38)**	**(33)**
TV003 Butantan (n=19)[5]	**(26%)**	**(16%)**	**(37%)**	**(0)**

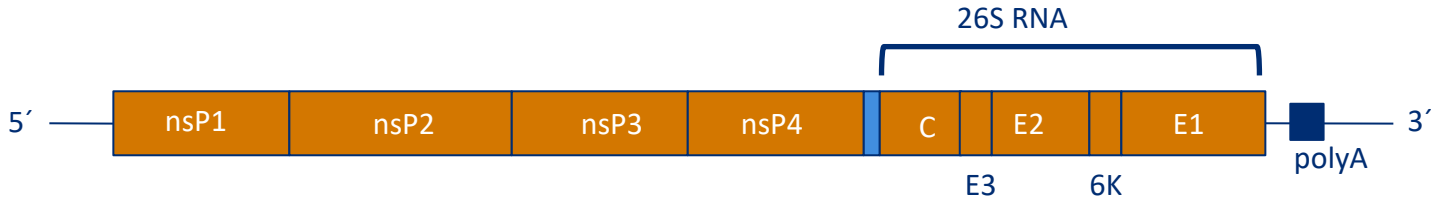
1. Torresi, et al 2017; CYD lot-to-lot consistency trial. Viremia measured on days 6, 8, 10, 14, & 20
2. Rupp et al 2015; Viremia measured on days 7, 9, 11, 14, &17
3. CIR323, unpublished, Viremia measured on days 0, 4, 6, 8, 10, 12, 14, 16.
4. Kirkpatrick, et al JID, 2015. Viremia measured by tissue culture, not by PCR on days 0, 4, 6, 8, 10, 12, 14, 16.
5. Kallas, et al Lancet, 2020. Viremia assess by culture from samples collected on days 3, 6, 9, 12, 15, and 21

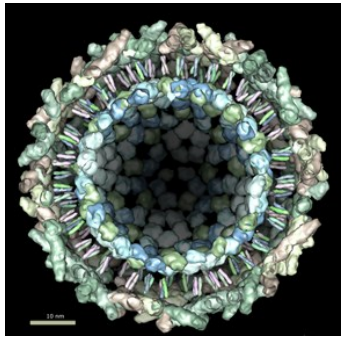
Summary of TV003 Butantan trial

- A single dose of TV003 provides very good efficacy against virologically-confirmed DENV-1 and DENV-2 through 2 years post-vaccination
- A single dose of TV003 provides excellent efficacy in all age groups, regardless of serostatus
- Licensed to several manufacturers (Instituto Butantan, Serum Institute of India, Panacea, Merck)
- Efficacy against DENV-3 and DENV-4 not known
- 5-year follow-up to be completed June 2024
  - Possible ANVISA submission Q4 2024

Chikungunya Virus

- Single stranded positive sense RNA
- Togaviridae family
  - Alphavirus genus
  - Enveloped virus of approx. 12,000 nucleotides
  - Subgenomic positive-sense RNA referred to as 26S RNA is transcribed from a negative-stranded RNA intermediate





Chikungunya epidemiology

- Chikungunya is an alphavirus
- Transmitted by *Aedes* mosquitoes
  - *Aedes aegypti* and *Aedes albopictus*
- Endemic to Africa, India, Southeast Asia, Indian Ocean
  - Most cases in the U.S. mainland are imported however local transmission of CHIK has occurred in Florida, Puerto Rico, and U.S. Virgin Islands
- Has re-emerged in recent years, infecting millions of people
- Outbreaks are unpredictable and sporadic
  - Difficult to conduct Phase 3 efficacy trial for vaccine development

Clinical manifestations

- Short incubation period (2 – 6 days)
- Acute stage
  - Sudden onset symptoms. High fever, incapacitating polyarthritis, skin manifestations
  - Can be confused with dengue
  - Acute arthralgia/arthritis mostly bilateral, symmetric, involving peripheral joints (wrists, hands, feet, and ankles)
  - Maculopapular rash, diffuse hyperemia, and edema of face and extremities
- Concern for persistence of the antigen in joints

Clinical manifestations

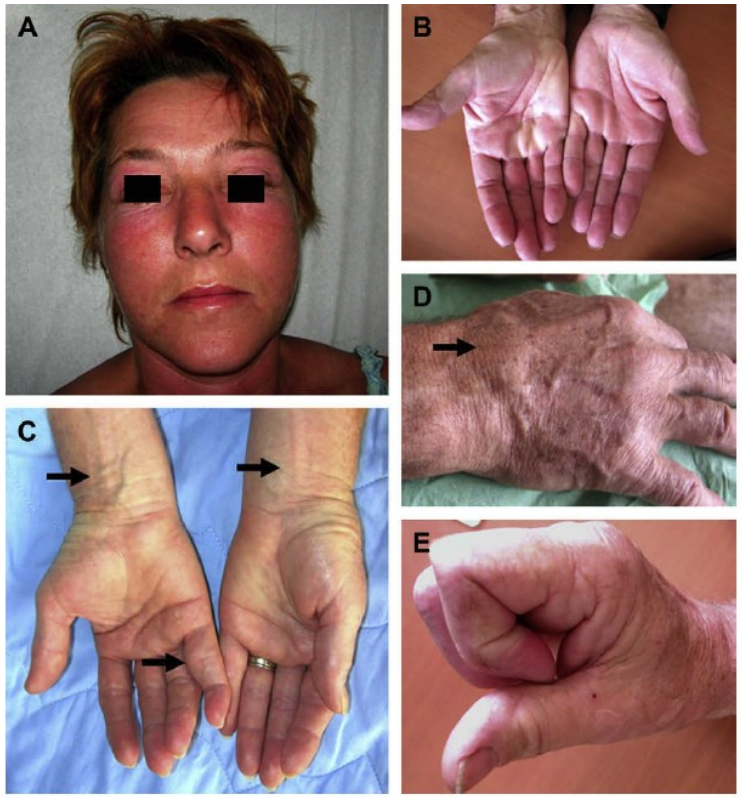


Fig. 4. Clinical manifestations of CHIK infection. (*A*) Edematous exanthema of the face (acute stage). (*B*) Raynaud's phenomenon at the third month after disease onset (chronic stage). (*C*) Polyarthritis in hands and hypertrophic tenosynovitis in wrists at the third month after disease onset (chronic stage). (*D*) Bursitis of dorsal side of the hand (chronic stage). (*E*) Chronic swelling and stiffness of the fingers with loss of grip strength (chronic stage).

Med Clin N Am 92 (2008) 1323-1343

Large outbreaks

- Occurred in 2006 on Reunion island, a French island in Western Indian Ocean
- High attack rate: 266,000 infected (34% population)
- 2006 had large outbreak of severe disease in India
- Disease more severe in elderly
  - CFR increased from 0.3 -1/1,000 to 47/1000 in patients older than 75

Chikungunya, dengue, Zika

	Chikungunya	Dengue	Zika virus
Fever, asthenia	Common	Common	Less common
Rash	Common	Common	Common
Conjunctivitis	None	None	Common
Retro-orbital pain	Rare	Common	Rare
Myalgia	Possible	Very common	Possible
Polyarthritis	**Very common**	None	None
Tenosynovitis	**Yes**	None	None
Hypotension	Possible	Common, days 5-7	None
Minor bleeding	Possible	**Common**	None
Second Stage	Chronic polyarthritis, tenosynovitis at M2-M3	Fatigue up to 3 months	GBS – can start 5 – 6 days after illness onset
CBC	Lymphopenia	**Neutropenia, Thrombocytopenia**	Normal

Treatment

- Empiric, supportive
  - Anti-inflammatory agents, steroidal or non-steroidal
  - Corticosteroid treatment should not be prolonged or repeated in elderly due to risks
  - People infected with CHIK should be protected from mosquito exposure during the first week of illness to reduce local transmission
- Vaccine development
  - Valneva live attenuated vaccine (VLA1553) completed Phase 3 clinical trial

Chikungunya vaccines

- A live attenuated vaccine was developed by WRAIR and advanced to Phase 2
  - Was safe and immunogenic but development stopped in 1998
- Emergent Biosolutions developed a VLP vaccine.
  - Well-tolerated and immunogenic after 2 vaccinations
  - Phase 3 trial was completed in April 2023
- Bharat Biotech is developing an inactivated vaccine (BBV87)
  - Completing Phase 2/3
- Valneva has completed Phase 3 of a live attenuated vaccine (VLA1553)
  - Based on the La Reunion strain

VLA1553 (Ixchiq)

- Attenuated by 61 amino acid deletion in the non-structural protein 3
- Induces transient viremia (live vaccine)
- Targets all Chikungunya strains
  - Comprehensive cross-neutralization to the rapidly spreading Asian lineage
- Viremia too low to result in transmission

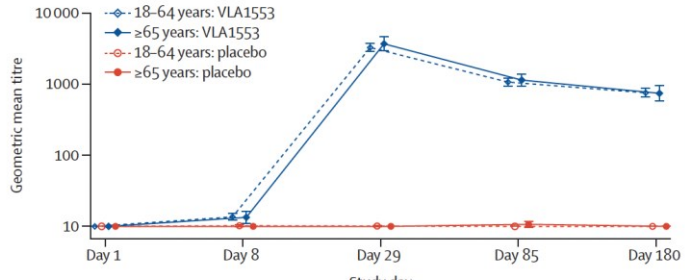
VLA1553 results

- Evaluated a dose of 1 x 10^4 $TCID_{50}$
- Evaluated in 18 – 64 years and ≥ 65 years old
- Both groups achieved > 98% seroprotection

	18–64 years (stratum A)		≥65 years (stratum B)		Total	
	VLA1553 (n=207)	Placebo (n=73)	VLA1553 (n=59)	Placebo (n=23)	VLA1553 (n=266)	Placebo (n=96)
Total* (n)	207	73	59	23	266	96
Participants with seroprotection, n (%)	204 (98·6%)	0	59 (100%)	0	263 (98·9%)	0
95% CI for seroprotection rate	95·8–99·7	0·0–4·9	93·9–100·0	0·0–14·8	96·7–99·8	0·0–3·8
p value†	<0·0001	>0·9999	<0·0001	>0·9999	<0·0001	>0·9999
Difference in seroprotection rate‡	98·6	..	100·0	..	98·9	..
95% CI	96·9–100·0	..	100·0–100·0	..	97·6–100·0	..
p value§	<0·0001	..	<0·0001	..	<0·0001	..

Data are in the per-protocol population. Percentages are based on the number of baseline negative participants with non-missing titres at the visit. Seroprotection was defined as $\mu PRNT_{50}$ titre ≥150 for µPRNT baseline negative participants (<20). Two-sided 95% exact (Clopper-Pearson) CIs are presented. Where the upper bound of the CI would be greater than 100%, the upper confidence limit is restricted to 100. $\mu PRNT_{50}$ titre=serum dilution with 50% plaque reduction in a micro plaque reduction neutralisation test. *Number of µPRNT baseline negative participants (<20) with non-missing titres on day 29. †p value from an exact binomial test for the null-hypothesis H0: seroprotection rate ≤70% against the alternative H1: seroprotection rate >70% with a one-sided significance level of 2·5%. ‡Differences, p values, and associated CIs are presented for the VLA1553 group minus the placebo group. §p value from Fisher's exact test.

Table 2: **Seroprotection rate for chikungunya virus-specific neutralising antibodies on day 29**



Number of participants					
18–64 years: VLA1553	207	198	207	194	184
18–64 years: placebo	73	70	73	69	68
≥65 years: VLA1553	59	53	59	52	58
≥65 years: placebo	23	23	23	22	23

Figure 2: **Assessment of neutralising antibodies after vaccination**
Line plot of chikungunya virus-specific neutralising antibodies geometric mean titres by study day and age stratum. Days shown in the figure refer to study days; day 1=day of vaccination. Error bars indicate 95% CIs. Neutralising antibodies to the vaccine were evaluated from clinical specimen (human serum) using a micro plaque reduction neutralisation test (µPRNT). A $\mu PRNT_{50}$ titre was defined as the dilution with 50% plaque reduction in the µPRNT.

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Approval of IXCHIQ

- Approved by US FDA Nov 9, 2023 by **accelerated pathway**
  - A correlate of protection was established by passive transfer of antibody from vaccine recipients to NHP and then challenging NHP
  - Correlate was µPRNT of ≥ 150
- Committee for Medicinal Products for Human Use (CHMP) of EMA recommended authorization of a single-dose of the vaccine for the prevention of CHIK in those ≥ 18 May 31, 2024
  - European Commission will review the CHMP recommendation

VLA1553 (Ixchiq)

- Indicated for those individuals ≥ 18 years of age at increased risk of exposure
- Single dose primary vaccine schedule
- Most adverse events were mild to moderate, but some chikungunya-like AEs were reported
- Vaccine viremia occurs in the first week following vaccination
- Post-licensure trials vaccine effectiveness trials planned
  - Current Phase 3 in adolescents – vaccine immunogenic and well tolerated
  - Case control study in Brazil in those ≥ 12 to start in 2026