Bringing Zika vaccines to licensure
Demonstration of efficacy and effectiveness

Zika vaccine and study designs
(with considerations to generating evidence that may contribute to inform regulatory review)

Ira Longini on behalf of R&D Blueprint
Clinical trials working parties
Current situation

• There are about 30 Zika vaccine candidates in various stages of development
  – Some have undergone animal challenge studies
  – One may be entering phase IIb efficacy trial
  – None in phase III efficacy trials
  – Some may have undergone human challenge studies

• There is no established immune correlate or surrogate of protection
Important caveat

The clinical development program and regulatory pathway for a Zika vaccine **must be tailored to the particular candidate vaccine** being evaluated and may differ from that of other candidate Zika vaccines.
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**TRADITIONAL APPROVAL**

RCT, clinical endpoint OR accepted correlate of protection
Placebo-controlled RCTs powered to demonstrate clinical efficacy.

**ACCELERATED APPROVAL**

Accelerated evaluation to treat a serious or life-threatening condition on one or more clinically significant endpoints. Well-controlled trials establishing an effect on a surrogate endpoint. Human challenge studies may support.

Require Post-licensure studies to verify clinical benefit

**ANIMAL RULE “Exceptional circumstances” EMA (only FDA)**

For serious/life threatening conditions, when efficacy studies are unfeasible or unethical. Product cannot be approved via traditional or accelerated approval. Immune markers in animal models reasonably likely to predict protection against Zika disease in humans

**EUAL* Listing (WHO)**

Special procedure. The disease has been declared PHEIC. Vaccine has oversight by a functional NRA. Basic evidence including but not limited to clinical data, safety data. Justify that immunogenicity data are sufficient, if no clinical data.

* WHO Emergency use assessment and listing procedures for medical products during public health emergencies.
Clinical disease endpoint

• Classical RCT with a valid comparator in multiple populations where future transmission is likely
  – Multi-arm trials
  – Combining information across trial populations, epidemics, vaccine candidates

Well-established marker of protection (or vaccine efficacy surrogate)

– There is no scientific well-established immune correlate or surrogate of protection for Zika
– However, there are known immune correlates for other live and inactivated flavivirus vaccines, e.g., yellow fever, JE
ACCELERATED APPROVAL

• Immune correlates or surrogates (immune marker or impact on another clinical marker)
  – Ideally we would have both efficacy and immunogenicity data from phase IIb or III vaccine trials
    • In the absence of this, human immunogenicity data from phase I and II trials

• [Human challenge studies]
Immune correlates

- Human and animal immunogenicity studies
- Immunogenicity from related flavivirus vaccine constructs
  - 17D live, attenuated yellow fever vaccine
    - High VE, near 100%
    - FDA approved antibody surrogate of infection
    - Neutralizing antibody titer > 10 is protective
    - Similar Zika vaccine construct may work
  - JE vaccines licensed may also be analogous
Human challenge studies

• Studies can directly assess many vaccine effects that cannot be observed in a typical Phase III trial
  – Includes detailed longitudinal data on viral load and persistence

• Approach has been used for bridging studies of vaccines for cholera, malaria, influenza and typhoid

• In 1998, FDA determined that human challenge would have been acceptable to demonstrate efficacy of a cholera vaccine (live oral CVD103-HgR)

• **Limitations:**
  – Extensive safety data still required for licensure
  – May be hard to replicate natural exposure (dose & pathway)

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What trial needs are anticipated post market authorization?

**TRADITIONAL APPROVAL**
Requires post marketing safety surveillance.

Additional effectiveness may be needed – rare outcomes

if there is an accepted correlate of protection, then a trial to show clinical efficacy might not be required.

**ACCELERATED APPROVAL**
Requires studies to verify clinical benefit - effectiveness.

Alternative designs suggested: e.g. cluster randomized.

Approval contingent on additional studies, usually underway.

**ANIMAL RULE**
Requires studies to verify clinical benefit - effectiveness.

Approval contingent on studies, studies are conducted if and when they become feasible and ethical.

**EUAL**
The manufacturer to submit human efficacy data and/or correlates of protection data ASAP. Plan to monitor quality, safety and efficacy in the field, and an undertaking to submit any new data ASAP.
Summary: Bringing Zika vaccines to licensure
Demonstration of efficacy and effectiveness

**TRADITIONAL APPROVAL**
RCT, clinical endpoint or accepted correlate of protection

These trials can be carried out by targeting populations that are soon to experience Zika outbreaks

**ACCELERATED APPROVAL**
It may be necessary to accumulate data on correlates and surrogates of VE from a large number of sources as trials and studies are carried out

Human challenge studies

**ANIMAL RULE**
(only FDA)
EXCEPTIONAL CIRCUMSTANCES
(only EMA)

This would be done if human phase IIb and III VE trials are not feasible

**EUAL**
(WHO)
This can always be done, but must have PHEIC
Some preliminary discussions at the R&D Blueprint ad hoc group on clinical trial designs
Designs we considered

• Individual RCT
  – Fixed populations sites
  – Reactive transmission clusters
  – Nested case control for rare outcomes, e.g. ZCS, GB

• Cluster RCT
  – Possible two-stage designs

• Case control studies
  – Test negative designs

• Observational studies
  – Historical controls
Individual randomization within sites

Multiple sites

Site: 1  2  ....................  n

Sites  Enrolled participants within sites

\[ VE = 1 - \frac{I_{vacc}}{I_{unvacc}}, \]  combined across the n sites
Outcomes we considered

• Primary outcomes
  – Laboratory confirmed Zika illness
  – Infection, conditional on appropriate serological diagnostics
  – May be possible to screen for infection, e.g., testing urine

• Secondary outcomes
  – Zika congenital syndrome
  – Guillain-Barré syndrome
  – Other surrogate endpoints
Considerations for site selection
Phase IIb or III VE trial

• Select 30 – 50 sites in the Americas that are likely to have Zika transmission in 2017-2018
  – Individual randomization within sites with blinded vaccine or placebo in 1:1 or 2:1 ratios
  – Predefined vs responsive vaccination
  – Expand sample size using conditional power arguments

• If transmission occurs in other parts of the world, additional sites could be added
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Thank you

Questions?