Reviewing the Clinical Development of Zika and Chikungunya Vaccines

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Division of Infectious Diseases
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October 2017

Discussion Topics

- Introduction
  - Virus, Disease, Epidemiology
- Requirement for vaccine development
- Vaccine development challenges
- Review of clinical development efforts

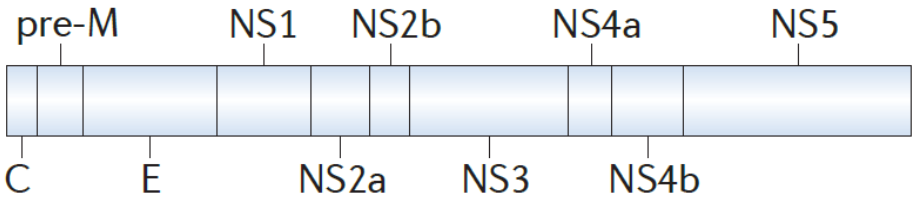
Zika

http://fortune.com/2016/03/03/google-zika-data/

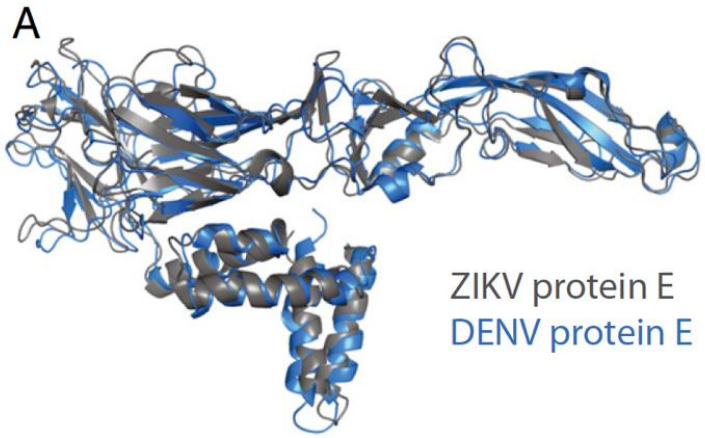
Introduction

- *Flaviviridae* – same family as DENVs, YF, JE, WNV, TBE
  - Antigenic complex: Spondweni

- RNA, icosahedral, enveloped, + single-stranded
  - Genome: 3 structural & 7 non-structural proteins



NATURE REVIEWS | IMMUNOLOGY
VOLUME 11 | AUGUST 2011



7852–7857 | PNAS | July 12, 2016 | vol. 113 | no. 28

ZIKV Transmission Cycles

The expanding spectrum of modes of transmission of Zika virus: a global concern

Alfonso J. Rodriguez-Morales[1,2*], Antonio Carlos Bandeira[3] and Carlos Franco-Paredes[4,5]

Rodriguez-Morales *et al.*
Ann Clin Microbiol Antimicrob (2016) 15:13

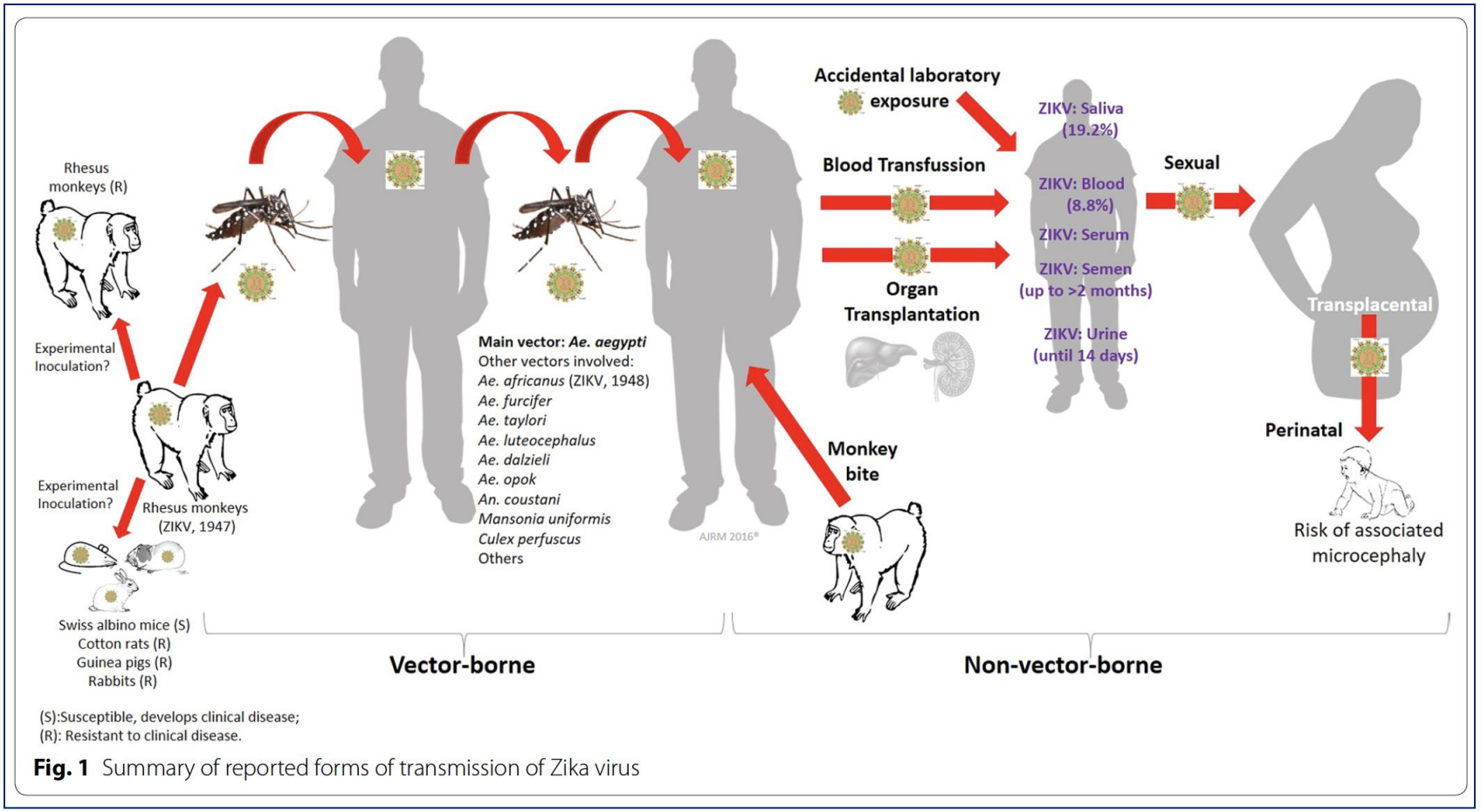
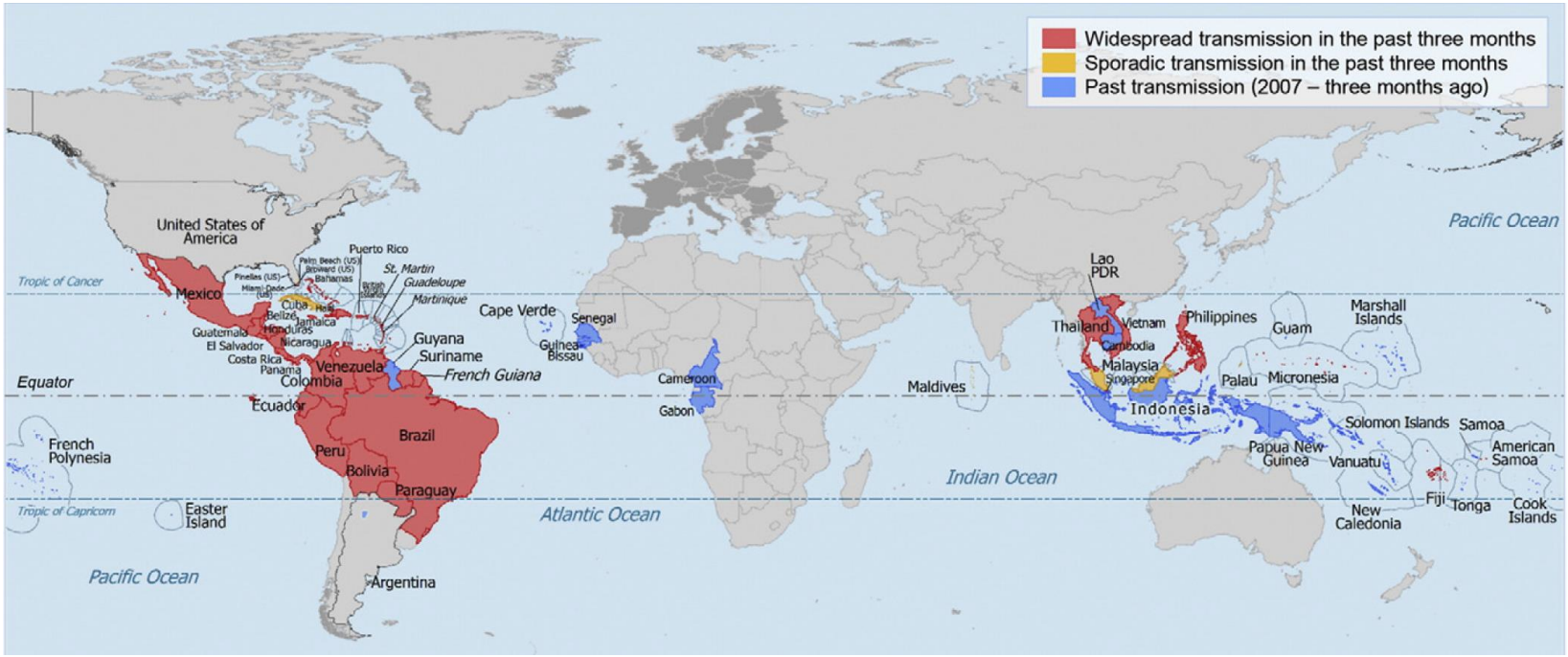


Fig. 1 Summary of reported forms of transmission of Zika virus

Zika's Clinical Epidemiology



B.-H. Song et al. / Journal of Neuroimmunology 308 (2017) 50–64

www.thelancet.com/infection Vol 17 October 2017

- Brazil (2015 – August 2017)
  - 231,725 suspected cases, 137,288 confirmed
  - 2,869 confirmed cases of Zika virus congenital syndrome
- USA
  - 2016: 5,102 symptomatic, 224 local, 36,079 in US territories
  - 2017 (1 JAN to 31 AUG) - 225, none local, 554 US territories

Typical Clinical Manifestations of Zika

Travel-Associated Zika Virus Disease Cases Among U.S. Residents — United States, January 2015–February 2016

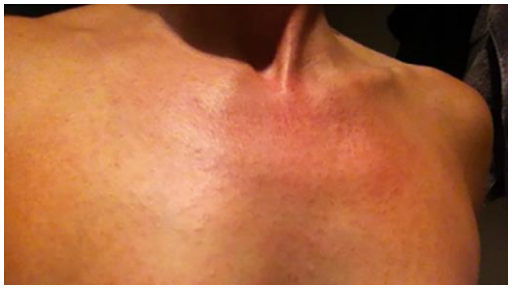
Paige Armstrong, MD[1]; Morgan Hennessey, DVM[1]; Monica Adams, PhD[1]; Cara Cherry, DVM[1]; Sophia Chiu, MD[1]; Alexia Harrist, MD[1]; Natalie Kwit, DVM[1]; Lillianne Lewis, MD[1]; Dana Olzenak McGuire, PhD[1]; Titilope Oduyebo, MD[1]; Kate Russell, MD[1]; Pamela Talley, MD[1]; Mary Tanner, MD[1]; Charnetta Williams, MD[1]; Zika Virus Response Epidemiology and Laboratory Team

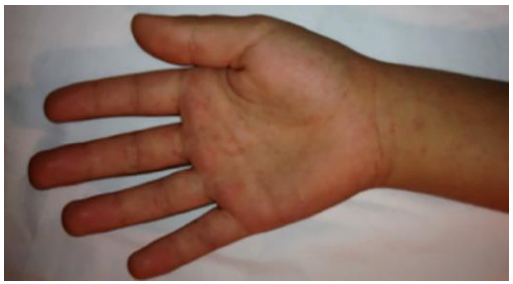
TABLE 2. Clinical signs and symptoms reported by 115 residents of U.S. states and the District of Columbia with laboratory evidence of Zika virus disease — January 1, 2015–February 26, 2016*

	Yes†	No	Unknown
Sign/symptom	**No. (%)**	**No. (%)**	**No. (%)**
✓ Rash	113 (98)	1 (1)	1 (1)
✓ Fever	94 (82)	20 (17)	1 (1)
✓ Arthralgia	76 (66)	33 (29)	6 (5)
Headache	65 (57)	37 (32)	13 (11)
Myalgia	63 (55)	38 (33)	14 (12)
Conjunctivitis	43 (37)	53 (46)	19 (17)
✓ Diarrhea	22 (19)	63 (55)	30 (26)
✓ Vomiting	6 (5)	79 (69)	30 (26)

* Testing performed at CDC's Arboviral Diseases Branch laboratory.
† Some patients had more than one sign and/or symptom.

MMWR / March 25, 2016 / Vol. 65 / No. 11





Clinical Microbiology Reviews July 2016 Volume 29 Number 3

Adverse Neurologic Outcomes

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Lancet 2016; 387: 1531–39

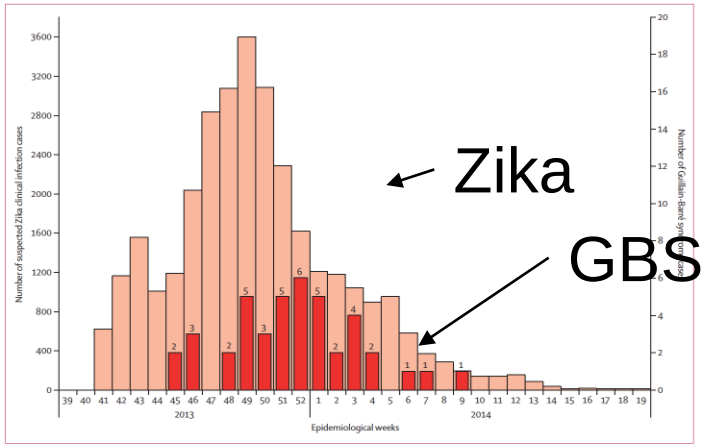


Figure: Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014

Johann Castro Hernandez, 18, is recovering from Guillain-Barre syndrome after he appeared to have fallen sick with Zika virus around New Year's. His mom, Janina Hernandez, is at right.

Becky Sullivan/NPR

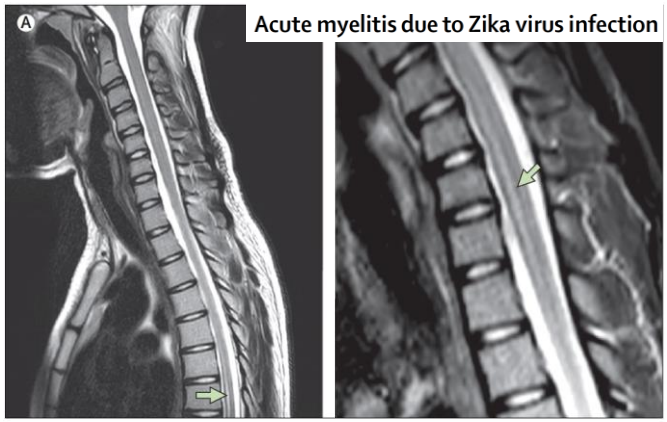


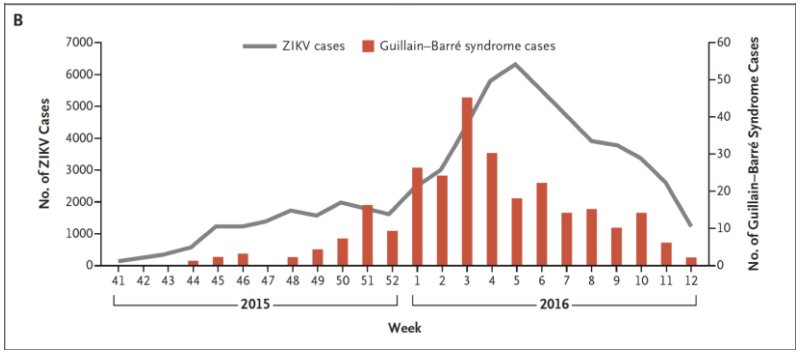
Figure: Magnetic resonance imaging (MRI) showing myelitis in Zika virus infection
(A) T2 sequences showing hypersignal in the thoracic cord T5–T8 (arrow) and enlargement of the cervical spinal cord. (B) Sagittal short time inversion recovery (STIR) sequences showing hypersignal in the cervical spinal cord C4–C7 (arrow).

Lancet 2016; 387: 1481

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 20, 2016 VOL. 375 NO. 16

Guillain–Barré Syndrome Associated with Zika Virus Infection in Colombia



Congenital Zika Syndrome

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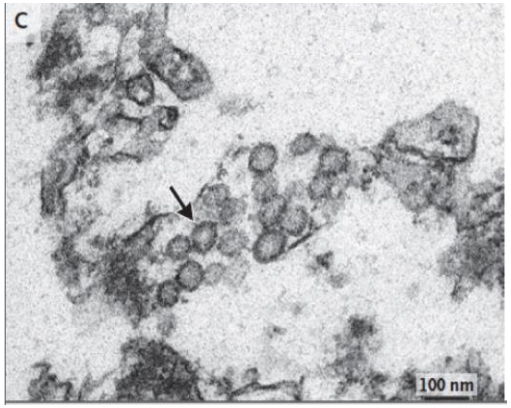
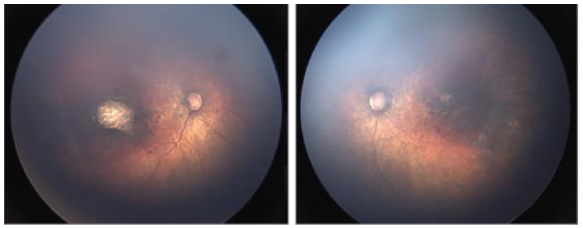
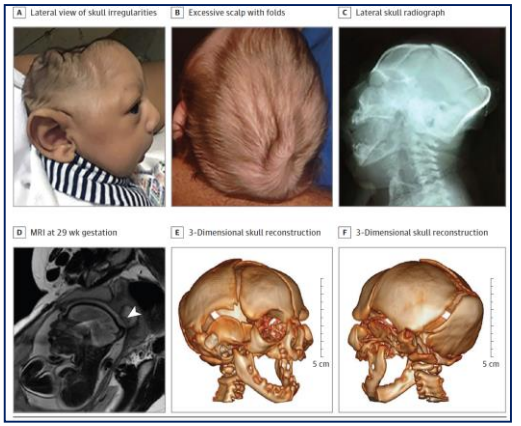
This article was published on February 10, 2016, at NEJM.org.

Zika Virus Associated with Microcephaly



JAMA Pediatr. doi:10.1001/jamapediatrics.2016.3982
Published online November 3, 2016.





JAMA Pediatr. doi:10.1001/jamapediatrics.2016.3982
Published online November 3, 2016.

Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study

www.thelancet.com Published online March 15, 2016

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

N Engl J Med. 2016 Apr 13.

Zika is Neurotopic

Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth

Cell Stem Cell *18*, 587–590, May 5, 2016 ©2016 Elsevier Inc. 587

"Here we show…ZIKV…efficiently infects human neural progenitor cells (hNPCs)... Infected hNPCs further release infectious ZIKV particles. Importantly, ZIKV infection increases cell death and dysregulates cell-cycle progression, resulting in attenuated hNPC growth. Our results identify hNPCs as a direct ZIKV target."

"Together, therefore, our findings identify a link between ZIKV-mediated TLR3 activation, perturbed cell fate, and a reduction in organoid volume reminiscent of microcephaly."

Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids through Activation of the Innate Immune Receptor TLR3

Cell Stem Cell *19*, 258–265, August 4, 2016 © 2016 Elsevier Inc.

Zika virus impairs growth in human neurospheres and brain organoids

13 MAY 2016 • VOL 352 ISSUE 6287 sciencemag.org SCIENCE

"…ZIKV targets human brain cells, reducing their viability and growth as neurospheres and brain organoids. These results suggest that ZIKV abrogates neurogenesis during human brain development."

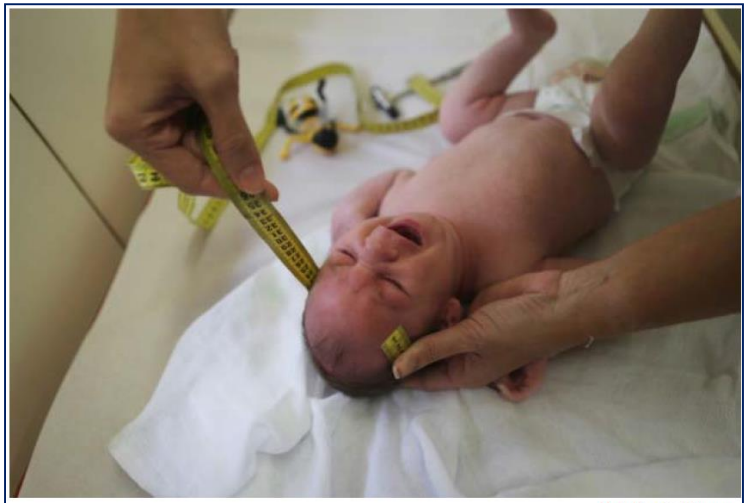
Requirements for a Zika Vaccine

- *Reduce clinical burden of infection*
  - *Microcephaly and other congenital disorders*
  - *Neurologic disorders*
- Generate herd immunity
- Interrupt transmission
  - Mosquito, sexual, maternal
- Public benefit
  - Reduce suffering
  - Reduce resource utilization
  - Restore normalcy

Editorial

Vaccine against Zika virus must remain a priority

www.thelancet.com/infection **Vol 17 October 2017**



Mario Tama/Getty Images

ZIKV Vaccine Development Challenges

Fast-Track Zika Vaccine Development — Is It Possible?

Stephen J. Thomas, M.D., Maïna L'Azou, M.Sc., Alan D.T. Barrett, Ph.D., and Nicholas A.C. Jackson, Ph.D.

N ENGL J MED 375;13 NEJM.ORG SEPTEMBER 29, 2016

Table 2. Zika Virus (ZIKV) Vaccine Challenges.*

Action and Challenge	Solutions for Accelerating Research, Development, and Licensure
Defining a target product profile	
Unknown severe disease incidence; unknown spectrum of ZCS	Early commitments to epidemiologic and natural history studies
Diverse cocirculating flaviviruses	Early inclusion of trial subjects with range of prior flavivirus exposure Efforts to find serologic assay able to distinguish prior exposure
Planning and executing preclinical and clinical studies	
Translating preclinical studies to clinical trials	Preclinical and clinical studies conducted in parallel
Long clinical development pathway	Broader and expanded early clinical studies Adaptive trial designs
Clinical trial design and completion if outbreak subsides or becomes sporadic	Field epidemiologic studies across multiple regions Modeling to predict epidemiologic situation
Relevant and measurable clinical end points	Establishing mild disease as a primary end point and rarer outcomes as secondary end points or focus of postlicensure studies
Unknown full spectrum of ZCS	Prospectively designed studies to confirm incidence of long-term sequelae not detected at birth
Incidence and cause of ZIKV-related GBS	Studies to elucidate pathology and incidence Clinical study end points related to GBS
Theoretical concerns about disease enhancement	Use animal models to test whether in vitro studies translate to in vivo If animal models suggest disease enhancement, use field studies to evaluate theory

ZIKV Vaccine Development Challenges

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Vaccine production and scale-up	
Process development and scale-up	Manufacturing processes and analytic capabilities developed before knowing a vaccine is successful
Capacity in time for licensure	Early investment in manufacturing capacity
Licensing strategy	
Requirement for efficacy trials	Preclinical and natural history studies to identify immune correlate or surrogate of protection; demonstrating effectiveness postlicensure Epidemiologic studies performed early to inform design
Seeking innovative registration pathways	Early engagement with regulatory agencies Address registration procedures for emergency or conditional use

* GBS denotes Guillain–Barré syndrome.

The virus has been linked to a massive rise in microcephaly cases in South America. Mario Tama/Getty

Zika Vaccine Candidates

WHO reported more than 40 Zika vaccine candidates under development. Twelve phase 1 trials including 6 candidates are near completion.

Table 1

ZIKV vaccine candidates entering humans in 2016–2017

Vaccine name	Technology	Target	Strain	Sponsor	Clinical trial identifier	Phase	Citation
VRC-ZKADNA085-00-VP	DNA vaccine	prM-E	H/PF/2013	NIH Vaccine Research Center	NCT02840487	1	[56,58]
GLS-5700	DNA vaccine	prM-E	ZIKV consensus	GeneOne Life Science	NCT02887482 NCT02809443	1	[59]
VRC-ZKADNA090-00-VP	DNA vaccine	prM-E	H/PF/2013	NIH Vaccine Research Center	NCT02996461	1	
ZPIV	Inactivated virus vaccine	Whole virion	PRVABC59	WRAIR/NIAID	NCT02937233 NCT02952833 NCT02963909 NCT03008122	1	[56,58,60]
MV-ZIKA	Viral vector (measles)	E		Themis Bioscience	NCT02996890	1	
mRNA-1325	mRNA vaccine	prM-E	Micronesia 2007	Moderna Therapeutics	NCT03014089	1/2	[54]

Zika Vaccine TPP

WHO/UNICEF Zika Virus (ZIKV) Vaccine Target Product Profile (TPP): Vaccine to protect against congenital Zika syndrome for use during an emergency

World Health Organization

Updated February 2017

unicef

A healthy volunteer receives the NIAID Zika virus investigational DNA vaccine as part of an early-stage trial to test the vaccine's safety and immunogenicity. This is the first administration of this vaccine in a human.

Indication: Prevention of Zika virus-associated clinical illness of any severity in subjects 9 years of age or older
Contra-indication: No contraindication for use during pregnancy

***Target population**: Women of reproductive age (adolescent and pre-adolescent girls ≥9 years of age), and boys/men of the same ages*

Efficacy: Prevention of virologically confirmed illness in 80% of recipient
Preparation: single dose
Durability of protection: At least 1 year

Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys

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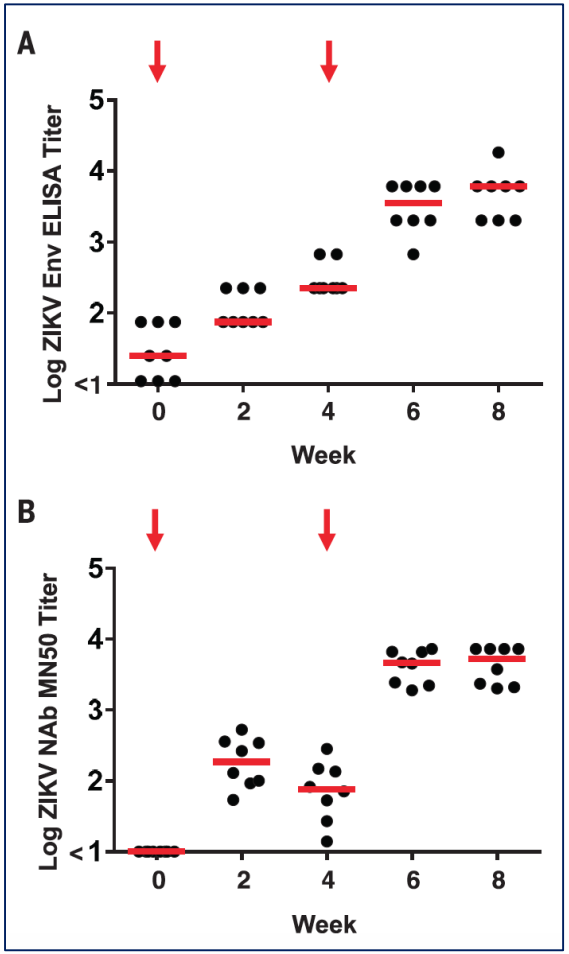
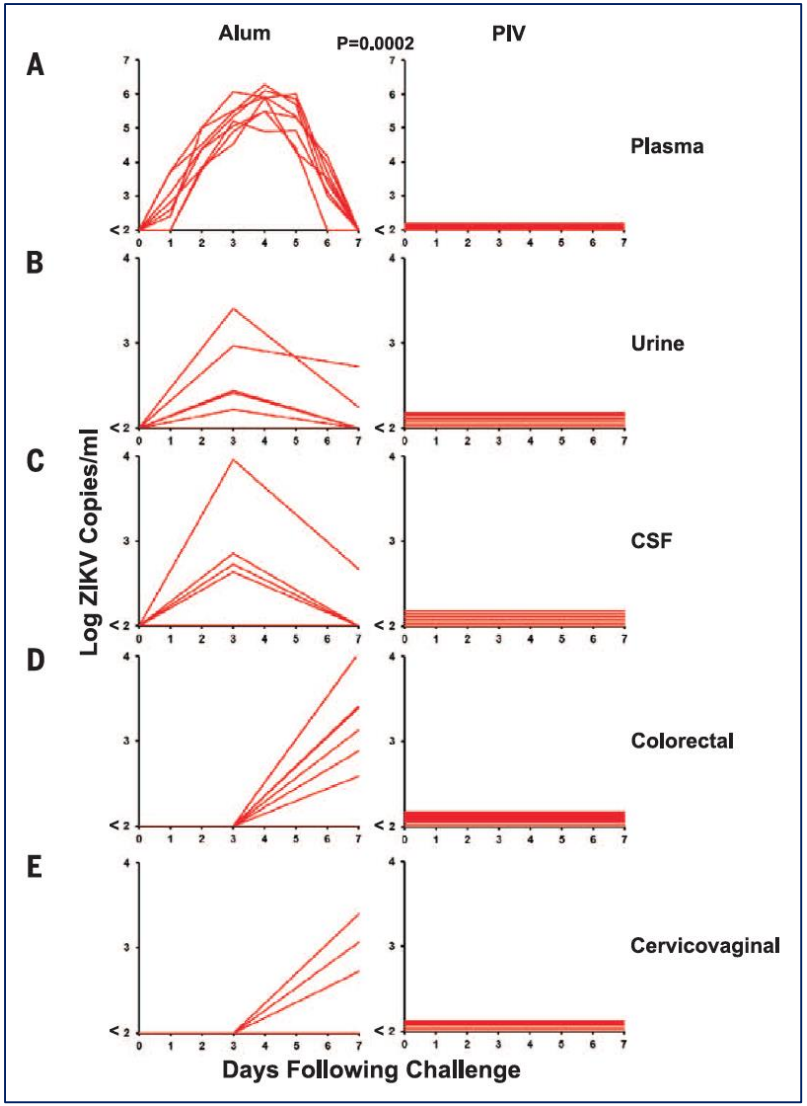
9 SEPTEMBER 2016 • VOL 353 ISSUE 6304

Immunogenicity



Efficacy vs. Challenge



Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys

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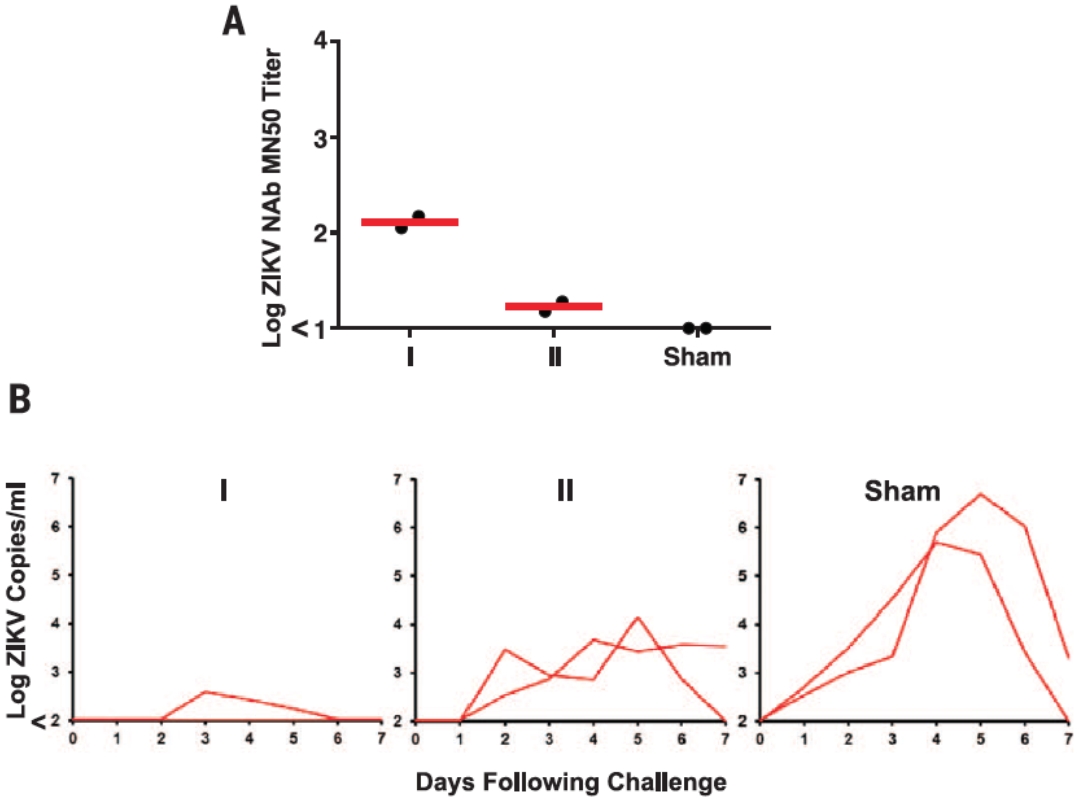
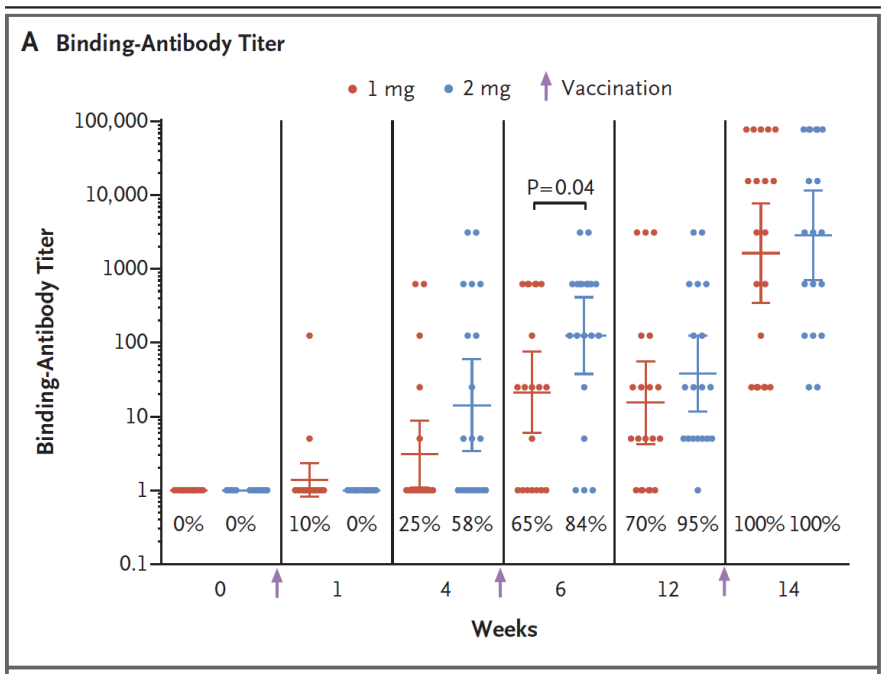


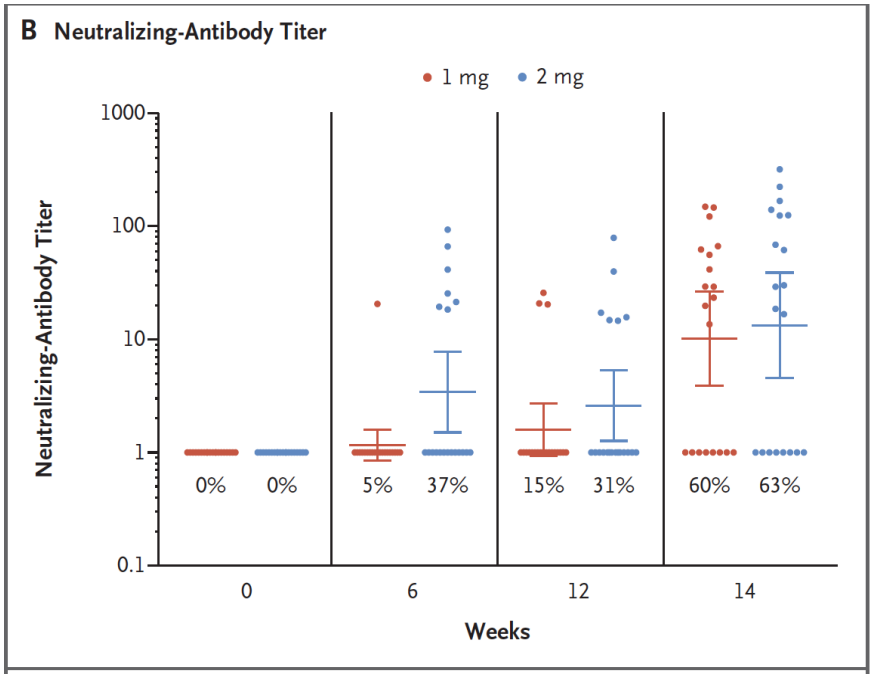
Adoptive transfer studies in NHPs. (A) ZIKV-specific MN50 titers in serum from recipient NHPs (n = 2 per group), measured 1 hour after adoptive transfer of five-fold dilutions of IgG purified from PIV-vaccinated NHPs (groups I and II) or sham controls. (B) Plasma viral loads in rhesus monkeys after challenge with 10^6 vp (103 PFU) of ZIKV-BR.
Red bars reflect medians.

Safety and Immunogenicity of an Anti–Zika Virus DNA Vaccine — Preliminary Report

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on October 4, 2017, at NEJM.org.





100% develop binding antibody after 3 vaccinations and 60-63% develop neutralizing abs.

Safety and Immunogenicity of an Anti–Zika Virus DNA Vaccine — Preliminary Report

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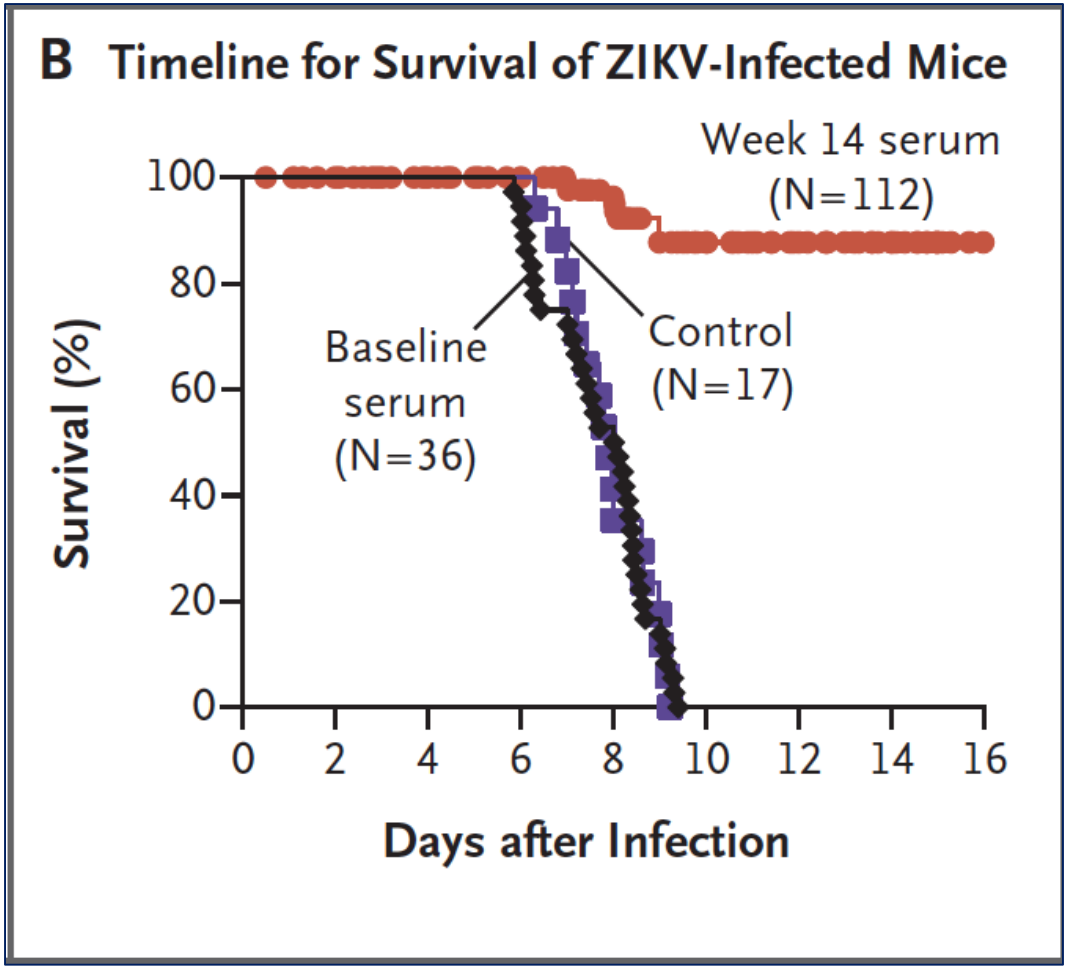


Passive transfer of human ab induced after 3 doses of vaccine protect 92% of mice from challenge.

ZIKV Immune Enhancement- Fact or Philosophy?

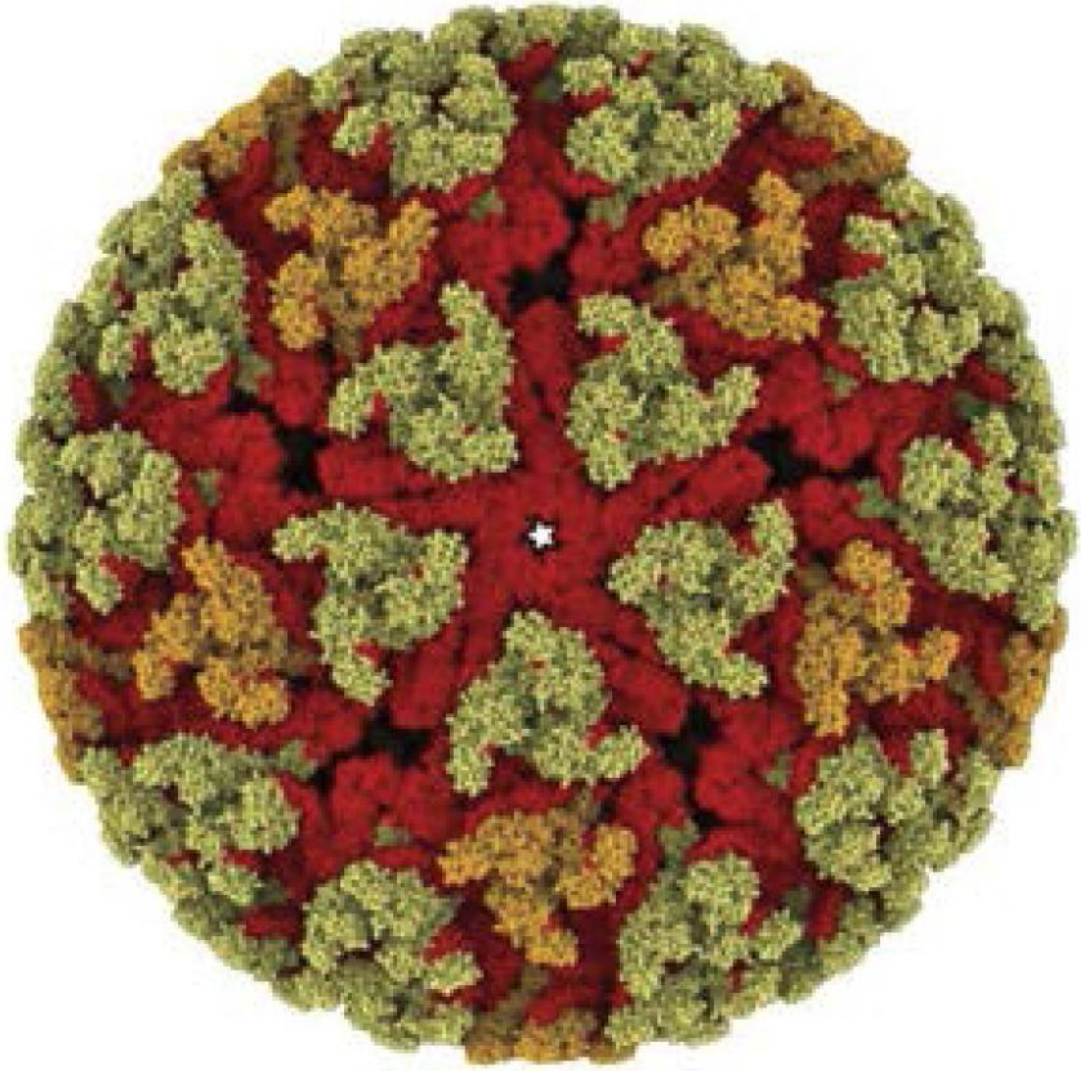
- Facts
  - Some % of ZIKV infections have severe outcomes
  - ZIKV co-circulates with numerous other flaviviruses
  - *In vitro* flavivirus cross reactivity exists
  - *In vivo* enhancement in small animals exits
  - *In vitro* / small animal data not translating to NHPs
  - *In vitro* / small animal data not translating to humans

Prospective studies aligning closely-in space and time-pre-existing immune profiles with infection and associated clinical outcomes will provide the data and reagents required to separate ZIKV enhancement "fact from philosophy."

Zika's Legacy

https://img.washingtonpost.com/rf/image_1484w/2010-2019/WashingtonPost/2016/02/12/Foreign/Images/2016-02-12T004906Z_01_NAC10_RTRIDSP_3_HEALTH-ZIKA-BRAZIL.jpg

Chikungunya

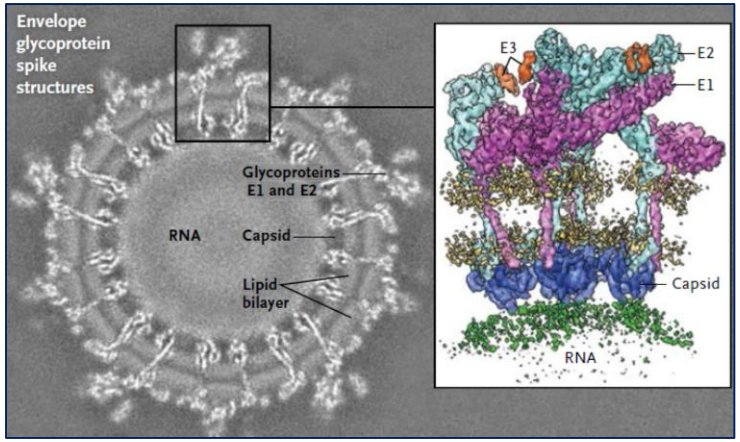


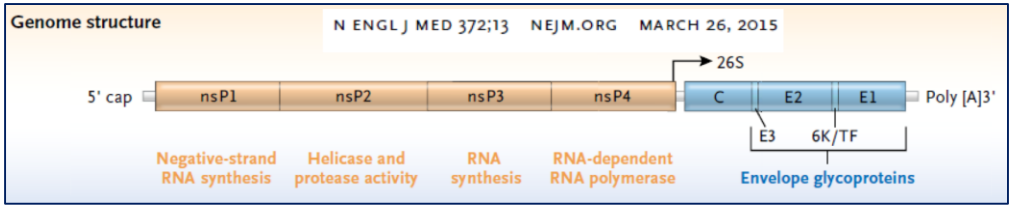
Felix Rey, Institut Pasteur,

Introduction

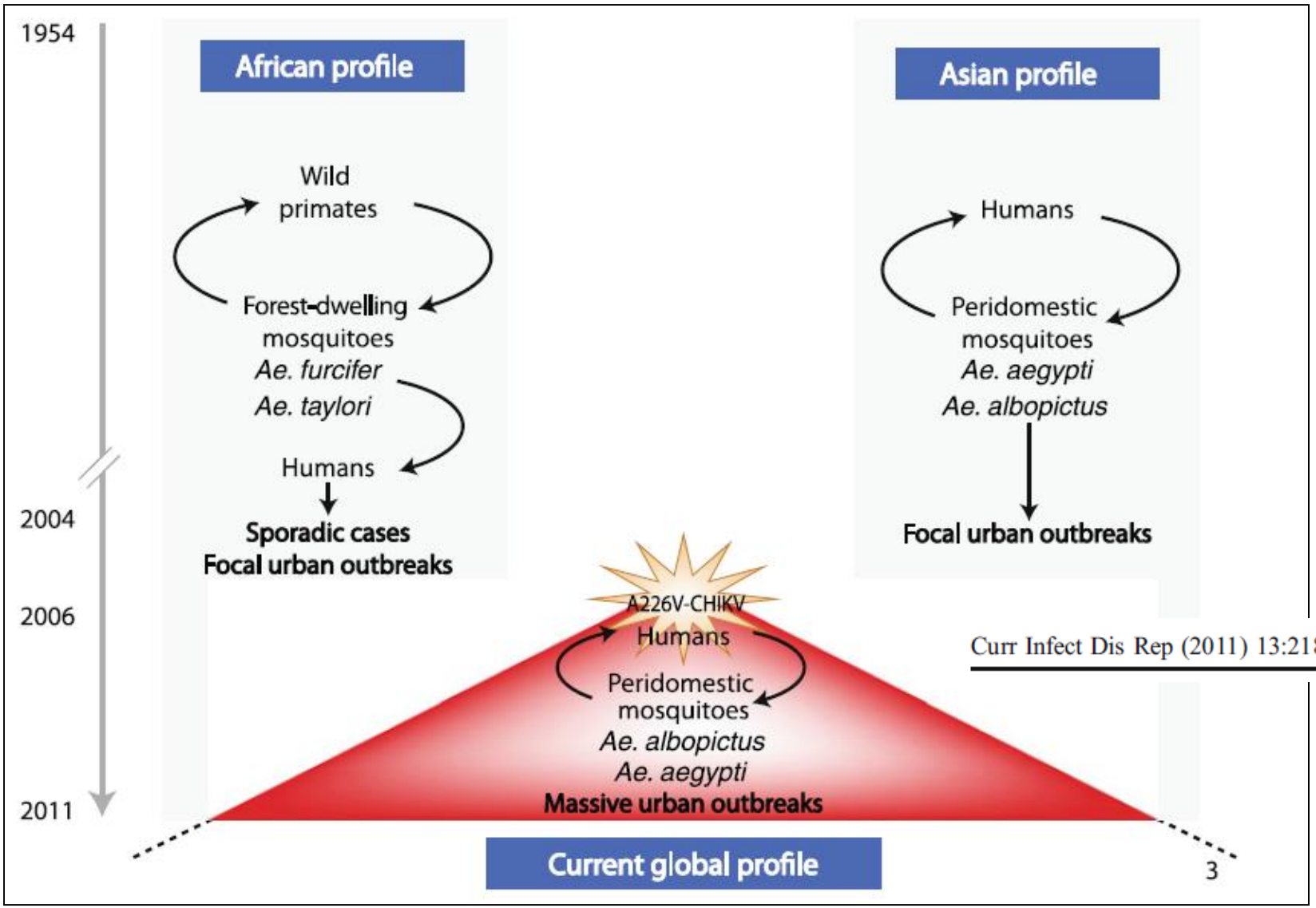
- *Togaviridae* family, Alphavirus genus
  - Positive-sensed, single stranded genomic RNA

- Three genotypes (84.5%–97.8% amino acid identity)
  - Asian, East/Central/South African (ECSA), West African



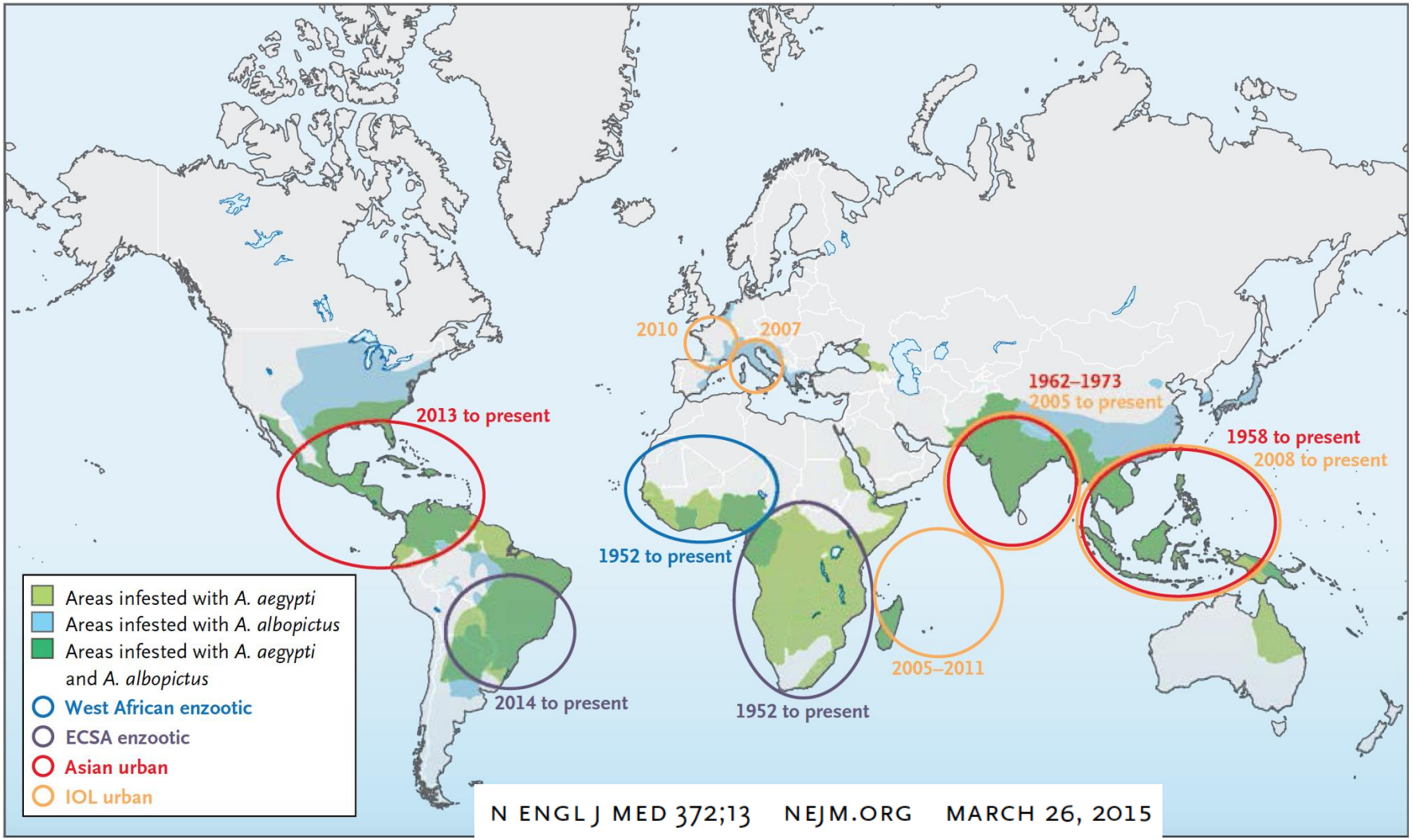


Chikungunya Transmission Cycles



Curr Infect Dis Rep (2011) 13:218–228

Chikungunya Clinical Epidemiology



N ENGL J MED 372;13 NEJM.ORG MARCH 26, 2015

Understanding Clinical Attack Rate

Table adapted from
R. Tan et al, "Findings of Endemic Transmission of Chikungunya Virus in Yogyakarta, Indonesia"

	Positive Chikungunya IgG Serology		
	Baseline n = 800	12 Months n = 528	24 Months N=504
	147 / 800 (18.4%)	26 / 528 (4.92%)	36 / 504 (7.1%)
Percent of seroconverters reporting CHIK-like episode in the interval period	20 / 147 (13.6%)	6 / 26 (23.1%)	7 / 36 (19.4%)

RESEARCH ARTICLE

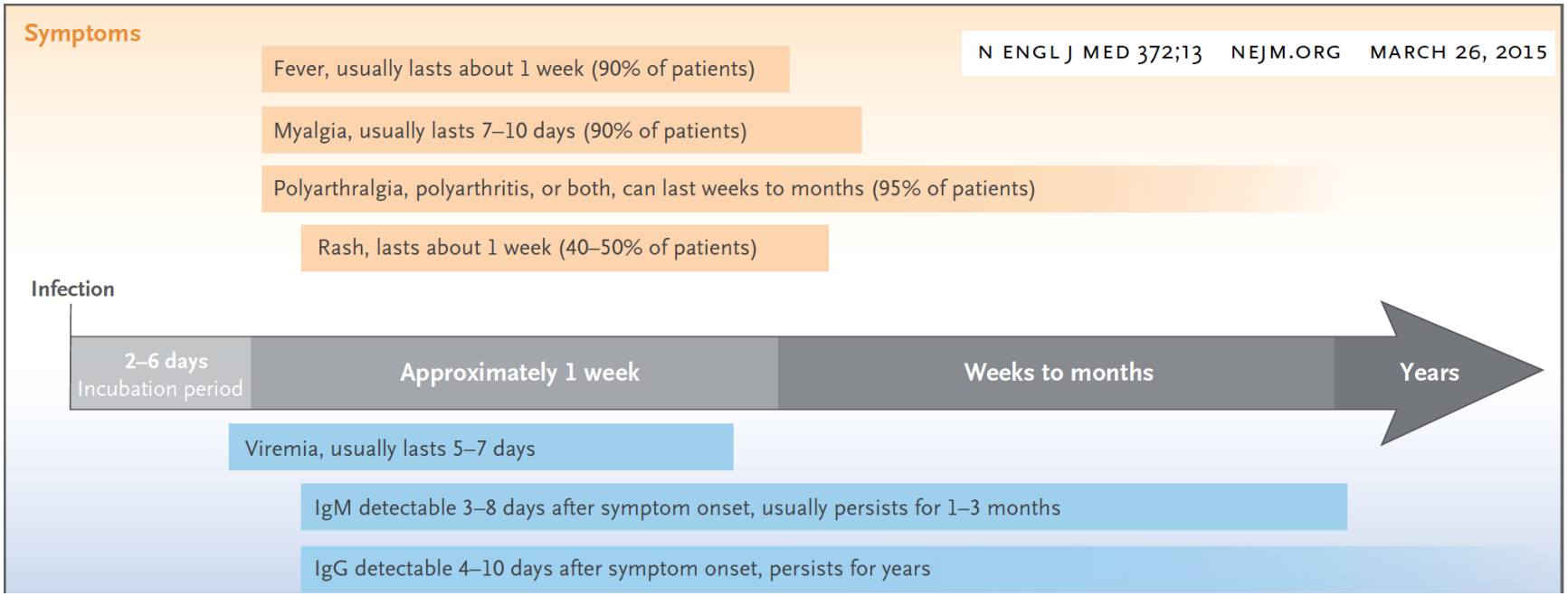
High Rate of Subclinical Chikungunya Virus Infection and Association of Neutralizing Antibody with Protection in a Prospective Cohort in The Philippines

In-Kyu Yoon[1]*, Maria Theresa Alera[2], Catherine B. Lago[2], Ilya A. Tac-An[3], Daisy Villa[3], Stefan Fernandez[1], Butsaya Thaisomboonsuk[1], Chonticha Klungthong[1], Jens W. Levy[1], John Mark Velasco[2], Vito G. Roque, Jr.[4], Henrik Salje[5], Louis R. Macareo[1], Laura L. Hermann[1,6], Ananda Nisalak[1], Anon Srikiatkhachorn[7]

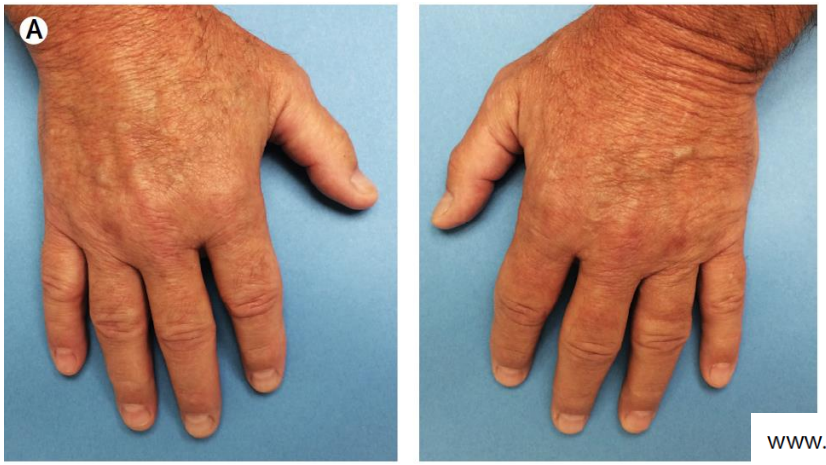
PLOS Neglected Tropical Diseases | DOI:10.1371/journal.pntd.0003764 May 7, 2015

- Subclinical : Symptomatic = 4.6:1
  - 2:1 in 6m-5 year olds
  - 12:1 in >50 year olds

Chikungunya Clinical Burden



N ENGL J MED 372;13 NEJM.ORG MARCH 26, 2015



www.thelancet.com/infection Vol 17 April 2017

Table 1. Typical and atypical manifestations of CHIKV disease in patients

Organ/System	Typical	Atypical
Systemic	Fever; asthenia	Lymphadenopathy
Musculoskeletal	Arthralgia; arthritis; myalgia; joint edema; tenosynovitis; backache; persistent or relapsing-remitting polyarthralgias	Chronic inflammatory rheumatism; articular destruction
Dermatological	Rash; erythema	Bullous dermatosis; hyperpigmentation; stomatitis; xerosis
Neurological	Headache	Meningoencephalitis; encephalopathy; seizures; sensorineural abnormalities; Guillain-Barré syndrome; paresis; palsies; neuropathy
Gastrointestinal		Nausea; vomiting; abdominal pain; anorexia; diarrhea
Hematological	Lymphopenia; thrombocytopenia	Hemorrhage
Ocular	Retro-orbital pain; photosensitivity	Optic neuritis; retinitis; uveitis
Cardiovascular		Myocarditis; pericarditis; heart failure; arrhythmias; cardiomyopathy
Hepatic		Fulminate hepatitis
Pulmonary		Respiratory failure; pneumonia
Renal		Nephritis; acute renal failure

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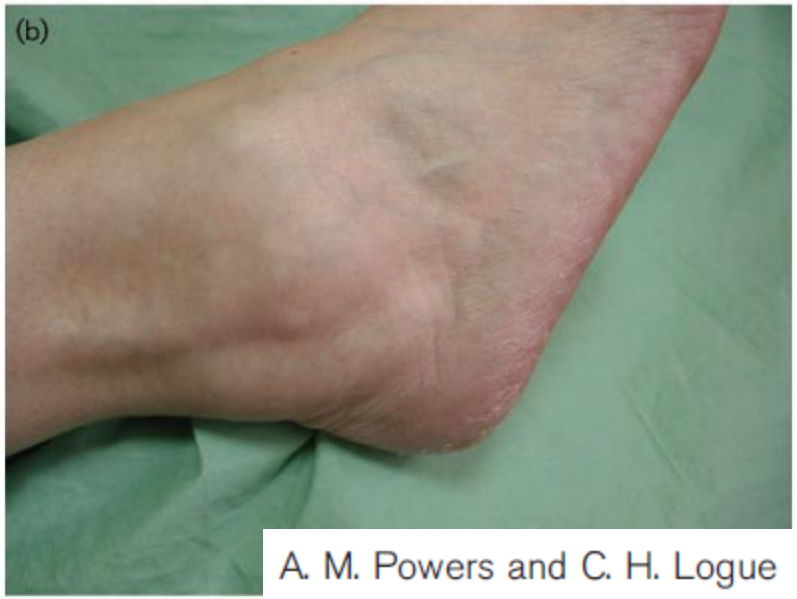
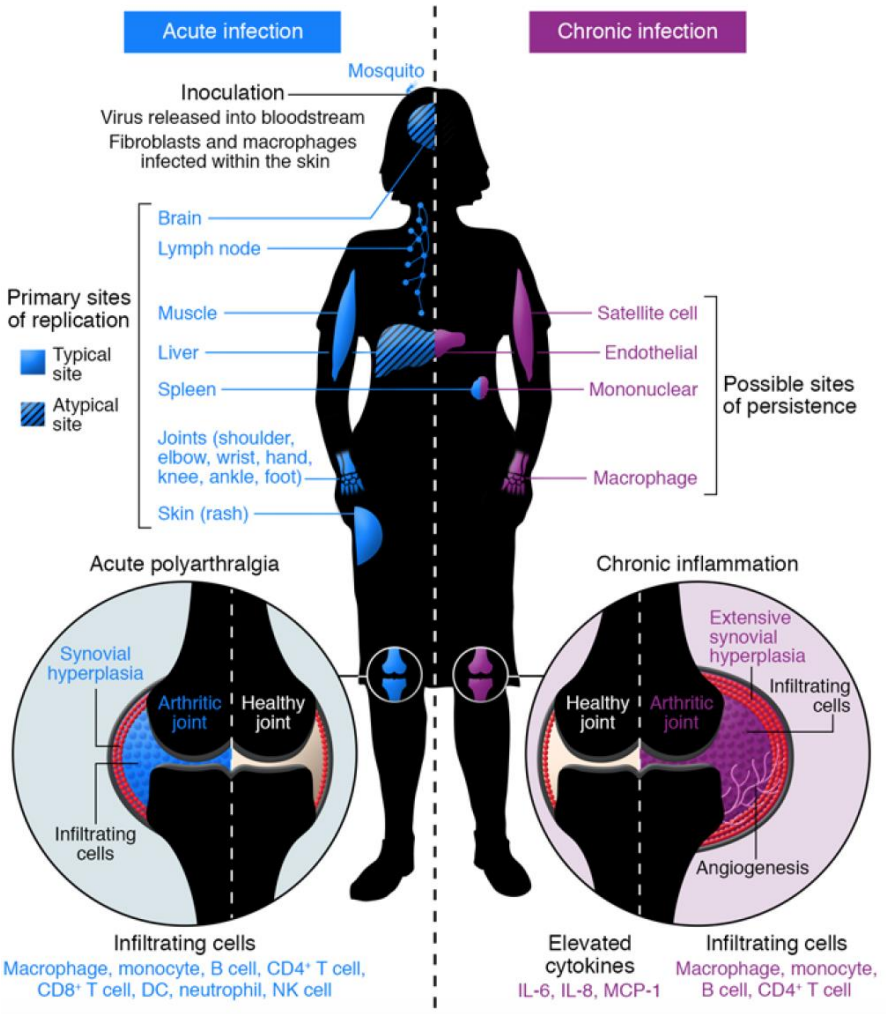
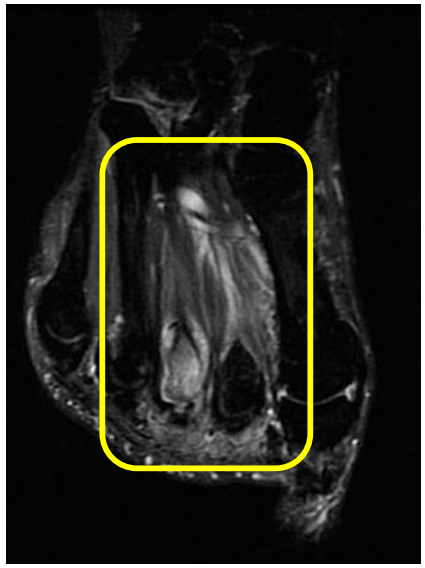
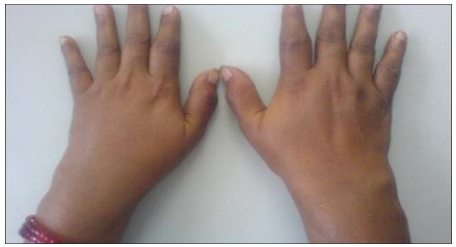
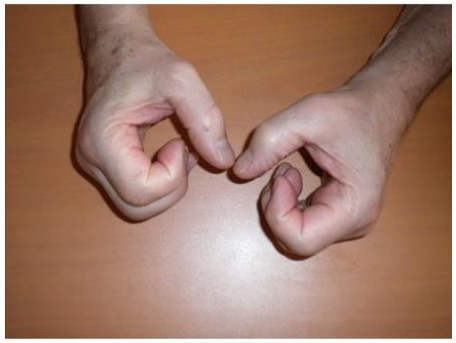


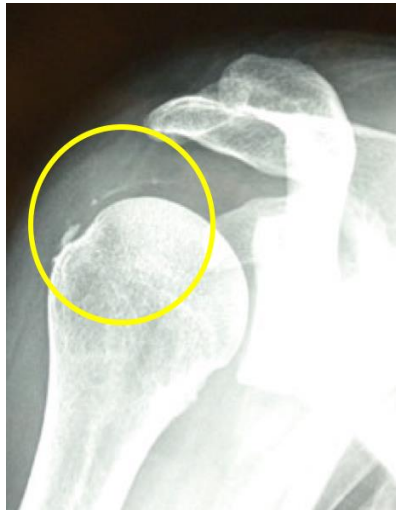
Requirements for a Chikungunya Vaccine

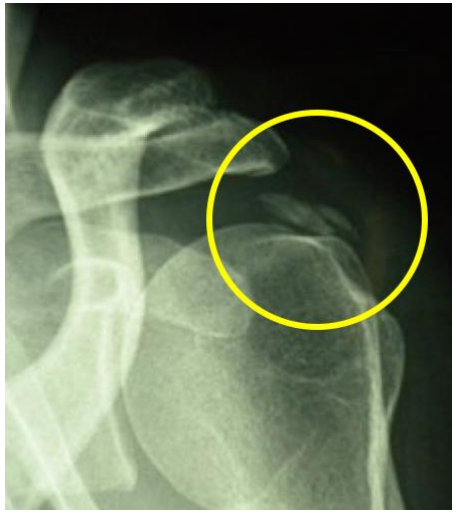












jci.org Volume 127 Number 3 March 2017

Vaccine Development Challenges

- Epidemiology
  - Sporadic outbreaks, long absence prior to return
    - *How do you plan clinical endpoint studies?*
  - Unclear infection : clinical attack rate ratio
    - *How do you properly power an efficacy trial?*
- Clinical disease phenotypes
  - Mild disease, Severe disease, Chronic disease
    - *Which endpoint, selection will impact study design?*
- Incomplete understanding of disease pathogenesis
  - Chronic infection, retained nucleic acid, autoimmunity
    - *May impact construct selection, safety evaluations.*
- No known correlate of protection or risk.

Chikungunya Vaccine Pipeline

VACCINE TYPE	STUDY TYPE	MODE	REFERENCE
LIVE ATTENUATED	Mice Primates	Subgenomic promoter replaced by IRES from encephalomyocarditis virus	Plante et al. 2011[135] Roy et al. 2014[115]
→	Mice Humans: Phase I Humans: Phase II	Passages in green monkey kidney cells and MRC 5 cells	Levitt et al. 1986[163] McClain et al. 1998[131] Edelman et al. 2000[132]
	Mice	Deleting E2 and passages in baby hamster cells and mosquito cell lines	Piper et al. 2013[164]
	Mice	Passage in Chinese hamster ovarian fibroblasts and mosquito cells	Gardner et al. 2014[173]
	Mice	Deleting nsP	Hallengärd et al. 2014[22]
	Mice	Deleting 6K	Hallengärd et al. 2014[22]
INACTIVATED →	Humans: Phase I	Formalin inactivated	Harrison et al. 1971[128]
	Primates	Formalin or UV-light inactivated	Nakao and Hotta 1973[165]
	Mice	Formalin inactivated	Tiwari et al. 2009[125]
	Mice	Formalin inactivated	Kumar et al. 2012[124]
	Mice	BPL inactivated	Kumar et al. 2012[124]
SUBUNITS	Mice	Bacterially produced E1	Khan et al. 2012[123]
	Mice	Bacterially produced E2	Khan et al. 2012[123]
	Mice	Bacterially produced E2	Kumar et al. 2012[124]
DNA	Mice	Expression of E1, E2, E3	Muthumani et al. 2008[166]
	Mice	Expression of C, E1, E2	Mallilankaraman et al. 2011[167] Bao et al. 2013[168]
	Mice	Expression of nsP3	Hällengard et al. 2014[22]
	Mice	Expression of 6K	Hällengard et al. 2014[22]
	Mice	Immunization DNA encoding the full length infectious genome	Tretyakova et al. 2014[122]
	Mice	Expression of 6K, E1, E2, E3	Hällengard et al. 2014[22]
VIRUS-LIKE PARTICLES/SUBUNITS	Mice Primates Humans: Phase I	Transfection of human embryonic kidney cells with plasmid DNA encoding C, 6K, E1, E2, E3	Akahata et al. 2010[139] Akahata and Nabel 2012[169] Chang et al. 2014[133]
→	Mice	Production in insect cells (Baculovirus)	Metz et al. 2013[138]
RECOMBINANT VECTOR	Mice	Eastern equine encephalitis virus as vector	Wang et al. 2008[117]
	Mice	Adenovirus as vector	Wang et al. 2011[118]
	Mice	Vesicular stomatitis virus as vector	Chattopadhyay et al. 2013[119]
	Mice	Poxvirus as vector	Garcia-Arriaza et al. 2014[120]
	Mice Humans: Phase I	Measles virus as vector	Brandler et al. 2013[48] Ramsauer et al. 2015[127]
→			

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 3, 716–731

Formalin Inactivated Chikungunya Vaccine

THE JOURNAL OF IMMUNOLOGY
Vol. 107, No. 3, September 1971

PRODUCTION AND EVALUATION OF A FORMALIN-KILLED CHIKUNGUNYA VACCINE[1]

V. R. HARRISON, K. H. ECKELS, P. J. BARTELLONI AND C. HAMPTON

From the Walter Reed Army Institute of Research, Washington, D. C. 20012, and the United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland 21701

Received for publication April 28, 1971

Production methods and immunogenic characteristics of a formalin-inactivated Chikungunya vaccine prepared in bank-frozen green monkey kidney tissue culture were described. The total absence of untoward reactions or side effects and the excellent immunogenic response in volunteers attested to the safety and immunogenicity of this vaccine.

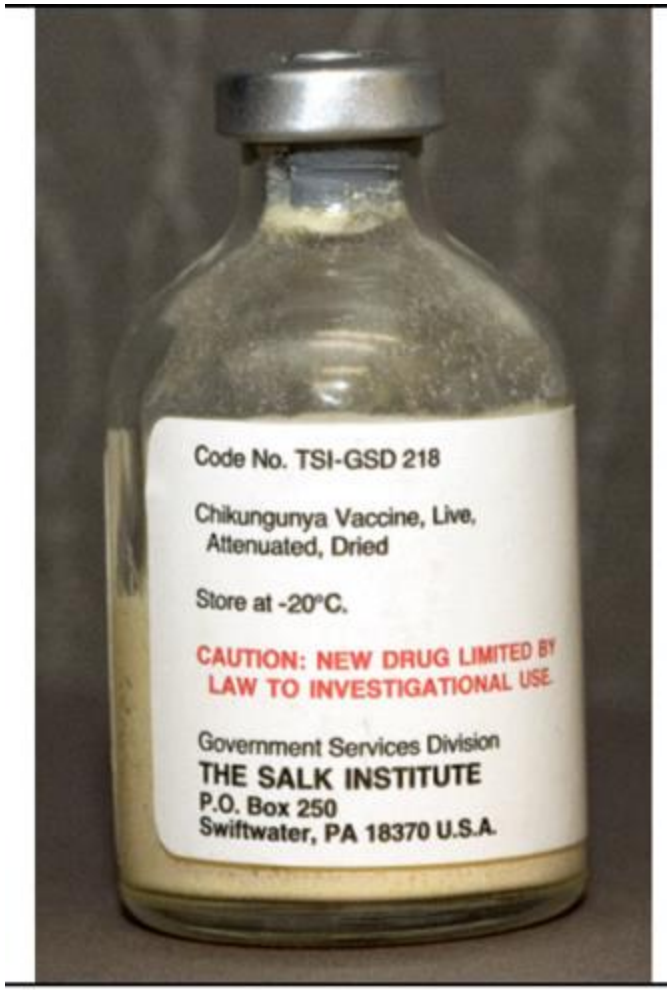
Serologic responses of volunteers without prior CHIK experience to administration of two doses of CHIK vaccine

Group (Dosage Schedule)		Mean Responses by Day after First Dose (Range)			
		0	14	28	42
ml					
I	HI[a]	<10	18 (<10–80)	15 (<10–40)	49 (<10–320)
(0.5 + 0.5)	LNI[b]	0	1.8 (0.7–2.7)	1.9 (1.3–3.0)	2.7 (2.0–3.5)
	CF[a]	2 (<4)	2 (<4–8)	2 (<4–4)	7 (<4–16)
II	HI	<10	11 (<10–20)	9 (<10–10)	26 (10–80)
(1.0 + 1.0)	LNI	0	1.9 (1.3–2.5)	1.9 (1.0–3.0)	1.7 (2.0–3.5)
	CF	2 (<4)	2 (<4–8)	3 (<4–8)	6 (<4–8)

[a] HI and CF test results are reciprocals of geometric mean titers.
[b] Log_{10} serum neutralization index.

US Military contributions to the global response to pandemic chikungunya☆

Charles H. Hoke Jr.[a,*], Judy Pace-Templeton[a], Phillip Pittman[b], Frank J. Malinoski[b], Paul Gibbs[b], Tracy Ulderich[c], Michelle Mathers[a], Beverly Fogtman[b], Pamela Glass[b], David W. Vaughn[d]



Code No. TSI-GSD 218

Chikungunya Vaccine, Live,
Attenuated, Dried.

Store at -20 C or lower

CAUTION: NEW DRUG LIMITED BY
FEDERAL LAW TO INVESTIGATIONAL USE.

THE SALK INSTITUTE
Government Services Division
P.O. Box 250
Swiftwater, PA 18370 U.S.A.

Chikungunya virus (CHIK 181/Clone 25), prepared in MRC-5 cell culture. After reconstitution, the vaccine contains less than 0.02 µg Neomycin base and 0.25g% human serum albumin U.S.P. per mL.

For reconstitution: Add 21 mL of Sterile Water for Injection, U.S.P.

Dose: 0.5 mL subcutaneously.

After reconstitution: Store at +4 C and use within 3 hours.

CAUTION: This vaccine vial contains live virus. Autoclave before discarding.

Live Attenuated Chikungunya Vaccine

Table 4
Proportion of alphavirus naïve recipients of chikungunya vaccine that developed plaque reduction neutralizing antibody ($PRNT_{50 \text{ or } 80}$)[b] antibody, and geometric means of maximum titers.

Study	Number with antibody/number of alphavirus naïve recipients	% Developing neutralizing antibody between days 15 and 32	Geometric mean of maximum titer on days 11–38 (95% CI)
A	29/30	97	305 (189–494)
C	19/19	100	297 ([a])
D	3/3	100	640 (114–3580)
F	21/21	100	110 ([a])
G	57/58	98	582 ([a])
Total	131	98	

[a] Not available because only GMT data (not individual data) reported.
[b] PRNT 80 for trials A, C, D, and F, and PRNT 50 for trial G.

Hoke et al, Vaccine 2012

PHASE II SAFETY AND IMMUNOGENICITY STUDY OF LIVE CHIKUNGUNYA VIRUS VACCINE TSI-GSD-218

Am. J. Trop. Med. Hyg., 62(6), 2000, pp. 681–685

TABLE 1

Number of volunteers developing clinical reactions during the first 28 days after immunization with the chikungunya (CHIK) vaccine

Reaction	CHIK vaccinees* n = 59 No. showing reaction (%)	Placebo recipients n = 14 No. reaction (%)
Local symptoms and signs†	12 (20)	3 (21)
Any systemic symptoms and signs‡	34 (58)	9 (64)
Systemic symptoms possibly associated with immunization§	19 (32)	4 (29)
Arthralgia in isolation	5 (8)	0
Flu-like symptom(s)	13 (22)	4 (29)
Urticaria	1 (2)	0

* All differences between CHIK and placebo groups were NS ($P > 0.58$, Fisher's exact test). Clinical reactions were graded and associated with immunization in a blinded fashion before vaccine code was broken.
† Pain, tenderness, erythema, induration, and restricted arm motion.
‡ Malaise, fever, chills, headache, photophobia, myalgia, arthralgia, anorexia, nausea, vomiting, pruritis, and rash.
§ Based on temporal association with immunization 28 days before onset of symptom, and by the absence of another identifiable condition that may have accounted for symptom or symptoms.

TABLE 2

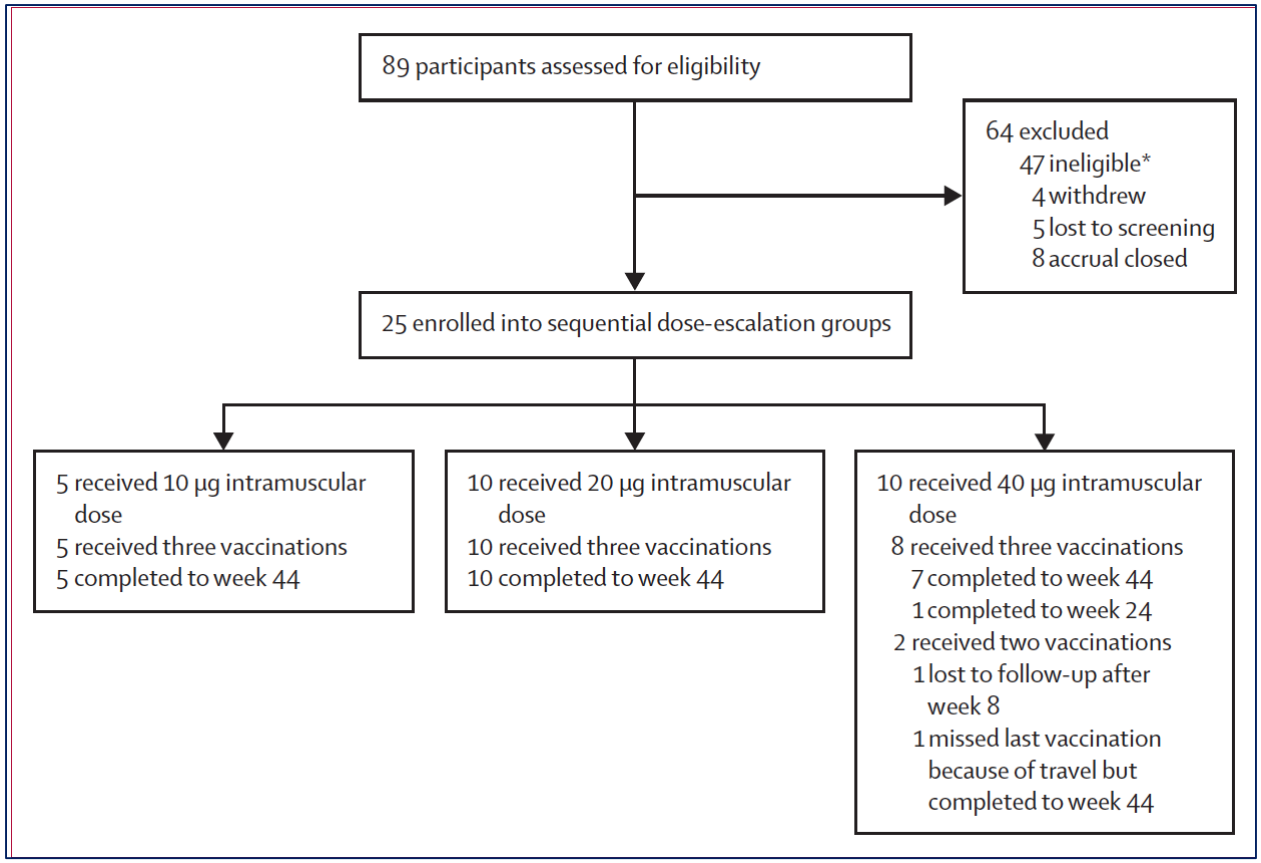
Arthralgia in volunteers immunized with the chikungunya vaccine

Volunteer no.	Description of arthralgia
11	Mild intermittent pain in the left elbow beginning Day 4 (lasted 24 hours)
19	Moderate pain in the left wrist on Day 1 (lasted 10 minutes)
22	Mild arthralgia in the left hand on Day 13 (lasted 3 hours)
32	2–3 bouts of episodic pain lasting 15 minutes in left elbow and wrist on Days 1, 2, and 4 that limited typing
43	Mild left knee and thigh pain on Day 1 (lasted 6 hours)

Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial

Lee-Jah Chang, Kimberly A Dowd*, Floreliz H Mendoza, Jamie G Saunders, Sandra Sitar, Sarah H Plummer, Galina Yamshchikov, Uzma N Sarwar, Zonghui Hu, Mary E Enama, Robert T Bailer, Richard A Koup, Richard M Schwartz, Wataru Akahata, Garv I Nabel, John R Mascola, Theodore C Pierson, Barney S Graham, Julie E Ledgerwood, and the VRC 311 Study Team*

www.thelancet.com **Vol 384 December 6, 2014**



Virus Like Particle

	ELISA titre (strain 37997)			Neutralisation IC_{50} titre (strain OPY1)		
	10 µg group (n=5)	20 µg group (n=10)	40 µg group (n=10)	10 µg group (n=5)	20 µg group (n=10)	40 µg group (n=10)
0*†	..	..	..	50 (50–50)	51 (49–52)	52 (50–54)
4*	160 (19–1317)	278 (98–788)	424 (134–1338)	188 (30–1179)	236 (90–614)	346 (120–999)
8	3378 (358–31 856)	5881 (2026–17 077)	20 480 (12 144–34 539)	2688 (885–8166)	1775 (1129–2791)	7246 (4512–11 637)
20*	2560 (758–8645)	1114 (557–2229)	4740 (1852–12 133)	650 (251–1680)	510 (288–901)	1485 (831–2655)
22	31 042 (14 378–67 021)	13 512 (4852–37 626)	14 482 (4362–48 073)	NA	NA	NA
24	40 960 (40 960–40 960)	15 521 (6058–39 763)	34 443 (22 862–51 890)	8745 (1514–50 516)	4525 (2252–9093)	5390 (1865–15 573)
44	4457 (442–44 860)	5881 (2026–17 077)	8611 (2730–27 161)	940 (141–6254)	717 (267–1927)	1385 (605–3171)

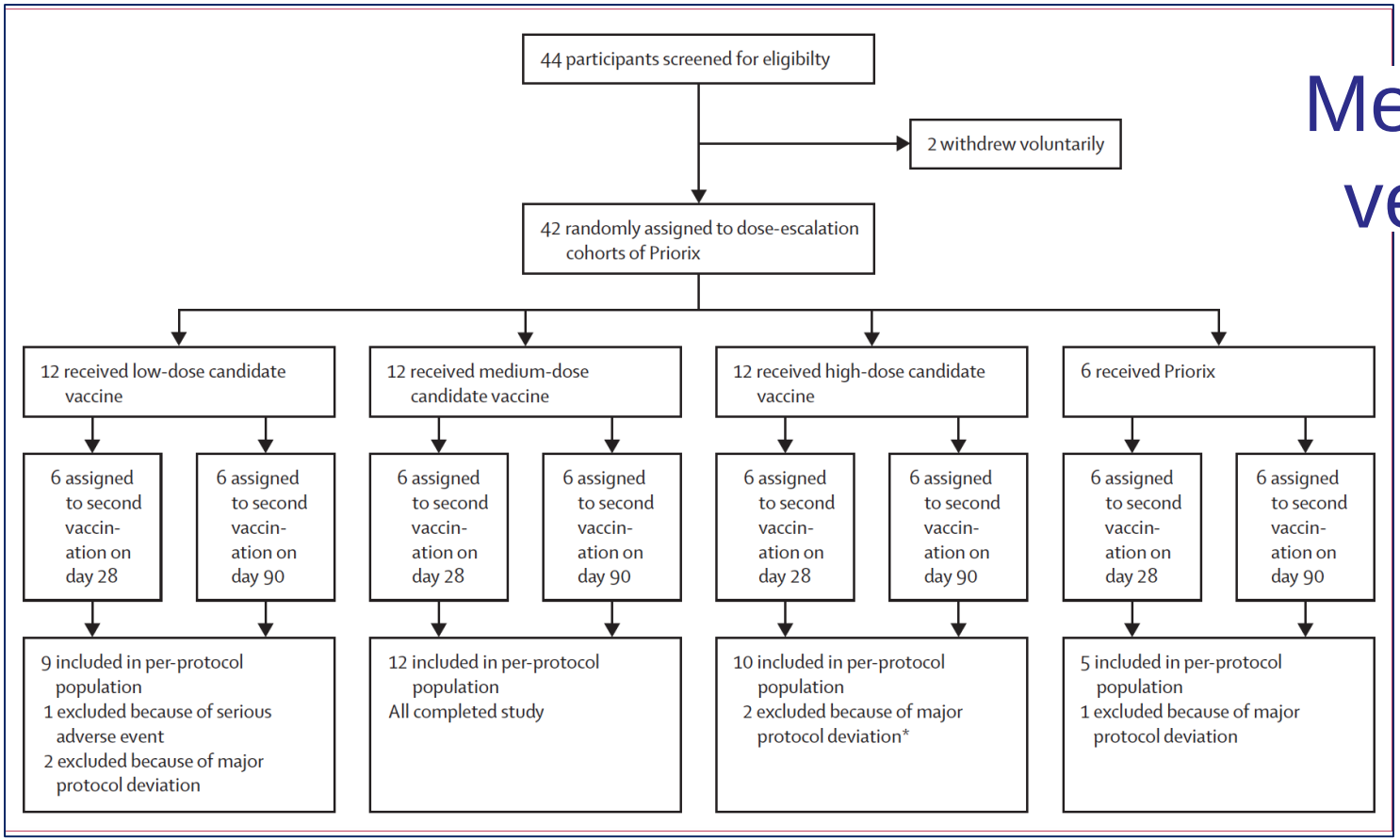
Data are the geometric mean titre (95% CI). All available samples were used for each reported result. IC_{50}=half maximum inhibitory concentration. NA=not assessed. *Visit at which vaccine was administered. †For ELISA, week 0 values were used to background correct titres for subsequent weeks.

Table 3: **Antibody titres**

Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial

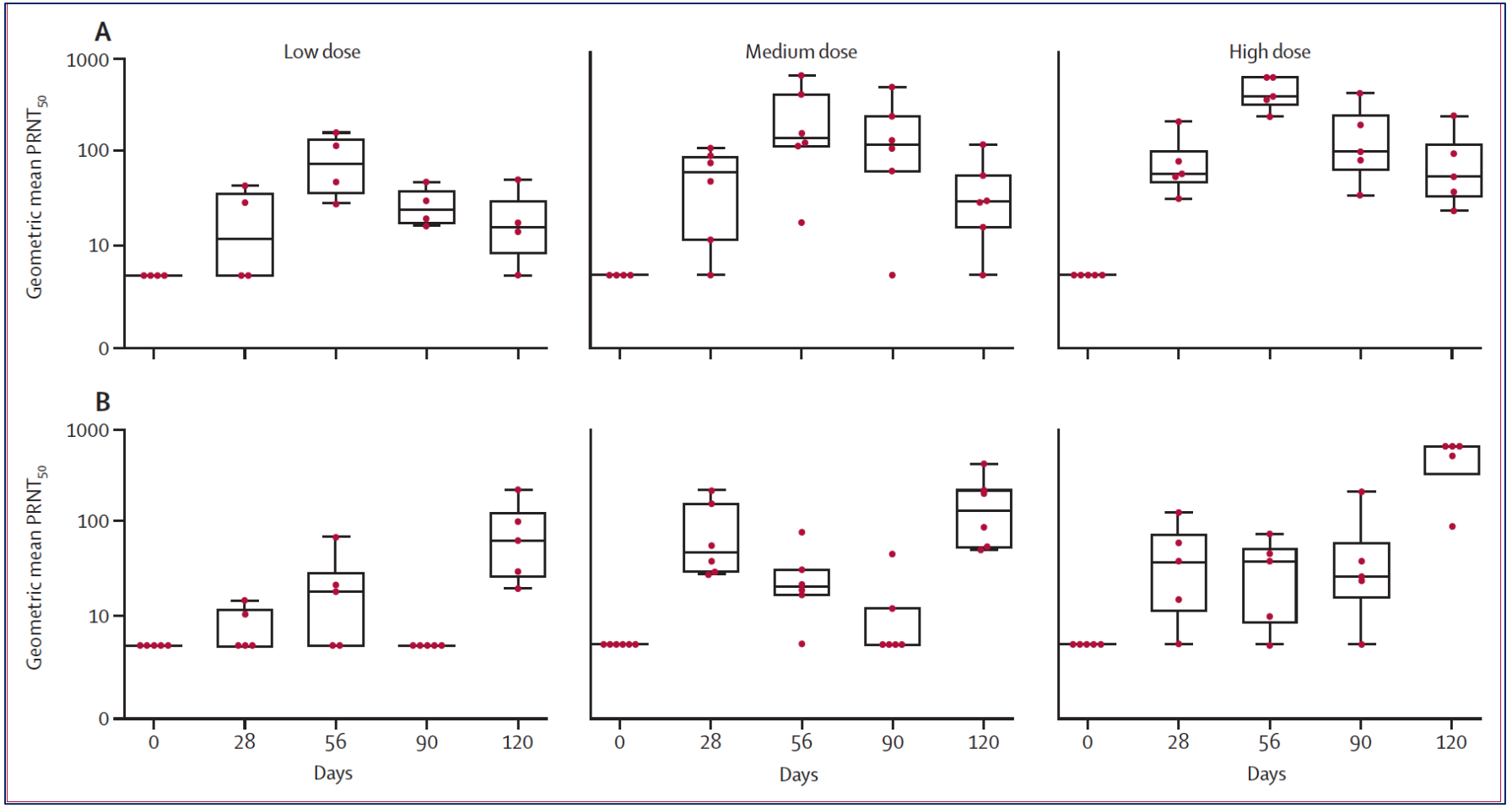
www.thelancet.com/infection Vol 15 May 2015

Katrin Ramsauer, Michael Schwameis*, Christa Firbas, Matthias Müllner, Robert J Putnak, Stephen J Thomas, Philippe Desprès, Erich Tauber, Bernd Jilma, Frederic Tangy*



Measles vector

MVV-Chikungunya Vaccine Recipients



	Boost on day 28				Boost on day 90			
	Low-dose group (n=4)	Medium-dose group (n=6)	High-dose group (n=5)	Priorix group (n=2)	Low-dose group (n=5)	Medium-dose group (n=6)	High-dose group (n=5)	Priorix group (n=3)
Day 0	5 (5–5)	5 (5–5)	5 (5–5)	8 (0–2017)	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)
Day 14	16 (4–57)	31 (8–131)	34 (7–174)	10 (0–93 360)	6 (4–8)	32 (17–62)	31 (6–147)	5 (5–5)
Day 28	14 (2–86)	36 (10–136)	73 (31–172)	9 (0–21 940)	7 (4–14)	63 (25–158)	29 (6–140)	5 (5–5)
Day 56	73 (21–257)	150 (41–552)	433 (262–713)	23 (0–5)	15 (4–61)	21 (8–54)	23 (6–95)	14 (0–1105)
Day 90	27 (13–57)	91 (17–478)	123 (38–397)	10 (0–66 827)	5 (5–5)	8 (3–22)	15 (4–49)	5 (5–5)
Day 120	16 (4–75)	28 (9–90)	66 (22–203)	8 (0–2017)	63 (19–208)	130 (53–316)	416 (145–1192)	5 (5–5)

Data are geometric mean titre (95% CI). Assessed by 50% plaque reduction neutralisation test.

***Table 2*: Geometric mean antibody titres by treatment group in the per-protocol population**

Regulatory

Regulating vaccines at the FDA: development and licensure of Zika vaccines

EXPERT REVIEW OF VACCINES, 2017
VOL. 16, NO. 6, 525–527
https://doi.org/10.1080/14760584.2017.1324304

Regulatory considerations in development of vaccines to prevent disease caused by Chikungunya virus ☆

Vaccine 35 (2017) 4851–4858

Pathways to Licensure:
Clinical Trials, Accelerated Approval, Animal Rule

Speak to your regulators

Summary

- Zika and chikungunya virus infections have the potential for rapid and significant infection attack rates resulting in morbidity and human suffering.

- Development of safe and efficacious vaccines designed to prevent clinically relevant disease appears feasible.

- Nuances of zika and chikungunya virus transmission and pathogenicity introduce numerous complexities into vaccine development plans.

Thank you!

Upstate Medical University, Syracuse, NY