Considerations for Zika Vaccine Trial Design

M. Elizabeth Halloran

Fred Hutch Research Center
Department of Biostatistics, University of Washington
Seattle WA USA

Thanks to NIH R37 AI032042, U54 GM111274
www.cidid.org
Collaborators

Ira Longini (UF), Natalie Dean (UF), Alessandro Vespignani (NEU)

Center for Inference and Dynamics of Infectious Diseases
www.cidid.org

Laboratory for Modeling of Biological + Socio-technical Systems (NEU)
www.mobs-lab.org

Discussions with individuals from CDC, NIAID, others
WHO Blueprint for Research and Development to prevent epidemics
Blueprint Working Groups
Group 1 Members

Ira Longini* (UF) Director
Natalie Dean* (UF)
Betz Halloran* (UW, FHCRC)
Martha Nason* (NIH)
Judith Mueller (Inst Pasteur)
Ximena Riveros (WHO)

Ron Brookmeyer (UCLA)
Christl Donnelly (Imperial Col)
Momodou Jasseh (Gambia, MRC)
Conall Watson* (LSHTM)
James Russell (NERC, Sierra Leone)
Victor De Gruttola (Harvard)

*Worked specifically on the Zika pathogen profile and/or possible vaccine trial design
Zika Spread in Americas

- 48+ countries
- As of May 25, 2017, PAHO (WHO) reported
  - 563,960 suspected and 211,695 confirmed locally-transmitted Zika cases
  - 5,515 imported cases in the US and Canada
  - 20 total deaths among Zika cases
  - 3,231 confirmed congenital syndrome associated with Zika virus infection (2,698 in Brazil)
Zika Vaccine Development

- 45 vaccine candidates in the pipeline
- Traditional approval: Clinical endpoint or well-established marker of protection (none for Zika currently, but for other flaviviruses) RCT (my focus here)
- Accelerated approval
- Animal rule (FDA only)
- Both require post-licensure studies to verify clinical benefit
- EUAL listing (WHO)
Challenges for Zika Vaccine Trial Design

- Seasonal transmission
- Unknown infection attack rate in Americas, 2\textsuperscript{nd} wave attack rate likely lower
- Spatial spread challenging to predict
- 10-23 day serial interval between cases
- How many vaccine doses and how far apart?
- Serological diagnoses challenging
Challenge: Where will Zika transmission be?

• In planning for the vaccine trials, it is important to predict where transmission will be.

• Vaccine efficacy trials based on clinical outcomes need to go where the transmission is.

• Idea being discussed: Plan for 30-50 trial sites where transmission will likely occur
Where has Zika transmission been?

• Where transmission will be is in part dependent on where transmission has been.

• If a large number of people in a population have already been infected, then there might not be sufficient susceptible individuals left to maintain transmission or to run a vaccine trial.

• Problem of underreporting and asymptomatic infections, so the infection attack rate up until now is unknown.
Zika model

• Detailed spatial and temporal modeling of Zika spread in the Americas fit to available data.

• Includes detailed human and mosquito population information, climate data, human transportation data, among others: GLEAM + mosquitos

• Zhang et al, The spread of Zika virus in the Americas, PNAS 2017

• www.gleamviz.org, www.zika-model.org
Posterior Density of Time and Place of Zika Introduction in Brazil (Zhang et al, PNAS 2017)
Model-projected symptomatic cases with projected cumulative infection incidence ≥ 5% in 2017*

*Source for model: Zhang, et al. Projected spread of Zika virus in the Americas. PNAS 2017
Challenge: Where will Zika transmission be?

• Predicting where transmission will be.

• Laura Rodrigues: Ongoing data needs:
  
  • (1) repeat, multi-site sero-prevalence surveys; (2) sero-conversion cohorts to get distribution of immune/susceptibles; (3) mosquito density information

• Cases: monitor incidence of Zika disease

• Congenital Zika syndrome: monitor incidence

• Data from the field combined with simulation results
Zika vaccine trial design

- Individual RCT
- Fixed sites, reactive transmission clusters, nested case control for ZCS, GB
- Cluster RCT: possibly two-stage: Laura Rodrigues warns that transmission is very patchy
- Test-negative design (observational)
- Designing a trial in an epidemic versus endemic situation
Considerations for site selection

- Select 30 – 50 sites that are likely to have Zika transmission in 2017-2018
- If transmission occurs in other parts of the world, additional sites could be added
- Accumulating evidence across sites/outbreaks/trials needs development of statistical methodology to be acceptable for regulatory agencies
Individual randomization within sites

Multiple sites
Site:  1  2  ………………..  n

Sites  Enrolled participants within sites

VE = 1 – incidence in vaccinated / incidence in unvaccinated, combined across the n sites
Predefined vs responsive vaccination

• Should enrollment and vaccination occur in sites where it is hoped (expected) that transmission will occur?

• Or should one wait until some transmission is documented at a site, then begin to vaccinate?

• Can mosquito infection monitoring give an early signal of transmission?

• The number and timing of the doses required could be on the order of the season of transmission.
Predefined vs responsive vaccination

- “Expected” Zika disease cumulative incidence
  - Moderate to high, > 3% (or some other threshold value)
    - Predefined vaccination
  - If low, ≤ 3%
    - Responsive vaccination
      - Enroll participants where transmission is occurring
      - Targeted vaccination of households and neighborhoods
      - Conditional expansion of sample size
    - Could also consider some mix of predefined and responsive (e.g. a small number vaccinated in advance), but spread of an outbreak triggers responsive vaccination
Primary and secondary analyses

- **Primary** = per protocol (X days after last dose) or ITT?

- **Secondary**
  - Predefine additional secondary analyses if there are multiple doses (e.g., after second dose in a three dose series)
  - Rare outcomes such as Guillain-Barré syndrome and Zika congenital syndrome – nested case control analysis
Primary outcome

- Primary outcome: lab-confirmed Zika by RT-PCR (blood, urine, other bodily fluid) (Stephen Thomas and others)

- Challenge: If ascertainment on disease, many infections will be missed.

- Role of asymptomatic infection on transmission and in producing Zika congenital syndrome currently unknown, and effect of vaccination on these outcomes hard to evaluate.

- How to ascertain Zika on asymptomatic infection? Monthly bleeds? (NIH study)
More on outcomes

• Active versus passive surveillance?

• Likely (very) active for Phase IIb or III

• Will there be enough transmission to use clinical outcome (disease and or infection) as the primary outcome? Or will it be necessary to use immunological surrogates as the primary outcome?

• Would the trials be held in different places if immunological outcomes rather than clinical outcomes were chosen?
Baseline samples

• Take baseline samples
  • Baseline immunity could be important (dengue experience) – assumes a serological test will be developed
  • Could be used to identify immune correlates or surrogates of VE

• Prof. Villar: missed opportunity in dengue vaccine trials

• Will vaccine trials include people who have already been infected with Zika? Should Zika-positive be excluded?
Statistical analysis

- Estimate vaccine efficacy
  - Frailty regression model (i.e., Cox model or logistic regression)

- Adjusting for site in the analysis expected to improve precision (controls for a large source of heterogeneity)

- Sites with no Zika spread (no cases among participants) will be dropped from the analysis

- Sites with few Zika cases can still contribute to the analysis, but sites may need to be collapsed to support estimation of random effects
Data monitoring

- Data monitoring should be event driven (total number of events across all sites)
  - Combining information across sites may require thought

- Do we need to predefining a strategy for trial closure if the epidemic ends before events accrued, or can the trial be expanded if the epidemic takes off in a new region?
Sample size

- Power and sample size calculations should consider both the expected event rate AND the probability of no outbreak
- The number of sites AND the number enrolled at each site are important considerations
  - Fewer large sites more cost-effective
  - Bigger site provides more lead time if vaccinating responsively
  - Many smaller sites may be more likely to accrue target number of cases (distributes risk of no outbreak)
- Simulation model of Zhang et al will be used to help design trials
Choosing among many candidates

- Framework for a pre-selection of most promising candidates (out of current 45)
- Perspectives of testing several vaccines at the same time
- Difference in testing two at same time or 10 at same time
- Who should decide which candidates should move forward for further testing in larger populations?
- Are there limits on the number of trial sites and candidates?
Zika vaccine WHO TPP

- Living document
- Outbreak vs Routine (or endemic) situation
- WHO TPP focuses on the outbreak setting
- Public health goal: prevent congenital ZIKV syndrome in outbreak setting
- Should trials focus on women of childbearing years (and men) say 9 years and older? Flavivirus or Zika + or -?
- Non-replicating platforms preferred.
Further considerations

• Should trials be powered around current TPP (80% clinical efficacy or 70% on immune surrogate)

• Would be underpowered for lower efficacies (Phil Krause).

• Regulatory expectations of Zika virus vaccines during an emergency vs during endemic use
Eventual Target Population

• Vaccinate just pre-adolescent girls to prevent Zika in pregnancy?

• Vaccinate young children routinely with an initial vaccination of broad age group to reduce transmission?

• Similarity to two different policies for rubella vaccination in different countries.
Path to Licensure Needs Clarity

• Rigid regulatory pathway to licensure from the regulatory agencies.

• Thus, design and plan for the statistical analysis must be rigorous and anticipate the unexpected.

• The rVSV- Ebola vaccine efficacy is still not licensed.
Conclusions

• Need for better communication between the modelers, planning of vaccine trials, and the ongoing field studies (ZIP, other cohorts)

• Laura Rodrigues’ suggestion of a Task force

• Better communication about development of various lab tests
Thank You!

9th Summer Institute for Statistics and Modeling of Infectious Diseases July 10-26, 2017
University of Washington, Seattle
sismid.uw.edu
Immunological measures

- Screening for pre-existing flavivirus infection
- Measure Zika vaccine induced immune response
- Distinguish vaccine from natural infection (NS1?)
- Neutralizing antibody testing, functional quantitative assay may be a correlate of protection (PRNT, MN, RVP)
- Methodology for comparing neutralization titer data across flaviviruses is needed
Role of Simulations in Trial Design

- Model by Zhang et al, PNAS 2017, will be used to
- generate simulated data that can be used in sample size calculations
- and in developing novel methods of analysis for the novel trial designs