Dengue, Japanese Encephalitis, West Nile, Chikungunya, and Yellow Fever

Challenges for the Development and Use of Vaccines

Thomas P. Monath MD
### Vaccines against Vector-Borne Diseases with Potential for Introduction and Spread in the US

<table>
<thead>
<tr>
<th>Disease</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved ex US</th>
<th>Approved US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
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<td>Japanese encephalitis</td>
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<td>West Nile</td>
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<tr>
<td>Chikungunya</td>
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<tr>
<td>Yellow fever</td>
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<tr>
<td>Ross River</td>
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<td>VEE</td>
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<td>Rift Valley</td>
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<td>TBE</td>
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<td>Zika</td>
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<tr>
<td>Sindbis</td>
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</tbody>
</table>
West Nile and Chikungunya
Common Threads

- Cyclical or intermittent epidemics
- Absent for a long period and then reappear in explosive form
- Changing geographical distribution, rapid spread
- Overwintering, transovarial transmission
- Potentially severe, life-threatening
- Sequelae, chronic disease syndrome in 20-30%
- Threat to blood supply
- No specific treatment
- Regulatory pathway challenging
- Uncertain recommendations and sustainable market for vaccines
- High cost of vaccine development, limited access to capital
West Nile Emerging Disease Threat
Decision on Vaccine Initiatives

• West Nile virus identified in September
• Outbreak limited to NYC area
• Humans, horses, birds affected
• First vaccine initiatives

• Established zoonotic cycle
• Overwintering
• Continued geographic spread
• Virgin soil outbreaks
• NIH funds multiple vaccine grants

• CDC predicts WN could pose a nationwide problem within 3 years
• First vaccine for horses approved by USDA
• At least 6 pharma and biotechs engaged in human WN vaccine R&D
<table>
<thead>
<tr>
<th>Company/Institute</th>
<th>Vaccine</th>
<th>Pre clin</th>
<th>Ph 1</th>
<th>Ph2</th>
<th>Ph3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acambis/Sanofi</td>
<td>Live, attenuated chimeric WN/YF</td>
<td></td>
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<tr>
<td>NIAID</td>
<td>Live, attenuated, chimeric WN/DEN4</td>
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<tr>
<td>Vical</td>
<td>DNA</td>
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<tr>
<td>Hawaii Biotech</td>
<td>Subunit E protein</td>
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<tr>
<td>Inviragen/Takeda</td>
<td>Live, attenuated WN/DEN2</td>
<td></td>
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<tr>
<td>J&amp;J (Crucell)</td>
<td>Inactivated whole virion</td>
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<tr>
<td>Intercell</td>
<td>Inactivated whole virion</td>
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<tr>
<td>Baxter</td>
<td>Inactivated whole virion</td>
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<tr>
<td>L2 Diagnostics</td>
<td>Subunit E (Sf9 cells)</td>
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<tr>
<td>NIAID</td>
<td>Virus-like particles</td>
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<tr>
<td>UTMB</td>
<td>Replicon</td>
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<tr>
<td>Inst Pasteur</td>
<td>Recombinant measles vector</td>
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</tr>
</tbody>
</table>

Legend:
- Industry
- Academia, government

Human WN Vaccine Competitive Landscape 2014
Vaccine Development against West Nile and Chikungunya

- The obstacles are not technological
- Established antigenic target (E proteins)
- Single serotype, no significant antigenic variability
- Multiple applicable vaccine platforms
- Well understood mechanisms of action and immune correlates
- Animal models of immunization and protection
- Suitable manufacturing methods and analytics
Vaccine Development against West Nile

• The main obstacles are
  – Commercial market risks
  – High development costs
  – Uncertain indications and target populations
  – Uncertain regulatory pathway, including
    • Feasibility and timelines of pivotal trials
    • Animal rule
  – Timing risks
    • Vaccine available after emergency subsided
  – Financial risks
    • Access to capital and strategic partnerships
  – Uncertain ACIP recommendations
Who is Developing Vaccines in the Emerging Disease Space?

• NIAID
  – Seeks licensing partners
  – Won’t develop past Phase I/II

• Biotech companies
  – Cash constrained
  – Investors seek high returns, low risk:reward
    • Vaccines viewed as difficult, costly, long timelines
  – High cost of capital
  – Uncertain strategic partner interest
    • If we make it who will buy it?
  – Not orphan indications
  – Not on the list for Priority Review Vouchers

• Large pharma
  – Limited interest, early stage, watch/wait

• Developing world entities
  – Target local/regional markets
ChimeriVax™-WN Target Product Profile

- Live, attenuated virus vaccine
- WN/YF 17D chimera
- Single inoculation
- Rapid onset of neutralizing antibodies
- Efficacy (immunogenicity) >90%
- Established immune correlate (PRNT\textsubscript{50} >10)
- Specific CD4+ and CD8+ T cell response
- Durable immunity (>5 years)
- Safe and well tolerated for all ages >9 mos.
- Cannot be transmitted by mosquitoes
- No anti-vector immunity
Neutralizing antibody responses after single dose, and geometric mean, ChimeriVax™-WN02

Monath T et al. PNAS 2006:103:6694-9
Chronology of Development of ChimeriVax™-WN

1999
- YF 17D vector with WN99 transgene constructed (4Q99)

2000
- Attenuating mutations inserted
- Preclinical studies (mice, hamsters)
- NIH RO1
- Corporate approves advanced development

2001
- GMP manufacturing
- Preclinical studies (monkeys, baboons)
- Horse immunization, challenge studies
- Virus-vector studies
Chronology of Development of ChimeriVax™-WN

2002
- GMP vaccine clinical trial material
- GLP Toxicology
- Intervet licenses horse vaccine
- Vaccine virus provided to CDC as diagnostic

Year 3

2003
- Pre-IND meeting
- IND filed
- Phase 1 initiated

Year 4

2004
- Phase 1 completed
- Manufacturing at final scale, >10,000 doses/L
- Market survey

Year 5
WN Vaccine Market Projection 2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Market doses</th>
<th>Market US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>1,928,468</td>
<td>$57,854,031</td>
</tr>
<tr>
<td>2010</td>
<td>3,411,866</td>
<td>$102,355,974</td>
</tr>
<tr>
<td>2011</td>
<td>4,815,754</td>
<td>$144,472,632</td>
</tr>
<tr>
<td>2012</td>
<td>6,122,152</td>
<td>$183,664,565</td>
</tr>
</tbody>
</table>

Doses sold vs Market US$
West Nile Market Survey (2004) at Peak of the Epidemic

Concern about vaccine safety among consumers

% of consumers
Extremely/Very Concerned About the Safety of Vaccines

50%

(Among people who worry about the safety of vaccines)

Reasons Worry About Vaccines

- I don’t want to introduce a virus from the vaccine into my body 57%
- I am worried that a vaccine may give me the disease it is meant to prevent 51%
- I have had a negative reaction to vaccines in the past 27%
- Vaccines are only important for children 19%
- I have decided not to be vaccinated in the past because I don’t like needles 18%
**Most health care providers and consumers do not feel that West Nile poses risks (2004 survey)**

<table>
<thead>
<tr>
<th>% that Report:</th>
<th>Consumers</th>
<th>Health Care Providers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low incidence is a <em>barrier to prescribing</em> West Nile vaccine</td>
<td>n/a</td>
<td>High(^2)</td>
</tr>
<tr>
<td>Feeling at least very <em>concerned</em> about West Nile</td>
<td>Low</td>
<td>Low(^3)</td>
</tr>
</tbody>
</table>

The following *attitudes* related to prevalence:

- Threat is over-hyped                                                       | High      | Mod                   |
- There is very little I can do to protect my patient/myself                  | Low       | Low                   |
- If infected I/my physician could treat it                                   | High      | Mod                   |

Legend:
- High = 66+
- Mod = 36-65
- Low = <36
Consumers view PCPs as the key physician type for a West Nile vaccination (2004 survey)

Type of Physician that Consumers Would Go to to Receive West Nile Vaccine

ACIP recommendation will be key: likely a “permissive” recommendation, leaving the decision to vaccinate to physician/patient
Chronology of Development of ChimeriVax™-WN

2005
• Phase 2A dose, young->elderly
• Public private partnership sought

Year 6

2006
• Phase 2A completed
• Push to gain USG support for Phase 3
• Vet vaccine (Prevenile®) launched by Intervet

Year 7

2007
• Licensed to Sanofi ($10M up-front, $70M milestones +royalties)
• Phase 2B – adults >50 in 11 states

Year 8
Chronology of Development of ChimeriVax™-WN

**2008**
- Medical impact declining
- Sanofi acquires Acambis

Year 8

**2009**
- Medical impact declining
- High cost of further development
- Market size not a good fit
- Animal Rule unlikely

Year 9

**2010**
- Further development ceases

Year 10

Development stalls due to financial, regulatory and market risks
West Nile virus neuroinvasive disease incidence reported to CDC by year, 1999-2013

Vaccine development
West Nile Re-emerges (Predictably!)
Texas, 2012
1,868 cases

- But vaccine developers do not respond
- Very hard to restart a dead program

Past will be prologue for the future
Is a vaccine stockpile useful for emergency response?

CDC, 2013
Pharmaco-economics

• Universal WN vaccination not justified (Zohrabian et al. EID 2006;12:375)

• As an emergency measure, in areas of repeatedly high incidence, or for high risk individuals (advanced age)?
  – Dallas Co., Texas, 2012
  – Persons >65: 133 cases in 208,000 pop.
  – Cost $156,000/case averted assuming all immunized, $100/person, 100% efficacy
Emergency Use Vaccine for West Nile: Challenges

- Short window for a vaccination intervention

- The US has no experience with mass immunization campaigns involving adults
WN Regulatory strategy

**ANIMAL RULE**
- Robust animal models
- Pathogenesis well understood
- Endpoint well understood
- Immune correlate
- Dose response similar to humans
- Clinical trial showing safety feasible (~5000 subjects)
- Phase 4 commitment (effectiveness)

**FIELD TRIAL (EFFICACY)**
- FDA preference
- Definitive data on clinical efficacy
- Large sample size
- Likely to require multiple years/transmission seasons
- Geographic uncertainty-matching clinical sites to incidence
Field Trial for WN Vaccine Efficacy

Feasible?

- Possibly, but cost not justified by market size
- Would require support from USG based on public health need
Incidence WN Neuroinvasive Disease, United States and South Dakota, 1999-2012

Cases per 100,000 population

Year


South Dakota

US
West Nile virus neuroinvasive disease incidence reported to ArboNET, by county, United States, 2013
## Phase 3 Trials for Vaccine Marketing Approval

<table>
<thead>
<tr>
<th>Product (indication)</th>
<th>Company</th>
<th>Incidence of disease in placebo group</th>
<th>Subjects in Phase 3 trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zostavax® (Herpes zoster)</td>
<td>Merck</td>
<td>0.7%</td>
<td>38,501</td>
</tr>
<tr>
<td>Rotateq® (Rotavirus)</td>
<td>Merck</td>
<td>0.02%-1% (different serotypes)</td>
<td>68,038</td>
</tr>
<tr>
<td>Havrix® (Hepatitis A)</td>
<td>GSK</td>
<td>0.3%</td>
<td>40,119</td>
</tr>
<tr>
<td>Prevnar® (Pneumococcus)</td>
<td>Pfizer</td>
<td>0.2%</td>
<td>37,868</td>
</tr>
<tr>
<td>Gardasil® (HPV)</td>
<td>Merck</td>
<td>0.5%</td>
<td>17,683</td>
</tr>
<tr>
<td>Cervarix® (HPV)</td>
<td>GSK</td>
<td>0.32%</td>
<td>17,350</td>
</tr>
<tr>
<td>CYD (Dengue)</td>
<td>Sanofi</td>
<td>Est. 1%</td>
<td>40,000+</td>
</tr>
<tr>
<td>West Nile, neuroinvasive</td>
<td>Acambis-&gt;Sanofi</td>
<td>0.06%</td>
<td>38,500</td>
</tr>
</tbody>
</table>
Fully Loaded Cumulative Cost of Development of ChimeriVax™-WN

- Research: $6M
- Development, Manufacturing: $28M
- NIH grants: $3M
- Intervet license: $0.5M
- Development stalls: $45M
- Sanofi license: $10M + $70M
- Clinical: $300M
- Regulatory: $350M
- Launch: $375M

Total costs:
- 8 years: $45M
- 4 years: $335M
- Total: $375M
Justification for Continued WN Vaccine Development

• Management of future outbreaks
• Neurological sequelae
• Evidence for persistent infection and chronic disease
  – Animal studies (NHP)
  – Chronic renal disease in humans (including persons asymptomatically infected)?
  – Chronic fatigue-like syndrome?
Prolonged fatigue, depression and chronic symptoms following West Nile

- 31% of WN patients had >6 mo. chronic fatigue
- Average duration of symptoms 5 years
- Pro-inflammatory cytokines significantly elevated in symptomatic subjects

Garcia MN et al. Viral Immunol 2014, Jul 25
How Does The WN Experience Inform The New Threat Of Chikungunya?
Chikungunya at the Door — Déjà Vu All Over Again?

David M. Morens, M.D., and Anthony S. Fauci, M.D.
CHIKUNGUNYA 2014

As of Sept, 2014
- > 700,000 cases reported in Americas
- > 1,000 imported cases in US
West Nile and Chikungunya Common Threads

• Cyclical or intermittent epidemics
• Absent for a long period and then reappear in explosive form
• Changing geographical distribution, rapid spread
• Overwintering, transovarial transmission
• Potentially severe, life-threatening
• Sequelae, chronic disease syndrome in 20-30%
• Threat to blood supply
• No specific treatment
• Regulatory pathway challenging
• Uncertain recommendations and sustainable market for vaccines
• High cost of vaccine development, limited access to capital
# West Nile and Chikungunya

Differences: □ Favors vaccine development

<table>
<thead>
<tr>
<th></th>
<th>West Nile</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human-mosquito-human</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>transmission</td>
<td></td>
<td></td>
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<tr>
<td>Subclinical infections</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Very large human epidemics</td>
<td>No</td>
<td>Ex US</td>
</tr>
<tr>
<td>Epidemics in US?</td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Explosive outbreaks, AR up to 90%, burns itself out (herd immunity)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Veterinary disease vaccine required</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Animal models/animal rule</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
CHIKV-associated rheumatism

polyarthritis and multiple tenosynovitis of wrists and fingers; carpal tunnel syndrome

20% with persistent arthritis

hypertrophic tenosynovitis of one ankle
(Dr. F Simon, Laveran Military Hospital, Marseille, France)

swelling observed in the right knee of a CHIKV infected patient
(Dr Adil Fakim, Mauritius)
# CHIK Vaccine Competitive Landscape 2014

<table>
<thead>
<tr>
<th>Company/ Institute</th>
<th>Vaccine</th>
<th>Pre clin</th>
<th>Ph 1</th>
<th>Ph2</th>
<th>Ph3</th>
</tr>
</thead>
<tbody>
<tr>
<td>USAMRIID</td>
<td>Live, attenuated (empirical)</td>
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<tr>
<td>Themis Bio GmbH</td>
<td>Live, attenuated, measles vector</td>
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<tr>
<td>Inviragen/Takeda</td>
<td>Live, attenuated, (rational)</td>
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<tr>
<td>Karolinska</td>
<td>Live, attenuated, (rational)</td>
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<tr>
<td>NIAID</td>
<td>Virus-like particles (HEK293 cells)</td>
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<tr>
<td>TI Pharma (Holland)</td>
<td>Virus-like particles (insect cells)</td>
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<tr>
<td>Merck</td>
<td>Virus-like particles (insect cells)</td>
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<tr>
<td>Baxter</td>
<td>Inactivated whole virion</td>
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<td>USAMRIID</td>
<td>Inactivated whole virion</td>
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<td>Indian Immuno</td>
<td>Inactivated whole virion</td>
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<tr>
<td>Bharat Bio</td>
<td>Inactivated whole virion</td>
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<tr>
<td>Defense Res Estab (India)</td>
<td>Subunit E (E coli)</td>
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<tr>
<td>UTMB</td>
<td>DNA launch, live</td>
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</tbody>
</table>

Legend:
- Orange: Industry
- Blue: Academia, government
Vaccine Development against West Nile and Chikungunya

• The obstacles are not technological
• Multiple applicable platforms
• Well understood mechanisms of action and immune correlates
• Applicable manufacturing methods and analytics
Chikungunya virus-like particle (VLP) produced by transfection of HEK293 cells, expression of the viral structural protein genes

Monkey model

- Broadly neutralizing responses with or without adjuvant
- No viremia after high dose CHIKV challenge
- Serum antibody from vaccinated NHP protects IFN-/- mice against lethal CHIK infection

Phase 1 trial

- Safety and Immunogenicity N=25
- Dose-escalation, open label
- 10, 20, 40 µg IM (no adjuvant)
- Schedule: 0, 1, 5 months
- Well-tolerated
- Robust N titers after 2nd dose; no dose effect

Do the challenges for WN vaccine apply to Chikungunya?

- Commercial market risks
- High development costs
- Uncertain indications and target populations
- Uncertain regulatory pathway, including
  - Feasibility and timelines of pivotal trials
- Timing risks
  - Vaccine available after emergency subsided
- Financial risks
  - Access to capital and strategic partnerships
- Uncertain ACIP recommendations
CHIKUNGUNYA VACCINE
COMMERCIAL CASE

Opportunities

- Continued spread, becomes permanently established

TRAVEL VACCINE
- 16 M US travelers to Latin Amer & Caribbean/year
- 282 imported cases (July14) versus vs. 149 for dengue
- Chronic disease in 20%
- High attack rates and low infection:illness ratio may facilitate trials
- Trials in travelers may be feasible
- Adult indication, peds later
- Non-dilutive funding

ENDEMIC MARKET
- Potential endemic market vaccine regional (Asia, Brazil, Mexico) and global partners

Challenges

- FDA (EMA) license, pivotal efficacy trials required
- High attack rate, burn out may hinder trial logistics
- Limited interest from investors, large pharma (travel vaccine)
- 6-10 year development time, with uncertain epidemiology
- Not an orphan indication
- Not currently on Priority Review Voucher list
RISK REWARD PROFILE

Risk Reward

Probability of success

Market size/Return

CHIK

WEST NILE

?
Summary

**West Nile vaccine**
- Strong technology basis for vaccines
- Lead in advanced Phase 2
- Industry engaged early but dropped out as medical impact subsided
- Limited market
- Pharmacoeconomics unfavorable
- Emergency use challenging
- ROW market uncertain (except veterinary)

**CHIK vaccine**
- Strong technology basis for vaccines
- Lead in early Phase 1
- Multiple industry candidates, but all small companies
- Sustainability dependent on epidemiology
- Significant financial and market risk
- Unlikely to be a significant US market except for travel
- ROW market potential but pricing constraints
Solutions?

• Vector-borne emerging diseases are challenging targets for the vaccines industry
• Government pull/push incentives required
  – These were insufficient to enable licensed WN vaccines
• Need to develop priorities for vaccine investments against natural disease threats
  – Priority Review Vouchers
  – Direct funding for advanced development (BARDA)
  – Stockpiles for emergency use (under EUA)
  – Change the rulebook for regulatory approval
    • Reduce cost of development and improve ROI
    • Conditional approvals (like veterinary vaccines)
    • Innovative approval strategies
Innovative ‘One Health’ Vaccine Approaches
Immunization of Animals to Prevent Human Diseases

• Much faster and less expensive regulatory path for animal vaccines
• Vaccination of animals involved in virus amplification and spill over to humans
  – Examples of existing and investigational vaccines
    • Domesticated animals (Injected vaccines)
      – Rift Valley fever (cattle, sheep, goats)
      – Venezuelan equine encephalitis (equids)
      – Leishmaniasis (dogs)
      – Hendra (equids)
    • Wild animals (oral bait vaccine)
      – Lyme disease
        » Field mice, OspA vaccine
Potential Future Targets

• Lyme disease
  – Oral bait or ballistic anti-tick vaccine for deer (or mice)

• West Nile
  – Oral bait vaccine for birds