Vaccines against emerging & re-emerging viruses

Monica McArthur, MD PhD
PREV 627 Vaccinology
08 May 2017
Outline

• Definitions
• Discuss importance of vaccine development for emerging and re-emerging viruses
• Discuss vaccine efforts against specific viruses:
  – Dengue (DENV)
  – Zika (ZIKV)
  – Chikungunya (CHIKV)
Emerging infectious diseases

- Infectious diseases leading cause of death globally
- 3rd leading cause of death in US
- Emerging infectious diseases:
  - Have not occurred in humans before
  - Have occurred previously but affected only small numbers of people in isolated places
  - Have occurred throughout human history but have only recently been recognized as distinct diseases due to an infectious agent
Reemerging infectious diseases

• Reemerging infectious disease
  – Diseases that were once major public health problems, then declined dramatically, and are again becoming health problems for a significant proportion of the population
## Determinants of emergence & reemergence

<table>
<thead>
<tr>
<th>The Microbial Agent</th>
<th>The Human Host</th>
<th>The Human Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic adaptation and change</td>
<td>Human susceptibility to infection</td>
<td>Climate and weather</td>
</tr>
<tr>
<td>Polymicrobial diseases</td>
<td>Human demographics and behavior</td>
<td>Changing ecosystems</td>
</tr>
<tr>
<td></td>
<td>International trade and travel</td>
<td>Economic development and land use</td>
</tr>
<tr>
<td></td>
<td>Intent to harm (bioterrorism)</td>
<td>Technology and industry</td>
</tr>
<tr>
<td></td>
<td>Occupational exposures</td>
<td>Poverty and social inequality</td>
</tr>
<tr>
<td></td>
<td>Inappropriate use of antibiotics</td>
<td>Lack of public health services</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Animal populations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>War and famine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of political will</td>
</tr>
</tbody>
</table>

Dengue virus
Disease manifestations

• Asymptomatic
• Undifferentiated febrile illness
• Classic dengue fever (DF)
• Severe dengue
  – Dengue hemorrhagic fever (DHF)
    • Fever or h/o fever, hemorrhagic tendencies, thrombocytopenia, and evidence of plasma leakage
  – Dengue shock syndrome (DSS)
    • Above + rapid, weak pulse with narrowing of pulse pressure or hypotension
• New classification system/treatment algorithm (2009)
  – DEN with or without warning signs and severe DEN
Dengue Viruses

- Mosquito-borne flaviviruses
- 4 genetically related serotypes
- Positive strand RNA genome ~11kb
- 3 structural proteins
  - E protein is major surface protein
  - Domain III exposed on virion surface
  - Contains multiple type-specific neutralizing epitopes
  - Major immunogen
- 7 NS proteins
  - Likely play a role in T cell mediated immune responses
Need for vaccine

• No specific antivirals
• Supportive care is effective, but not always available
• Economic impact
• Limited success of vector control
Vaccine impediments

• Epidemiology
• Immunology
• Lack of known correlate of protection
• No animal model that faithfully recapitulates human disease
Mosquito vector

*Aedes aegypti* primary vector
*Aedes albopictus* secondary vector
Immune mediated enhancement

- Antibody Dependent Enhancement (ADE)
  - Secondary infection or primary infection in infants with maternal antibody
  - Non-neutralizing/weakly neutralizing cross-reactive Ab facilitate viral entrance into Fc receptor bearing cells

http://www.nature.com/scitable/content/model-of-antibody-dependent-enhancement-of-dengue-22403433
Immune mediated enhancement

• Cytokine storm
  – Heterologous T cell responses
  – High levels of pro-inflammatory cytokines released

• Complement
  – High plasma levels of terminal complement associated with increased disease severity
Characteristics of an ideal DEN vaccine

• Cheap
• Easy to administer
• 1-2 dose(s)
• Tetravalent
• Protective in naïve individuals
• Safe in infants and children
• Compatible with EPI
Vaccine candidates in clinical trials

- Live Attenuated Virus
  - CYD (Sanofi Pasteur) → Dengvaxia (licensed in Mexico Dec 2015)
  - TV003 & TV005 (NIH)
  - DENVax (Takeda)
  - F17 & F19 (WRAIR-GSK)
- Purified Inactivated Virus
  - TDEN-PIV (WRAIR-GSK)
- Subunit
  - V180 (Merck)
Live attenuated TDV candidates

Pros
• Related flaviviruses use live-attenuated vaccines (YFV & JEV)
• Inexpensive to manufacture
• Replicate within the host improving duration of immunity and frequently require fewer doses

Cons
• Interference due to multiple viruses replicating simultaneously
• Reversion to virulence/transmission to mosquitoes
• Can’t be used in immunosuppressed individuals
Flavivirus genome

A) 
CAP → 5'UTR → STRUCTURAL → NON-STRUCTURAL → 3'UTR

B) 
C → E → NS1 → NS2A → NS2B → NS3 → NS4A → NS4B → NS5

prM → M

Region substituted into YF17D backbone for CYD TDV, DEN4Δ30 for Tetra-vax-DV, or DENV2 PDK-53 for DENVax

C) 
CAP → 5'UTR → STRUCTURAL → NON-STRUCTURAL → 3'UTR

prM/E

Site of 30 nucleotide deletion in Tetra-vax-DV (Δ30)
CYD-TDV (Sanofi Pasteur)

- prM/E in YF 17D backbone
- Given in 3 doses at months 0, 6, and 12
- Furthest along vaccine pipeline
- Phase IIb and III clinical trials in long-term f/u
- Licensed in Mexico Dec 2015, no WHO prequalification
Phase IIb immunogenicity

<table>
<thead>
<tr>
<th>Dengue vaccine group (n=197)</th>
<th>Control group (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>m</td>
<td>GMT (95% CI)</td>
</tr>
<tr>
<td>-----</td>
<td>--------------</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Serotype 1</td>
<td>197</td>
</tr>
<tr>
<td>Serotype 2</td>
<td>197</td>
</tr>
<tr>
<td>Serotype 3</td>
<td>197</td>
</tr>
<tr>
<td>Serotype 4</td>
<td>197</td>
</tr>
<tr>
<td>28 days after first injection</td>
<td></td>
</tr>
<tr>
<td>Serotype 1</td>
<td>197</td>
</tr>
<tr>
<td>Serotype 2</td>
<td>197</td>
</tr>
<tr>
<td>Serotype 3</td>
<td>197</td>
</tr>
<tr>
<td>Serotype 4</td>
<td>197</td>
</tr>
<tr>
<td>28 days after second injection</td>
<td></td>
</tr>
<tr>
<td>Serotype 1</td>
<td>94</td>
</tr>
<tr>
<td>Serotype 2</td>
<td>94</td>
</tr>
<tr>
<td>Serotype 3</td>
<td>94</td>
</tr>
<tr>
<td>Serotype 4</td>
<td>94</td>
</tr>
<tr>
<td>28 days after third injection</td>
<td></td>
</tr>
<tr>
<td>Serotype 1</td>
<td>95</td>
</tr>
<tr>
<td>Serotype 2</td>
<td>95</td>
</tr>
<tr>
<td>Serotype 3</td>
<td>95</td>
</tr>
<tr>
<td>Serotype 4</td>
<td>95</td>
</tr>
<tr>
<td>1 year after third injection</td>
<td></td>
</tr>
<tr>
<td>Serotype 1</td>
<td>95</td>
</tr>
<tr>
<td>Serotype 2</td>
<td>95</td>
</tr>
<tr>
<td>Serotype 3</td>
<td>95</td>
</tr>
<tr>
<td>Serotype 4</td>
<td>95</td>
</tr>
</tbody>
</table>

m = number of participants per protocol at that point in the study and for whom data are available for that endpoint. PRNT<sub>60</sub> = plaque-reduction neutralisation test. GMT = geometric mean titre. * Titre 10 or higher.

Table 6: Geometric mean PRNT<sub>60</sub> antibody titre against vaccine parental dengue strains at baseline and after each injection (per-protocol immunogenicity analysis)

Sabchereon Lancet 2012;380:1559
Despite neutralizing antibody titers against DENV-2 that were equivalent to those against other serotypes, there was no efficacy against DENV-2.
Phase III clinical trials

**Asia**
- Observer-masked, randomized controlled multicenter phase III trial
- **5 Asian countries**
- CYD-TDV or placebo @ 0, 6, and 12 months
- Children ages **2-14** years
- 25 month follow-up

**Latin America**
- Observer-masked, randomized controlled multicenter phase III trial
- **5 Latin American countries**
- CYD-TDV or placebo @ 0, 6, and 12 months
- Children ages **9-16** years
- 25 month follow-up
Phase III clinical trials

25 month analyses
- Asia → vaccine efficacy against severe disease was 80.8% after 3 doses
- Latin America → Vaccine efficacy against severe disease 95.5% & against hospitalization 80.3%

3 year analyses
- Increased risk of severe disease in vaccine group (participants < 9 yrs)
- Fewer than expected cases of severe DEN in controls
Questions remaining

- Is vaccine efficacy of ~60% sufficient for public health?
- Is protection against severe disease enough?
- Could waning protection lead to enhanced disease?
- Are neutralizing antibodies a correlate of protection?
- Are different levels of neutralizing Ab necessary for different serotypes?
- What is the role of anti-NS protein T cell responses in protection?
- Can this vaccine protect travelers?
Additional vaccine candidates in pre-clinical and clinical trials

• Virus vectored and virus-like particle (VLP)-based vaccines
  – VLP utilize carriers which self-assemble into VLPs and display Ag of interest on the surface of the particle (successfully used for HPV vaccine)
  – HepB core Ag is a carrier capable of expressing DENV E DIII
    • Modest immunogenicity in mice
  – Adenoviral vectors (AdV5)
  – VEE virus replicon

• DNA
  – Selected gene sequence cloned into a plasmid backbone
  – Plasmid is injected allowing DNA to taken up by APC → express plasmid-encoded genes to generate target Ag
  – DNA vaccine candidates focusing on prM/E and NS1 are in pre-clinical trials and Phase I clinical trials are underway
Outlook for DENV vaccine

• Live attenuated vaccine candidates furthest along the pipeline

• Human challenge model may accelerate vaccine development

• Likely that multiple vaccines will be needed for different target populations
Zika virus

Flavivirus transmitted primarily by Ae. Aegypti

Spreading rapidly

Cause of significant neurological manifestations

From the CDC
Current Epidemiology of Zika Virus

• As of March 10, 2017 Zika virus transmission has been reported in >80 countries, territories, and subnational regions

• In the US local transmission has occurred in TX and FL

• In the US as of May 3, 2017
  – 4,973 travel associated cases
  – 224 locally transmitted mosquito-borne cases (FL: 218, TX: 6)
  – 77 cases acquired through other routes (congenital: 29)
Modes of ZIKV Transmission

- Bite of infected mosquito (Ae. *aegypti*, Ae. *albopictus*)
- Vertical transmission
- Sexual transmission
  - Male-female
  - Male-male
  - Female-male
- Blood transfusion
- Laboratory transmission
- Person-to-person via unknown route
Clinical Manifestations of Zika Virus Infection

Red eyes
Fever
Joint pain
Rash

Neurological Manifestations of Zika Virus Infection in Adults

• Guillain-Barré Syndrome
  – Most frequent neurological sequela reported following ZIKV infection
  – Risk increases with age
• Encephalitis
• Meningoencephalitis
• Acute myelitis
Pregnancy Associated Outcomes

- Fetal loss/miscarriage
- Fetal growth and brain abnormalities (microcephaly, hydrocephalus)
- Ocular findings
- Hearing loss
- Neurologic abnormalities
Congenital Zika Syndrome

- Destruction of existing CNS tissue and disruption of future development
- Loss of brain volume/neurologic dysfunction
  - Hearing
  - Vision
  - Swallowing problems
  - Limb contractures
  - Developmental impairment
Immunology of ZIKV Infection

• Innate Immunity
  – Interferon response

• Humoral Immunity
  – Neutralizing Ab
  – Antibody dependent enhancement (ADE)

• Cell Mediated Immunity
  – T cell responses against DENV contribute to protection and/or disease enhancement
  – Anti-ZIKV T cell responses demonstrated in animal models and human infection
Clinical ZIKV Vaccine Development

• Successful vaccines against other flaviviruses
• Proof-of-concept from pre-clinical anti-ZIKV vaccine studies
• Theoretical safety advantages of non-replicating vaccines in pregnant women
• Current clinical trials of anti-ZIKV vaccine candidates
Vaccine Platforms in the Pipeline

• Purified Inactivated Virus (PIV)
• DNA
• RNA
• Recombinant viral vector
• Live-attenuated virus (LAV)
• Recombinant subunit
• Peptide
• ZIKV exosome

http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/
ZIKV Genomic Structure & Candidate Vaccine Immunogens

Adapted from: Barouch et al., Immunity, 2017 46(2):176-182
• Modified mRNA vaccine encoding prM/E protects in 3 different mouse strains
• High titers of nAb
• Sterilizing immunity with single prime-boost
• Fusion loop mutant reduced production of anti-DENV cross-reactive Ab
Evaluation of the vaccine properties of rVSV-ZIKV constructs in C57BL/6 mice

Betancourt et al., J Immunol 2017; published online MAR 13
Offspring of VSVm-ZprME– vaccinated female mice are protected from lethal ZIKV challenge

Betancourt et al., J Immunol 2017; published online MAR 13
Clinical Trials

• DNA vaccines (VRC & Inovio)
• PIV vaccines (WRAIR/BIDMC/Harvard/NIAID/Sanofi Pasteur)
• mRNA (Valera (Moderna))
• Synthetic peptide (SEEK/NIH)
Difficulties in Clinical Development of ZIKV Vaccines

• Animal models
• Induction of sterilizing immunity
• Vaccine safety
  – Women of child-bearing potential
• Demonstration of efficacy
  – Non-specific symptoms (20% of infected individuals)
  – Limitations of diagnostic tests
  – Unclear transmission patterns
• ADE
Chikungunya virus
Chikungunya fever

**Symptoms**
- Fever, usually lasts about 1 week (90% of patients)
- Myalgia, usually lasts 7–10 days (90% of patients)
- Polyarthralgia, polyarthritis, or both, can last weeks to months (95% of patients)
- Rash, lasts about 1 week (40–50% of patients)

**Infection**
- 2–6 days Incubation period
- Approximately 1 week
- Weeks to months
- Years
- Viremia, usually lasts 5–7 days
  - IgM detectable 3–8 days after symptom onset, usually persists for 1–3 months
  - IgG detectable 4–10 days after symptom onset, persists for years

**Biomarkers**

**Figure 3. Timeline of Infection, Symptoms, and Biomarkers.**
Shown is the chronology of viral replication in relation to the clinical and biologic signs of disease, including the biomarkers used in diagnostic assays to detect chikungunya virus infection (adapted from Suhrbier et al.\textsuperscript{28}).

Weaver NEJM 2015; 372:1231
Chikungunya virus

- Alphavirus
- 11.5kb genome, (+)-strand RNA
- 3 structural genes
- 4 non-structural genes

Figure 1. Chikungunya Virus Genetic and Physical Structure.
Panel A shows the organization of the chikungunya virus genome, including its nonstructural proteins 1 through 4 (nsP1–nsP4) and structural proteins C (capsid), E1–E3 (envelope glycoproteins), and 6K/TF (6K and TF [transframe] are alternative translation products of the same gene). Panel B shows the structure of the virion (image courtesy of Felix Rey, Institut Pasteur, Centre National de la Recherche Scientifique). Panel C shows spike-protein predicted structures based on atomic resolution structures of the envelope glycoproteins and high-resolution cryoelectron microscopic reconstructions of chikungunya virus and other alphavirus particles.

Weaver NEJM 2015; 372:1231
Figure 2. Origin, Spread, and Distribution of Chikungunya Virus and Its Vectors.
The map shows the African origins of enzootic chikungunya virus strains and the patterns of emergence and spread of the Asian lineage and Indian Ocean lineage (IOL) of the virus during epidemics since the 1950s, based on phylogenetic studies.4,5 The distributions of the peridomestic vectors, *Aedes aegypti* and *A. albopictus*, are also shown. ECSA denotes eastern, central, and southern African.
Clinical Trials

• Passive immunization (anti-CHIKV hyperimmune human IV Ig to neonates) - ongoing
• Live attenuated vaccine (LAV)
• Virus-like particle (VLP)
• Recombinant measles-CHIKV vaccine
Pre-clinical vaccine candidates

- Formalin-killed
- Chimeric alphavirus
- DNA
Outlook for CHIKV vaccines

• Immunogenic vaccine candidates
  – Unknown correlate of protection
• Dependent on political will
Conclusions

• Emerging and re-emerging viruses pose a significant threat to public health
• Vaccines are needed to combat the continued spread of these viruses
• Many promising vaccine candidates exist for these important pathogens
• Political will and funding play a major role in which vaccines are developed
Thank you!