Revisiting
generic protocol(s)
elements for Phase 2b or 3
Epidemiology – key messages

- Heterogeneity  Granularity
- Several knowledge gaps

- Synthesis, Collection and of data from all serosurveys and cohorts to inform vaccine studies is required.
- Generic protocol for serosurveys
- Prospectively, and within individuals use of same protocol and compare results (use same test for all or some of samples)

Flavivirus epidemiology experts – a consultation?
Study design – primary end point

**PRIMARY END POINT**

Infection related outcome +
include samples and data to be able to
contribute to surrogate of protection definition.
Study design – primary end point

CASE DEFINITION

Choice between mild and frequent and rare severe and atypical

ANY Disease ANY severity—
Infection – challenges lab test....molecular testing

Complications– desirable BUT probably not feasible (rare)

Asymptomatic disease – assess infection by serum testing, viremia, what is known about risk of severe complications in this group? A test not affected by vaccination?
Study design – primary end point

CASE ASCERTAINMENT

Test for pathogen—preferred?

Test for immune response—seroconversion? over time, what testing schedule?

Combined?
Study design – Randomization

LEVEL OF RANDOMIZATION

Individual randomization – preferred
  o Within transmission sites/areas/locations

Cluster randomization – x
  o Clusters of similar incidence required
  o Heterogeneity of transmission
  o Risk of contamination- vector control measures
Study design – Target population

RISK TARGET

General population—preferred
  o WCBA (TPP only priority if vaccine supply issues)
  o How to deal with seropositives? Strata analysis plan?

Geographic—xx
  o Sites may have different levels of transmission
  o Start early on in the outbreak
  o But...how to decide when to start...?
Study design – Comparator

BLINDING OF CONTROL

Placebo– preferred

Active control– xx
  o Adjuvant only?
  o If vaccine is highly reactogenic... blinding?
  o If in pregnant women... no?
Lab tests

- Screening
- Measure of vaccine response
- Confirm infection
- Differentiate vaccine induced immunity from wild type infection

Challenges - besides those intrinsic to the tests development and validation

SPECIFICITY??

Testing schedule

Time from onset (beyond 4-7 days most negative?)

Other?

Lots of progress !!!
Still challenging...Difficult to compare results as different test and approaches being used.....
Multicenter studies

• Use available evidence – ongoing transmission, past transmission??

• One protocol, standardised procedures

• A priori define analysis plan

• One DSMB
Site selection

• Heterogeneity
• Distribution of immune susceptible
• A balanced approach -- Being able to start study early on...which indicator? Vector density, evidence of virus in vectors? Evidence of severe Cxnes (maybe too late?)

• Review + Access to data from existing cohorts and surveys

• Modelling can contribute to site(s) selection
  o Current models can forecast:
  o geographic heterogeneity,
  o pregnancies that can be affected in first trimester
  o Temporal changes
  o UPDATE WITH EMERGING DATA
Correlates of protection

• Challenging – but probably addressed/informed by some of ongoing research

• Standardization of neutralization tests
• Interpretation of results in animal studies and translation to humans
• Definition of disease/infection outcomes

• Desirable and work is ongoing, data from vaccine studies would contribute, therefore it should be planned for...
Other key topics that we discussed...

- Dengue vaccine experience
- Human challenge studies
- Vector information ...
- Surveillance can it help? Before and during...
- Multi candidate vaccines study designs
Next steps
Data needs

• NIH and other groups to be contacted to share results of cohort studies...serosurveys...other relevant available data to inform trial designs (in real time...)

• Update model predictions using existing and emerging data

WHO must facilitate this work
Data analysis

• Develop an analytical strategy and approach to make available the data to help inform trial designs ...

• Trial simulator ....

• Share lab test..retesting at same lab..other...
Other

• (what did I miss ?)

• Lots of networking took place .....