Emerging Infectious Disease – Chikungunya as a Public Health Threat and Introduction to a Novel Vaccine Candidate (VLA1553)

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Conflict of Interest Statement

Honoraria for consultancies, lectures

and as principal investigator in studies from

Abbott, Astra Zeneca, Bavarian Nordic, Baxter, Boehringer Ingelheim, Clover Pharmaceuticals, Crucell, Dr. Falk, Emergent, GSK, Glenmark, Hermes Arzneimittel, Hoffmann LaRoche, Janssen Cilag, Medicago, Novartis Vaccines, Pfizer, r-biopharm, Sanofi Pasteur, MSD Sharp & Dohme, Sekizui-Virotech, Sigma Tau, Takeda, Themis Bioscience, Valneva

This presentation is sponsored by Valneva.

Case Report

- In late 2013, a 54yo man presents in our outpatient clinic with ongoing arthralgia, esp. hands & wrists
- Previous stay in Dominican Republic, works there as a journalist for German press. Cannot type, ergo cannot work.
- Dx of Chikungunya is established (serology)
- I tell him that symptoms will go away, give symptomatic treatment.
- Patients presents again every 2 years, latest visit 2021. Symptoms did not go away. Patient is incapacitated, unable to work since 2013. Had to quit his job and to sell his house in Dominican Republic.
  Developed depression. Dire financial situation.

Chikungunya is becoming an increasing global health issue as it spreads across the world

- Chikungunya, a mosquito-borne viral disease caused by Chikungunya virus (CHIKV), is characterized by acute febrile polyarthralgia and inflammatory arthritis and other systemic manifestations
  - ➢The joint pain can be severe, debilitating, and long-lasting
- The disease name is the Kimakonde word for "to become contorted," describing the stooped appearance of sufferers with severe chronic incapacitating arthralgias

- Chikungunya was first described in 1952 during an outbreak in Tanzania.[1,2] Initially, the virus appeared stable but has evolved and spread across the globe.[3]
  - ➢Outbreaks have occurred across 6 continents
- Epidemics are characterized by large explosive outbreaks with high attack rates between years-long periods of quiescence[4-6]
  - ➢Affecting 1/3 to 3/4 of the population in areas where the virus is circulating
  - ➢High attack rates often overwhelm local health care systems

1. Robinson MC. Trans R Soc Trop Med Hyg. 1955. 49:28-32. 2. Lumsden WH. Trans R Soc Trop Med Hyg. 1955. 49:33-57. 3. Nsoesie, EO et al. Euro Surveill. 2016; 21:doi: 10.2807/1560-7917.ES.2016.21.20.30234. 4. Staples et al. CDC Yellow Book 2020, Chapter 4. 5. CDC Arboviral Diseases Branch, Division of Vector-Borne Diseases. Chikungunya in the United States, April 8, 2015. 6. Paul BJ. Rheumatol Ther. 2018. 5:317-326.

CHIKV is a single-stranded RNA alphavirus[1]

Phylogenetic analysis has revealed 3 distinct strains[1,2]

- ✓ **West African**
- ✓ **East-Central-South African (ECSA)**
- ✓ **Asian**

- CHIKV is spread by the same mosquitoes that transmit dengue and Zika viruses.
- The symptoms of these diseases are similar, leading to misdiagnosis and delays in treatment in areas where they are common[3]

1. Da Cunha RV, Trinta, KS. Mem Inst Oswaldo Cruz, Rio de Janeiro. 2017;112:523-531.
2. Sahadeo et al. PLOS Neg Trop Dis 2015;9: e0004199.
3. https://www.cdc.gov/chikungunya/hc/diagnostic.html, accessed 8/26/2020.

Transmission of CHIKV

CHIKV is transmitted to humans through mosquitoes that belong to the Aedes genus[1,2]

- The primary vectors of CHIKV are ***Aedes aegypti*** and ***Aedes albopictus*** mosquitoes
- These are aggressive daytime-biting mosquitoes but also active at night

Aedes aegypti

Aedes albopictus

During quiescent periods, CHIKV is maintained in the environment between humans or other animals and mosquitoes[3,4]

- Africa: sylvatic cycle between monkeys, rodents, and birds and multiple Aedes mosquitos
- Asia: urban cycle between *Aedes aegypti* mosquitoes and humans

1. https://www.ecdc.europa.eu/en/disease-vectors/facts/mosquito-factsheets/aedes-aegypti, accessed 8/20/2020.
2. https://www.ecdc.europa.eu/en/disease-vectors/facts/mosquito-factsheets/aedes-albopictus, accessed 8/20/20.
3. Thiboutot M, et al. PLoS Negl Trop Dis. 2010;4:e623 4. https://www.who.int/news-room/fact-sheets/detail/chikungunya, accessed 8/3/2020.

Chikungunya Epidemiology

Risk to travelers: historical spread

For 5 decades, only periodic outbreaks of CHIKV were reported	The 2006-2007 mutated strain with enhanced fitness for Aedes albopictus quickly became predominant and generated an explosive outbreak	By 2007, the disease was no longer considered a tropical illness, as it had spread to several non-tropical and temperate areas	In late 2013, the first locally acquired cases in the Americas were reported on Caribbean islands	Since 2013, CHIKV has spread to 45 countries and territories in North, Central, and South America	By the end of 2017, more than 2.6 million suspected cases were reported in the Americas

2006 **2007** 2008 2009 2010 2011 2012 **2013** 2014 2015 2016 **2017**

> **"Further spread and establishment of the disease in the Americas is likely, given the high number of travelling between the affected and non-affected areas and the widespread occurrence of efficient vectors"**
>
> *Van Bortel W et al. Euro Surveill. 2014;19: 20759*

Eurosurveillance

ECDC Chikungunya virus disease. Annual epidemiological report for 2018.

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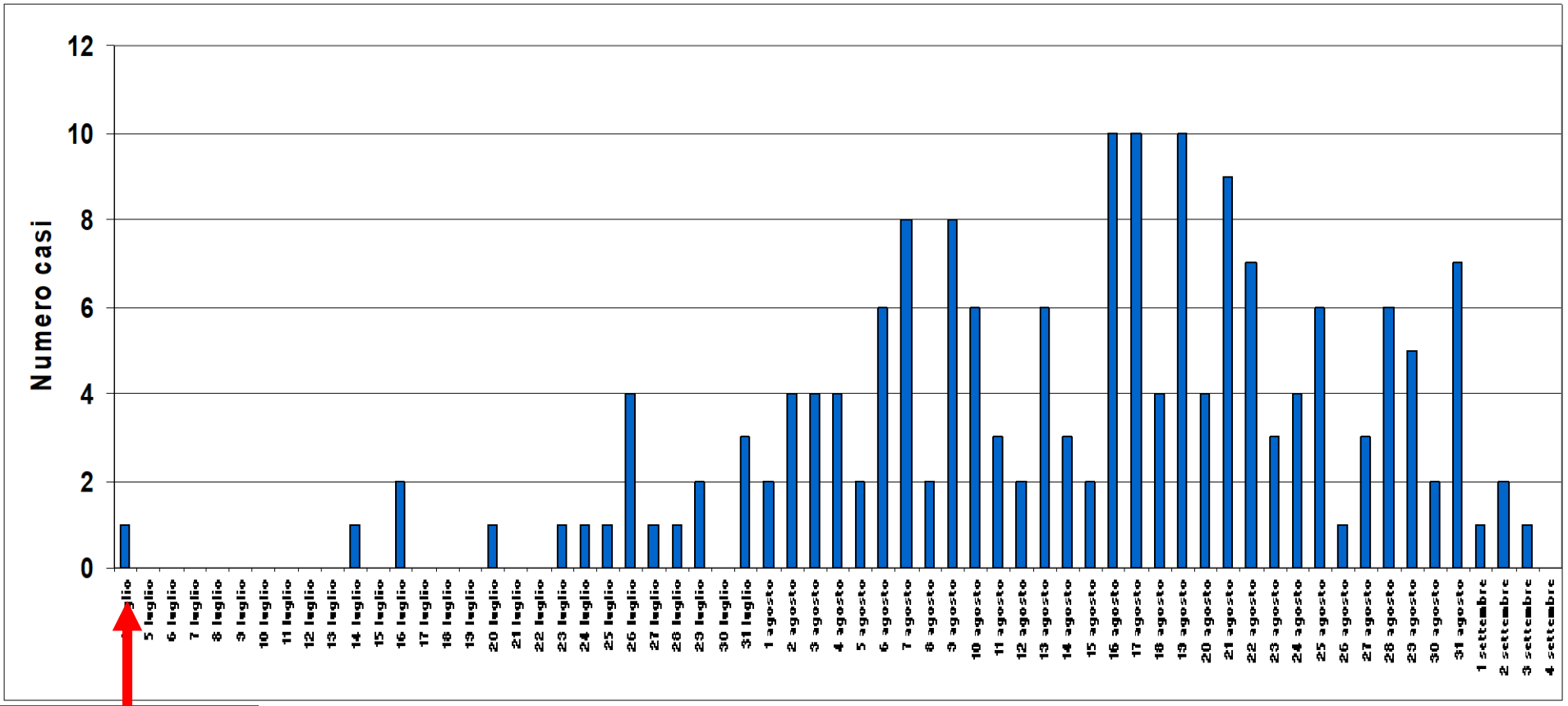
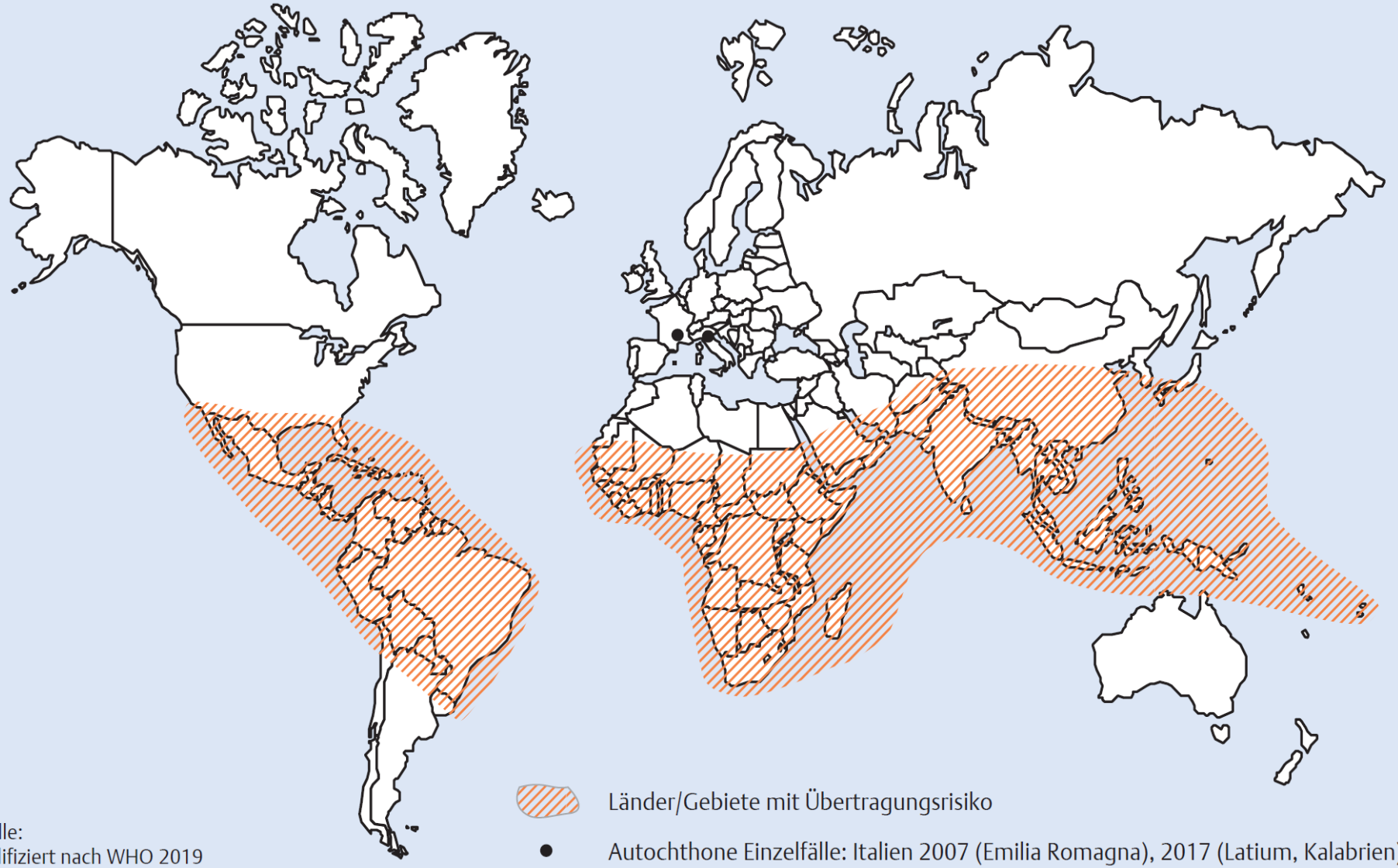
First CHIKV-Outbreak in Italy

4th july-4 september 2007 – total cases n° 176



Index case ?

Chikungunya



Quelle:
modifiziert nach WHO 2019
+ Ergänzungen CRM

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Source: CRM Handbuch Reisemedizin

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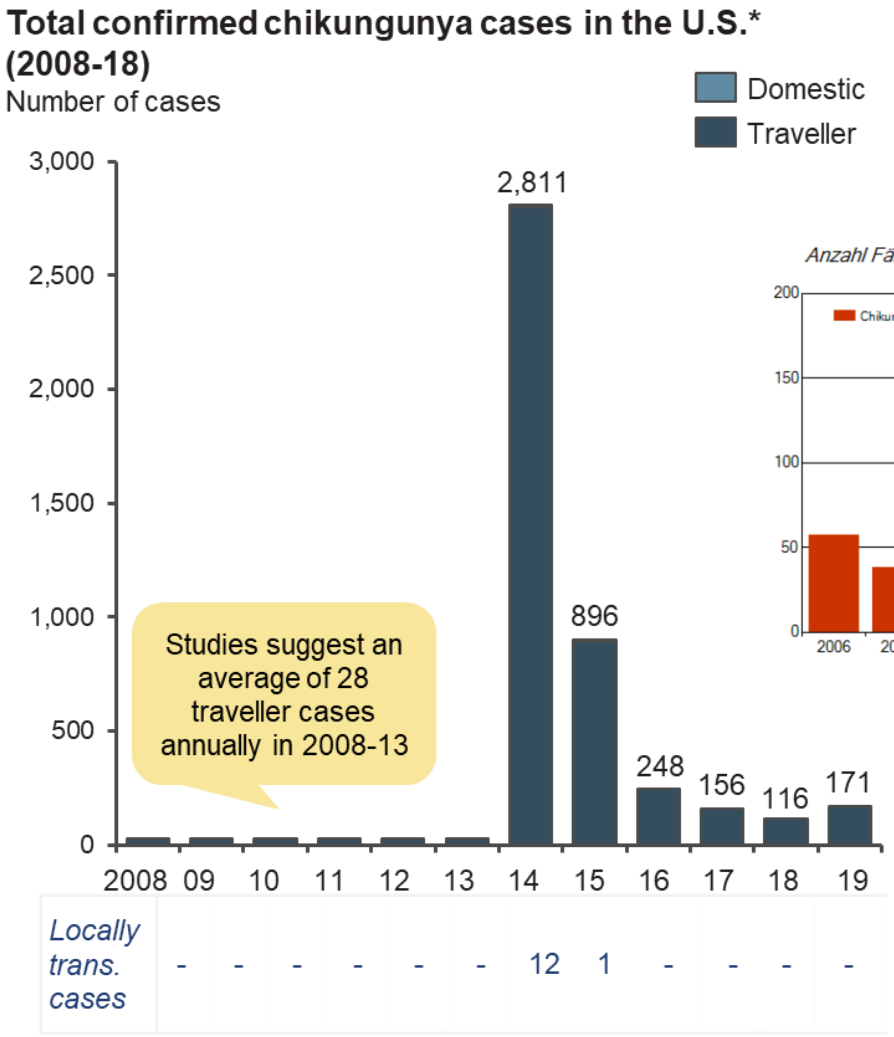
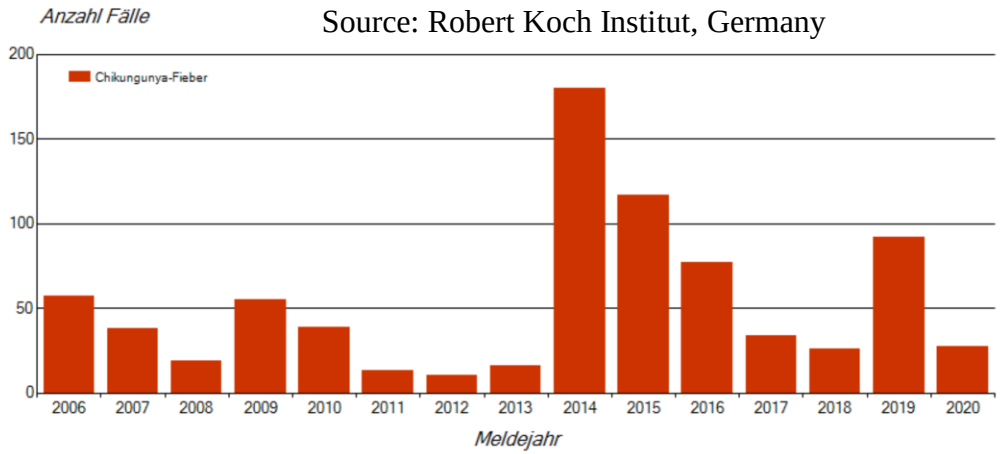
Chikungunya: Imported Cases



*Chikungunya became a nationally notifiable condition in 2015

Source: Robert Koch Institut, Germany



*CDC Arboviral Diseases Branch, Division of Vector-Borne Diseases. Chikungunya in the United States, April 8, 2015. 2. https://www.cdc.gov/chikungunya/geo/index.html, accessed 3 August 2020.

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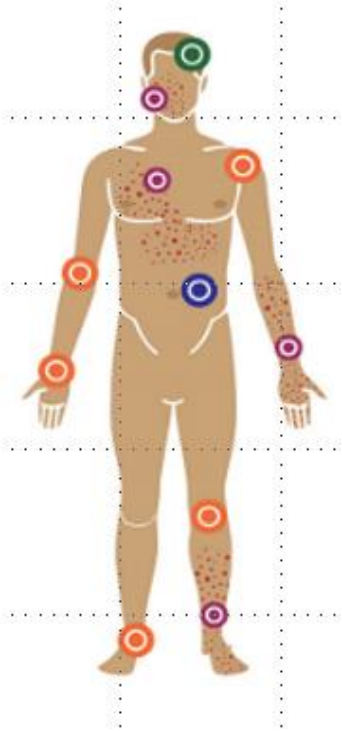
Symptoms of Chikungunya

- Millions of cases of CHIKV occur annually worldwide[1,2]
  - Up to 97% of infected individuals are symptomatic1,2
  - Low mortality rate; estimated case-fatality rate of ~0.1%

- Chikungunya has ACUTE (< 3 months) and CHRONIC (> 3 months) phases of disease[2]

- Primary symptoms include acute onset of fever and polyarthralgia[1,2]
  - Polyarthralgia is described in 87% to 98% of cases
  - Usually bilateral and symmetric
  - Joint symptoms are typically severe and can be debilitating

- Other symptoms may include headache, myalgia, arthritis, conjunctivitis, nausea, vomiting, or a maculopapular rash[1]



1. Thiberville SD, et al.. Antiviral Res; 2013 99:345-370. 2. Queyriaux B, et al. Lancet Infect Dis 2008;8:2-3.

Chikungunya Disease Process

Acute Phase
(up to 97%)[1]

- Symptoms typically begin 3–7 days after being bitten by an infected mosquito[1]
- Viremic for 5-10 days[2,3]
- Acute symptoms typically resolve in 7–10 days[1]
- Sub-acute post-viremic state (6-21 days) can occur[3,4]
  - Persistent articular symptoms
  - Tenosynovitis and bursitis

Chronic Phase
(4% to 78%)[5,6]

- Pattern similar to Rheumatoid Arthritis
  - Characterized by peripheral spondylarthritis, undifferentiated arthritis, fibromyalgia, neuropathic chronic pain
- Fatigue is other main persistent symptom, can last for months to years[7,8]
- Risk factors for developing chronic symptoms:[(6,9)]
  - >45 years of age
  - high viral load during acute phase
  - severe immunologic response in post-viremic phase

1. Staples et al. CDC Yellow Book 2020, Chapter 4. 2. Rudolph KE, et al. Am J Trop Med Hyg. 2014;90:882-891. 3 Suhrbier A et al. Nat Rev Rheumatol. 2012;8:420-429. 3. Thiberville SD et al. PLoS Negl Trop Dis. 2013; 2014;7:e2004-e2004. 4. Stalkowsky F et al. PLoS one 2009;4:e7603-e7603. 5. Rodríguez-Morales AJ et al . Arthritis Care Res 2016;68:849-58 6. Martí-Carvajal A et al. PLoS One 2017;12:e0179028 7. Manimunda SP, et al. Trans R Soc Trop Med Hyg 2010; 104: 392–99. 8. Soumahoro MK, et al. PLoS One 2009;4:e7800. 9. Zaid A et al. Arthritis Rheumatol 2018;70:484-95

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Chikungunya: Rheumatologic Disease

Post-CHIKV Rheumatism - 2 forms -	Effect of Arthritis/Polyarthritis	Impact on Quality of Daily Life
Mechanical musculoskeletal disorders	Long-term joint pain	• **Rising from chair** • **Walking** • **Picking up objects** • **Opening a bottle** • **Self care** • **Physical impact on leisure time and limitations on activity**
	Stiffness after immobility[1,4]	
	Multiple joints affected, ie, spine, shoulder, elbow, wrist, hand, hip, knee, ankles, feet	
Chronic inflammatory arthritis	Can be triggered by change in temperature and physical effort[5]	
	May require surgery	

Carpitis and thumb arthritis (left) – Multiple tenosynovitis of fingers and wrist (right)[1]

2 years after CHIKV infection: Intense arthritis of metacarpophalangeal joints and wrist[3]

Symmetrical inflammatory polyarthritis[2]

1. Simon F., et al. Medicine: 2007;86:123-137. 2. Mohan A, et al. Indian J Dermatol. 2010; 55: 54–63. 3. Amaral J, et al. Viruses. 2019;11:289. 4. Tritsch S. et al. J Rheum. 2020;47:1267-74. 5. Schilte C. et al. PLOS Negl Trop Dis. 2013;7:e2137.

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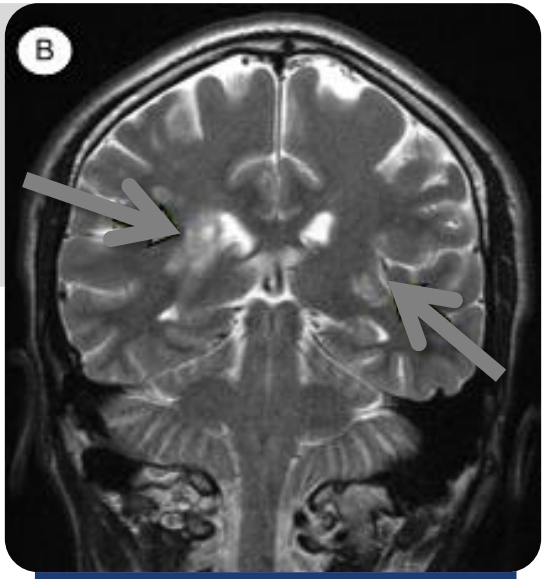
Chikungunya: Persistent Rheumatologic Disease is Common

Outbreak	Year	Number of Patients	Observation Period	% Patients Affected	Post-Chik Chronic Disorders	Source
Réunion	2005	662	6 months	93.7	Rheumatic symptoms	Queyriaux et al. *Lancet Infect Dis* 2008
Italy	2007	250	12 months	66.5	Myalgia, asthenia or arthralgia	Moro et al. *J Infect* 2012
Réunion	2005	88	18 months	63.6	Persistent arthralgia	Borgherini G et al. *Clin Infect Dis* 2008
Italy	2007	180	36 months	60	Arthralgia	Schilte et al. *PloS Negl Trop Dis* 2013
Réunion	2005	147	15 months	57	Rheumatic symptoms	Sissoko et al. *PLoS Negl Trop Dis* 2009
Kerala, India	2007	1396	15 months	57	Polyarthralgia	Mathew et al. *Int J Clin Pract* 2011
Aruba	2014	248	>6 weeks >12 months	43.8 26.3	Chronic polyarthralgia	Huits et al. *PLOS One* 2018
French Guyana	2014	168	3 months 6 months	40.4 31.3	Rheumatic or musculoskeletal pain	Bonifay et al. *Eur J Clin Microbiol Infect Dis* 2018
South Africa	1975-1977	107	3-5 years	12	Residual joint symptoms such as stiffness, swelling, and pain	Brighton et al. *S Afr Med J* 1983

Chikungunya: Neurological Complications

Neurologic disorders — one of the most common severe complications of chikungunya

- Approximately 0.1% of chikungunya infections
- The primary issue in 61%-79% requiring ICU care



Acute disseminated encephalomyelitis in a patient with systemic Chikungunya

Encephalitis
1/3 patients die and 1/3 are left with cognitive sequelae[1]

Encephalopathy
Altered mental state, ie, confusion, disorientation, behavioral changes[1]

Guillain-Barré Syndrome[2]
(1 in 5 people have long-term problems) May require acute to sub-acute invasive support
Long-term sequelae

Myelitis
Potential for direct viral infection or post-infectious response to the infection causing transverse myelitis

1. Matos, A. et al. https://www.encephalitis.info/chikungunya-encephalitis, accessed 4 June 2020. Mehta R et al. 2018. 2. PLoS Negl Trop Dis. 2018;12;e0006212 3. Mehta 2018 Rev Med Virol 2018;28:e1978.

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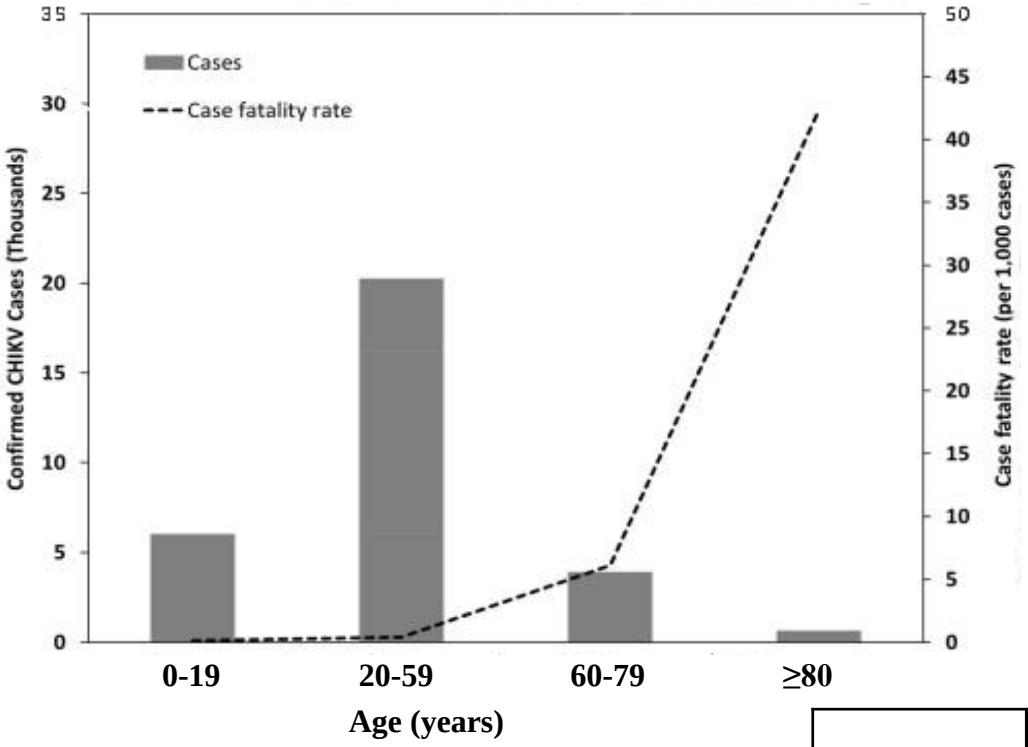
Chikungunya: Mortality



	Age			
Days	**0-19**	**20-59**	**60-79**	**80 or more**
0-6	1	7	19	15
7-14	1	5	17	17
15-21	0	1	4	9
22-29	0	2	5	12
≥ 30	0	7	25	22
Total deaths	**2**	**22**	**70**	**75**

Interval between onset of symptoms and death

Lima Neto, et al. PLoS Negl Trop Dis 2019;13:e0007575.

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Chikungunya: Treatment

No cure – Symptomatic treatment only

There is no vaccine to prevent or medicine to treat chikungunya virus[1,2]	**Treatment for symptoms can include rest, fluids, and use of analgesics and antipyretics[2]**	**Physical activities tend to aggravate the joint inflammatory process, contributing to local wear and thus to prolonging the clinical condition[3]**	**Treatment of the acute phase is limited to painkillers and nonsteroidal anti-inflammatory drugs (NSAIDs)[4]**

Persistent joint pain may benefit from use of:[2]

- Anti-inflammatories/inflammatory mediators: NSAIDs, corticosteroids, DMARDS, biologics
- Physical and occupational therapy
- Psychological support
- Surgery may be required – tendon release to joint replacement

1. Thiberville SD, et al. Antiviral Res; 2013;99:345-370. 2. Staples et al. CDC Yellow Book 2020, Chapter 4. 3. Da Cunha RV, Trinta, KS. Mem Inst Oswaldo Cruz, Rio de Janeiro. 2017;112:523-531. 4 Simon et al. Curr Infect Dis Rep. 2011;13:218-228.

Chikungunya

Etiology & Epidemiology

- Mosquito-borne disease occurring worldwide
- Humans are the primary host
  - ➢ Human to mosquito to human transmission
- Expanding geographic distribution of CHIKV-carrying mosquito
- Americas, parts of Africa and Southeast Asia are the highest risk areas
- Millions of cases worldwide
- Epidemics of large, explosive outbreaks with high attack rates
- Outbreaks often overwhelm local health systems

Disease and Disease Burden

- Low mortality, high morbidity
- Up to 97% of infected individuals are symptomatic
- Up to 98% experience acute onset of polyarthralgia
- Up to 4 of 5 people experience chronic arthralgia
- Disease manifestations typically last months to years
- Low proportion of patients return to previous health status
- Significant individual and societal costs
- Negative impact on quality of life, with altered daily and long-term patterns of living

Patient Management

- No vaccine at present
- No cure, treatment is symptomatic and supportive only
- Ongoing case importation and local disease transmission within the continental US likely from travelers to affected areas

Clinical features of dengue, Zika and chikungunya viral infection

Features	Zika	Dengue	Chikungunya
Fever[1]	++	+++	+++
Rash[1]	+++	++	++
Joint pain[1]	++	+	+++
Conjunctivitis[1]	++	-	-
Muscle pain[1]	+	+++	+
Headache[1]	+	++	++
Hemorrhage	Rare	++	Rare[2]
Shock[1]	-	+	-
Guillain-Barré syndrome	Rare[3]	Very rare[4]	Very rare[5]
Neurological infection	Rare	+	+
Case fatality rate	Very rare[6] (Except fetal loss)	<1%[7]	0.1%[8]

1. Rabe, *et al.* Zika Virus – What Clinicians Need to Know? Clinical Outreach and Communication Activity (COCA) Call, January 2016, Atlanta, GA
2. World Health Organization. Guidelines for Prevention & Control of Chikunyunga Fever. 2009
3. Gold, *et al. Jama Neurol* 2016;73:905–6
4. Fragoso, *et al. Arq Neuropsiquiatr* 2016;74:1039–40
5. Villamil-Gómez, *et al. Enferm Infecc Microbiol Clin* 2016;34:140–1
6. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=38229&lang=en Accessed 25/10/2017
7. Shepherd. Dengue, Prognosis. Updated 2017. Available at: https://emedicine.medscape.com/article/215840-overview#a6 Accessed 02/11/2017
8. Mavalankar, *et al. Emerg Infect Dis* 2008;14:412–15

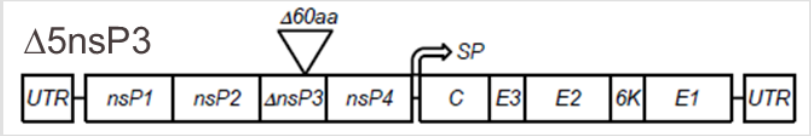
VLA1553 - Chikungunya vaccine candidate

Attenuation Principle

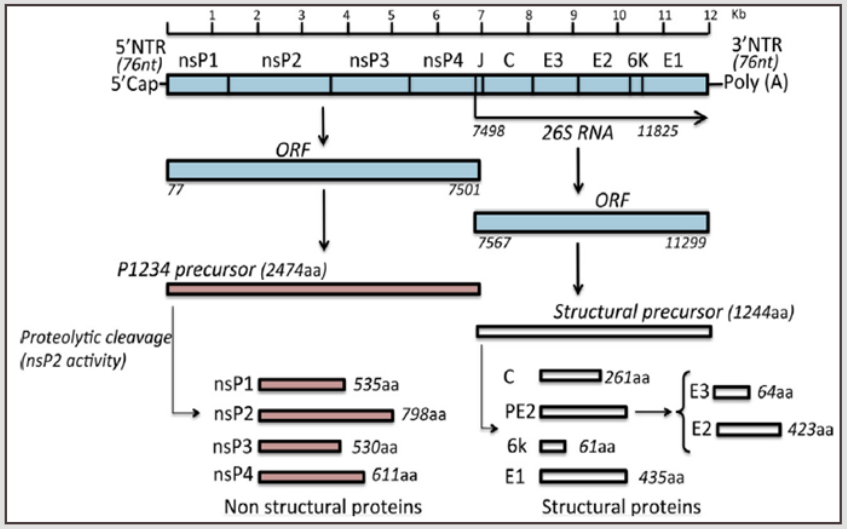
CHIKV Δ5nsP3 (VLA1553) vaccine is based on ECS African strain of Indian Ocean lineage and is designed to protect against other strains such as the Asian isolate which is now rapidly spreading across the Americas.

- **60 aa deletion in gene encoding nsP3**
- No change of deletion detectable after up to 20 passages on Vero cells
- Slightly reduced plaque size as compared to CHIKV clone LR2006-OPY1
- Reduced replication (1.2×10^7 pfu/mL) as compared to CHIKV clone LR2006-OPY1 (4.4×10^8 pfu/mL)

Vaccine construct



CHIKV genome



Hallengärd et al. 2013, J Virol. 88(5):2858-66.

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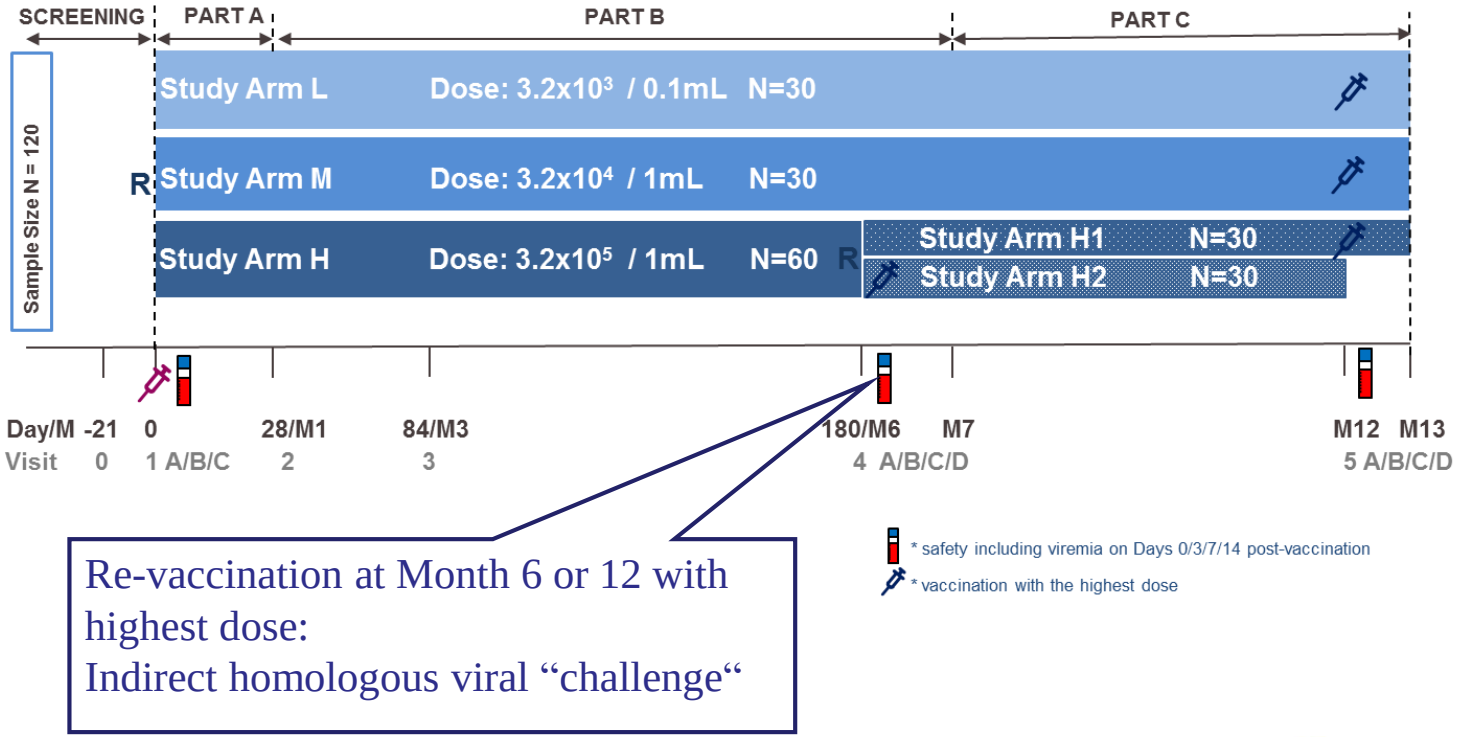
Phase 1 Study VLA1553-101 – Study Design

- Observer-blinded, randomized, multicenter, dose-escalation study
- Study Population: 120 healthy volunteers aged 18 to 45 years
- Study Location: US (2 sites)
- Dosage: $3.2x10^3$ $TCID_{50}$ (0.1ml), $3.2x10^4$ $TCID_{50}$ (1ml), $3.2x10^5$ $TCID_{50}$ (1ml), liquid formulation
- Immunization route: i.m.



Re-vaccination at Month 6 or 12 with highest dose:
Indirect homologous viral "challenge"

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

Single-shot live-attenuated chikungunya vaccine in healthy adults: a phase 1, randomised controlled trial

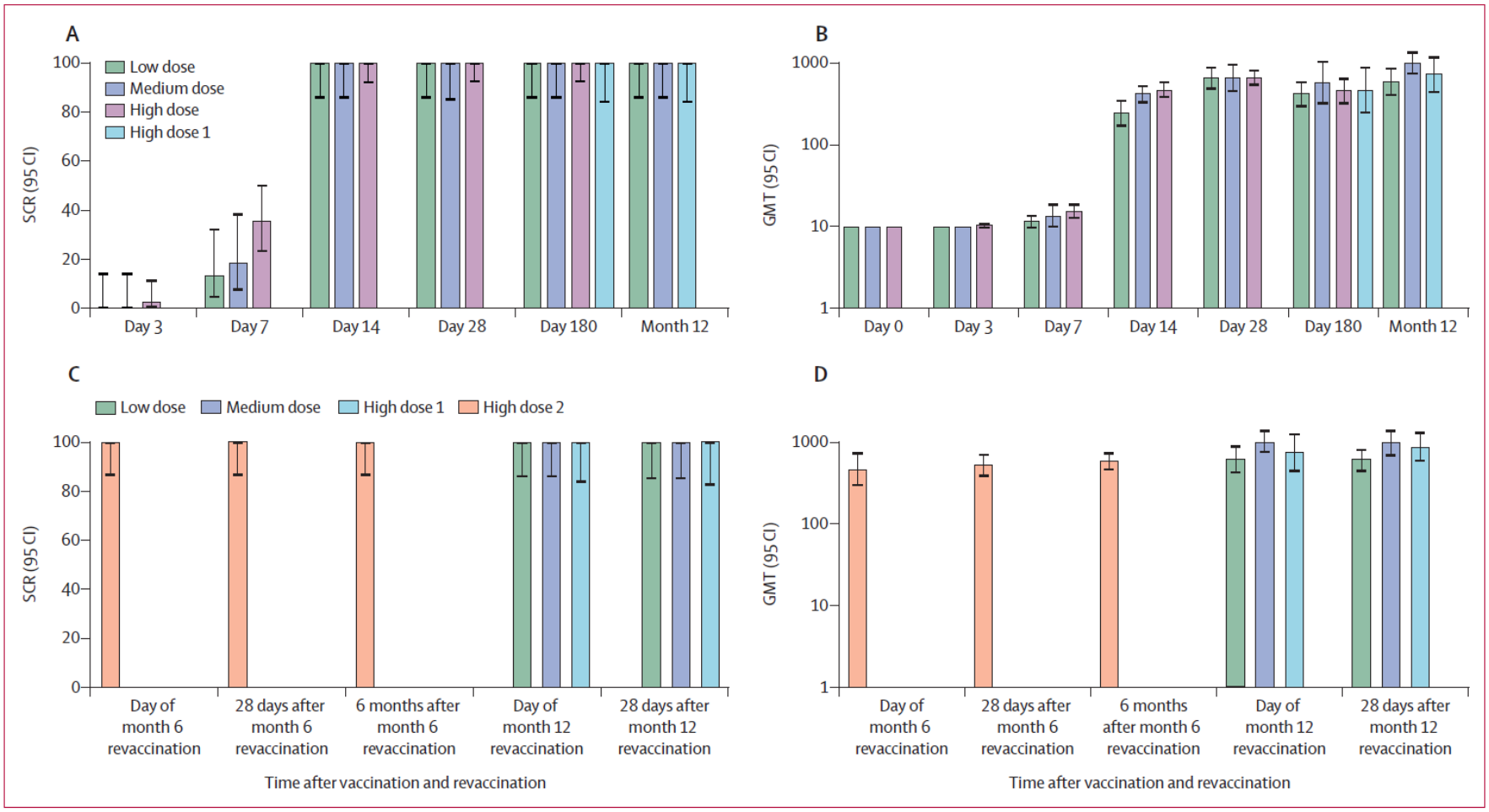
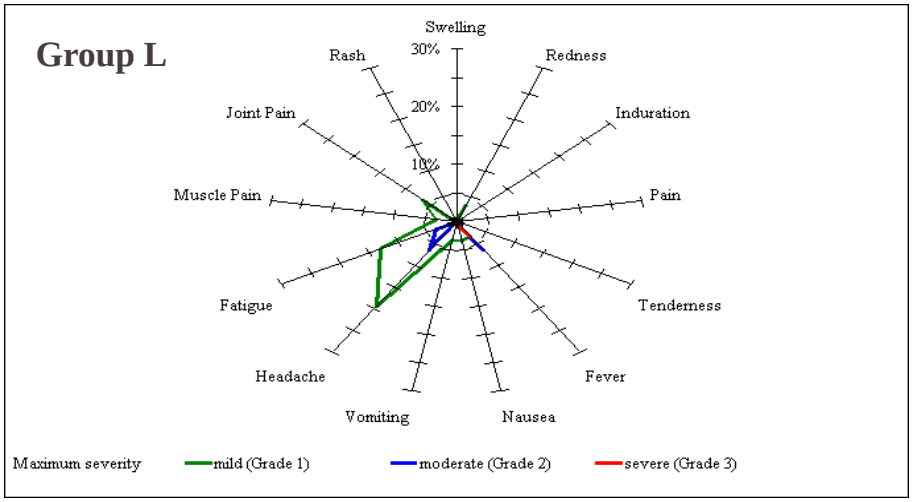
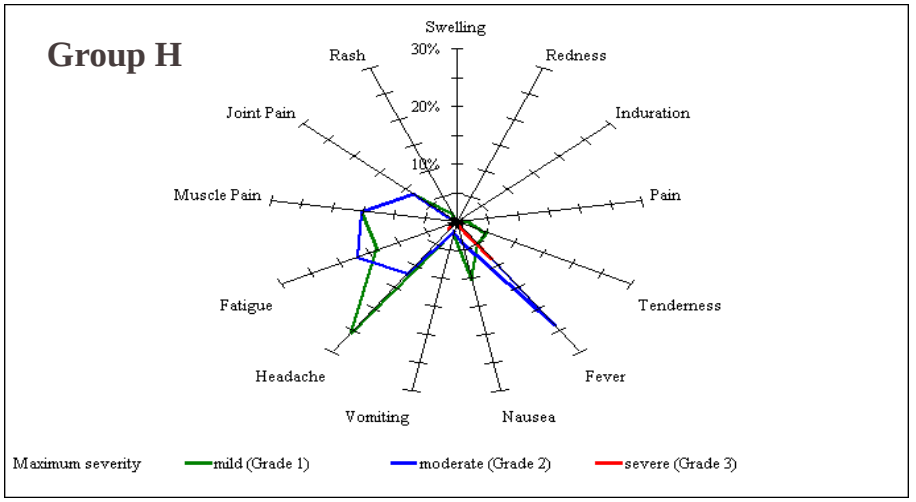


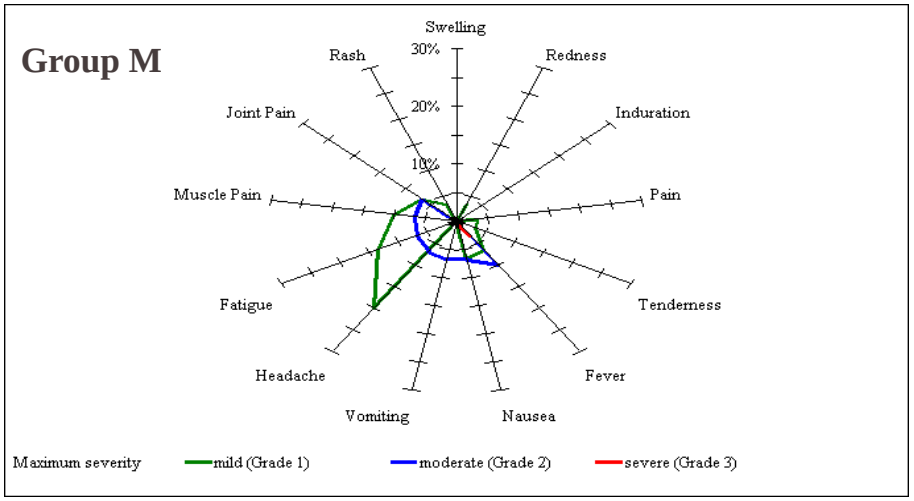
Figure 4: **Assessment of neutralising antibodies after vaccination and revaccination**
SCRs (A, C) and GMTs (B, D) after vaccination (A, B) and revaccinations (C, D) by study groups. Seroconversion is defined as proportion of participants achieving a chikungunya virus-specific antibody titre of at least 20 (neutralisation titre ≥20). SCR=seroconversion rate. GMT=geometric mean titres.

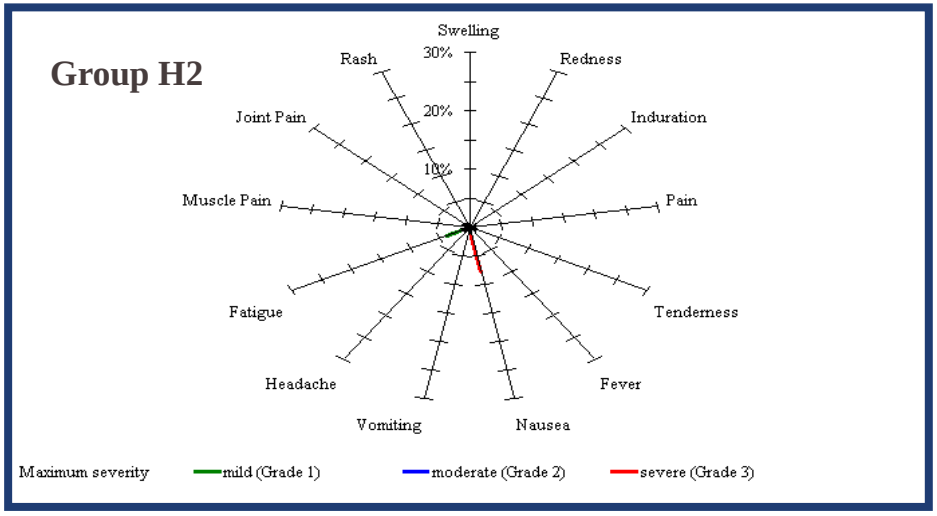
Chikungunya Phase 1 - Safety

Subjects with solicited AEs after Vaccination by Maximum Severity





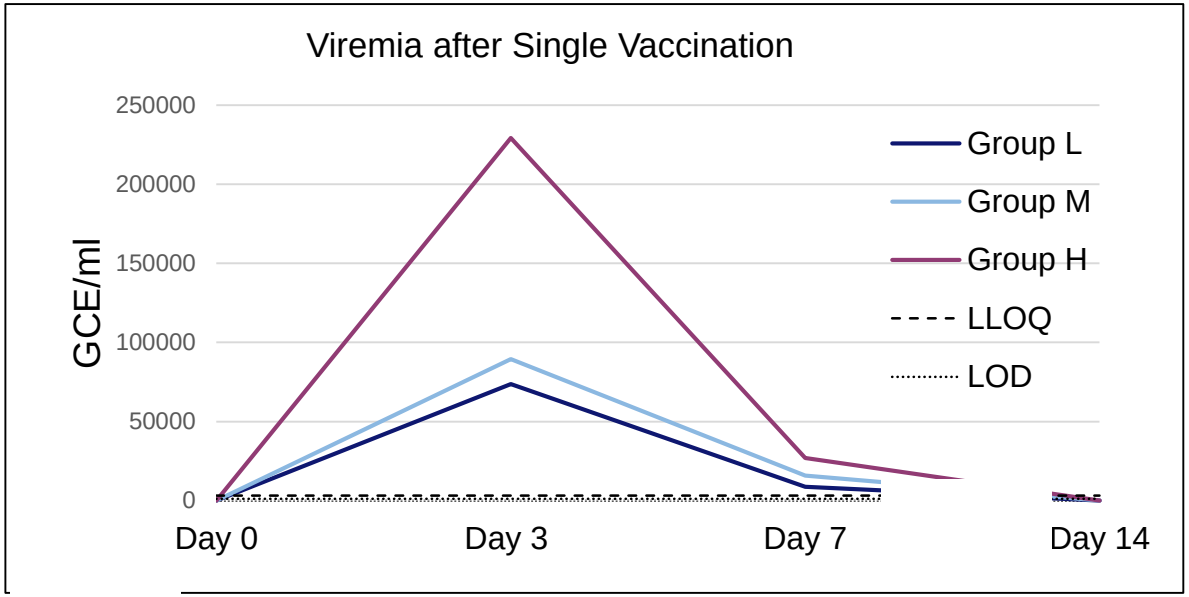


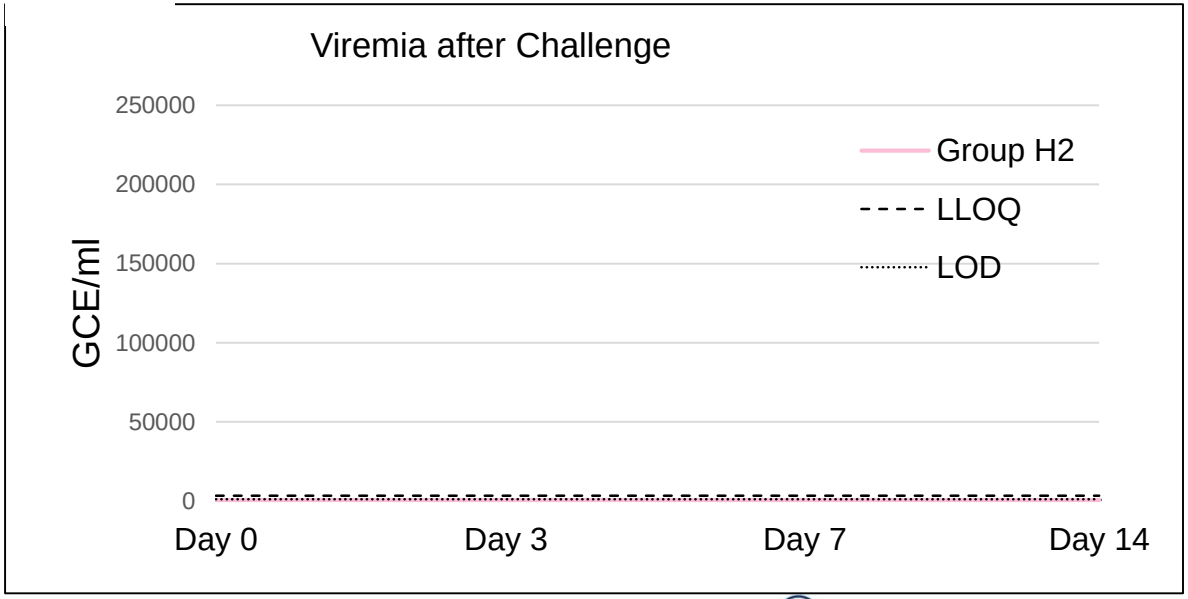


Radar plots of solicited injection site and systemic AEs within 14 days after Single Vaccination (Groups L, M, H) and Challenge (Group H2).

Chikungunya Phase 1 - Safety

Viremia in plasma at Days 0, 3, 7 and 14 after Single Vaccination and Challenge (B).
Limit of Detection (dotted line): 1087 GCE/mL, Lower Limit of Quantification (dashed line): 3261 GCE/mL.
Time points with no available results in the treatment group are imputed with 500. GCE/mL – Genome copy equivalents per mL determined by quantitative real-time PCR





1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

VLA1553: Summary of Phase 1 Clinical Data

Clinical Study VLA1553-101 [1]

Immunogenicity

- 100% Seroconversion Rate achieved at Day 14 after a single vaccination in all dose groups; fully sustained at 100% by Month 12
- A single vaccination of VLA1553 was sufficient to induce sustaining, high-titer, neutralizing antibodies at all dose levels one year after priming
- Upon Re-Vaccination ("Challenge"):
  - —No anamnestic response
  - —No vaccine-strain viremia

Highly immunogenic after single vaccination

Safety

- Acceptable safety profile, well-tolerated in the low and medium doses
- Excellent local tolerability
- Systemic adverse events included short-term fever, headache and fatigue, muscle pain
- No vaccine related Serious Adverse Events or Adverse Events of Special Interest

Safety profile supported Phase 3 progression with medium dose

BCRT Berliner Centrum Reise- und Tropenmedizin

Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

CRM Centrum für Reisemedizin

Questions?
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