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JOHNS HOPKINS
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Dengue Infection Model

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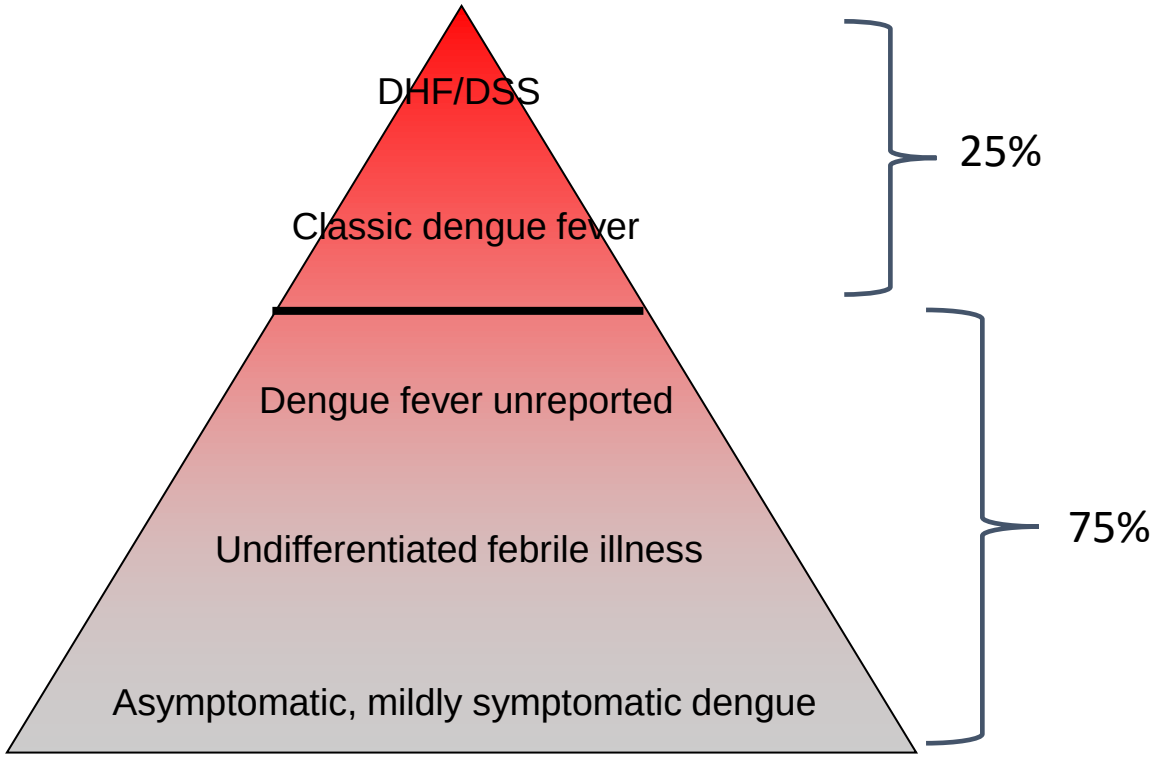
Dengue Background

- Mosquito-borne disease caused by any one of 4 dengue serotypes
- Dengue can range from asymptomatic or mild disease to severe disease with vascular leak syndrome
  - Most severe disease associated with second, heterotypic DENV infection
- Most DENV infections (~ 75%) do not present for clinical care



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Types of challenge models

- Infection Model
  - Endpoint is verification of infection, not disease
  - Pathogen is generally recovered from the blood to determine infection
  - The malaria CMHI is the prototype of infection model
- Disease Model
  - Endpoint is specified clinical illness
  - Typically used when systemic infection is difficult to measure (respiratory, enteric infections)
  - Enteric challenge models are the prototype disease models

Characteristics of ideal challenge model

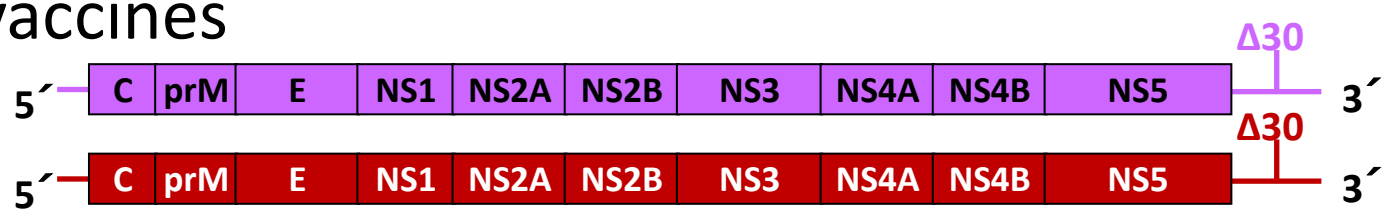
- Induce ***reproducible*** endpoints with a sufficient frequency that studies can be powered with relatively few numbers of volunteers to achieve primary aim
- Challenge must be done in a safe & ethical manner
  - Risk:benefit of study must be balanced
  - Primary aims of study should be obtained while minimizing risk to volunteers
- Dengue CHIM: the majority of dengue infections are asymptomatic or mildly symptomatic – ***infection model vs disease model***

Dengue infection model

- Only ~ 25% of dengue infections are symptomatic
  - A successful dengue disease model requires achieving dengue illness with high frequency and reproducibility
    - Achieving this may lead to severe disease in some subjects
- Goal of the dengue infection model is to pattern the majority of natural dengue infections Primary endpoint of dengue infection model
  - Recovery of virus from the blood
  - Secondary endpoints can include: objective clinical / laboratory signs (rash, neutropenia, thrombocytopenia) of infection
  - Dengue fever is not an endpoint

Dengue infection model

- Challenge strains were derived from human isolates that were described as causing low viremia and mild illness during outbreaks
  - DENV-2 Tonga/74
  - DENV-3 Sleman/78
- Both challenge strains were initially developed as candidate DENV-2 and DENV-3 vaccines
  - DENV2Δ30
  - DENV3Δ30



- Both were ***not attenuated*** compared to recombinant wild-type virus in the NHP model

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Approach to development of challenge strain

- Must fully characterize the infectivity profile of challenge virus:
  - Infectivity rate of virus (is it reproducible?)
  - Incidence of viremia
  - Peak virus titer achieved (how easily measured?)
  - Duration of viremia
- Characterize the clinical spectrum of illness induced
  - What monitoring and support will be needed?
- Characterize the transmissibility to mosquitoes

Dengue infection model

- Goal was to induce viremia in high proportion of subjects without inducing dengue fever
  - Started with low dose (10^3 PFU) with plan to dose escalate if primary endpoint was not met (viremia by culture in ≥ 80% of subjects)
  - Included placebo group to better assess subjective complaints
  - Hoped for peak viremia 10 to 100-fold higher than that obtained with vaccine candidates (3 – 5 PFU/mL)
- Depending on clinical symptoms / viremia induced, future trials could be conducted as outpatient studies
  - Increased capacity and cohort sizes
  - Reduced cost

Dengue infection model

- Both DEN2Δ30 and DEN3Δ30 induced viremia in 10/10 subjects in pilot study
  - Rash was induced in 8/10 for both challenge viruses
- Evaluated the protective efficacy of LATV dengue vaccine against viremia (primary endpoint) and rash/neutropenia (secondary endpoints)
  - Studies were powered for 60% efficacy against viremia with power of 0.8 with initial assumption of viremia in only 80% of controls.
    - Required < 10 subjects in vaccine and control arm
  - Secondary endpoint of 60% efficacy against rash with power of 0.8 required fewer than 20 subjects

Viremia induced by rDEN2Δ30 is highly reproducible

Virus	Dose (log_{10} PFU)	N	% with viremia	Mean peak titer[1] ± SE (range)	Mean day of onset ± SE	Mean # days of viremia ± SE
rDEN2Δ30	3	10	100	2.5 ± 0.2 (1.2 – 3.3)	4.6 ± 0.4	5.8 ± 0.6
rDEN2Δ30	3	20	100	2.3 ± 0.1 (1.5 – 2.9)	4.7 ± 0.6	5.6 ± 0.5
rDEN2Δ30	3	21	100	2.23 ± 0.2 (0.5 – 3.2)	4.95 ± 0.4	4.62 ± 0.3

1. Log_{10} PFU/mL
2. Mean peak titer of DENV-2 candidate vaccine rDEN2/4Δ30 is 0.5 log_{10} PFU/mL

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Viremia induced by DEN3Δ30

Virus	Dose (log_{10} PFU)	N	% with viremia	Mean peak titer[1] ± SE (range)	Mean day of onset ± SE	Mean # days of viremia ± SE
rDEN2Δ30	3	10	100	1.77 ± 0.2 (0.5 – 2.1)	4.6 ± 0.5	3.4 ± 0.5
rDEN2Δ30	4	21	85	1.0 ± 0.2 (0.5 – 2.2)	4.6 ± 0.4	1.9 ± 0.4

1. Log_{10} PFU/mL
2. Mean peak titer of DENV-3 candidate vaccine rDEN3Δ30 is 0.6 log_{10} PFU/mL

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Dengue CHIM summary

- Viremia induced in 85 - 100% of control subjects
  - Mean peak titer induced by challenge strain is high enough to evaluate ability of vaccine or therapeutic to decrease titer of challenge strain without
  - Reduced risk of transmission with mean peak titer ≤ 2.5 $\log_{10}$ PFU/mL
  - Increasing dose of DEN3Δ30 did not increase mean peak titer – no advantage
- Rash induced in 80 – 100% of control subjects
- Adverse events induced by both challenge strains were mild or moderate (subjects maintained ability to perform ADLs – no missed work)

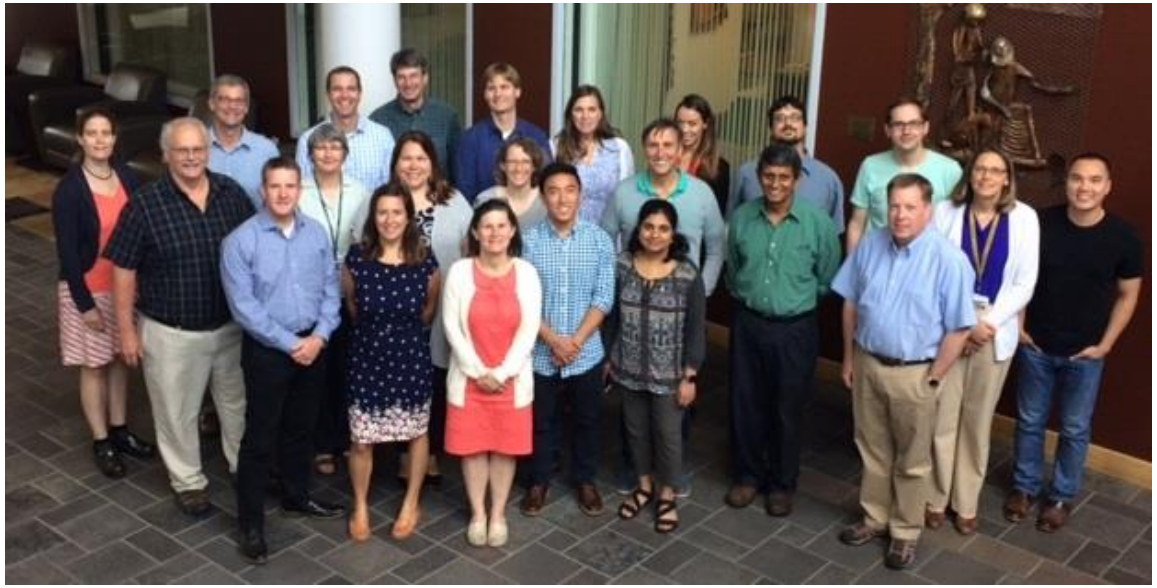
Dengue CHIM limitations

- Difficult to study pathogenic mechanisms of dengue fever and severe dengue
  - Mediators of inflammation produced in infection model but not sufficient to cause symptomatic illness
- Cannot evaluate therapeutics designed to prevent progression from dengue to severe dengue
- DENV-1 and DENV-4 strains for dengue CHIM need to be developed

Dengue CHIM conclusions

- Prevention of infection highly stringent criteria for vaccine
  - Prevention of infection would prevent disease
- High incidence and reproducibility of these outcomes allow studies to be powered for significant efficacy with relatively few subjects
  - Prevention or reduction in incidence of viremia
  - Reduction in peak viremia or improved clearance of viremia (therapeutics)
- Trials can be conducted as outpatient trials
- DENV-1 and DENV-4 strains for dengue CHIM need to be developed

Dengue CHIM group



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ATRECA

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Why do we need a controlled Dengue Human Infection Model?

- Down selection of candidate vaccines before Phase 3 efficacy trials in endemic countries. Issues of vaccine acceleration and safety.
  - A dengue vaccine that fails to protect may not just fail to reduce disease incidence but ***may actually pose a greater risk of more severe disease*** to those vaccinated over time
- Platform upon which to understand immune correlates of protection.
  - Clear CoP are important for bridging studies for future or second generation vaccines.
  - Need to understand immunologic responses in naïve vs. experienced individuals.
  - Explore development and components of protective responses
- Testing of therapeutics.