

Vaccines and Therapeutics: Key Issues

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Potential Role of Vaccines in Pregnancy

- **Pregnant women as a target:** Prevention of microcephaly is a primary goal, but several expressed concern about use of vaccines in pregnancy:
 - Need for demonstrated safety in non-pregnant adults before testing in pregnant women
 - Potential need for sterilizing immunity
 - Rapidity of immune response
 - Limits approaches – e.g., live-attenuated
- Several invoked **rubella** approach (target broad population in order to protect)

Preclinical development issues

- **Strain selection** – data showing excellent cross-reactivity
- **Immune correlates** – have one for JE and recently for dengue (both neutralizing Ab titers)
- **Harmonized assays** – e.g., reporter virus particles for neutralization
- **Animal models** – good model for viremia curves in NHPs; gap for pathogenesis

Clinical development issues

- **Potential trial pathways:** traditional vs. Phase 2b vs. human challenge/Phase 2
- Key questions about **efficacy endpoints**, particularly given current diagnostics
- Need to locate trials well for high incidence
- Potential role of **human challenge**
 - Could provide immune correlate (at least immune profile)
 - Could offer demonstration of sterilizing immunity
 - Efficacy in small N
 - Questions about GBS, sexual transmission and prevention of pregnancy

Other questions and critical gaps

- Potential role of prior flavivirus exposure
- Pathogenesis and risk of Guillain-Barré syndrome
- Critical gaps for vaccine developers:
 - Viral samples from endemic settings
 - Sera from endemic settings, particularly to define likely neutralizing Ab target
 - Standardized assays
 - Well characterized animal models
 - More information on viral structure and contact points for neutralizing antibodies

Use of drugs in pregnancy

- Outlined specific considerations for drugs in pregnancy
 - **Impact of pregnancy physiology**
 - **Specific preclinical information needed** (special tox, placental transfer)
 - **Ethical considerations**
- Potential use cases – chemoprophylaxis vs. treatment after infection
- Approved drugs vs. novel drugs (including monoclonals)

Other issues/critical gaps

- Kinetics of viral infection and disease; implications for therapeutic window
- Replication sites in humans
- Potential use of monoclonals – early stage but could be long-lasting; concerns about cost and placental transfer
- Animal models – including microcephaly, accurate placental transfer