An R&D Blueprint
for action to prevent epidemics

Phase IIb and III
Chikungunya Vaccine Trials Design

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CHIKV vaccine – product profile

Emergency setting (Reactive/Outbreak use):
Protection of at-risk persons in the area of an ongoing outbreak of chikungunya.

Non-emergency setting (Preventive Use):
Populations living in areas where chikungunya is endemic.
Reactive vaccination should be possible

- Serial interval is long \( \approx 23 \) days

*Trapeang Roka, Cambodia, February and March 2012*

*CDC, Morbidity and Mortality Weekly Report (MMWR), September 21, 2012 / 61(37);737-740*
CHIKV – target vaccine population

Healthy adults and children, excluding pregnant and lactating women, people with comorbidities (immunodeficiencies, rheumatic conditions, diabetes).

Latin America, Southeast Asia, Asia Pacific, Africa
CHIKV – vaccine trial design

A prospective, randomized, double-blind, placebo-controlled, efficacy trial

Individual randomization (2:1) in geographic clusters in areas mapped to have transmission, mixture of

- Closely monitored high-risk clusters with responsive vax
- Responsive addition of clusters with transmission

When transmission is detected, start community-based (e.g. door-to-door) enrollment of participants
CHIKV – vaccine site selection

Suggest closely monitoring high-risk sites in participating countries in Latin America, Southeast Asia, and Africa.

High-risk sites have high circulation of Aedes-borne diseases, but seroprevalence of CHIKV <50%.
CHIKV – important considerations

Screening at baseline

Bleed all of the trial participants before vaccination to determine baseline seropositivity.

All individuals are randomized and vaccinated, but only baseline seronegative individuals contribute to the primary analysis.

Baseline sample could contribute to design an immune correlate of protection if the vaccine works.
CHIKV – endpoint considerations

Primary endpoint
Laboratory-confirmed acute clinical illness

Secondary endpoints
• Subacute clinical illness
• Chronic clinical illness
• Immunological correlates of risk and surrogates of protection, i.e., surrogates for vaccine efficacy
CHIKV – analysis considerations

Primary analysis
Vaccine efficacy (VE) for the prevention of laboratory-confirmed acute clinical illness among seronegatives

Key secondary analyses
• VE for the prevention of acute clinical illness in overall population
• VE for prevention of subacute and chronic clinical illness, and other complications.
Statistical analysis

The primary analysis will be the estimated vaccine efficacy against confirmed Chikungunya illness:

\[ \hat{VE} = 1 - \frac{\hat{\lambda}_1}{\hat{\lambda}_0} \]

- \( \hat{\lambda}_1 \) = estimated hazard of illness for individuals who receive vaccine.
- \( \hat{\lambda}_0 \) = estimated hazard of illness for individuals who receive placebo.

One-sided hypothesis test for the primary outcome:

- \( H_0: \hat{VE} \leq 0.3 \) versus \( H_a: \hat{VE} > 0.3 \). In addition, a lower 95% confidence bound will be calculated for \( \hat{VE} \).

Secondary analyses using same setup

Statistical method: Cluster-stratified, Cox proportional hazards model, with appropriate \( \alpha \) – spending for interim analyses.
Testing more than one vaccine

• We can test $m$ vaccines against a single placebo arm, using Bonferroni or a more complex correction for $\alpha$
• e.g., two vaccines would be randomized in a 1,1,1 pattern with two hypothesis tests, each at $\alpha = 0.025$
Individual randomization within sites

Multiple sites/outbreaks

Sites  Enrolled participants within sites

VE = 1 - \frac{\lambda_1}{\lambda_0}, \text{ combined across the } n \text{ sites as stratification or regression}
Sample Size for Primary Outcome With One Vaccine

90% power, 2:1 vaccine to placebo, $\alpha = 0.05$ one-sided, VE = 0.3 lower bound, 20% loss-to-follow-up

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<th>Cumulative attack rate in placebo arm</th>
<th>Cumulative attack rate in vaccination arm</th>
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Sample size considerations

The sample size must be further expanded if seropositives are excluded from the primary analysis.
The case of CHIKV vaccine trials

Emergency setting (Reactive/Outbreak Use)
- It may be possible to accumulate enough data to assess VE in a single local outbreak

Non-emergency setting (Preventive Use)
- It will probably involve several years and a variety of locations to accumulate enough cases to assess VE
- We could combine data from the preventive and reactive trials to get an answer sooner
Data monitoring strategy

Interim analyses to assess efficacy or futility can be timed to occur after reaching a targeted number of events, e.g., 50%

Study data would not be released unless the trial was stopped, for efficacy, futility, or reaching its targeted number of endpoints
“Master protocol” approach

The protocol should ideally be generalizable to all countries where CHIKV is endemic

Where outbreaks in other countries occur, the trial structure should allow new sites in affected areas to be added

Researchers and national representatives from affected countries should be engaged early on

A clear and transparent mechanism for achieving consensus regarding elements of the protocol is required (e.g. managing data, sharing samples, mediating disagreements)
Thank you