Chikungunya Vaccine Pipeline Assessment and Outcomes from NIH/WHO Consultation on Chikungunya

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Overview

• Chikungunya virology and disease.
• Immunity to CHIKV.
• Status of CHIK vaccine development.
• Outcomes from NIH/WHO consultation on CHIKV in the Americas.
Chikungunya virus (CHIKV)

• Mosquito-borne virus.

• Family *Togaviridae*, genus *Alphavirus*.

• First isolated from human samples obtained during outbreak of febrile disease with debilitating joint pains and rash in Tanganyika Territory (now Tanzania), 1952.

• Chikungunya – derived from Makonde language; meaning “that which bends up”.

• Requires BSL3 containment.
CHIKV – virion structure

- Icosahedral virus particle, ~65nm diameter
- External envelope comprised of trimeric spikes of 240 E1/E2 protein heterodimers embedded in lipid membrane.
- E1 involved in membrane fusion; E2 involved in receptor binding.
- Envelope surrounds icosahedral nucleocapsid comprised of single copy of RNA genome with 240 capsid proteins.

Siyang Sun et al. eLife Sciences 2013;2:e00435
CHIKV phylogenetics

- 3 major genotypes
  - West African
  - ECSA
  - Asian

- plus Indian Ocean lineage (IOL);
  subtype of ECSA
Transmission cycles

1. Spillover from enzootic cycle

2. Human urban amplification

3. Spillback into enzootic cycle

Control of urban vectors or modulation of urban vectorial capacity; Immunization of urban populations

Control of arboreal vectors or modulation of their vectorial capacity; Immunization of enzootic NHP hosts

Targeted vaccination of people exposed to enzootic spillover; reduction of exposure to enzootic vectors

Chikungunya disease

- Attack rates can be very high – 70-90% reported in some outbreaks.
- Estimates of subclinical infection rates vary but are generally low (5-25%).
- Incubation period is typically 3-7 days, followed by onset of clinical signs.
Chikungunya disease

• **Acute disease** (~2-3 weeks) characterized by fever with inflammatory arthralgia/arthritis, accompanied by other non-specific symptoms – e.g. myalgia, headache, rash.

• **Post-acute phase** (4 wks to 3 months) occurs in ~50% of patients and involves persistent joint pain.

• **Chronic phase** (>3 months to years) occurs in a small proportion of patients. In most it involves various musculoskeletal features treatable with NSAIDs, analgesics, physiotherapy; some (~5%) have chronic inflammatory rheumatism.

(Simon et al., 2015, French guidelines for the management of chikungunya).
Severe forms of Chikungunya disease

• Atypical, severe presentations reported in ~0.5-5% of cases, including encephalopathy, encephalitis, myocarditis, hepatitis.

• Fatal outcomes associated with CHIKV infection have been described in recent epidemics. (CFR <1% in most).

• Most severe/fatal cases associated with other underlying morbidity.

• Mother to neonate transmission frequent if viremic at delivery and associated with high rates (>50%) of clinical disease in neonates with severe presentation.
Diagnosis and case definitions

• Clinical diagnosis is complicated by presence of similar febrile viral diseases – dengue, Zika, others?

• Laboratory diagnosis typically on the basis of pathogen detection (virus isolation; qRT-PCR) or serology (IgM and/or neut antibodies; increases in IgM/IgG titer in paired sera)

• Varying case definitions have been employed during outbreaks to date. Some recent attempts to standardize definitions for possible/suspect, [probable,] confirmed cases.
Re-emergence and spread of CHIKV
Chikungunya burden of disease - LMIC

Countries and territories where chikungunya cases have been reported*
(as of March 10, 2015)

*Does not include countries or territories where only imported cases have been documented. This map is updated weekly if there are new countries or territories that report local chikungunya virus transmission.

http://www.cdc.gov/chikungunya/geo/index.html
Chikungunya burden of disease - LMIC

101 countries/territories; ~2/3rds are LMIC

~1.66M suspected, 42,721 confirmed cases and 252 deaths in the Americas to 28 August, 2015 (PAHO figures);
>3/4 of cases are in LMIC

http://www.cdc.gov/chikungunya/geo/index.html
Chikungunya burden of disease - LMIC

Are other control measures effective?

Following the 2005-06 outbreak in La Reunion:

“[By] September 2007, no epidemic resurgence had been recorded in Reunion with an attack rate remaining below 40%, despite sporadic circulation of chikungunya virus. The lack of resurgence may well have been due to collective and individual vector control measures, and especially to effective use of repellents and destruction of domestic and peridomestic larval shelters by the population and authorities. It is also possible that attack rate in Reunion masks a certain heterogeneity, with very high rates of acquired seroprotection in places where the inhabitants were most vulnerable in 2005 and 2006.”

Flahault et al., 2012. “An interdisciplinary approach to controlling chikungunya outbreaks on french islands in the south-west indian ocean”. Médecine Tropicale. 72:66-71
Immunity to CHIKV

- Robust IgM/IgG antibody responses following CHIKV infection in humans and animal models.
- Neutralizing antibodies primarily target E1/E2 structural proteins and are protective in passive transfer studies.
- Suggestion that early production of neutralizing IgG3 antibodies may be associated with reduced risk of prolonged disease; additional studies of Ig subclasses and infection outcome possibly warranted.
- Cytotoxic T cells contribute to but not necessary for virus clearance. Unclear whether CMI may contribute to immunopathology of CHIK disease.
- Natural infection results in lifelong immunity.
“An attenuated live vaccine was pursued because of decreased production costs and possible reduced risk that might be associated with handling large quantities of un-attenuated vaccine prior to inactivation.”

“The unpredictable epidemiology of chikungunya, the associated challenges of demonstrating efficacy in the field, the lack of evidence that chikungunya virus was a biological threat agent, and reduced budgets together led to program termination.”
Live attenuated TSI-GSD 218 vaccine (CHIK 181/clone25)

Good immunogenicity.

Generally well tolerated by recipients. Transient arthralgia in ~10%.

Subsequent molecular studies determined that attenuation was due to only 2 mutations; potential risk of reversion to virulence?

Technology transferred to five developers since 2006 for evaluation.

Table 4
Proportion of alphavirus naïve recipients of chikungunya vaccine that developed plaque reduction neutralizing antibody (PRNT_{50 or 80})⁵ antibody, and geometric means of maximum titers.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number with antibody/number of alphavirus naïve recipients</th>
<th>% Developing neutralizing antibody between days 15 and 32</th>
<th>Geometric mean of maximum titer on days 11–38 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29/30</td>
<td>97</td>
<td>305 (189–494)</td>
</tr>
<tr>
<td>C</td>
<td>19/19</td>
<td>100</td>
<td>297 (⁴)</td>
</tr>
<tr>
<td>D</td>
<td>3/3</td>
<td>100</td>
<td>640 (114–3580)</td>
</tr>
<tr>
<td>F</td>
<td>21/21</td>
<td>100</td>
<td>110 (⁴)</td>
</tr>
<tr>
<td>G</td>
<td>57/58</td>
<td>98</td>
<td>582 (⁴)</td>
</tr>
</tbody>
</table>

Total  | 131                                                        | 98                                                    |                                                     |

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

## Current CHIK vaccine candidates

<table>
<thead>
<tr>
<th>Entity</th>
<th>Vaccine type</th>
<th>Pre-clinic</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valneva/Karolinska Inst.</td>
<td>Live, attenuated (CHIKV-Δ5nsP3)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takeda/UTMB</td>
<td>Live, attenuated (CHIK/IRES)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arbovax/NC State Univ</td>
<td>Live, attenuated (transmembrane deletion)</td>
<td>X</td>
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<td></td>
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<tr>
<td>UTMB</td>
<td>Live, attenuated chimeric (various alphavirus backbones)</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Themis Bioscience/Inst. Pasteur</td>
<td>Live, vectored (measles virus)</td>
<td></td>
<td>X</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>Profectus/Yale/UTMB</td>
<td>Live, vectored (VSVΔG-CHIKV)</td>
<td>X</td>
<td></td>
<td>2016?</td>
<td></td>
</tr>
<tr>
<td>Karolinska Inst./CSIC Madrid</td>
<td>Live, vectored (MVA-CHIKV E1E26KE3)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univ. Wisconsin/Takeda</td>
<td>Live, vectored (MVA-CHIKV E2E3)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIAID</td>
<td>Virus-like particle (mammalian cells)</td>
<td>X</td>
<td></td>
<td>2015-16</td>
<td></td>
</tr>
<tr>
<td>Ti Pharma/Wageningen Univ.</td>
<td>Virus-like particle (insect cells)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merck</td>
<td>Virus-like particle (insect cells)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bharat Biotech</td>
<td>Inactivated (various strains, various methods)</td>
<td>X</td>
<td></td>
<td>2016?</td>
<td></td>
</tr>
<tr>
<td>Indian Immunological</td>
<td>Inactivated (formalin-treated 181/25 from US Army)</td>
<td></td>
<td>X</td>
<td>2016?</td>
<td></td>
</tr>
<tr>
<td>DRDE, India</td>
<td>Inactivated (formalin treated Indian 2006 isolate)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanotherapeutics Inc. (from Baxter)</td>
<td>Inactivated</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medigen</td>
<td>DNA (plasmid-launched 181/25 live attenuated)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRDE, India</td>
<td>Recombinant subunit (E. coli expressed E1/E2)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Inst. Virology, India</td>
<td>Recombinant subunit (E. coli expressed E2)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>
Gaps and Opportunities in Chikungunya Research: Expert Consultation on Chikungunya Disease in the Americas

Date: 30 June-2 July 2015
Location: Rockville, Maryland

Co-hosts: This interdisciplinary research workshop is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health within the U.S. Department of Health and Human Services (NIAID/NIH/HHS) in partnership with the Pan American Health Organization (PAHO/WHO) and the World Health Organization (WHO/HQ).

Purposes:

- Share knowledge about chikungunya disease, epidemiology and pathogenesis;
- Assess the chikungunya epidemic risk throughout the Americas;
- Identify critical gaps in knowledge, technologies, and research infrastructure needed to interrupt the epidemic;
- Discuss potential collaborative research opportunities to address the prevention, diagnosis, treatment and control of chikungunya disease.
NIAID VLP vaccine candidate

- VLPs (10-20mg/L) produced by transfection of 293T cells with plasmid expressing CHIKV structural proteins (strain 37997, WA genotype)

- GMP production in characterized VRC293 cells for clinical trials; multi-step purification from culture supernatants.

NIAID VLP vaccine candidate

- Immunogenic and protective in mice and NHPs during nonclinical evaluation.

![Graphs showing antibody titers and neutralization activity.](c) Neut. activity of sera from immunized rhesus macaques against (c) lentivirus pseudotypes or (d) CHIKV.

- Phase 1 trial – 12/2011 to 03/2012 (USA)
  - Dose escalation in 25 healthy adults (18-50 years old)
  - Three doses (IM; 10, 20, 40 µg/dose) at wks 0, 4, 20
  - Well tolerated; only mild local or systemic symptoms reported
NIAID VLP vaccine candidate - immunogenicity

Indirect ELISA using VLP antigen, anti-IgM/IgG/IgA secondary Ab. Neutralization using SINV/CHIKV-GFP chimeric virus on Vero cells; 50% cutoff.

Themis Bioscience/Inst. Pasteur
MV-CHIK vaccine candidate

- Recombinant measles virus (Schwarz strain) expressing CHIKV structural proteins (strain 06-49; IOL). Grown on Vero cells.
- Infection of cells by MV-CHIKV results in production of CHIKV VLPs.
- 1 or 2 10E5 TCID50 doses protected mice against lethal CHIKV challenge
Phase 1 dose-escalation trial - Nov13 – Feb14 (Austria)

- 42 healthy adults, 18-45 years old
- Two doses of $1.5 \times 10^4$, $7.5 \times 10^4$, or $3.0 \times 10^5$ TCID50 MV-CHIK, on days 0 and 28 or 90
- Well tolerated
  - Headache, injection-site pain, influenza-like illness in ~50%
  - More common with higher doses
- No significant effects on tolerability/immunogenicity associated with pre-existing immunity to MV
Humoral immune response to CHIKV vaccine candidate


Neut. testing against 181/25 vaccine strain (Asian genotype).
Also measured HI antibodies against an ECSA genotype strain.
Immunization strategies and schedules for CHIK vaccines?

• How would CHIKV vaccines be utilized in LMIC?
  • Part of regular immunization schedule or targeted campaigns in endemic areas
  • Available to individuals - user pays
  • Stockpiled for outbreak response

• Can a single CHIK vaccine candidate meet the likely requirements of LMIC and HIC markets?
Target populations for CHIK vaccines?

• Are they the same in HIC versus LMIC countries?

• During epidemics, all age groups appear to be at risk.

• High risk groups for prolonged or severe disease:
  • Older age (>65 years?)
  • Underlying health problems
  • Pregnant women (risks for maternal-fetal transfer)

• Traveler and military populations.

• What are appropriate populations for phase 2 studies? How different will responses be in vaccinees in endemic areas?
1. Clinical efficacy trials

- Significant logistical challenges for demonstrating efficacy due to sporadic incidence of outbreaks.
- Unclear what to expect for ongoing CHIK disease incidence in the Americas.
- Can any current vaccine candidates be evaluated during ongoing epidemic? Where?
- What is the likelihood for demonstration of efficacy in Phase 2/3 trials in endemic (post-epidemic) areas (Africa/India/SE Asia?)
Pathways to licensure

1. Clinical efficacy trials

If vaccine efficacy testing occurs in outbreak scenario, other key issues are:

- Study site preparedness: diagnostics and lab infrastructure for early detection, and to support testing of trial samples
- Cumbersome IRB approval processes. How do we streamline reviews? Who is responsible for driving this change? Inadequate expertise of (some) approval committees?
Pathways to licensure

2. Approval via neut. antibodies as a correlate of protection

- Good evidence from animals and humans that neut. antibodies provide protection against infection/disease.

- [One candidate vaccine shows protection (in mice) with very low or absent neutralizing antibodies.]

- What titer(s) correlate with protection?

  - Some data from passive transfer studies in mice, e.g. PRNT$_{80} \geq 35$
  
  - Presence of measurable neut Abs (PRNT$_{50} \geq 10$) associated with protection against CHIK infection/disease in human cohort in Philippines.
2. Approval via neut. antibodies as a correlate of protection

- Are human challenge studies relevant (and feasible) to investigate a correlate of protection? Significant ethical questions.

- Definition of a correlate may be platform/vaccine-specific, at least for first candidate(s).
How to measure antibody responses?

- Wide range of assay types/formats currently being used to assess total or neutralizing antibodies.

- Neutralization assays use differing cell substrates, virus/antigen types, time/temp conditions, readouts.

- Lack of standardization makes comparison of data difficult.

- Testing against multiple strains/lineages may be necessary, depending upon what titer(s) is/are considered “protective”.
NIH/WHO consultation - Recommendations related to prevention

• Need for more surveillance. Utilizing current surveillance resources for dengue?
• Need for prospective cohort studies in different areas.
• Consensus/formalization around case definition.
• Investigate how we can facilitate/streamline IRBs and accelerate timelines for study approvals.
• Facilitate comparability of neutralization data between studies/sites. Development of reference reagents (positive control sera).
• Cost/resources to move candidate vaccines forward. How to attract large pharma?
Summary

• The CHIK vaccine development pipeline appears robust – many candidates based on a range of platforms/approaches.

• Two candidates with positive Phase 1 data; others following.

• Path forward to licensure and ongoing burden of disease appear less clear.

• Need for guidance regarding deployment strategies, target populations and indications for use of vaccines in LMIC; and for definition of correlates of protection.
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