



Desafios para o desenvolvimento de uma vacina para o Zika vírus

Challenges for the development of a vaccine for Zika virus

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Viral Vaccine Program

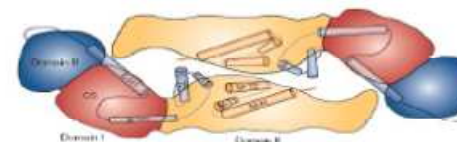
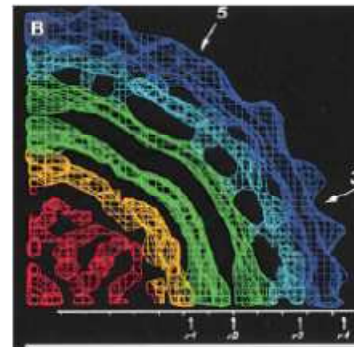
R&D Vice-Directory

Bio-Manguinhos/Fiocruz – Rio de Janeiro

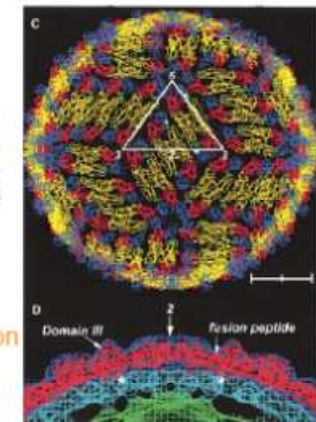
Flavivirus Vaccines

- Most neutralizing antibodies are induced against E protein, and all approved and most developing flavivirus vaccines contain E antigens

60-70nm, 11.7kb (+)RNA



Envelope protein — DI - structural
Membrane protein — DII - dimerization, fusion
Lipid bilayer — DIII - Ig-like, R binding
Capsid protein shell
RNA



Flavivirus Infections in Humans

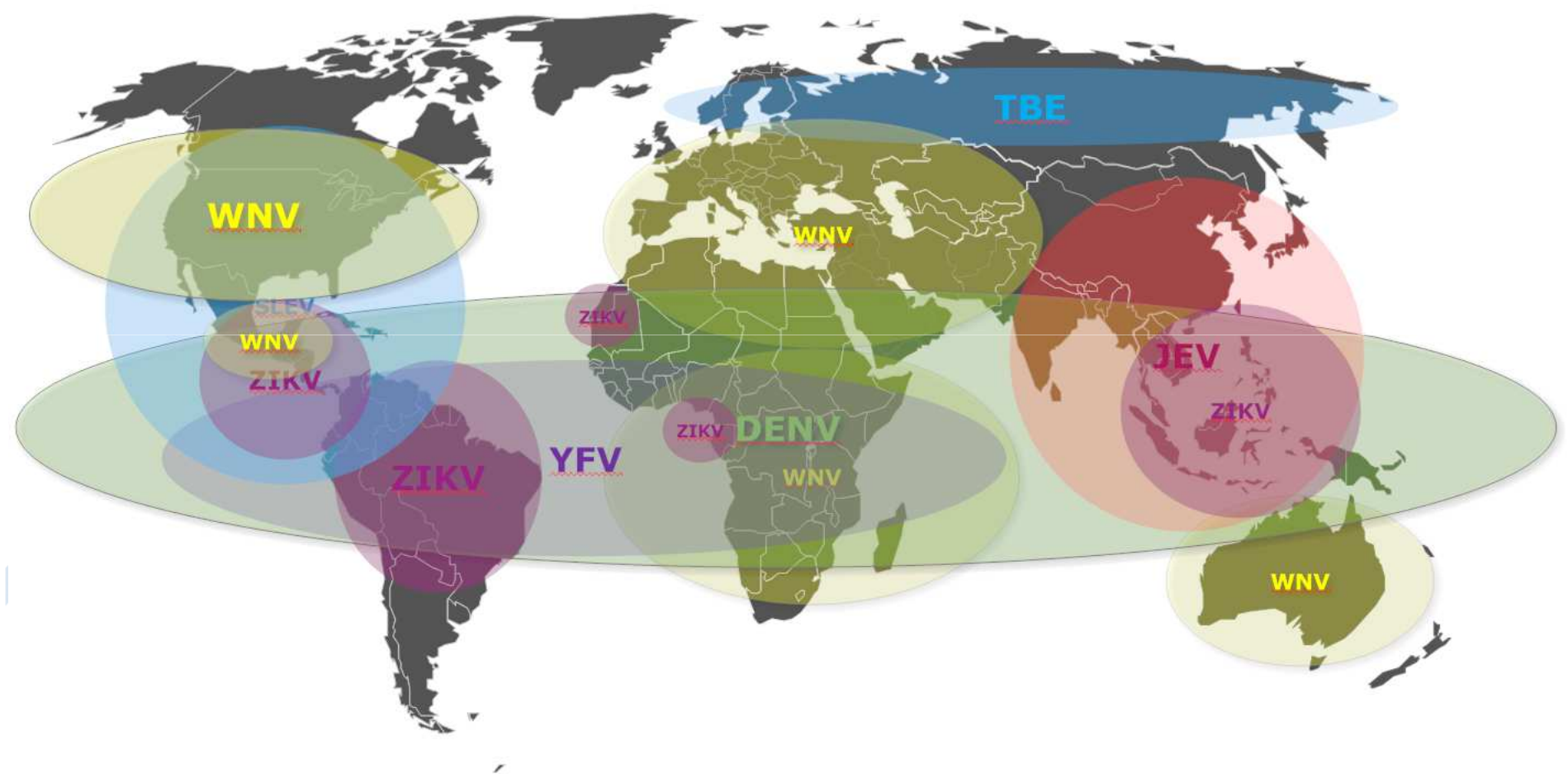


- Mosquitoes-transmitted viruses:
 - Yellow Fever,
 - Dengue Fever,
 - Japanese encephalitis,
 - West Nile viruses,
 - St. Louis encephalitis
 - Zika virus



- Flaviviruses transmitted by ticks:
 - Tick-borne Encephalitis (TBE),
 - Kyasanur Forest Disease (KFD)
 - Alkhurma disease,
 - Omsk hemorrhagic fever

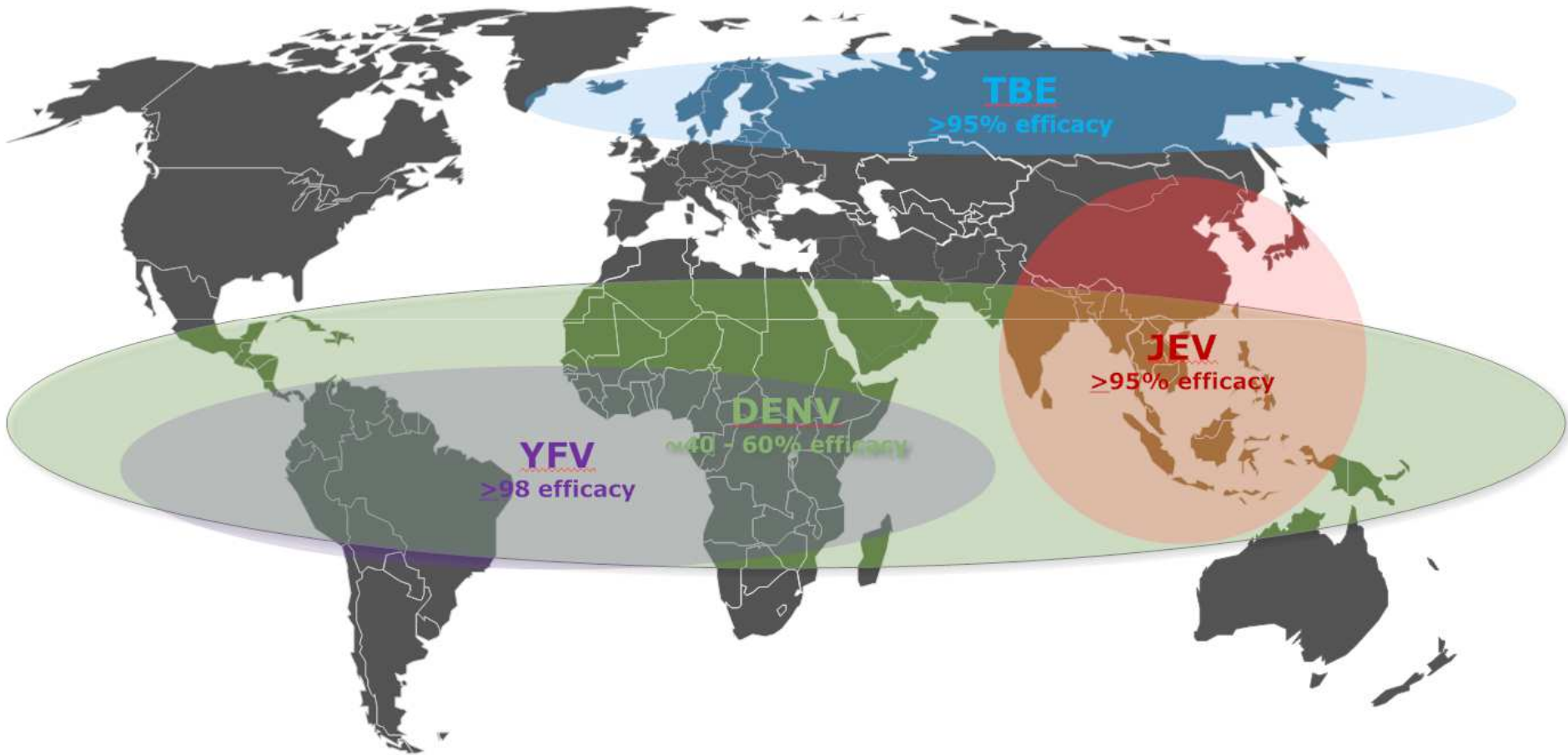
Worldwide distribution of flaviviruses



Adapted from T. Ishikawa et al. / Vaccine 32 (2014) 1326–1337



Flaviviruses Vaccines



Adapted from T. Ishikawa et al. / Vaccine 32 (2014) 1326–1337



Flavivirus Vaccines

- Flavivirus vaccines against YFV, JEV TBEV and DENV infections have been developed using different platforms.

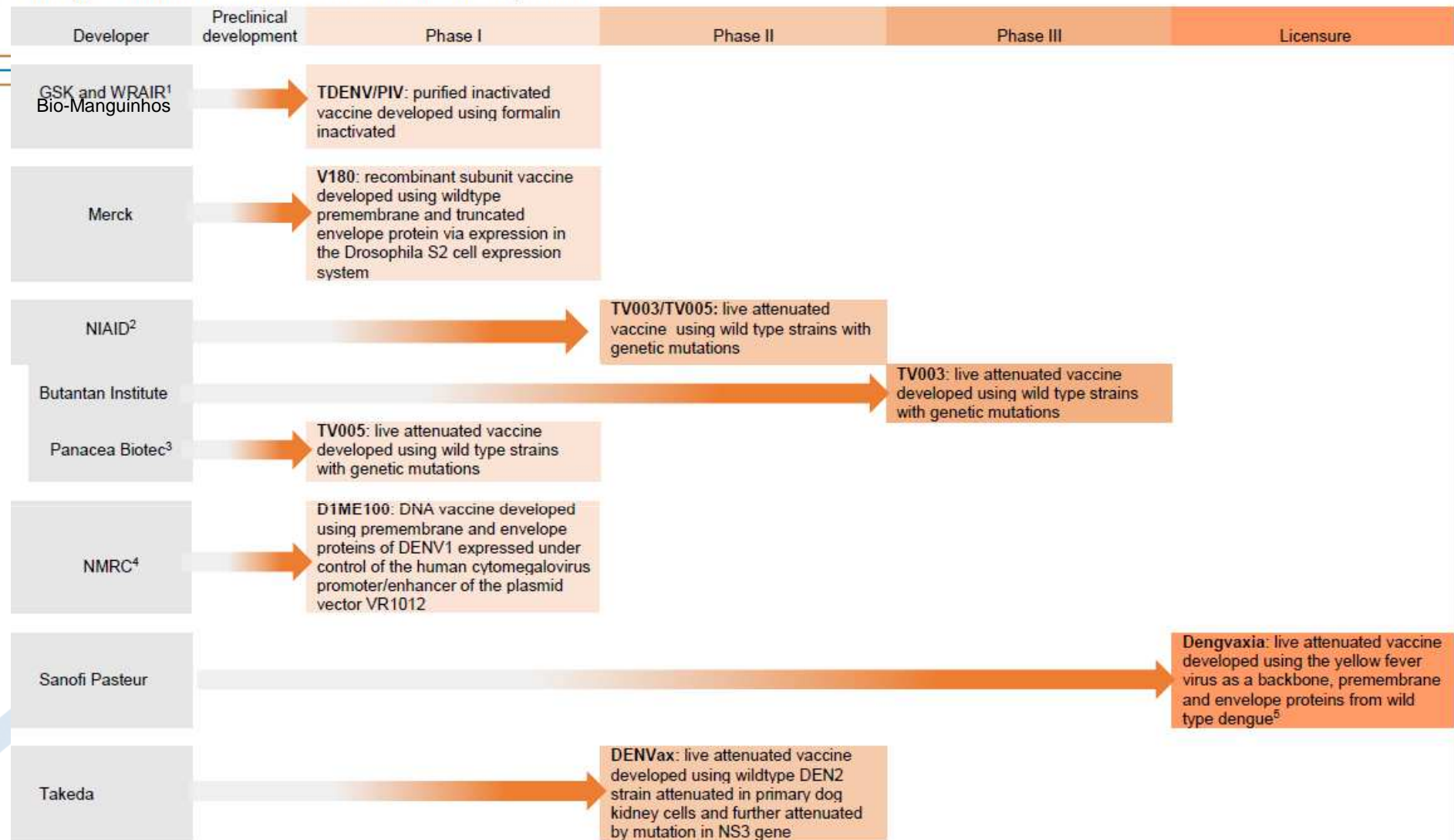


Flavivirus Vaccines



Disease	Vaccine type	Strain	Substrate	Adjuvant	Immunization schedule	Manufacturer(s)	Status
YFV	Live attenuated vaccine	17DD and 17D-204	SPF embryonated chicken eggs	no	One dose, 10 years	Brazil (Bio-Manguinhos/Fiocruz); France (Sanofi Pasteur); Senegal (The Institute Pasteur in Dakar); Russia (Chumakov Institute of Poliomyelitis and Viral Encephalitis)	Licensed in 1937
	Inactivated (β -propiolactone) vaccine	17D-204	Vero cell (bioreactors)	Alum	Two doses, 4wks apart	Xcellerex/GE HealthCare (US)	Phase 1
JEV	Inactivated (formalin) vaccine	Nakayama Beijing-1 (P1)	Mouse brain	no	Two doses, 4wks apart	Green Cross (South Korea), Central Research Institute (India), Adimmune corp (Taiwan), Government Pharmaceutical Organization (Thailand), Vabiotech (Vietnam)	Licensed in 1930
	Inactivated (formalin) vaccine	Beijing-1 (P3)	Primary hamster kidney cell (PHK)	no	Two doses, 1wk apart	Beijing, Shanghai, Wuhan and Changchun Institute of Biological Products (China)	Licensed in 1968
	Live attenuated vaccine	SA14-14-2	Primary hamster kidney cell (PHK)	no	One dose Booster 7 yrs	Chengdu Institute of Biological Product (China)	Licensed since 1988
	Inactivated (formalin) vaccine	SA14-14-2	Vero cell	Alum	Two doses, 4wks apart	Valneva SE (France) Biological E (India)	Licensed since 2009 WHO prequalified
	Inactivated (formalin) vaccine	Beijing-1	Vero cell	Alum	Two doses, 4wks apart	Biken (Japan)	Licensed in Japan since 2009
	Live-attenuated chimeric vaccine	SA14-14-2 prM/E genes replaced YFV-17D genes	Vero cell	no	Single dose Booster dose have not yet been determined	Sanofi Pasteur (France)	Licensed in Australia and Thailand since 2010
TBE	Inactivated (formalin) vaccine	Neudorf (TBEV-Eu)	Primary chicken embryo cell (PCEC)	Alum	Three doses	Baxter AG, Austria	Licensed since 1976
	Inactivated (formalin) vaccine	Sofjin (TBEV-Fe)	Primary chicken embryo cell (PCEC)	Alum	Three doses	Chumakov Institute of Poliomyelitis and Viral Encephalitis, Russia	Licensed since 1982
	Inactivated (formalin) vaccine	German K23 (TBEV-Eu)	Primary chicken embryo cell (PCEC)	Alum	Three doses	Novartis, Switzerland	Licensed since 1991
	Inactivated (formalin) vaccine	205 (TBEV-Fe)	Primary chicken embryo cell (PCEC)	Alum	Three doses	Microgen, Russia	Licensed since 2001
DENV	Live-attenuated chimeric vaccine	DENV 1, 2, 3 and 4 prM/E genes replaced YFV-17D genes	Vero cell	no	Three doses six months apart	Sanofi Pasteur	Licensed since 2015

Dengue Vaccine Candidates in Clinical Development*



*Table last updated January 4, 2016

¹ GlaxoSmithKline and Walter Reed Army Institute Research.

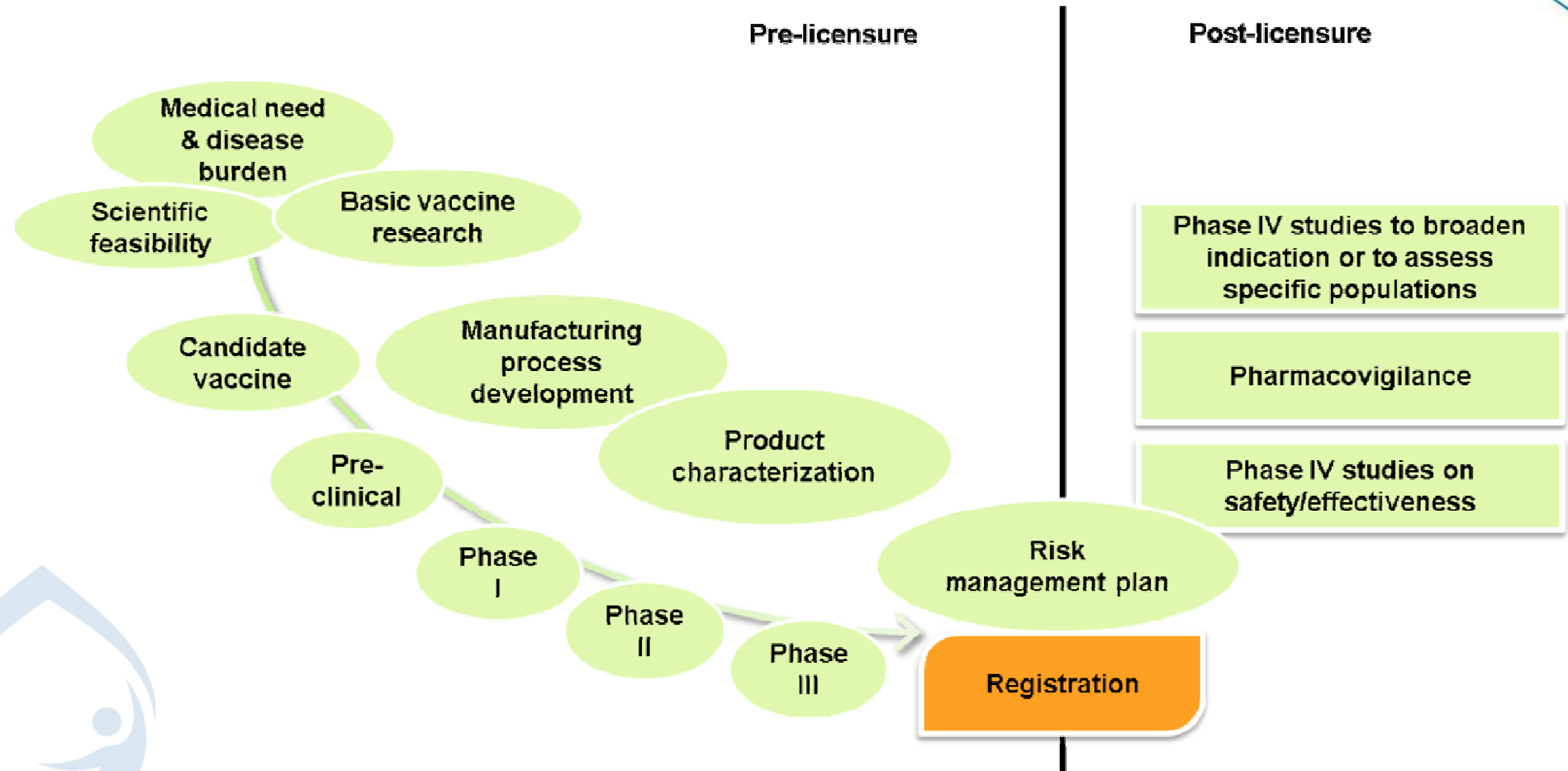
² National Institute of Allergy and Infectious Diseases, US NIH: National Institutes of Health. NIAID licensed its strains to several [developing country manufacturers](#) on a non-exclusive basis.

³ Both Butantan Institute and Panacea Biotech use NIAID vaccine formulation.

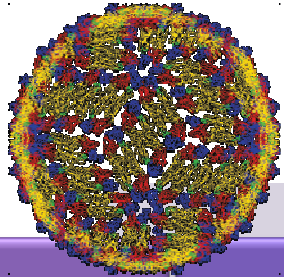
⁴ US Navy Medical Research and Development.

⁵ Dengvaxia has been approved by Mexico, the Philippines and Brazil for 9 to 45 year olds living in dengue endemic areas.

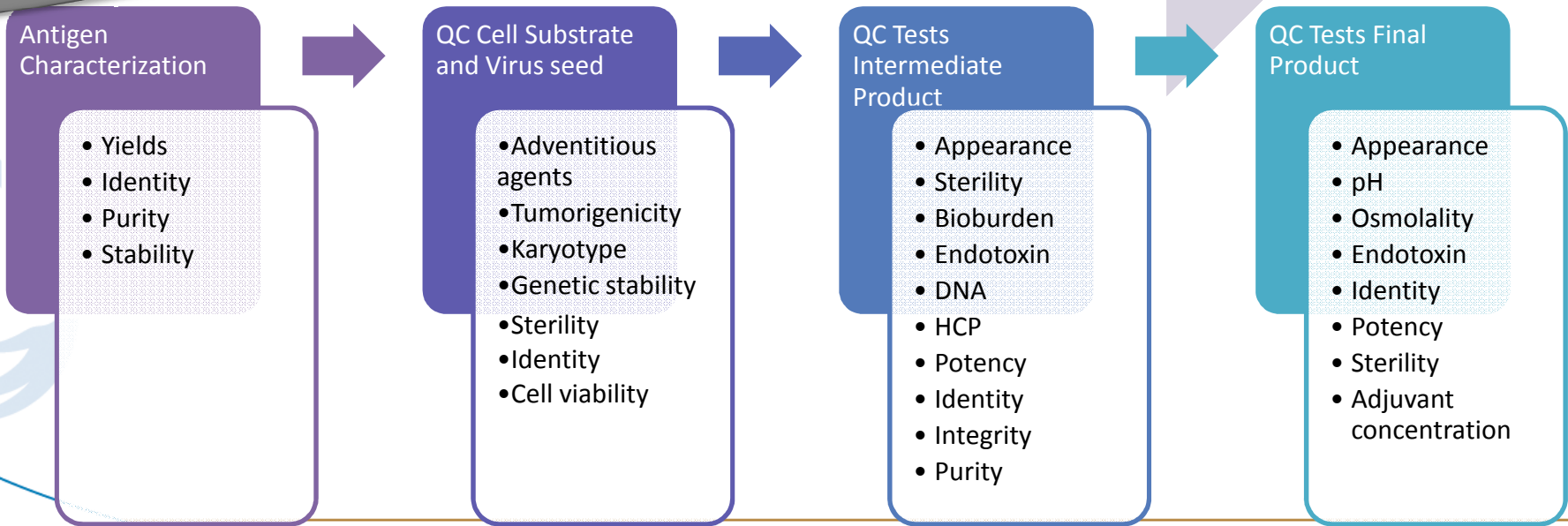
Vaccine development activities



Manufacturing Process Development



Quality Control



Antigen Characterization

- Yields
- Identity
- Purity
- Stability

QC Cell Substrate and Virus seed

- Adventitious agents
- Tumorigenicity
- Karyotype
- Genetic stability
- Sterility
- Identity
- Cell viability

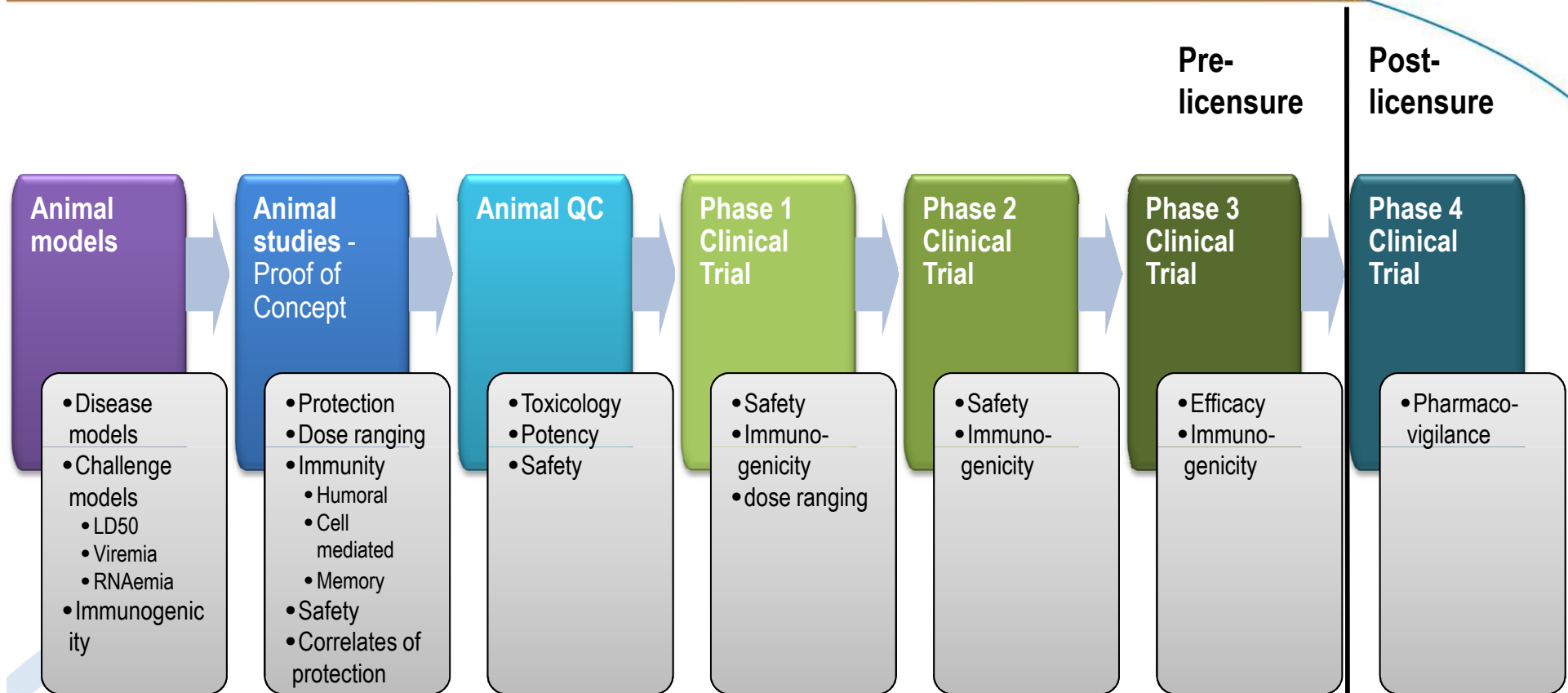
QC Tests Intermediate Product

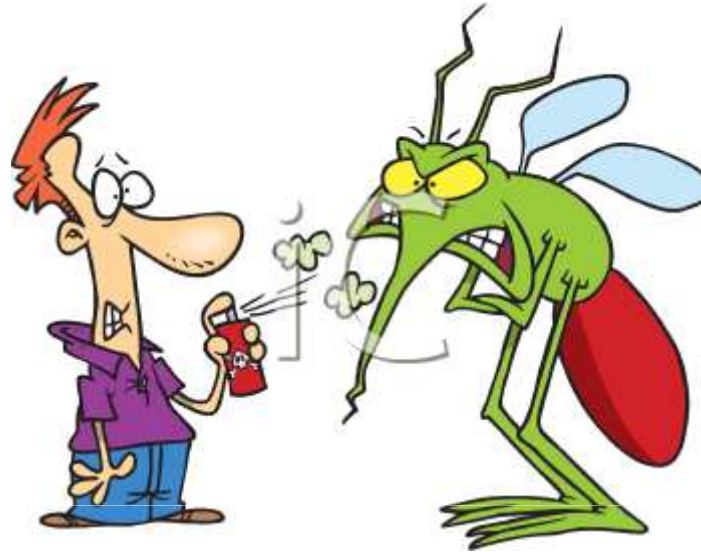
- Appearance
- Sterility
- Bioburden
- Endotoxin
- DNA
- HCP
- Potency
- Identity
- Integrity
- Purity

QC Tests Final Product

- Appearance
- pH
- Osmolality
- Endotoxin
- Identity
- Potency
- Sterility
- Adjuvant concentration

Pre-Clinical and Clinical Phases





Use insect repellents!
Thank you!

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