Zika - Regulatory approval strategy for/lessons learned/precedence from other licensed flaviviruses

H. Meyer, June 2016
Flavivirus vaccines

Phylogenetic analysis of mosquito- and tick borne flaviviruses

**Licensed vaccines**

- **Dengue:**
  - Chimeric tetravalent vaccine

- **Japanese encephalitis:**
  - Live attenuated
  - Chimeric
  - Inactivated whole virion (+/- adjuvans)

- **Yellow fever:**
  - Live attenuated

- **TBE:**
  - Inactivated whole virion, adjuvanted

*Heinz and Stiasny, 2010*
Tick borne encephalitis (TBE) vaccines
Tick Born Encephalitis Virus

- Transmission via ticks (*Ixodes ricinus*, *Ixodes persulcatus*) and rarely via consumption of non-pasteurized dairy products (e.g. raw goat milk)
- Vertical transmission and transmission via blood transfusion have not been observed
- Three subtypes of TBEV exist: Western, Far Eastern and Siberian
- Approximately two-thirds of infections are asymptomatic
- Acute neuroinvasive disease including aseptic meningitis, encephalitis, or myelitis is the most commonly recognized clinical manifestation
- CFR between 1-2% for Western type and ~20% for Far Eastern type
TBE vaccines

- First TBE vaccine approved in 1941 in Russia produced from mouse brain
- Currently four vaccines licensed in Europe and Russia
- All inactivated, cell-culture derived, whole virion, alum adjuvanted, 2 vaccines use Western strains and 2 vaccines use Far Eastern strains
- European vaccines (Western strains):
  - FSME Immun (strain Neudörfl) licensed 1976 in Austria
  - Encepur (strain K23) licensed 1994 in Germany
  - Manufacture of vaccine antigens is similar but vaccine formulation differs in strain, antigen content and use of excipients
  - Age indication for adult and pediatric vaccine formulation varies between two vaccines
TBE vaccines

- Various vaccination schedules approved

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Accelerated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FSME-Immun</strong></td>
<td>0, 1-3, 5-12 months</td>
<td>0, 14 days, 5-12 months</td>
</tr>
</tbody>
</table>
<pre><code>      | First booster: 3 years                            | First booster: 3 years                          |
</code></pre>
<p>| <strong>Encepur</strong>      | 0, 1-3, 9-12 months                               | 0, 14 days, 9-12 months                         |
| First booster: 3 years                            | First booster: 3 years                          |
|          |                                                   | or                                              |
|                                                   | 0, 7, 21 days                                   |
|          |                                                   | First booster: 12-18 months                     |</p>

- Subsequent booster vaccinations: every 3-5 years depending on age
- Antibody persistence data indicate possibility for booster intervals of 10 years
TBE Vaccines

- No controlled efficacy trials were conducted for TBE vaccines.
- However, data from an uncontrolled cohort study of an experimental TBE vaccine (Neudörfl strain) performed in Austria suggested protective vaccine efficacy:
  - High risk group of 30,000 forest workers and farmers having a 3 times increased risk of contracting TBE disease were vaccinated between 1973-1976.
  - No case of TBE reported in vaccinees in subsequent years.
- This experimental vaccine was further developed and licensed in Austria (FSME-Immun) (Heinz 2003)
Based on animal models as well as on clinical vaccine trials, a threshold of neutralizing antibodies ≥ 1:10 has been accepted as evidence of protection.

- Seroprotection rates of 97-100% after primary vaccination.
- Long-term antibody persistence indicate that >94% are seroprotected after first booster vaccination independent of vaccination schedule.
- Crossreactive neutralizing antibodies against all TBEV subtypes.
- Different formats of serological assay used by different companies.
TBE vaccines

Number of TBE cases in Austria and CZ from 1979 to 2001

Vaccine coverage:
Austria: increased from 6% in 1980 to 86% in 2001
Czech Republic: up to approx. 10%

(Kunz 2003)
TBE vaccines

Estimated field effectiveness in Austria from 2000-2006:
• Across all age groups: 96-100%
• Regularly vaccinated: ~99%
• After 2 doses within the 1st year of vaccination: 100%

• Breakthrough cases are rare
• Occur more often in older age groups

(Heinz et al. 2007)
Vaccine safety
Fever is reported in 1-3% of vaccinees, but it is more frequent in children 1-2 years of age

Impact of vaccine formulation on safety profile
- FSME Immun: Removal of HSA from vaccine formulation led to increased rate of high fever including fever convulsions in infants
  - HSA was reintroduced
- Encepur: Polygeline in vaccine formulation led to high number of spontaneous reports on febrile reactions and on suspected allergic reactions especially in children
  - Polygeline was replaced by sucrose
TBE vaccines and pregnancy

- No clinical trials in pregnant women
- No reproductive and developmental toxicity studies performed
- Pregnancy is not a contraindication for vaccination
- Vaccination of pregnant women could be considered, but only after careful benefit-risk assessment
- Very limited post marketing data do not indicate any untowards risk in pregnant women
Summary TBE vaccine

- Inactivated TBE vaccines are highly efficacious
- Primary immunisation schedule consists of 3 doses
- However, 2 doses provide short term protection for a period of 1 year
- A NT titer of 1:10 is considered protective
- Use in pregnancy not contraindicated
- No studies in pregnant women
Japanese encephalitis (JE) vaccines
JE vaccines

- Inactivated mouse brain derived (JE-VAX)
- Inactivated Vero cell derived alum adsorbed (Ixiaro)
- Live attenuated vaccine (CD.JEVAX)
- Chimeric vaccine (IMOJEV)

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Immunogenicity data</th>
<th>Efficacy data</th>
<th>Effectiveness data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated mouse brain vaccines</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Inactivated Vero cell vaccines</td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live attenuated vaccines</td>
<td>×</td>
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<td>×</td>
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<tr>
<td>Chimeric vaccines</td>
<td>×</td>
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</tr>
</tbody>
</table>

- All internationally approved prequalified vaccines are made from attenuated JE strain SA-14-14-2
- Mouse brain derived vaccine JE-VAX derived from Nakayama strain
JE Vaccines

Protective efficacy of the MBDV JE-VAX was shown in Thailand with about 65 000 children to be 91% (Hoke et al 1988).

The generally accepted immunological surrogate of protection is a serum neutralizing antibody titer of at least 1:10 as determined in a 50% plaque reduction neutralization assay (PRNT50).

Immunogenicity analyses are influenced by the virus strain used in the PRNT50 assay (homologous vs. non-homologous) as well as the cell substrate.

Approval of recent JE vaccines (e.g. Ixiaro, Imojev) were supported by
- Challenge studies in animals
- Passive human antibody transfer studies in animal challenge models
- Demonstration of crossneutralising capacity of various strains
## JE vaccines

### Vaccination schedules

<table>
<thead>
<tr>
<th></th>
<th>Primary vaccination</th>
<th>Booster</th>
</tr>
</thead>
</table>
| **Vero cell derived, inactivated** | Children (≥12 mo) and adults 0, 28 days | Adults:  
First booster: 12-24 months  
Second booster: 10 years  
**Children:**  
Not established yet |
| **Live attenuated** | Children (≥8 mo)  
Single dose  
(no adult data) | Not established |
| **Chimeric** | Children (≥9 mo)  
and adults  
Single dose | Not established |
Inactivated Vero cell derived JE Vaccine

Seroprotection rates:
- One month after completion of two-dose primary series
  - High seroprotection rates in all studies and age groups: ≥95%
- Antibody persistence:
  - Children aged 1-17 years in endemic area
    - Limited data indicate that 3 years after primary vaccination high seroprotection rates (~90%) maintained
    - No booster vaccination recommended
  - Adults in non-endemic area
    - 2nd booster dose 10 years after 1st booster recommended
# Live attenuated JE vaccine

## Effectiveness of CD.JEVAX (Case-Control Studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ages @vax</th>
<th>1W-1M</th>
<th>6M</th>
<th>1YR</th>
<th>Up to ~3YR</th>
<th>5YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bista 2001</td>
<td>Nepal</td>
<td>1-15Y</td>
<td>99.3%</td>
<td></td>
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<td></td>
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<td></td>
<td>(94.9-100%)</td>
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<tr>
<td>Kumar 2009</td>
<td>India</td>
<td>1-15Y</td>
<td></td>
<td>94.5%</td>
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<td></td>
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<td></td>
<td>(81.5-98.9%)</td>
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<tr>
<td>Ohrr 2005</td>
<td>Nepal</td>
<td>1-15Y</td>
<td></td>
<td></td>
<td>98.5%</td>
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<td></td>
<td></td>
<td></td>
<td>(90.1-99.2%)</td>
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<tr>
<td>Murhekar 2014</td>
<td>India</td>
<td>16-24M</td>
<td></td>
<td></td>
<td></td>
<td>84%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(53-95%)</td>
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<tr>
<td>Tandan 2007</td>
<td>Nepal</td>
<td>1-15Y</td>
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</tbody>
</table>

Hills, SAGE Meeting 2014
Live attenuated JE vaccine

Seroconversion rates in children aged 8-24 months:

- One month after a single dose
  - Across clinical trials in endemic areas: 80-99%
- Antibody persistence:
  - Follow-up study
    - 3 years: 79%
  - Observational study
    - 4 years: 90%
    - 5.5 years: 64%

SAGE Meeting 2014
Chimeric JE Vaccine

Seroconversion rates:

- One month after a single dose
  - Children aged 12-18 months in endemic area: ≥95%
  - Adults 18-65 years: ~99% (81% - PRNT with heterologous strain)

- Antibody persistence:
  - Children aged 12-24 months in endemic area
    - 2 years: 80%
    - 5 years: 66%
    - In Australia a second dose is recommended
  - Adults in non-endemic area
    - 5 years: 94%
<table>
<thead>
<tr>
<th></th>
<th>Inactivated JE-VAX</th>
<th>Inactivated, adsorbed Ixiaro</th>
<th>Live attenuated SA14-14-2</th>
<th>Live chimeric Imojev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>Mouse brain</td>
<td>Vero cells</td>
<td>Primary hamster kidney cells</td>
<td>Vero cells</td>
</tr>
<tr>
<td>Excipients /residuals with known effects</td>
<td>Gelatine, thiomersal, residual mouse brain protein</td>
<td>Protamine sulphate as residual</td>
<td>Gelatine</td>
<td>Glutamic acids (?) Antibiotics (?)</td>
</tr>
<tr>
<td>Hypersensitivity including generalized urticaria, angio-oedema or respiratory distress</td>
<td>0.8/100,000 (Japan, mostly children) 6.3-8.4/100,000 (US, mostly adults)</td>
<td>3.6/100,000 (EU; US, Australia; mostly adults)</td>
<td>2.8/100,000 (mostly children)</td>
<td>?</td>
</tr>
<tr>
<td>Neurological AEs including encephalitis, encephalopathy, convulsions, peripheral neuropathy, transverse myelitis</td>
<td>2/1,000,000 (Japan, mostly children) 0.0 (US, mostly adults)</td>
<td>5/250,000 neuritis, meningism, headache (2x), migraine, <strong>only one</strong> case of neuritis considered serious)</td>
<td>1.3/1,000,000</td>
<td>? Limited postmarketing data</td>
</tr>
</tbody>
</table>
JE vaccines and pregnancy

- No studies in pregnant women

- Inactivated JE vaccines
  - Not contraindicated during pregnancy
  - Data from a reproductive and pre-/post-natal toxicity study showed no vaccine-related effects on reproduction, foetal weight, survival and development of the off-spring.

- Live attenuated vaccines
  - Vaccine is contraindicated
  - No data available for adult subjects, vaccine used primarily in children

- Chimeric vaccine
  - Vaccine is contraindicated
Summary JE vaccines

- High seroprotection rates induced by all vaccines
- Long-term antibody persistence data are limited
  - Insufficient evidence to indicate booster doses are needed in endemic regions
  - More data needed to fully assess need for a booster, especially
    - longer periods of follow-up
    - in different transmission settings
    - in routine immunization program use
- Acceptable safety profile
- Pregnancy
  - No studies in pregnant women
  - Only inactivated vaccines could be considered during pregnancy
  - Live attenuated and chimeric vaccines are contraindicated
Yellow Fever (YF) Vaccine
YF vaccine

- Live attenuated vaccines using various strains derived from 17D
- Single dose, no booster dose needed anymore
- Highly efficacious
- Correlate of protection: NT 1:10 – 1:20
- Rare but serious viscerotrophic and neurotropic side effects

**Pregnancy and breast-feeding:**
- Limited data on pregnant women from mass vaccination campaigns in Brazil provide no indication that in utero exposure to YFV carries an increased risk of major malformation
- One study from Brazil provides evidence that YF vaccination during early pregnancy might increase the risk of spontaneous abortion
- Transmission of YFV by breast-feeding vaccinated mothers to babys
- Cases of encephalitis in neonates following transmission reported
Tetravalent Chimeric Dengue Vaccine
Tetravalent Chimeric Dengue Vaccine

- Similar concept as IMOJEV
- Live attenuated YF virus 17D vaccine backbone + Dengue viral proteins M/E of serotypes 1-4
- Licensed in Mexico, Brasil, El Salvador, Paraguay, the Philippines
- Indicated from 9 to 45 (60) years
- Vaccination schedule: 3 doses given 6 months apart each
- Two efficacy trials in Latin America and Asia in 2-16 years old
- No correlate of protection established to date
**Tetravalent Chimeric Dengue Vaccine**

**Vaccine efficacy**

- Vaccine efficacy demonstrated against per protocol primary endpoint.
  - Pooled across two efficacy trials (ages 2-16 years) VE was 59.2%

- Protection was seen in 2 years following first dose
  - 2-16 years Pooled VE was 60.3%
  - 9-16 years pooled VE was 65.6%

- VE varied by infecting serotype, serostatus, age, and severity of disease.

- Variable efficacy by country, at least in part, due to these factors.
Tetravalent Chimeric Dengue vaccine

Safety

- Elevated risk of hospitalised and severe dengue among vaccinated seen in 2-5 year old age group in Year 3
- Trends in relative risk against dengue hospitalisation with time since vaccination suggest waning immunity

Pregnancy

Pregnancy is contraindicated