Ethics Considerations in Zika Vaccine research: An approach

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Introduction

- This presentation, as part of the WHO Zika vaccine TPP (June 2016), is a work in progress.
- It outlines an approach to the ethical issues rather than a resolution of those ethical issues identified to date.
- The approach is based on the well-known model by Emanuel et al (2004; 2008) outlining what makes clinical research in developing countries ethical.
Focus of this presentation

- In the interests of time only issues that are controversial/unique to emergency Zika vaccine research are highlighted.
- Take as given that most other usual ethical aspects of preventive vaccine trials should also be considered applicable to emergency use Zika vaccine research.
1) Community Engagement

- Probably needs to be much more rapid but as intense and thorough as for other vaccine trials in developing countries (See UNAIDS/AVAC 2011).
- Women’s rights/sexual and reproductive health/gender groups in particular should be included.
- Broader stakeholder consultation.
2) Social Value

• Uncontroversial, depending on state of the epidemic and/or epidemic predictions.
• What types of vaccines are local governments likely to support or have capacity to roll out?
3) Scientific validity

• Selection of appropriate trial designs is a key issue, including the use (or not) of placebo in emergency use. Alternate trial designs (e.g. challenge studies, cluster randomised, stepped wedge, adaptive designs or phased approaches, even though RCTs are scientifically most robust) must be considered.
3) Scientific validity 2

- Need for openness to innovative but ethical designs. Consultation required with regard to risks/benefits of each.
- Placebo use?
- Animal challenge data required?
- Review of the nature of the vaccine itself
  - live attenuated,
  - replication competent
  - replication defective
  - non-replicating
3) Scientific validity 3
- inactivated whole or split
- nucleic acid
- or subunit protein based

• Nature of the platform/vector
• Double or single dose?
• If double, same or different product?
• Suitable specified endpoints?
• Ideally, protocol should comply with the WHO TPP or a sound scientific rationale presented for deviation from the TPP.
• Duration of effect/durability?
4) Fair selection of study population

- Study population must be aligned with the scientific aims of the study and those most likely to benefit from an effective vaccine.
- Key population is characterised by women of childbearing age or pregnant women.
- There is no international ethics guidance on prevention research in pregnancy. JHU work has commenced: PI: Ruth Faden PhD
4) Fair selection 2

- Exclude especially vulnerable persons (such as those with mental health issues, concurrent disease).
- Specify minimum age of enrolment (mandatory reporting of underage sex?)
- Health system strengthening to roll-out an efficacious vaccine also needs to be considered and planned for.
- Other flaviviruses exposed or naïve?
- Men not excluded.
5) **Favourable risk/benefit ratio**

- Risk/benefit determination is complicated by having to simultaneously consider risks to mother and the foetus.

- There is currently no ethics framework providing guidance on balancing these issues. cf. Faden et al project at JHU...

- There is growing international pressure for a framework to facilitate research during pregnancy (e.g. PAHO June 2016)
5) Favourable risk/benefit ratio 2

- Local background rate of foetal abnormality needs to be known/established
- Zika risks appear to vary by trimester
- Safety and immunogenicity should ideally be shown in non-pregnant adults first – then women of childbearing age then pregnant women, with efficacy studies following in a delayed stepwise fashion.
6) Favourable risk/benefit ratio 3

- There should be no contra-indications of the vaccine technology for use by pregnant women for other vaccines.
- Effects of vaccine on participants receiving possible later alternate vaccine?
- Potential risk of vaccine-mediated enhanced disease? (Risk of ‘enhancement’).
6) Favourable risk/benefit ratio 4

• Standard of prevention to be provided during trials? (e.g., Education and advice; repellents, spraying of homes; bed nets (?); hormonal contraception, condoms, female condoms?; Faso soap?)

• Adherence to other prevention measures to be monitored.

• New methods to be introduced as they appear. Uptake to be recorded to detect confounders.
6) Favourable risk/benefit ratio 5

• Care and referral for all ‘cases’ (mother and child). Standard and site of treatment (provide or refer?), must be evidence-based.

• Specify testing for foetal abnormality – type and timing

• Access to abortion counselling and abortion if foetal abnormality is detected, if clinically feasible and legally permitted.
6) Favourable risk/benefit ratio 6

- Specify efficacy markers (disease reduction vs sterilising immunity)? Because foetal and neonatal abnormality incidence too low but important to follow-up.
- Close and extended monitoring and reporting of maternal, foetal and neonatal outcomes is essential.
- Impact on transmission desirable but not a prerequisite for emergency use.
6) Favourable risk/benefit ratio 7

- Extended follow-up of participants, neonates/children for adverse events.
- Data on inadvertent use in pregnancy must be collected and reviewed.
- Additional safety data will be required for live vaccines.
- Reviewers need to bear in mind that despite urgency of preventive vaccines, only about 10% of new molecular entities show efficacy after phase III trials.
7) Independent ethics review

- Rapid but competent ethics review is essential.
- Informed lay representatives on REC's NB.
- WHO should consider creating a specialist ethics advisory group that could pre-review any submitted protocols to guide and assist (but not replace) local REC review.
7) Independent ethics review

- Local REC's are likely to be under-resourced and may need capacity development, expert guidance and assistance.
- Consider centralised review if all stakeholders agree and if legislation allows it.
7) Voluntary informed consent

- Special attention will need to be paid to ensure that participants understand risks to mother and to foetus, in the language of the participating community.
- Intensive community engagement can assist with such understanding.
- Rigorous tests of understanding.
- Role of fathers re foetus? Local laws?
8) Ongoing respect for participants

• Usual issues relating to
  – Monitoring (e.g. of GBS/neurocognitive problems),
  – rapid post-trial access and local roll-out and surveillance of an effective vaccine.

• Collection and storage of samples

• Sharing of samples\(^{(13)}\) (Ideally, with broad consent)

• Dissemination of results
8) Ongoing respect for participants 2

- Data sharing (anonymised)
- International conventions on ownership of human and virus genetic material
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