Review of conclusions from prior Zika vaccine consultations

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WHO technical consultations on Zika vaccines

- March 2016: WHO global consultation on research related to Zika virus infection; 7-9 March 2016, Geneva, Switzerland; call for an emergency use vaccine TPP

- WHO Zika Virus (ZIKV) Vaccine Target Product Profile (TPP)
  - First iteration for emergency/outbreak scenarios published July 2016
  - Revised TPP published February 2017

- June 2016: WHO consultation on considerations for regulatory expectations of Zika virus vaccines for use during an emergency, 6-7 June 2016;

- October 2016: Mosquito-borne viruses: can we build on commonalities to pre-empt the future? 5-7 October 2016; London.

- January 2017: Scientific Consultation on ZIKV vaccine development; hosted jointly with US NIH/NIAID, 10-11 January 2017 in Rockville, MD, USA
**WHO Zika Virus Vaccine Target Product Profile (TPP) for Emergency Use**

“While this document contains assumptions with respect to regulatory considerations, in order to help frame the rationale for the proposed characteristics, this TPP should not be considered as a regulatory document.”

“The primary objective in the emergency/outbreak context will be prevention of CZS through protection of pregnant women through the duration of their pregnancy.”

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Possible regulatory implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for use</td>
<td>Prevention of virol. confirmed clinical illness; assumptions in relation to relevance to the public health objective</td>
</tr>
<tr>
<td>Target population</td>
<td>Age groups (above 9 years) and special populations (pregnancy), flavivirus exposed and unexposed</td>
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<tr>
<td>Vaccine platform</td>
<td>May have specific requirements for safety evaluation</td>
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<tr>
<td>Measures of efficacy</td>
<td>Consideration of clinical and surrogate endpoints, post-registration needs</td>
</tr>
<tr>
<td>Safety</td>
<td>Age groups, both sexes, flavivirus-naive and -exposed subjects, no contra-indication pregnancy &amp; lactation, post-registration needs</td>
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WHO consultation on considerations for regulatory expectations of Zika virus vaccines for use during an emergency, 6-7 June 2016, Geneva*

- Initial discussion of regulatory considerations, with reference to
  - Limited understanding of disease epidemiology, transmission (vector/sexual), and pathology;
  - WHO’s (draft) TPP for emergency use vaccines;
  - Preliminary data from animal models;
  - Potential data requirements, regulatory pathways and mechanisms to enable emergency use authorization by national regulatory authorities of a ZIKV vaccine

(Note: emergency use authorization may be less of interest today vs accelerated approval processes)

(*Vannice KS et al., Vaccine 2016)
Advantages and limitations of potential endpoints for clinical trials of ZIKV vaccines in support of emergency use (2)

<table>
<thead>
<tr>
<th>Clinical trial endpoint</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity</td>
<td>• Easily measured&lt;br&gt;• Does not enlarge sample size&lt;br&gt;• Short timeline to collect (e.g. 28 days post-vaccination)&lt;br&gt;• Could be done in a range of epidemiological settings</td>
<td>• Limitations of PRNT assay&lt;br&gt;• Unclear relationship between immunogenicity and protection (no correlate of protection established)&lt;br&gt;• Must be linked to convincing animal data, such as passive protection studies&lt;br&gt;• Effectiveness data must be collected post-introduction</td>
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<tr>
<td>ZIKV infection (viremia or seroconversion)</td>
<td>• Asymptomatic infection may be relevant for congenital Zika syndrome&lt;br&gt;• Sterilizing immunity would constitute an all-encompassing endpoint&lt;br&gt;• Smaller sample size needed</td>
<td>• As few vaccines confer sterilizing immunity, high bar for vaccine success&lt;br&gt;• Limitations of RT-PCR assays (duration of viraemia)&lt;br&gt;• Uncertainties of specimens needed&lt;br&gt;• Unpredictability of disease transmission&lt;br&gt;• Might need frequent sampling to detect asymptomatic infections, causing burden to trial participants</td>
</tr>
</tbody>
</table>
Advantages and limitations of potential endpoints for clinical trials of ZIKV vaccines in support of emergency use (2)

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| Laboratory-confirmed Zika disease | • Standard for efficacy trials in absence of a correlate of protection  
• Hypothesis that symptoms, viraemia, and transmission to infants are correlated | • Case definition unvalidated  
• Large sample size requirements  
• Unpredictability of disease transmission |
| Congenital Zika syndrome | • Outcome of greatest interest for public health | • Largest sample size requirements  
• Longest time for results to be available  
• Focus on enrolling women  
• Unpredictability of disease transmission |
Points to consider for regulatory expectations of ZIKV vaccines for use during an emergency

- Understanding of disease epidemiology, pathology and immune protective mechanism still incomplete

- A definitive regulatory strategy cannot yet be recommended

- While public health objective is the prevention of CZS, the indication could relate to prevention of illness/infection

- Clinical efficacy endpoints are the preferred option if feasible: prevention of ZIKV infection as well as prevention of virologically-confirmed ZIKV illness represent the two most likely options

- If clinical efficacy trials are not feasible, immunological endpoint studies combined with passive protection studies in animals, and possibly human challenge study results, may represent acceptable data sets

- Safety evaluation needs particular attention in relation to reproductive toxicology, and AESI’s will include GBS and the risk of enhanced disease due to pre-existing immunity to related flaviviruses

- Significant post-registration studies will be needed in relation to effectiveness and safety
Considerations for developing a Zika virus vaccine; Marston et al., NEJM 2016

Strategy 1a: Using phases 1, 2, 3
- Phase 1 safety and immunogenicity
- Phase 2 safety and immunogenicity in endemic settings
- Phase 3 efficacy in endemic settings, symptomatic infections

Strategy 1b: Using phases 1, 2, 2b
- Phase 1 safety and immunogenicity
- Phase 2 safety and immunogenicity in endemic settings
- Phase 2b safety, efficacy in endemic settings, asymptomatic and symptomatic infections

Strategy 2: Using human challenge
- Phase 1 safety and immunogenicity
- Phase 2 for safety and immunogenicity in endemic settings
- Human challenge for efficacy, additional human safety studies

Strategy 3: Animal rule
- Phase 1 safety and immunogenicity
- Phase 2 for safety and immunogenicity in endemic settings
- Challenge in animal model for efficacy, additional human safety studies
Animal models: As seen in vaccinated mice, adoptive transfer studies in vaccinated NHPs showed that vaccine-induced antibodies afford protection to naïve hosts. The data are qualitatively similar to those from other flaviviruses. The question remains whether neutralizing antibody is an immune correlate of protection for ZIKV. A clear methodology for comparing neutralization titer data is needed.

Efficacy endpoints to consider include infection, mild disease, severe disease, or a known correlate of protection. Secondary or supplemental endpoints could involve measuring reduction of viremia or RNAemia, attenuation of disease, or the performance of a vaccine against an established correlate of protection.

Zika virus vaccines could be licensed based on clinical endpoint efficacy studies, studies that show an effect on a marker reasonably likely to predict clinical benefit, or animal studies: “Traditional” Approval; Accelerated Approval; Animal Rule.

Conclusions from an ethical review of Zika human challenge convened by US NIH December 2016


Key Question: Are the risks reasonable, minimized, and justified by the potential social value of the trial?

Conclusion:

• There is substantial uncertainty about the risks to potential volunteers in Zika virus human challenge study.

• Particular concern about possible risks to third parties (foetuses, members of the community)

• Absence of a strong argument and evidence that a challenge study will accelerate vaccine development

• Absence of an indication that field trials will be prohibitively difficult to conduct

• The committee concluded that it is premature to proceed with a Zika virus human challenge trial

• It may become much more ethically acceptable in the future if conditions change or if more information is provided that changes the calculus