Outcome Endpoints for Dengue Vaccine Trials

Principles for the evaluation of the effectiveness of dengue vaccines
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Guidelines for Clinical Evaluation of Dengue Vaccines in Endemic Areas, 2008

• Background and Justification
  – Dengue is spreading rapidly in the world
  – Rapid progress of basic and clinical research on dengue
  – Growing financial support by industry, governments, WHO, PDVI
  – Many candidate vaccines are in pre-clinical or clinical development
Guidelines for Clinical Evaluation of Dengue Vaccines in Endemic Areas

• **Purpose**
  – Identify basic technical information required to design dengue vaccine field trials:
    • To support vaccine licensure
    • To support post-licensure field studies for long-term safety and protective efficacy
    • Follows international GCP guidelines (WHO, ICH)
    • Not intended to provide guidelines for the introduction of dengue vaccines into national immunization programs
  – **Written for:**
    • National health authorities in dengue-endemic countries
    • Vaccine developers
    • Research scientists
Guidelines for the Clinical Evaluation of Dengue Vaccines in Endemic Areas

• The 2008 revision emphasizes:
  – Vaccine trial endpoints, primary and secondary
  – Immune correlates of protection against dengue disease
  – Effect of other Flavivirus infections and vaccinations on dengue vaccine outcomes in endemic areas;
  – Long-term studies of vaccine safety, immunogenicity and protective efficacy.
    • Phase 2 or 3 bridging studies,
    • Phase 2 & 3 long-term follow-up safety studies,
    • Phase 4 post-licensure trials
  – Strong regulatory infrastructure
    • Local IRBs, DSMBs, internal QC and external QA, and NRAs.
Guidelines Consider *Unique Aspects of Dengue Vaccine Trials*

- Protect against four DENV serotypes simultaneously
- Provide precise vaccine efficacy and safety endpoints
  - Must develop new WHO classification of “severe dengue”
- Identify immune correlate of protection
  - Confirm the role of neutralizing antibody and protective titer against each DENV type
  - Immune correlate required for bridging studies
- Extended trial preparation timelines
  - Collect accurate dengue incidence data across multiple transmission seasons (1-5 years).
- Determine long-term vaccine safety and protective efficacy in areas endemic for flaviviruses
  - Maintain study site infrastructure and trial methods for 3-5 years after vaccination to permit extended follow-up of volunteers.
Guidelines for the Clinical Evaluation of Dengue Vaccines in Endemic Areas

- The potential trial sites should include the following desirable characteristics:
  - Endemic for one or more DENV types
  - At least 3 years of background data on the epidemiology of dengue.
  - Document all species of flaviviruses in circulation at the trial site.
  - The NRA and local authorities are firmly committed to conduct the trial.
  - NRA's should be competent to assess clinical trial protocols.
  - The study population are firmly committed to the trial and to long-term follow-up.
Guidelines for the Clinical Evaluation of Dengue Vaccines in Endemic Areas

• The potential trial sites should include the following desirable characteristics:
  – Sufficient medical infrastructure to assure adequate medical care and identification of adverse events.
  – Maximal involvement of in-country qualified investigators and field and laboratory teams
    • They should give the trial high priority
  – Reasonable expectation of social and political stability at the national and local levels for the duration of the trial.
Outcome Endpoints for Dengue Vaccine Trials

• Trial Endpoint
  – *Used to calculate sample size and estimate vaccine efficacy*
  – The only practical primary endpoint is:
    • detection of dengue virus in a patient,
    • with at least 2 days of fever,
    • irrespective of disease severity.

– Justification for including all dengue
  • The number of severe cases (e.g., DHF) is likely to be low
  • A low number of DHF cases will increase the size, duration and cost of Phase 3 efficacy trials
  • The public health impact (DALYS) of all dengue illness is significantly larger than the impact of DHF alone.
Outcome Endpoints for Dengue Vaccine Trials

- **Primary efficacy endpoint**
  - *Efficacy is a composite of all serotypes encountered during the trial*
  - Viremia during the first 5 days of infection
    - Virus isolation
    - RT-PCR
    - Surrogate DENV antigen marker such as NS1
  - An active surveillance system must identify all febrile participants and obtain blood to confirm DENV viremia no later than day 5 after illness onset.
Outcome Endpoints for Dengue Vaccine Trials

• **Secondary efficacy endpoints:**
  - Positive serology without viral isolation
    - Diagnosis complicated by serological cross-reactions found among all flaviviruses.
    - A four-fold rise in dengue neutralizing antibodies provides a presumptive diagnosis, not a definitive diagnosis.
    - Define as “possible” or “probable” dengue
  - Efficacy against each of the four distinct serotypes
  - Virologically-confirmed protective efficacy stratified by age group and gender
  - Dengue cases occurring after the first of two or more vaccinations
  - Severity of virologically-confirmed dengue cases.
  - Effect on duration of hospitalization for dengue
Outcome Endpoints for Dengue Vaccine Trials

• Phase 3 trial
  – The long-term objective: “demonstrate protective efficacy against each of the four dengue virus serotypes in the absence of any long-term safety concerns.”
  – Design a double-blind, randomized, vaccine-controlled or placebo-controlled trial (DB-RCT)
    • randomize individuals in the same community.
  – Identify an age-specific, high-risk cohort
    • analyze hospital and/or out-patient records obtained for the previous 1-5 years.
  – Measure protective efficacy within a single dengue transmission seasonal cycle
    • without significantly reducing dengue virus transmission.
Outcome Endpoints for Dengue Vaccine Trials

• **Phase 3 trial**
  – An active surveillance system must identify all febrile participants and all DENV viremia.
    • Study site must be endemic for at least one DENV type
    • Hospital-based study with enrollment criteria of <72 hours of fever
    • A school-based study where home visits are made within a day or two of school absence.
    • Home-based study with daily passive surveillance and weekly home visits.
Outcome Endpoints for Dengue Vaccine Trials

Vaccine safety

- Pre licensure - Phases 1, 2, 3: short term
  - Monitor AEs for 1 - 21 days after vaccination
  - Monitor wild dengue exposures

- Pre licensure - Phases 2, 3: long term
  - Monitor SAEs for $\geq$ 6 months after the last vaccination
  - Stop the Phase 3 trial after one year to assess efficacy
  - Monitor the relative risk of dengue disease and severity in vaccinees versus controls for 3 to 5 years.

- Post licensure:
  - Extend follow up of participants enrolled in Phase 3 and Phase 4 trials for 3-5 years
  - Include national/regional epidemiological surveillance for presumptive dengue.
  - Identify safety signals related to rare events.
Outcome Endpoints for Dengue Vaccine Trials

• **Vaccine bridging studies**
  – First, license a vaccine.
  – Confirm at least one immune assay, which predicts protection against dengue illness.
    • The immune threshold for protection (e.g., a specific antibody titer) may not be the same for all dengue serotypes
  – Conduct a head to head immunogenicity trial of a candidate vaccine with the licensed vaccine when both vaccines are based on the same technology.
  – Utilize the non-inferiority trial design to efficiently recruit a minimal number of volunteers.
Outcome Endpoints for Dengue Vaccine Trials

• **Phase 4 trial**
  • The NRA should determine if a Phase 4 trial will be needed immediately after licensure, and possibly as a condition for licensure.
  • *If trial is adequately designed and supported:*
    • Provides an additional robust assessment of vaccine safety
    • Provides an estimate of the long-term effectiveness of immunization against multiple dengue virus serotypes in large populations.
    • Helps establish the need for booster immunizations.
    • Provides additional data on possible interference between the newly licensed dengue vaccine and licensed pediatric vaccines (EPI).
    • Measures indirect vaccine effects, e.g., herd immunity
    • Measures safety and immunogenicity in HIV-positive and other at risk groups
Outcome Endpoints for Dengue Vaccine Trials

• **Phase 4 trials**
  • Conduct trials in a limited number of carefully selected countries having adequate resources and technical support
    – Phase 4 studies will not need to be repeated in each country introducing dengue vaccination.
  • Routine post marketing surveillance in most dengue-endemic is passive and unlikely to be effective for long-term monitoring for dengue enhancement.
    – Limited by incomplete data on cases, poor case verification, short follow-up and under-reporting
    – At most, passive surveillance data may generate vaccine safety signals that should be followed up with appropriately designed research.
Outcome Endpoints for Dengue Vaccine Trials

• **Phase 4 trials**
  – Establish a global coordination of Phase 4 studies for live dengue vaccines that provides support to national regulatory authorities to ensure adequate long term risk assessment for each type of vaccine.

  – Further work is warranted to ensure complete, accurate and harmonized classification of cases in order to monitor the long-term safety and effectiveness of dengue vaccines.
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References


Questions?