Can Partially Effective Vaccines be Safely Used to Prevent and Control Dengue?

Duane J Gubler, ScD, FAAAS, FIDSA
Professor and Founding Director
Signature Research Program in Emerging Infectious Diseases,
Duke-NUS Graduate Medical School, Singapore, and
Chairman, Partnership for Dengue Control

Public Health Impact of Vaccines, Annecy, France, 22-24 June, 2015

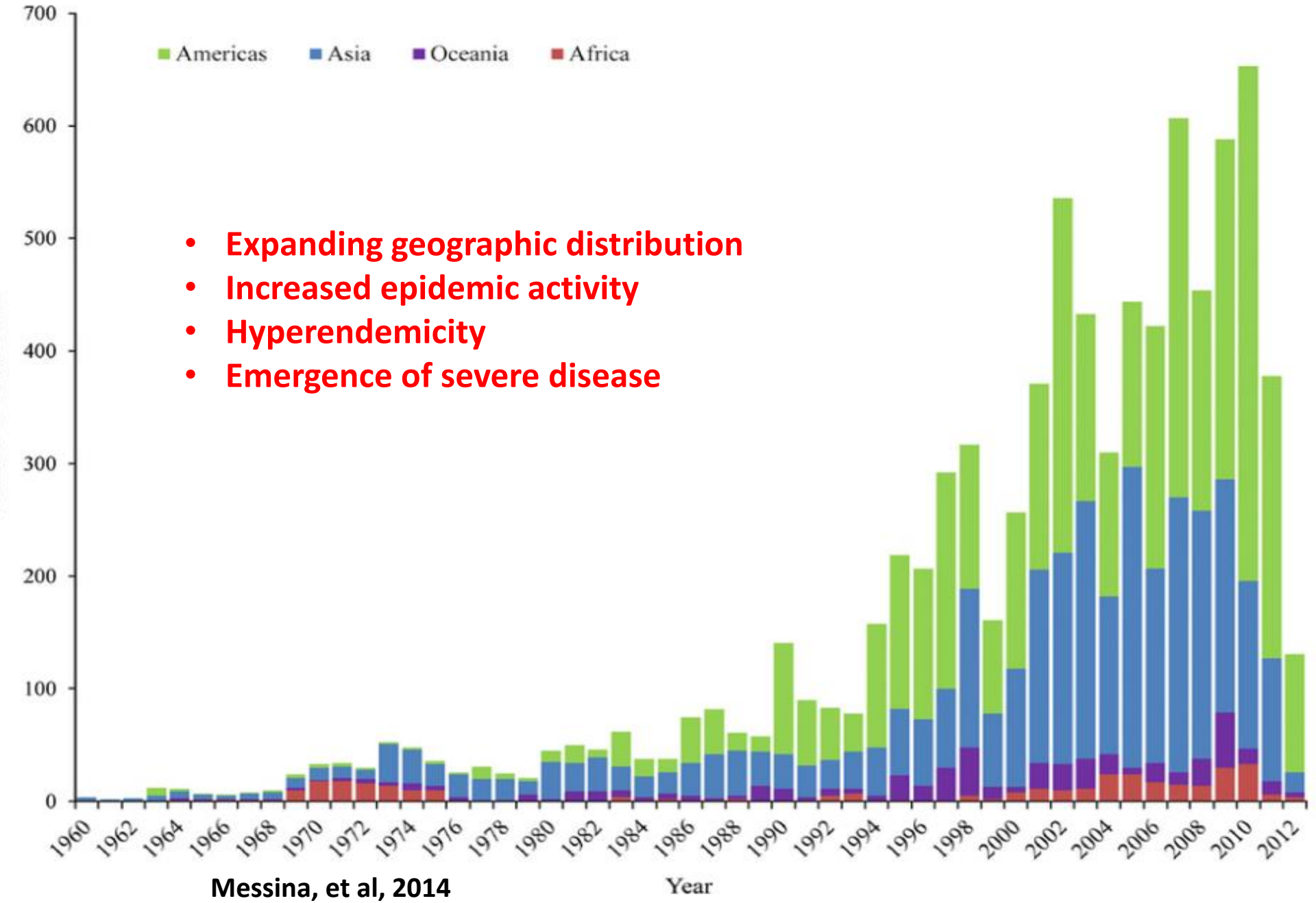
Disclosure

Provided consultation and advice on dengue to:

Sanofi Pasteur
Takeda
Inviragen
NIH
Merck
GSK
Globavir
Novartis
Hawaii Biotech

Patent holder of Takeda vaccine
Investor in Takeda Pharmaceuticals

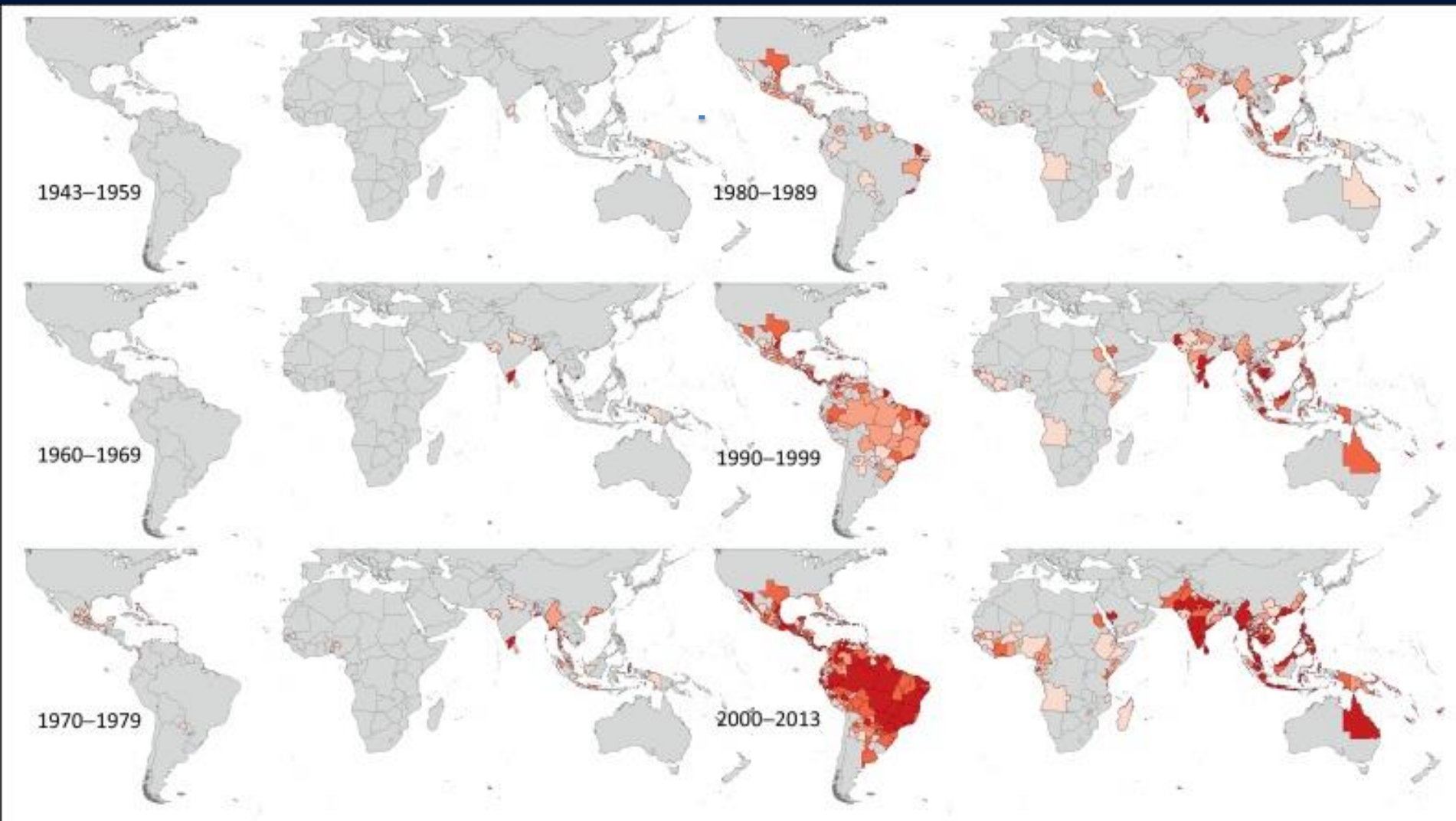
The Changing Epidemiology of Dengue



- Expanding geographic distribution
- Increased epidemic activity
- Hyperendemicity
- Emergence of severe disease

Messina, et al, 2014

Global Spread of Dengue Viruses



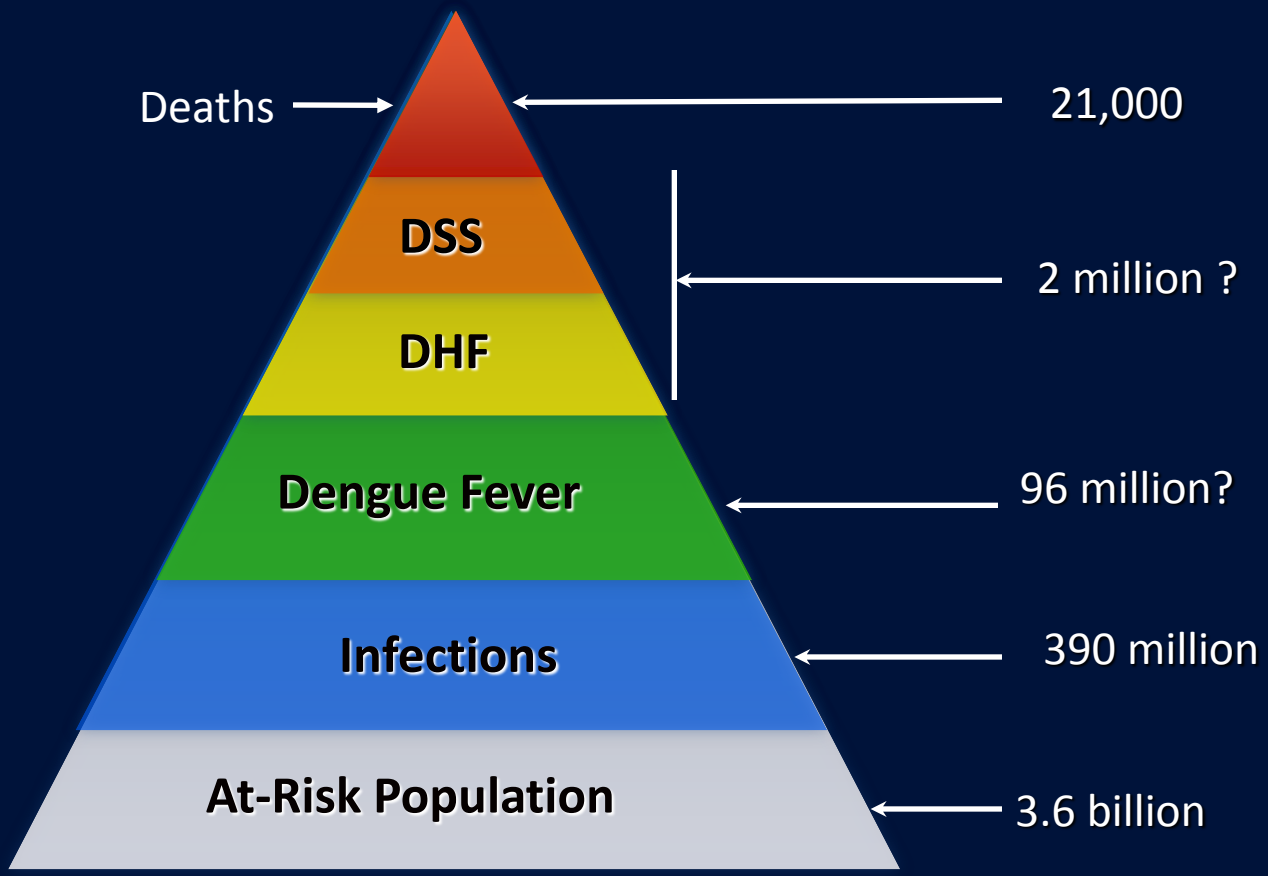
Messina, et al, 2014

Why have we seen such a dramatic increase in epidemic Dengue Hemorrhagic Fever?

Major Drivers

- Demographic Changes (Pop Growth)
- Environmental Change
  - Urbanization
  - Changing lifestyles
- Modern Transportation (Globalization)
  - Increased Movement of People, Animals, Commodities and pathogens
- Lack of Effective Mosquito Control

New dengue Disease Burden estimates



Beatty ME, Letson GW, Margolis HS.,
Phuket, Thailand October 17-19, 2008; Bhatt, et al, 2013.

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

What can we do to prevent Epidemic Dengue?

Mosquito Control

Efforts to prevent the spread of dengue viruses and control the disease in the past 40 years, have failed!

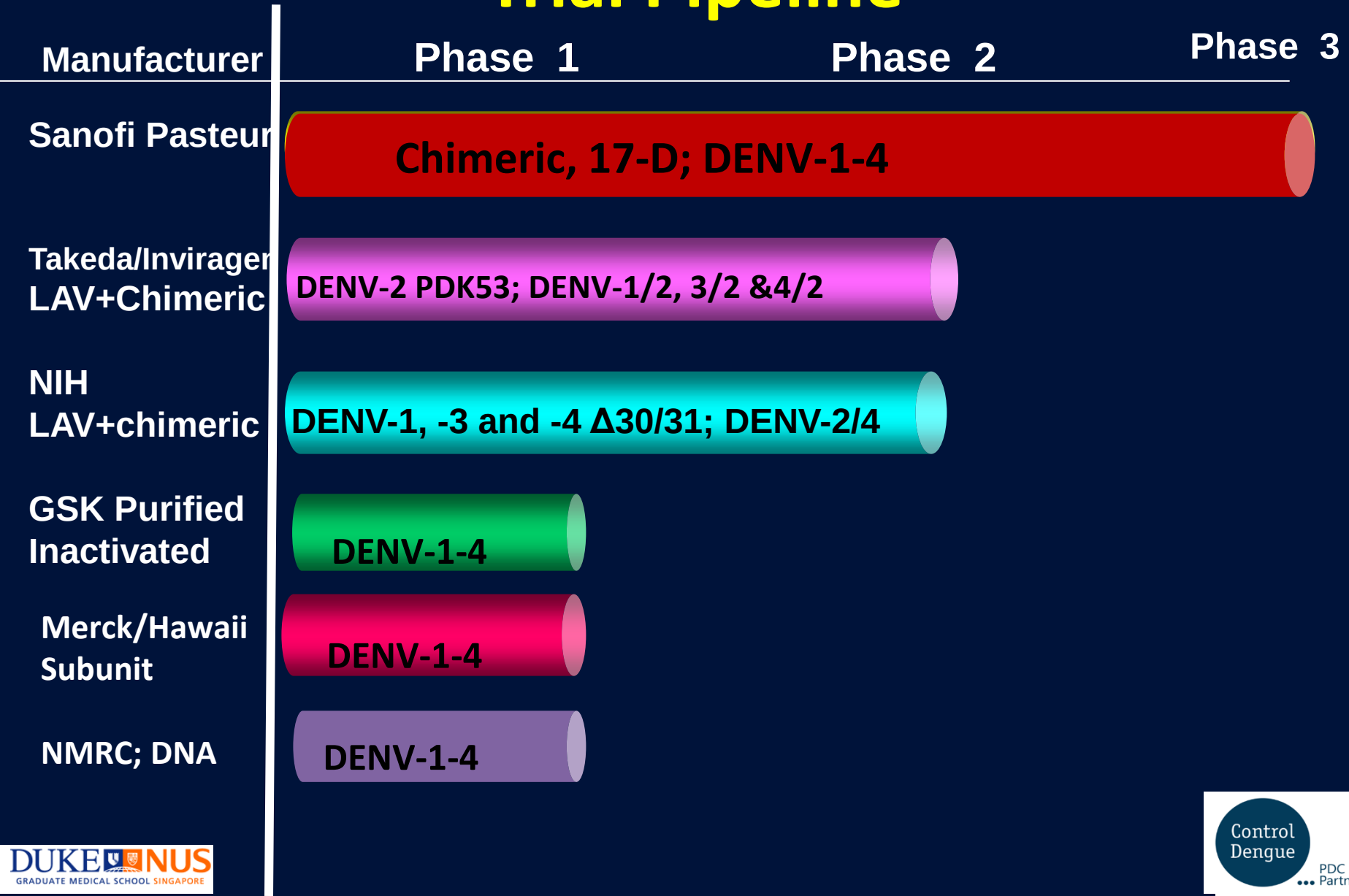
Promising New Tools in *Dengue* Control Pipeline

- Mosquito control
- Antiviral therapeutics
- Vaccines

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Tetravalent Dengue Vaccines in Clinical Trial Pipeline



DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Control Dengue PDC Partnership

Live attenuated dengue vaccines

	Sanofi-Pasteur	Takeda	NIH
Doses	3	2	1
Potency	5, 5, 5, 5	4, 4, 4, 5	3, 4, 3, 3
% tetravalent response (naïve subjects & SQ dosing)	78%*	100%**	90%
T-cell epitopes	YFV	DENV-2	DENV-1, -3, -4
Clinical phase	3	2	2
Overall efficacy	56% – 61%	?	?

* Villar, *et al*. 2011. *Ped. Inf. Dis. J.* Oct 2013.

** Takeda, internal data

Courtesy Steve Whitehead; modified

Uncertain whether any of the lead live attenuated candidate vaccines will provide balanced tetravalent protection

Question?

Can we use partially effective dengue vaccines to help control dengue in endemic countries?

Or do we continue to wait for the perfect tetravalent vaccine, which may never become reality?

Attributes of the Sanofi Vaccine

- Variable efficacy against four serotypes
- Overall efficacy of 56-61%
- Increased efficacy in people with prior dengue infection
- High efficacy in protecting against DHF
- Good efficacy in decreasing hospitalization
- Safe

Assumption

Assume we use a vaccine with atributes similar to the Sanofi vaccine

What do We Know?

- High seroprevalence in endemic countries
- Most (all?) severe dengue disease occurs during the 1st and 2nd dengue infections*
- 3rd and 4th dengue infections are mild or asymptomatic*
- Risk of ADE relatively low

* Gibbons, et al **Am J Trop Med Hyg November 2007 77:910-913**

* Olkowski, et al, **J. Infect. Dis. 2013. 208: 1026-1033.**

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Rationale for Public Health use of Partially Effective Dengue Vaccines

- Majority of children in hyperendemic areas have already had at least one dengue infection
- Protected against 2 and possibly 3 serotypes
- Protected against severe dengue disease
- Decreased hospitalization
- Priming effect of previous dengue infection
- Trivalent, possibly bivalent vaccine may do job

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Limitations To This Rationale

- A paucity of research on 3rd & 4th infections
- Poor surveillance doesn't allow accurate distinction of infection sequence
- Uncertain that the vaccine viruses will perform as wild type viruses
- Uncertainty about the role of the virus strain
- Uncertainty about the role of temporal distribution of infections

Is a Tetravalent Dengue Vaccine Really Necessary?

Based on what we think we know about dengue infection and immunity, and depending on the endpoint we want, the answer is

NO!

However, there are many unanswered questions.

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

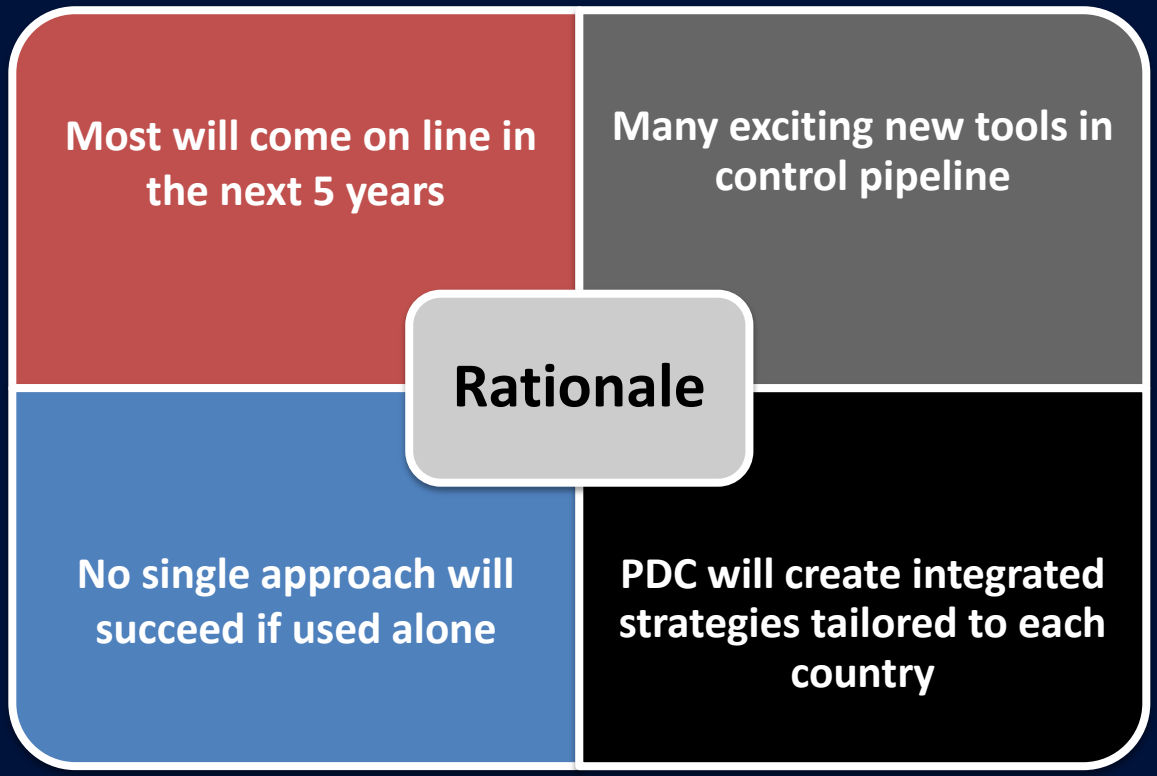
Dengue Prevention and Control Tools in the Pipeline

- New MosquitoTools being Developed
  - Residual insecticides
  - Genetic control
  - Biologic control
  - Other, eg, ITMs, traps, etc
- Therapeutic antibodies
- Antiviral drugs
- Vaccines
- Warning- no single panacea

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Partnership for Dengue Control (PDC)



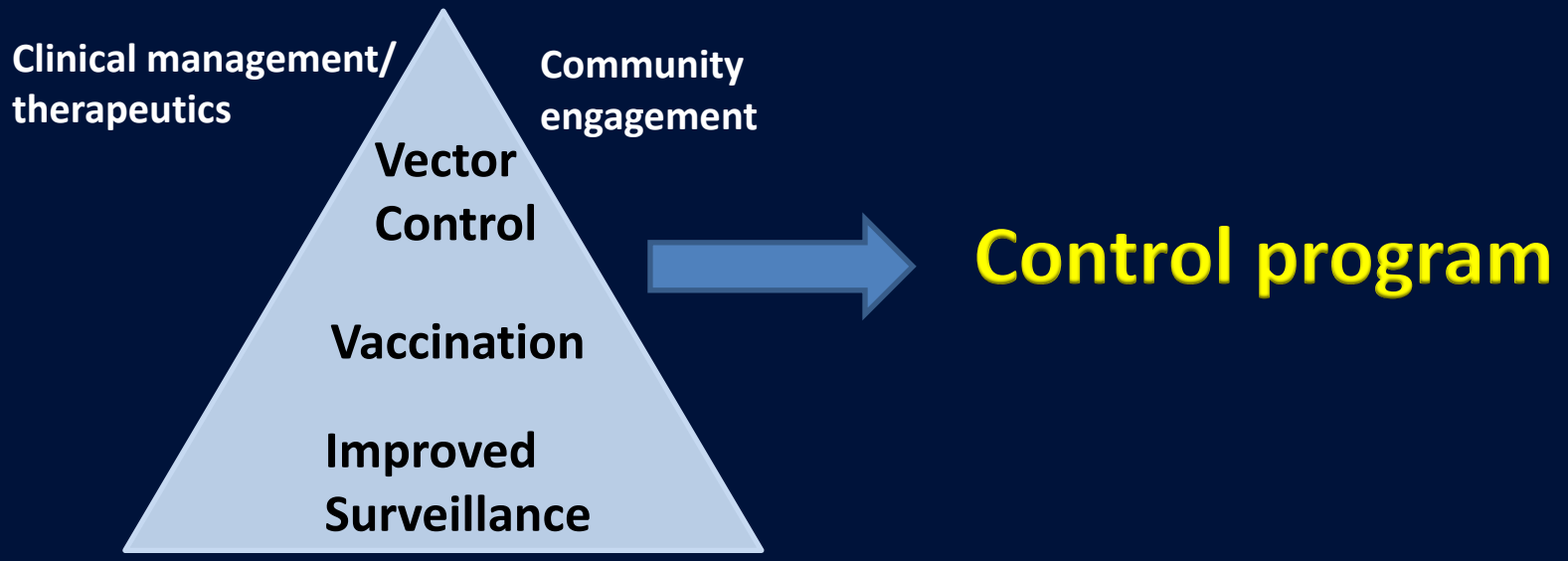
PDC was created in a consensus meeting in Annecy, France, July 2013, with the purpose of facilitating and synergizing dengue control efforts

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Entering a New Era that will Allow Us to Rollback Dengue Using New Tools in the Control Pipeline

Integration



International mobilization of resources

- Build public health capacity
- Fund program implementation
- Fund research

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Two Papers that have data on 3rd and 4th Dengue infections

Robert V. Gibbons, Siripen Kalanarooj, Richard G. Jarman, Ananda Nisalak, David W. Vaughn, Timothy P. Endy, Mammen P. Mammen, Jr, and Anon Srikiatkhachorn

Analysis of Repeat Hospital Admissions for Dengue to Estimate the Frequency of Third or Fourth Dengue Infections Resulting in Admissions and Dengue Hemorrhagic Fever, and Serotype Sequences

Am J Trop Med Hyg November 2007 77:910-913

Olkowski, S., B.M. Forshey, A.C. Morrison, C. Rocha, S. Vilcarromero, E.S. Halsey, T.J. Kochel, T.W. Scott, and S.T. Stoddard.

Reduced risk of disease during postsecondary dengue virus infections.

J. Infect. Dis. 2013. 208: 1026-1033.

Gibbons, et al, 2007

- Retrospective hospital admission study in Thailand specifically looking for DHF associated with 3rd and 4th dengue infections.
- Period covered: January 1994-Fedruary 2005
- **Conclusions:**

"Although no confirmed 3rd (or 4th) dengue admissions were found, our results suggest that 0.08% to 0.8% of dengue admissions may be caused by 3rd or 4th infections.

Control Dengue PDC Partnership

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

Olkowski, et al, 2013

- Two cohort studies in Peru covering all age groups from August 2006 to November, 2010.
- About 5000 people in two cohorts, visited 3 times per week to monitor febrile illness. Laboratory analysis included PRNT, Isolation and PCR. Two serotypes (DENV-3 and -4) transmitted during study period.
- No severe disease or patients hospitalized during study, but found that symptomatic disease in DENV-3 infections was reduced by 93% in 3rd and 4th infections compared to 1st and 2nd infections. For DENV-4, the reduction was 64%.
- **Conclusion: "Should a vaccine provide incomplete protection (ie, to only 2 or 3 serotypes)--- our analyses indicate that in a population where dengue is endemic, there may be a reduction in disease without a corresponding reduction in human infection and transmission to mosquitoes"**