

Dengue Vaccines: current status of development

ISID-NTD 2011 International Meeting, Boston

Satellite Symposium on Dengue Control, 10 July 2011

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WHO/IVB/IVR



Presentation Outline

- Summary of dengue candidate vaccines in development
- Update on the status of development and some of the characteristics of the Live attenuated tetravalent, ChimeraVax
- Some challenges to the future use of the tetravalent live attenuated vaccines
- Looking ahead-what WHO is doing to prepare for the introduction of dengue vaccine



"We can make this the decade in which we take full advantage of the technology of vaccines. By doing that, we will build an entirely new future based on the understanding that global health is the cornerstone of global prosperity"



Challenges to the development of dengue vaccines

- No animal model that reproduces human disease
- There is no known true correlate of protection
 - Neutralizing antibody appears to be an indicator of protection, however-
 - Absolute titer for protection is not known, and titer can vary between strains within a serotype and between serotypes
- The need for developing balanced immune response by the four serotypes whereby a protective immune response is induced against all four viruses simultaneously



Challenges to the development of dengue vaccines

- Life-long homotypic immunity but only short-term cross-protective immunity
- Immune enhancement, including antibody dependent enhancement
- Possibility of viral interference with a tetravalent vaccine (live)



Vaccine candidates in early clinical stage of development

Approach	Developer	DENV antigens	Status
Live attenuated, recombinant YF17D/DEN chimeric	Sanofi Pasteur	prM/E	Phase 3 tetravalent
Live attenuated	GSK/WRAIR	all DENV antigens	Phase 2 tetravalent
Live attenuated, recombinant mutations, DEN/DEN chimeric	NIH	all DENV antigens (DENV2 prM/E)	Phase 1 tetravalent
Live attenuated, recombinant DEN/DEN chimeric	CDC/Inviragen	all DENV antigens (DENV1,3,4 prM/E)	Phase 1 tetravalent
DNA	NMRC/WRAIR	prM/E	Phase 1 monovalent
Recombinant subunit	Merck	80% of E	Phase 1 monovalent

Candidate vaccines in preclinical stage of development

Approach	Developers	DENV antigens
Rec. subunit	ICGEB, IPK, VaxInnate	EDIII
DNA	CDC, Inovio, Kobe University, NMRC	EDIII or prM/E
VLP	Cytos, ICGEB, Kobe University	EDIII or prM/E
Virus-vectored	GenPhar (AV), Themis (MV), UNC (VEE), UTMB (WNV)	EDIII or prM/E
PIV	GSK/WRAIR/Fiocruz	all DENV antigens
LAV	Fiocruz Mahidol University/Chiang Mai University/BioNet-Asia	prM/E all DENV antigens

Dengue vaccine candidate in advanced clinical development stage

- The Sanofi Pasteur's tetravalent live attenuated candidate vaccine has advanced to Phase III clinical trial
- It is a YF-Dengue chimera based on the 17D Yellow Fever backbone wherein the *prM* and E genes are replaced by genes from each dengue serotypes and cultured on Vero cells and formulated as tetravalent ChimeriVax™ vaccine



Vaccine characteristics of ChimeriVax

- Live attenuated virus, tetravalent (4 vaccine strains cultured in serum free Vero cells)
- Injectable supplied as powder with solvent for suspension, dose 0.5 ml, to be administered Sub-cutaneous
- Recommended Schedule: 3 injections, 0 - 6 - 12 months
- Storage: +5°C
- Recommended for
 - Children aged 9 months & above (eventually),
 - Adults living in endemic areas, and those traveling to endemic areas

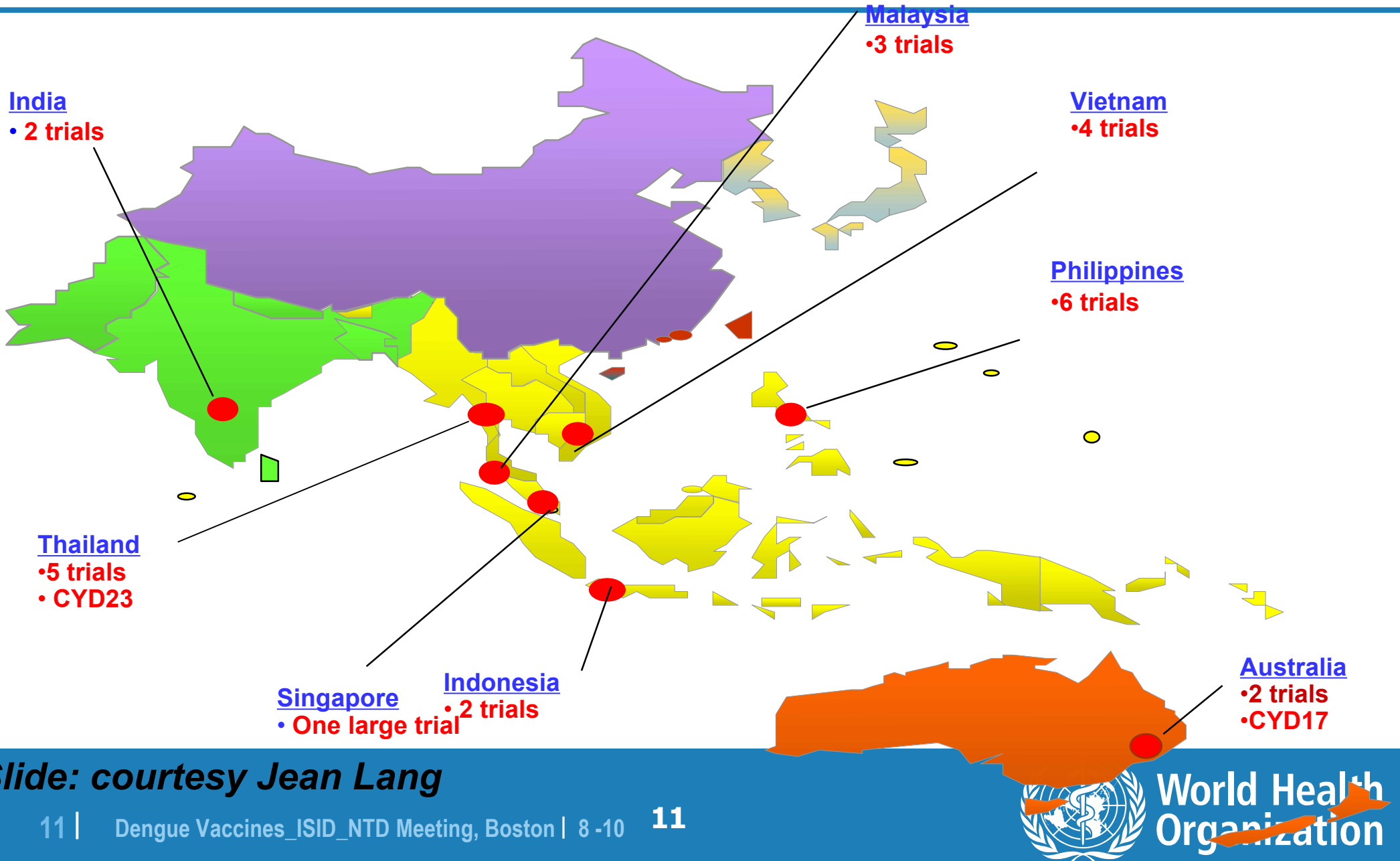
Dengue Phase I-III Clinical trials LatAm 2004-2014



Slide: courtesy Jean Lang



Dengue Phase I-III Clinical trials As Pac 2004-2014

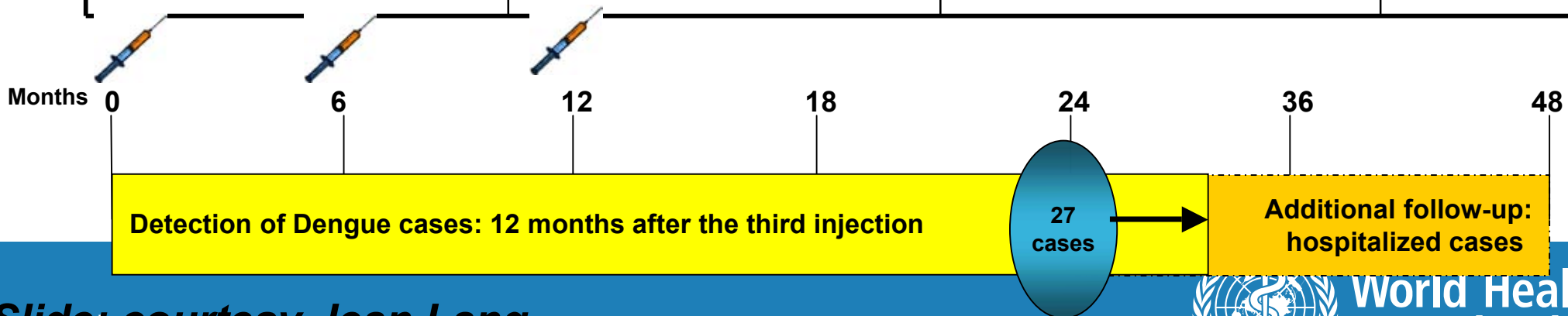


Slide: courtesy Jean Lang

CYD23 : First worldwide GCP efficacy trial in 4-11 yrs Thai Children

- Ratchaburi, Thailand, 3 sub-cutaneous injections at 0-6-12 month, Sample size: Based on 70% efficacy, lower bound of 0% (TBC) and attack rate of 1.3% , 57 schools, 28 vaccination sites
 - Primary endpoint
 - To assess the efficacy of dengue vaccine after three injections in preventing symptomatic, virologically* confirmed dengue cases, regardless of the severity, due to any of the four serotypes
 - Third vaccination completed February 2011
 - Estimate for efficacy results on 27 cases post dose 3 : Q4 2012
 - Subsets: immunogenicity n=300; viraemia n=100; reactogenicity n=1050
 - Laboratory confirmation of dengue will be performed in all febrile illness that requires hospitalisation for 3 years after completion of vaccination
- April 2011 : IDMC no evidence to suggest a safety concern with the vaccine

Population	Group 1 (Dengue Vaccine)	Group 2 (Control/placebo)	TOTAL
Children (4-11 years)	2668	1334	4002



Slide courtesy Jean Lang

Dengue Vaccines, ICD, NTD Meeting, Boston | 8-10

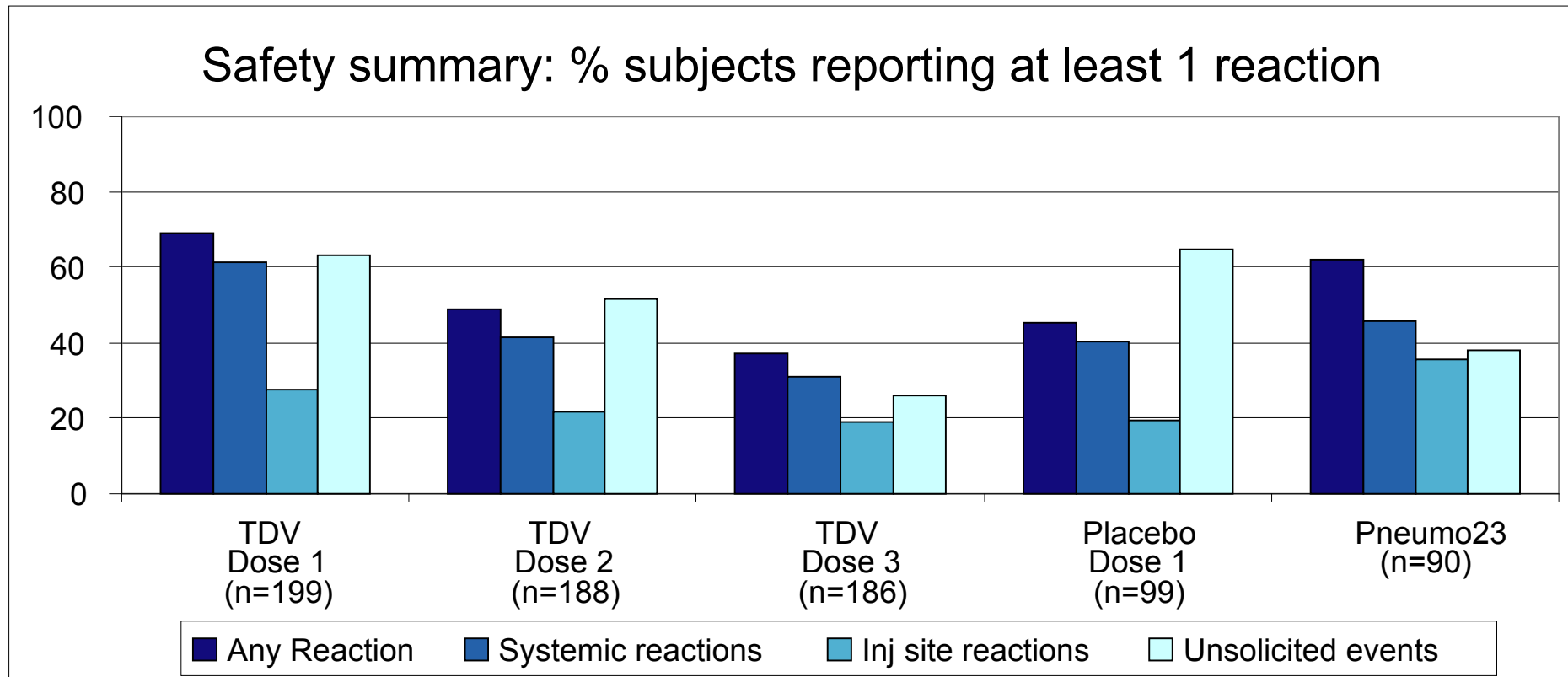
Challenges to the use of the live attenuated dengue vaccine...1/

● Safety

- Because of the theoretical risk of developing more severe disease upon subsequent infection by a wild type dengue virus, at least the early adopting countries will need a long term surveillance and risk assessment mechanisms in place
- Is there any possibility of return to virulence?
- Can the vaccine strains be transmitted to other people through mosquitoes?
- AEFI



Phase II Representative Safety overview following the vaccination 2-11 years Latin american subjects (YFV >0)



- Similar safety profile after the first vaccination (TDV dose 1 versus placebo dose 1)
- Trend for a decrease of systemic reactogenicity after TDV doses 2 and 3
- Pneumo23 licensed vaccine more reactogenic than TDV dose 3

Slide: courtesy Jean Lang



Challenges to the use of the live attenuated dengue vaccine...2/

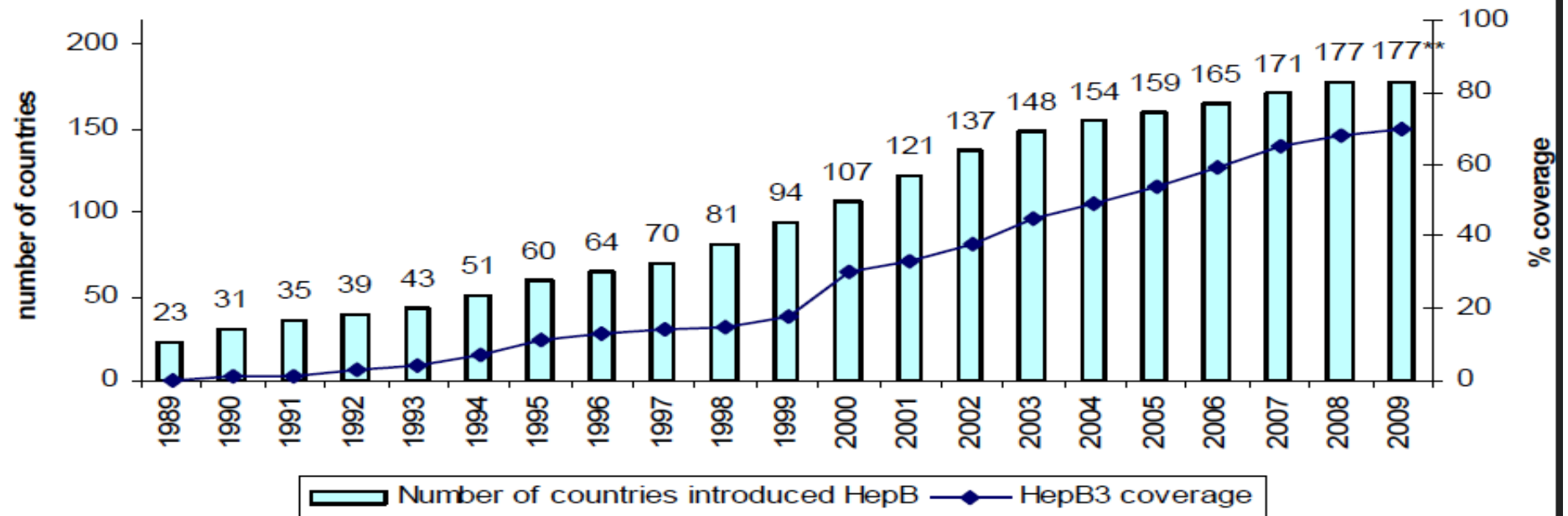
● Affordability

- Price is an important driver of uptake
- Dengue is a disease most common in low to low-middle income countries. Ability of governments in these countries to fund a full dengue immunization programme may be challenging
- However, low price of a vaccine does not guarantee rapid uptake



A low price does not necessarily guarantee rapid uptake of a vaccine

Number of countries that introduced HepB, 2009



Year of introduction can be the year of partial introduction

** Includes India and Sudan with partial introduction

excluding 3 countries where HepB administered for adolescents

Source: WHO/UNICEF coverage estimates 1980-2009, July 2010 and IVB Database, 193 WHO Member States.

Date of slide: 26 July 2010



World Health Organization



World Health Organization

Challenges to the use of the live attenuated dengue vaccine...3/

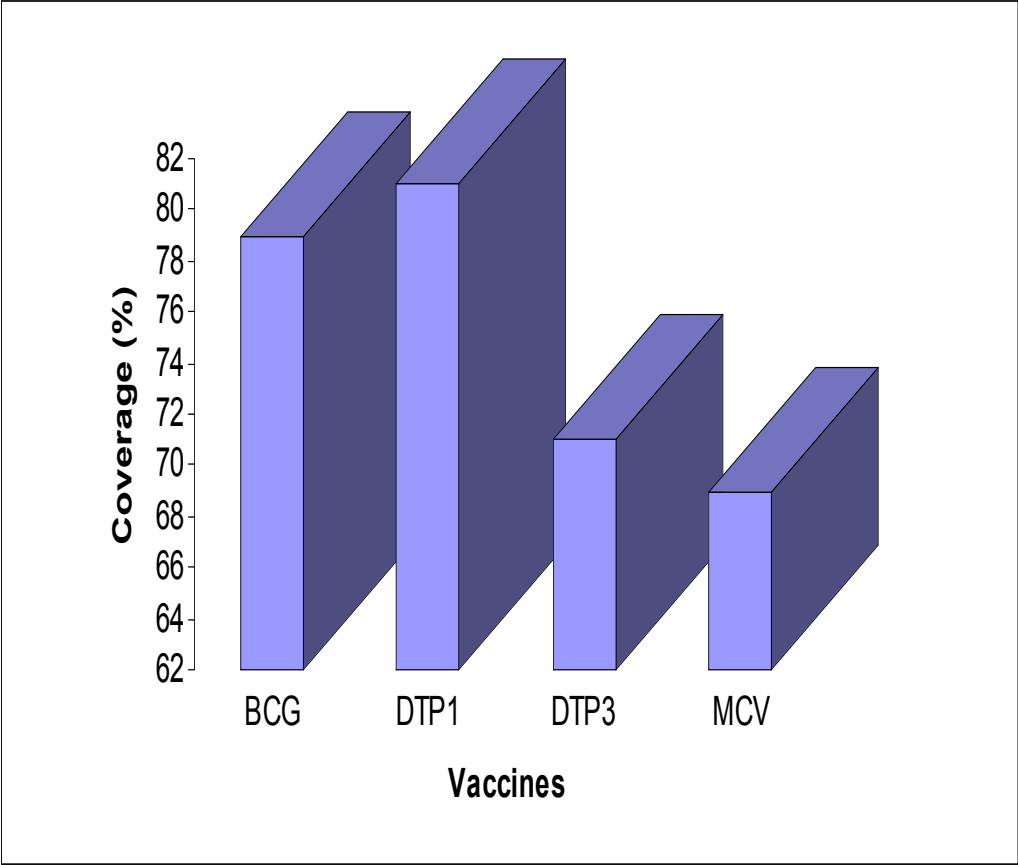
- Achieving high coverage

- Despite the billions spent in the last one decade on immunization, there are still more than 22 million children who do not even get the basic vaccines through routine programme
- The longer the interval between doses, the higher the chances of greater drop-outs between doses

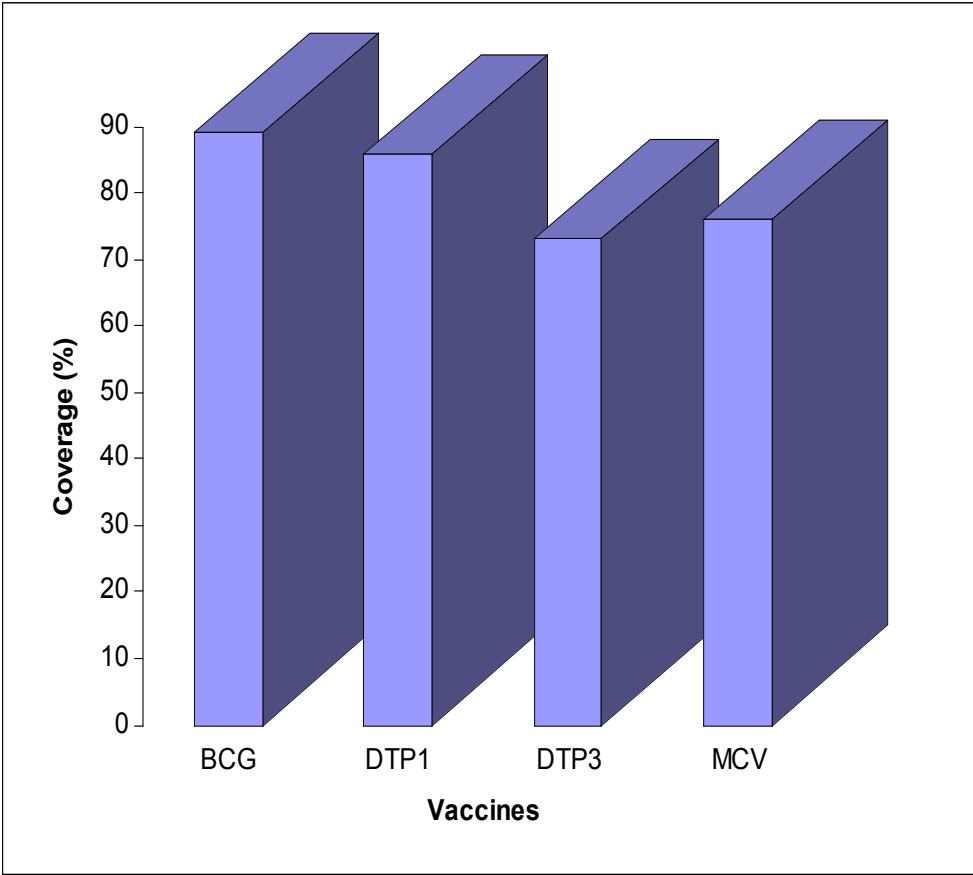


Interval between doses and Impact on coverage

Africa Region, 2009



South-East Asia Region, 2009



Source: WHO



Looking ahead- what WHO is doing to prepare countries for dengue vaccine introduction

- As part of the Dengue Vaccine Initiative Consortium, WHO is already working on the following:
 - Developing the policy process for dengue vaccine recommendations by SAGE
 - Dengue immunization and the impact of different strategies on the disease epidemiology
 - Dengue vaccine introduction guidelines
 - Update of written standards TRS 932, ready for submission to the Expert Committee on Biological Standardization (ECBS)
 - Framework for safety evaluation proposed in clinical evaluation guidelines
 - Supporting countries to strengthen their regulatory capacity



In Conclusion..

- Sanofi's efforts are commended and exciting for the dengue world
- But to meet the global demand and to enhance access to affordable vaccines, we need several other vaccines/ vaccine manufacturers,
- Particularly vaccine manufacturers in developing countries are needed,
 - NIH vaccine candidate Licensed to developing country manufacturers for further development
 - Butantan (Brazil)
 - Biological E (India)
 - Panacea (India)
 - VaBiotech (Viet Nam)
- CDC (Inviragen) candidate in contract manufacturing agreement with Shantha Biotec but ???



THANK YOU



ChimeriVax™

Yellow fever 17D genome cloned as cDNA

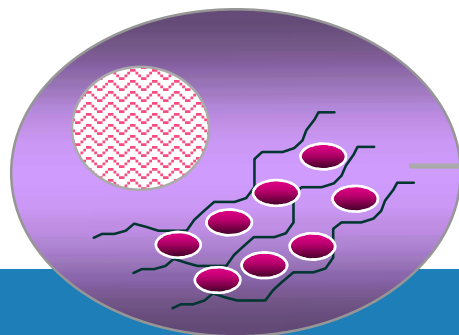


Chimeric cDNA → transcribe to RNA



Envelope is heterologous virus containing immunizing antigens

Transfect mRNA



Grow virus in cell culture



RNA replicative 'engine' is YF 17D