Zika Virus in the Americas: An HHS Expert Consultation to Accelerate the Development of Countermeasures

Flavivirus Vaccines: Current Status

Thomas P Monath MD
CSO & COO, Infectious Disease Division
NewLink Genetics Corp.

Vaccines Against 28+ Human Diseases

Viral diseases

Flaviviruses

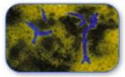

Yellow fever

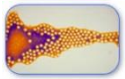

Japanese encephalitis

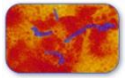

Dengue

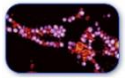

Tick-borne encephalitis

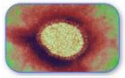

Kyasanur Forest disease

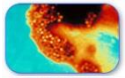

Mumps

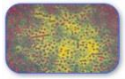

Poliomyelitis

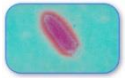

Measles

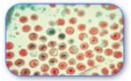

Rubella

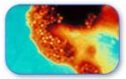

Influenza


Hepatitis A

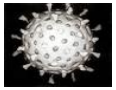

Hepatitis B

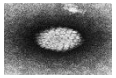

Rabies


Chickenpox/Zoster


Enterovirus 71

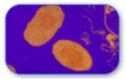

Hepatitis E

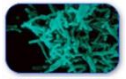

Rotavirus


Human Papillomas

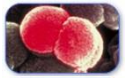

Smallpox

Bacterial diseases


Pertussis


Diphtheria

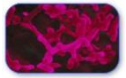

Haemophilus influenzae type b infections

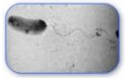

Meningococcal meningitis


Pneumococcal infections


Tetanus


Tuberculosis


Typhoid fever


Cholera

Flavivirus Vaccine Types

+ commercial (+) investigational, (v) veterinary

	YF	DEN	JE	WN	TBE
Live, attenuated	+	(+)	+, +(v)		
Live , flavi vector		+,(+) YF 17D	+ YF 17D	+(v) YF 17D	(+)
Defective, single cycle		(+)	(+)	(+)	(+)
Live non-flavi vector		(+)	(+)	+(v) canarypox	
Inactivated	(+)	(+)	+	+(v)	+
Subunit E		(+)		(+)	
Recombinant VLP				(+)	
DNA		(+)		+(v)	

Current Flavivirus Vaccines (Live, attenuated)
How well do the match the draft ZIKV TPP?

Characteristic	Yellow fever	Dengue	Japanese encephalitis	
Type	LAV (empirical)	LAV (recomb YF chimera)	LAV (empirical)	LAV (recomb YF chimera)
Monovalent	Yes	Yes (DEN 1-4)	Yes	Yes
Platform with no safety issue for pregnant or lactating women	No	No	No	No
Efficacy ≥80%	Yes	65%* (95%* *vs* severe)	>95%	Yes
Seroprotection ≥80%	>95%	(no correlate)	>95%	99%
Long duration of protection	>35 years	TBD	5y?	>5y, (>30 yrs modelled)
Boostable following primary series	Yes (blunted with LAV)	TBD	Yes	Yes (with PIV)
Single dose preferred, 2 dose acceptable	1 dose	3 doses (0,6,12m)	1 dose	1 dose
Administered ID, SC, IM or oral	SC	SC	SC	SC
Stable formulation (2-8C)	>2y Lyo	>2y Lyo	>2y Lyo	>2y Lyo

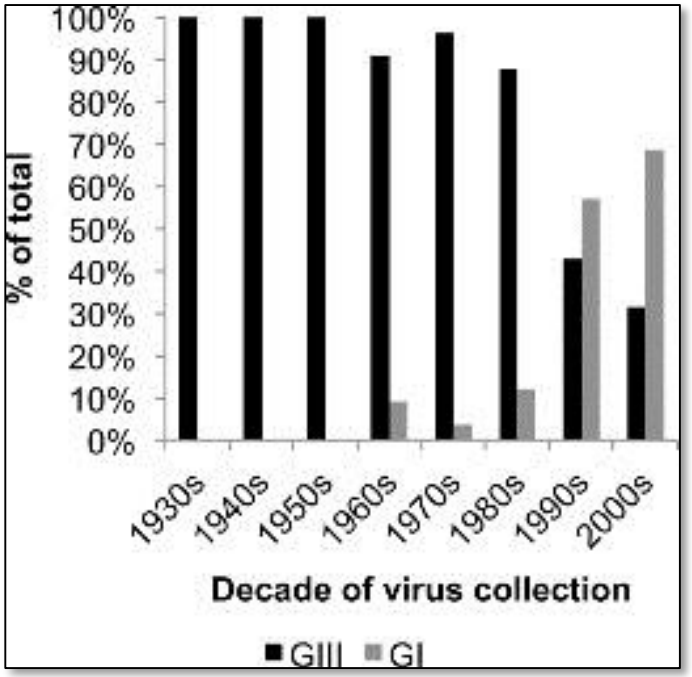
Current Flavivirus Vaccines (inactivated)
How well do the match the draft ZIKV TPP?

Characteristic	Japanese encephalitis		Tick-borne enc	Kyasanur Forest
Type (dose, adjuvant)	Inactivated ($F^{\Diamond}$) 6 mcg, Alum	Inactivated ($F^{\Diamond}$)	Inactivated ($F^{\Diamond}$) 1.5-2.5 mcg, Alum	Inactivated ($F^{\Diamond}$)
Monovalent (strain)	Yes (SA14-14-2)	Yes (Beijing-1 or Nakayama)	Yes (Neudorfl or K23)	Yes (KFDV)
No safety issue for pregnant or lactating women	Yes	Yes	Yes	Yes
Efficacy ≥80%		76-85%	97%	83%
Seroprotection ≥80%	96%	70-80%	99%	
Long duration of protection	No	No	No	No
Boostable following primary series	Yes (≥1y)	Yes (Multiple)	Yes (3y, then q5y)	Yes (6-9m, then q1y)
Single dose preferred, 2 dose acceptable	2 dose (0,28d)	2 dose (0,7-28d)	3 dose (0, 1-3m, 6-9m)	2 dose (0,28d)
Administered ID, SC, IM or oral	IM	SC	IM	SC
Stable formulation (2-8C)	>2y, Liquid	>2y, Liquid	>2y, Liquid	>2y, Liquid

($F^{\Diamond}$) formalin

Antigenic Variation

- General
  - Flavivirus species consist of a single serotype, multiple genotypes
  - Successful vaccines consist of a single virus strain
- Japanese encephalitis
  - 5 JE genotypes (G1 to G5)
  - All approved vaccines are a single genotype (G3)
  - G3 vaccines cross-protect against all genotypes
  - G3 being replaced by G1
    - Secondary vaccine failures (horses, humans), but at low incidence
- Zika
  - 3 genotypes
  - Less variable than JEV
  - Antigenic variation not a factor for vaccine development



Schuh et al. PLoS NTDS 2013;7:e2411

Flavivirus vector platform for developing a new flavivirus vaccine

Strengths

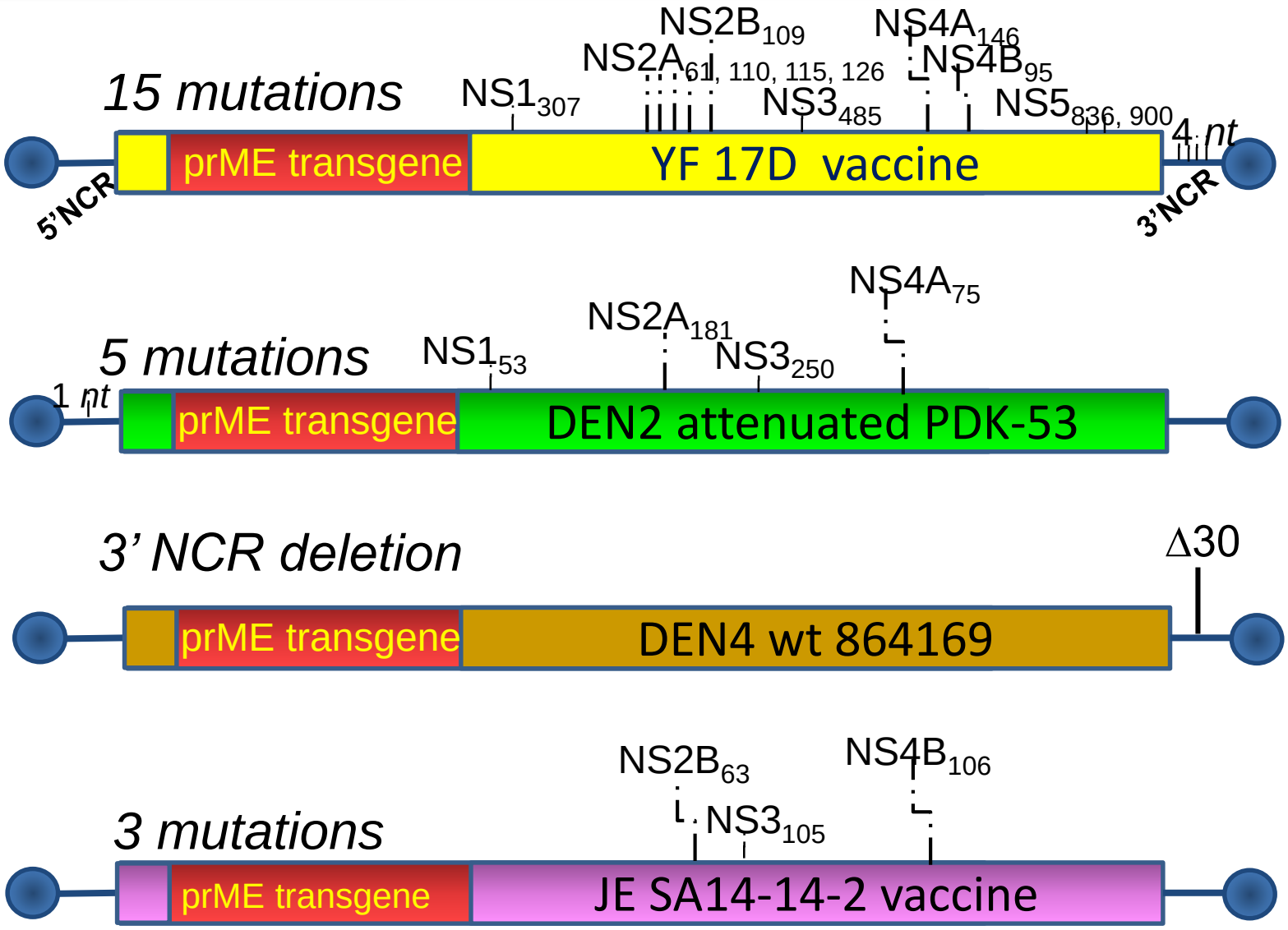
- Advantages of LAVs (single dose, immunogenicity, durability, low COGS etc.)
- Rapid development
  - Switch transgene
  - Similar manufacturing processes
- No anti-vector immunity (compared to adeno, measles, pox, etc)
- Improved safety profile
  - Chimerization is attenuating *per se*

Challenges

- Disadvantages of LAVs (precautions, contraindications, viremia)
- Safety profile in part dependent on transgene
  - No known attenuated transgene sequence
- Safety testing requires animal models recapitulating pathogenesis of wt virus

Flavivirus Vector Platforms

Chimeric viruses using attenuated flavivirus backbone



IMOJEV®, JE vaccine developed on ChimeriVax technology (Sanofi Pasteur)

- Attenuated YF 17D vector with attenuated JEV SA14-14-2 transgene
- Clinical studies in >15,000 people over the past 5 years
- Safe, well tolerated
- Single dose, >95% immunogenic, non-inferior to 3-dose inactivated JE vaccine
- Onset of immunity in <14 days
- Minimal, transient viremia
- Not infectious for mosquitoes
- Strong immunological memory
- Durable immunity
- Protects NHP against severe *intracerebral* challenge

15 000 Persons
in clinical studies

13
Registered Countries

WHO PQ
since 2014

1.7M doses
Sold since launch

Acknowledgement: N Jackson, Sanofi Pasteur

Flavivirus Inactivated Vaccines

Strengths

- Multiple vaccines developed, approved
- Multiple successful inactivation methods (formalin, BPL, H202)
- Epitopes preserved
- No issues with residual live virus
- Safe, well tolerated
- Immunogenic at low doses (2-6 mcg)
- Liquid formulation (no lyo req.)
- May be given with other vaccines
- Few contraindications
- Potential for use in pregnancy, breastfeeding

Challenges

- Multiple dose primary schedule (2-3 doses)
- Antibody levels often wane rapidly before first boost
- Boosters required for sustained immunity through child-bearing years
- Adjuvant may be required or desirable
- More challenging DSP, higher COGS
- *Requires upstream yields ≥8 logs for affordable vaccine*
- Complex DSP to remove DNA and protein

Dengue Vaccines in Advanced Development

Current Developer	Vaccine	Type	Stage
Sanofi Pasteur	Dengvaxia	Live, recombinant, YF chimeras	Approved/ registration
Takeda	DENVax	Live, recombinant, DEN2 chimeras	Phase II
NIH, Biologicals E, Butantan, Vabiotech	TV003	Live, recombinant, Δ30 deletion and 1 DEN2/DEN4 chimera	Phase II/III
Merck	V180	Subunit E, recombinant + Iscomatrix® adjuvant	Phase II
GSK, WRAIR	TDEN-PIV PIV	Inactivated + AS03 Inactivated + alum	Phase II Phase II
	TDEN	Live, empirical	Phase II
US Navy		DNA	Phase I

Immune Correlates

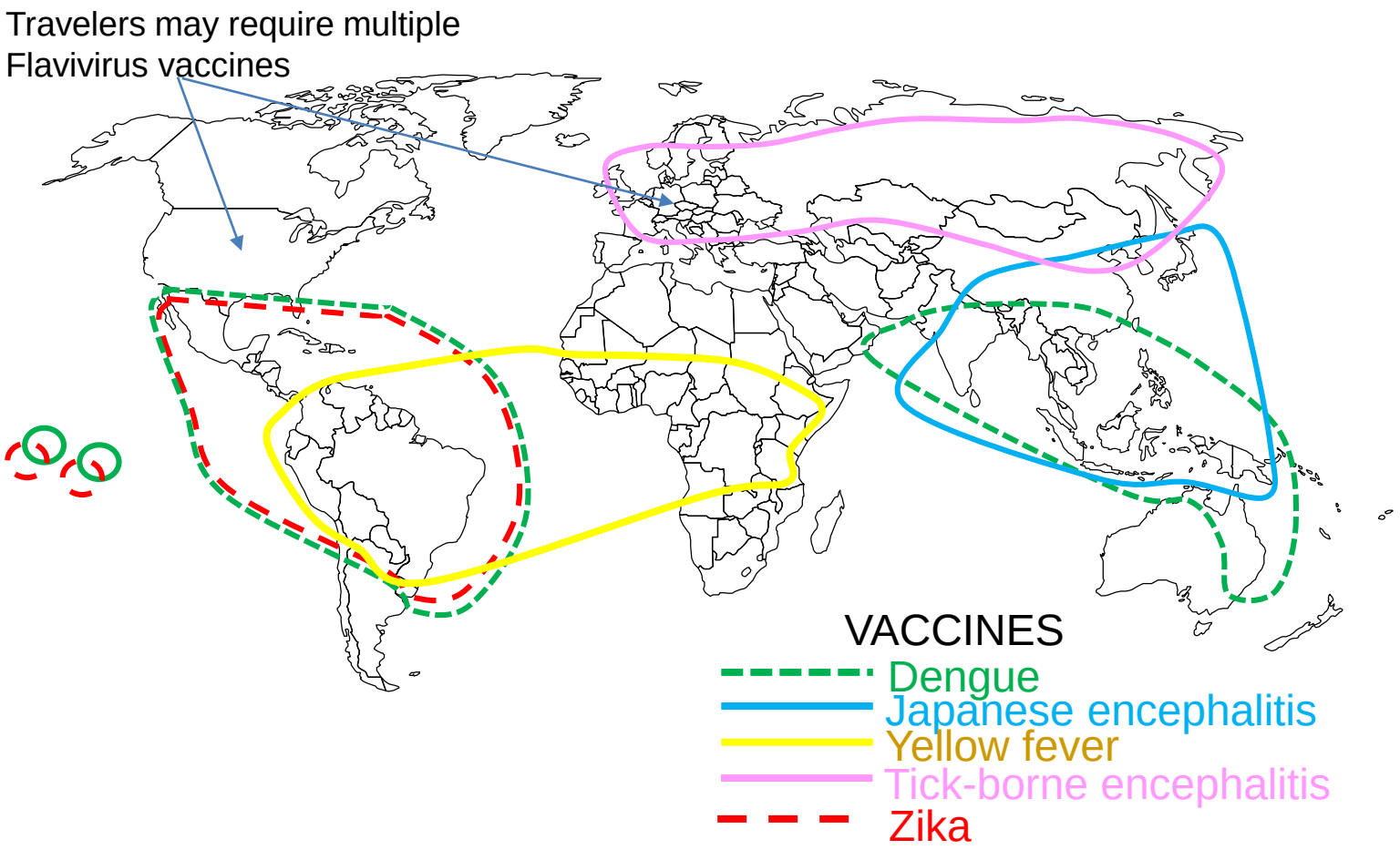
- Neutralizing antibodies mediate protection
- What is the level of N antibodies corresponding to protection?
- Established for JE and TBE only ($PRNT_{50}$ ≥10)
  - Minimum antibody required to prevent neuroinvasion when BBB intact
- Protection against systemic infection (YF, DEN) appears to require 4 to 10-fold higher levels of antibody
  - Likely true for ZIKV where objective is to abrogate viremia and protect placenta, fetus
  - The one inactivated vaccine against a severe systemic infection (KFD) has lower reported efficacy

Sterilizing Immunity

- Demonstrated by absence of post-challenge rise in antibody
  - Observed following *weak challenge* or in presence of *high antibody titers* (~50% in YF 17D revaccination, human dengue challenge)
- Difficult to achieve since primary site of replication is skin at site of mosquito bite
  - Some level of local replication may occur in face of pre-formed antibody
- Sterilizing immunity not a general requirement for Flavivirus vaccines
  - Pre-formed antibody protects against secondary viremia, infection of target organs, transmission
  - T cells clear virus before significant direct viral injury occurs
  - No mucosal portal of entry
- In contrast, a successful ZIKV vaccine may require sterilizing immunity or high grade protection against viremia
  - Low-level breakthrough viremia could infect small number of critical target cells (e.g. neural stem cells), cause injury before immune clearance
  - Infection via mucosal routes w/ lower immune barrier

Flavivirus Vaccine Interactions

- Background of artificial and natural immunity to multiple flaviviruses
- Immune response qualitatively different in naïve vs subjects with prior heterologous immunity
- May be difficult to differentiate homotypic from cross-reactive antibody



Thank you!