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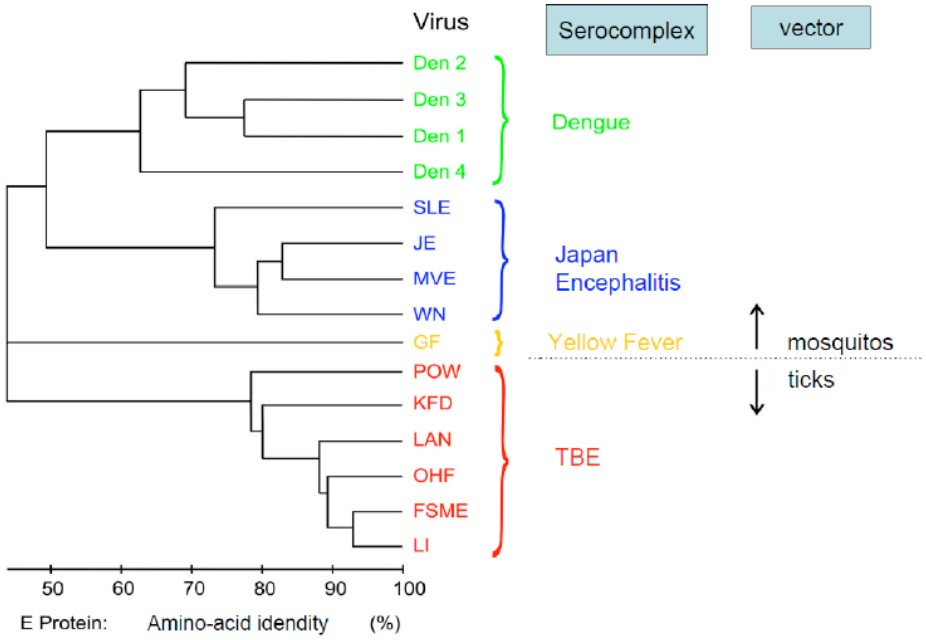
Zika - Regulatory approval strategy for/lessons learned/precedence from other licensed flaviviruses

H. Meyer, June 2016

Flavivirus vaccines

Phylogenetic analysis of mosquito- and tick borne flaviviruses



Heinz and Stiasny, 2010

Licensed vaccines

Dengue:
Chimeric tetravalent vaccine

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

Yellow fever:
Live attenuated

TBE:
Inactivated whole virion, adjuvanted

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 inactived, cell-culture derived, whole virion, alumn 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

	Conventional	Accelerated
FSME-Immun	0, 1-3, 5-12 months First booster: 3 years	0, 14 days, 5-12 months First booster: 3 years
Encepur	0, 1-3, 9-12 months First booster: 3 years	0, 14 days, 9-12 months First booster: 3years **or** 0, 7, 21 days First booster: 12-18 months

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

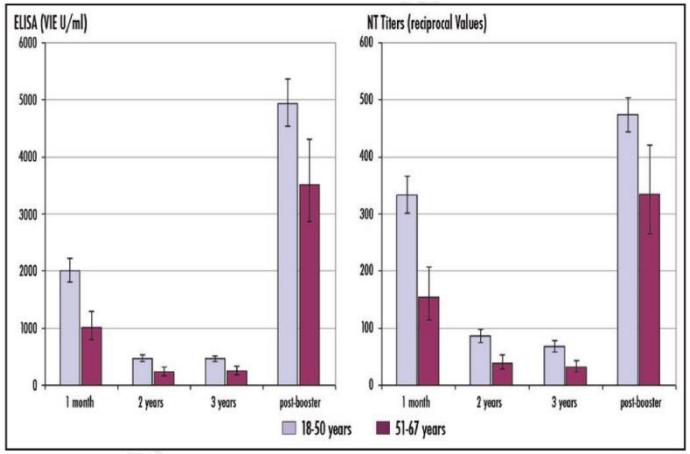
TBE Vaccines

- 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)

TBE vaccines

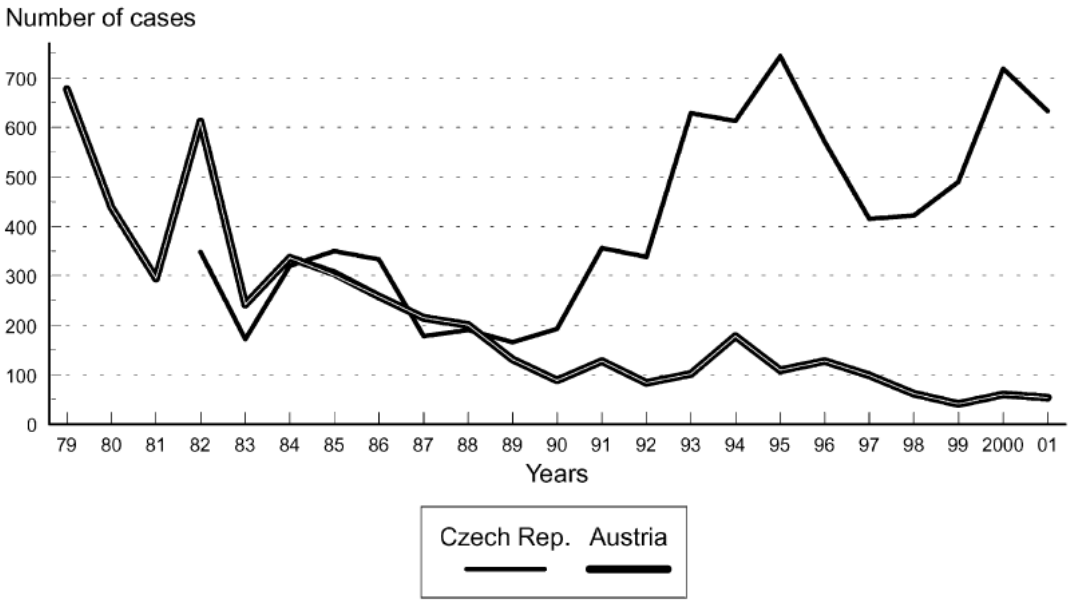
- Based on animal models as well as on clinical vaccine trials, a threshold of neutralizing antibodies ≥ 1:10 has been accepted as evidence of protection
- Seroprotection rates of 97-100% after primary vaccination
- Long-term antibody persistence indicate that >94% are seroprotected after first booster vaccination independent of vaccination schedule
- Crossreactive neutralizing antibodies against all TBEV subtypes
- Different formats of serological assay used by different companies



e 3. GMCs (ELISA) and GMTs (NT) and 95% CIs 1 month, 2 years and 3 years after the third vaccination, as well as post-booster by age group.
TBE SAGE meeting, Geneva, April 2011

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)

TBE vaccines

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 condraindication 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 efficacous
- 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)

	Immunogenicity data	Efficacy data	Effectiveness data
Inactivated mouse brain vaccines	✗	✗	✗
Inactivated Vero cell vaccines	✗		
Live attenuated vaccines	✗		✗
Chimeric vaccines	✗		

- 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**

	Primary vaccination	Booster
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)							
Study	Country	Ages @vax	1W-1M	6M	1YR	Up to ~3YR	5YR
Bista 2001	Nepal	1-15Y	99.3% (94.9-100%)				
Kumar 2009	India	1-15Y		94.5% (81.5-98.9%)			
Ohrr 2005	Nepal	1-15Y			98.5% (90.1-99.2%)		
Murhekar 2014	India	16-24M				84% (53-95%)	
Tandan 2007	Nepal	1-15Y					96.2% (73.1-99.9%)

Hills, SAGE Meeting 2014

Live attenuated JE vaccine

Seroprotection 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%

Chimeric JE Vaccine

Seroprotection 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%

	Inactivated JE-VAX	Inactivated, adsorbed Ixiaro	Live attenuated SA14-14-2	Live chimeric Imojev
Substrate	Mouse brain	Vero cells	Primary hamster kidney cells	Vero cells
Excipients /residuals with known effects	Gelatine, thiomersal, residual mouse brain protein	Protamine sulphate as residual	Gelatine	Glutamic acids (?) Antibiotics (?)
Hypersensitivity including generalized urticaria, angio-oedema or respiratory distress	0.8/100,000 (Japan, mostly children) 6.3-8.4/100,000 (US, mostly adults)	3.6/100,000 (EU; US, Australia; mostly adults)	2.8/100,000 (mostly children)	?
Neurological AEs including encephalitis, encephalopathy, convulsions, peripheral neuropathy, transverse myelitis	2/1,000,000 (Japan, mostly children) 0.0 (US, mostly adults)	5/250,000 neuritis, meningism, headache (2x), migrane, **only one** case of neuritis considered serious)	1.3/1,000,000	? Limited postmarketing data

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 viscerotropic 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 attentuated 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