NVAC and the Future of Vaccinology

Stanley A. Plotkin

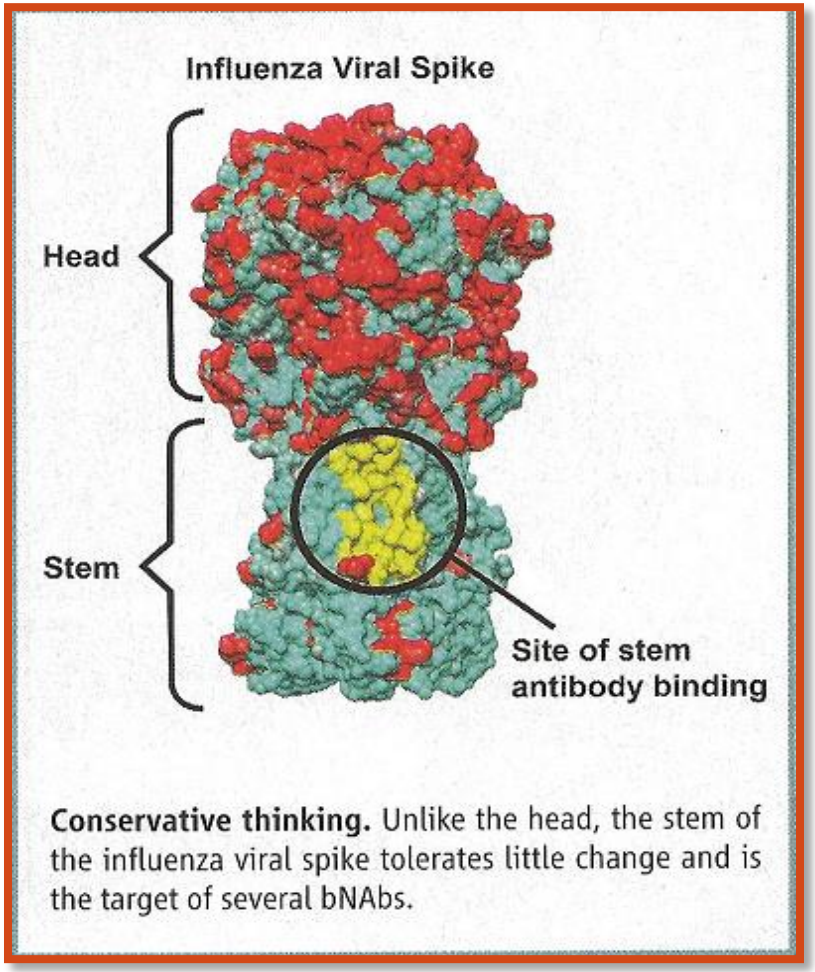
“The impact of vaccination on the health of the world’s peoples is hard to exaggerate. With the exception of safe water, no other modality has had such a major effect on mortality reduction and population growth.”

Susan and Stanley Plotkin,
in *Vaccines* 1st Edition, 1988

Influenza

Ways to Improve Efficacy of Influenza Vaccines

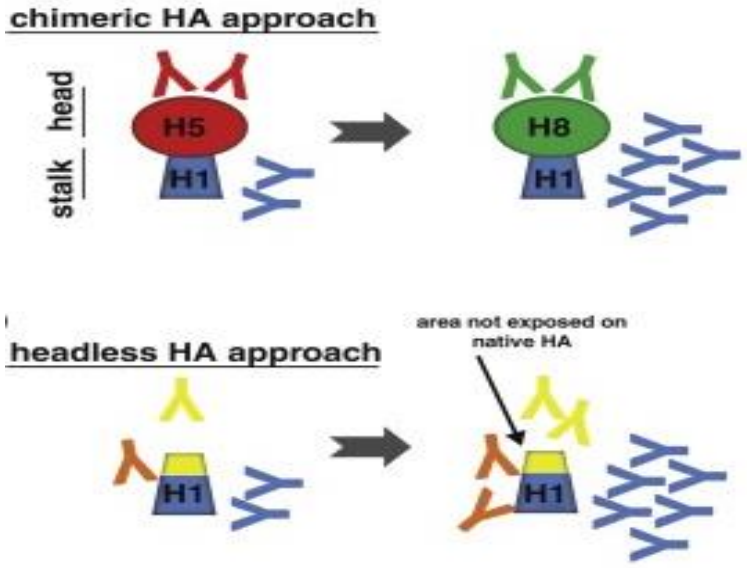
- Add second lineage of type B (done)
- High hemagglutin dose (done)
- Adjuvants such as MF-59 or AS01 or flagellin
- Add neuraminidase
- Add conserved epitopes NP, M2e, stalk HA
- Prime-boost (DNA, RNA, vector)
- Conserved stem antigen



Conservative thinking. Unlike the head, the stem of the influenza viral spike tolerates little change and is the target of several bNAbs.

Cohen J. Science 341:1171, 2013

Stalk-based Approaches



or prime-boost, peptides, VLPs

Short Effector Memory:

Pertussis

The Pertussis Problem

- Pertussis is serious in newborns, milder but common later in life.
- Replacement of WcP by AcP has eliminated serious reactions, but disease is resurgent in many countries because immunity wanes after AcP

Incidence of Pertussis in Wisconsin after TdaP

Years after TdaP	Vaccine Efficacy
1	75%
2	68%
3	35%
≥	12%

Koepke et al, JID 2014

Possible Improvements of Acellular Pertussis Vaccines

- Use newer circulating strains containing P3 + Ptx promoter
- Add stronger adjuvant to stimulate Th1/Th17 and Tfh cellular responses
- Use genetically or H_2O_2 detoxified PT
- Add other virulence factors:
  e.g. adenylate cyclase, tracheal cytotoxin, LPS
- DNA prime, AcP boost
- Live, attenuated *B. pertussis*

Obtaining the Right Functional Response:

HIV

Why was Thai Trial Successful?

- **Induced antibody-dependent cellular cytotoxic antibody against V1-V2 loop of IgG3 Isotype**

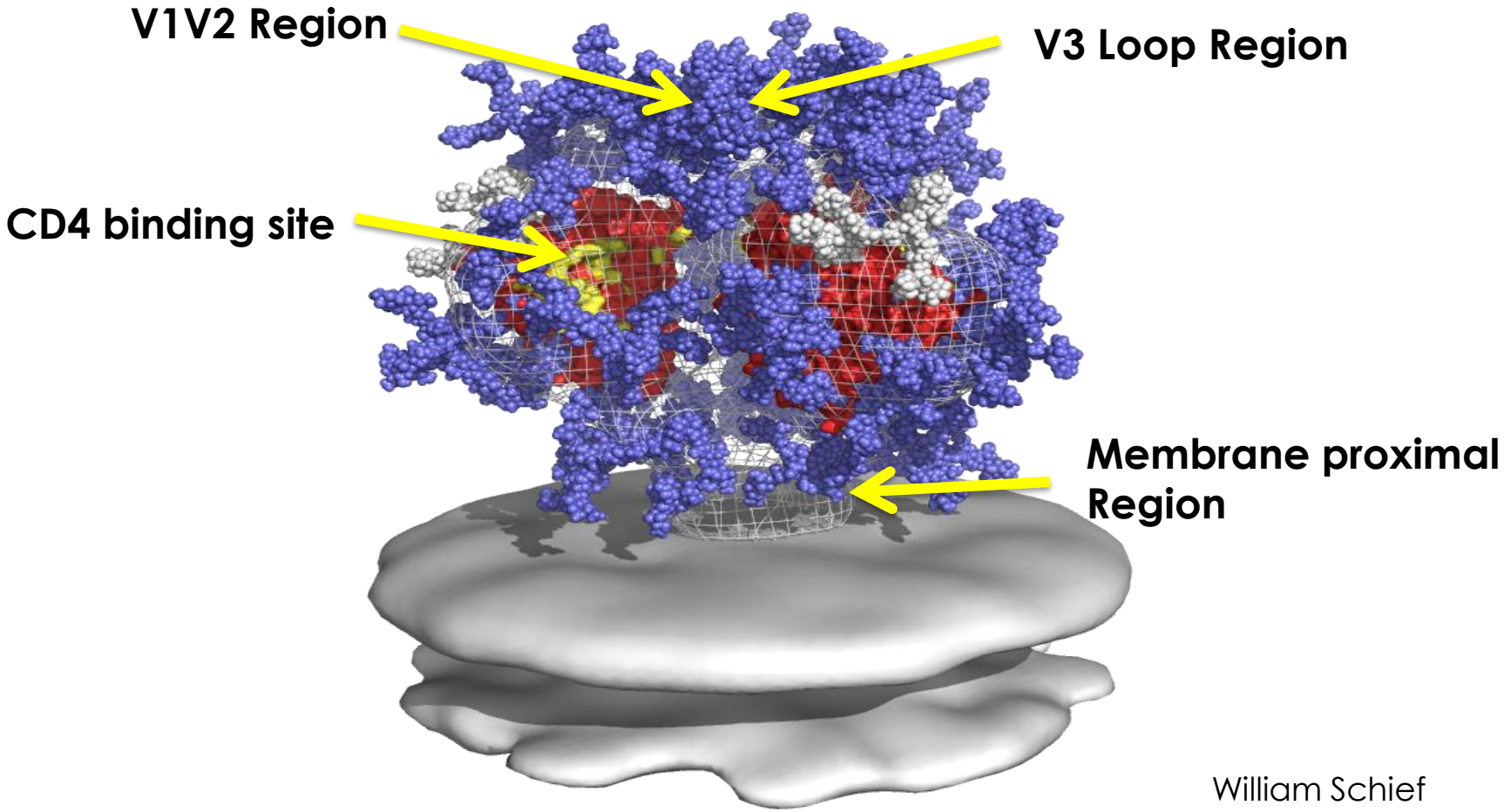
but

- **Efficacy was high early after vaccination and in low-risk groups, but faded with time.**

Importance of Non-Neutralizing Antibodies

- **Influenza – Infection induces ADCC antibodies, TIV does not. ADCC antibodies are strain cross-reactive.**
- **Other examples of important nNAb: Sindbis, Dengue, Rotavirus, LCMV**

Jegaskanda et al, J Virol 2013
Excler et al, ClinVacc Immunol 2014



William Schief

What is the Way Forward for an HIV Vaccine ?

- Induction of broadly neutralizing antibodies through envelope trimer structures
- Building on prime-boost ADCC induction with better vector/adjuvants
- Induction of effector CD8+ cells to kill first infected cells using CMV vectors

Population – Specific Challenges:

Rotavirus

Effect of Rotavirus Vaccination in the U.S.

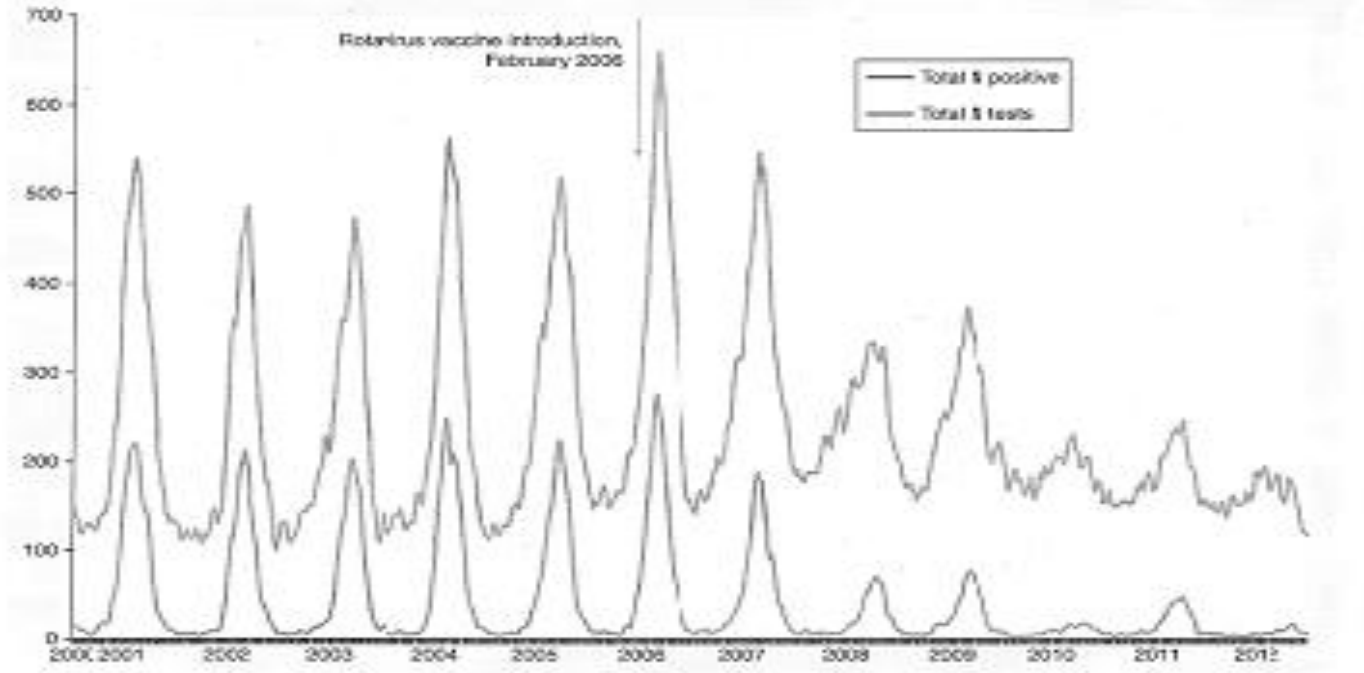
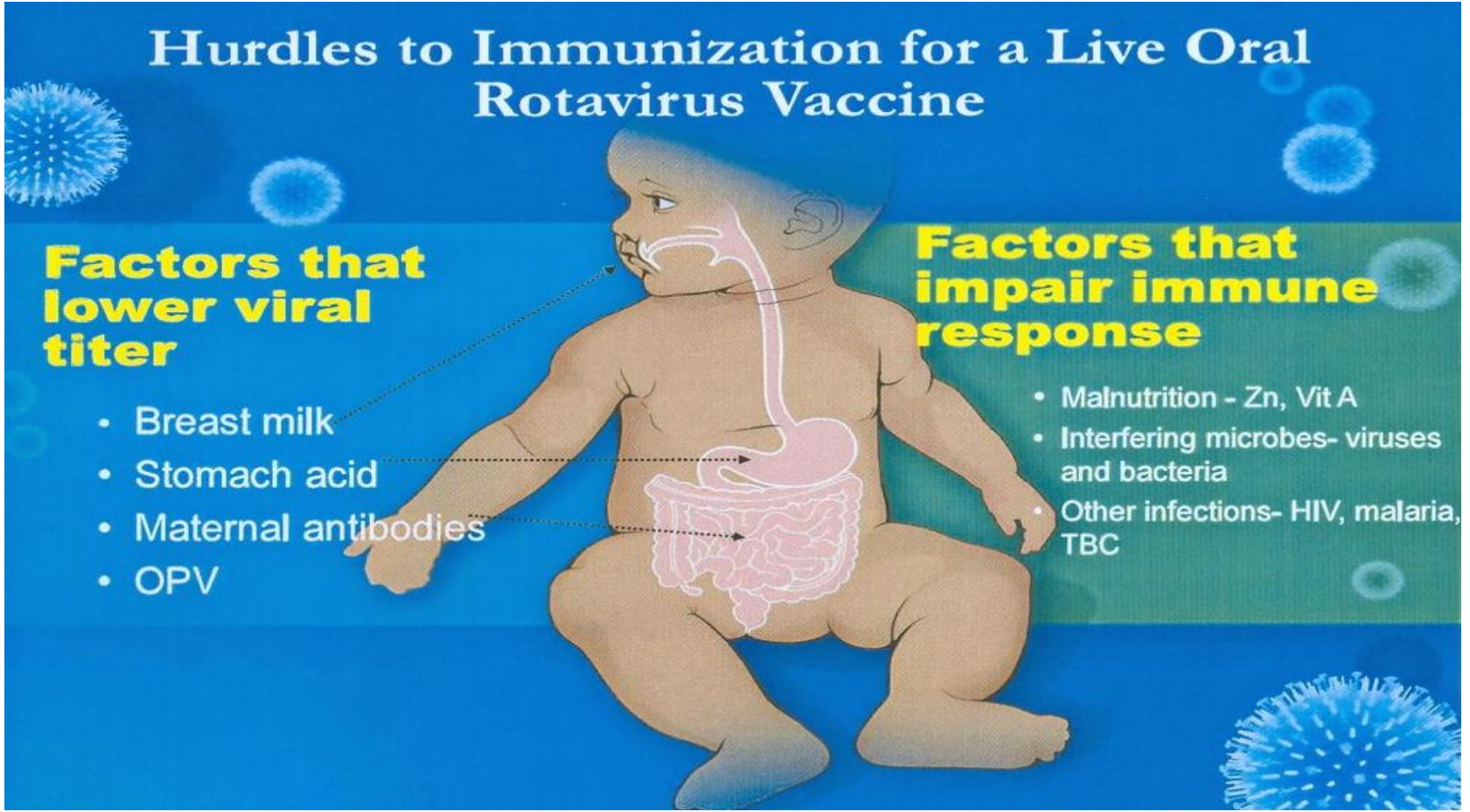


Figure 1. Number of positive and total rotavirus tests from 25 continuously reporting National Respiratory and Enteric Virus Surveillance System laboratories, by week of year and region, June 2000–July 2012, 5-week moving average.

Rotavirus Vaccine Efficacy Against Severe Disease in Tropical Countries

Vaccine	Country	Efficacy
RV1	Brazil	77%
	Malawi	49%
	South Africa	77%
RV5	Nicaragua	77%
	Kenya	83%
	Ghana	65%
	Viet Nam	73%
	Bangladesh	46%

Hurdles to Immunization for a Live Oral Rotavirus Vaccine



Importance of the Microbiome to Oral Vaccination

- **Infections change morphology of the intestinal mucosa**
- **Antibiotics decreased rotavirus infection in mice but increased antibody responses**
  (Uchiyama et al, J. Inf. Dis. 2014)
- **Or call prior infections modify immune responses ?**

Uncertain Correlates of Protection:

Dengue

Efficacy of Chimeric Dengue Vaccine in Thailand - Phase 2 + 3

Serotypes	Phase 2 Efficacy (C.I.)	Phase 3 Efficacy (C.I.)
All	35% (6.7-54)	57% (44-64)
1	61% (17-82)	50% (25-67)
2	3.5% (-60-41)	35% (-9-61)
3	82% (39-96)	78% (53-91)
4	90% (11-100)	75% (55-87)

Sabcharoen, Lancet 2012 Capeding, Lancet 2014

Possible Explanations for Low Efficacy of Chimeric Dengue Vaccine

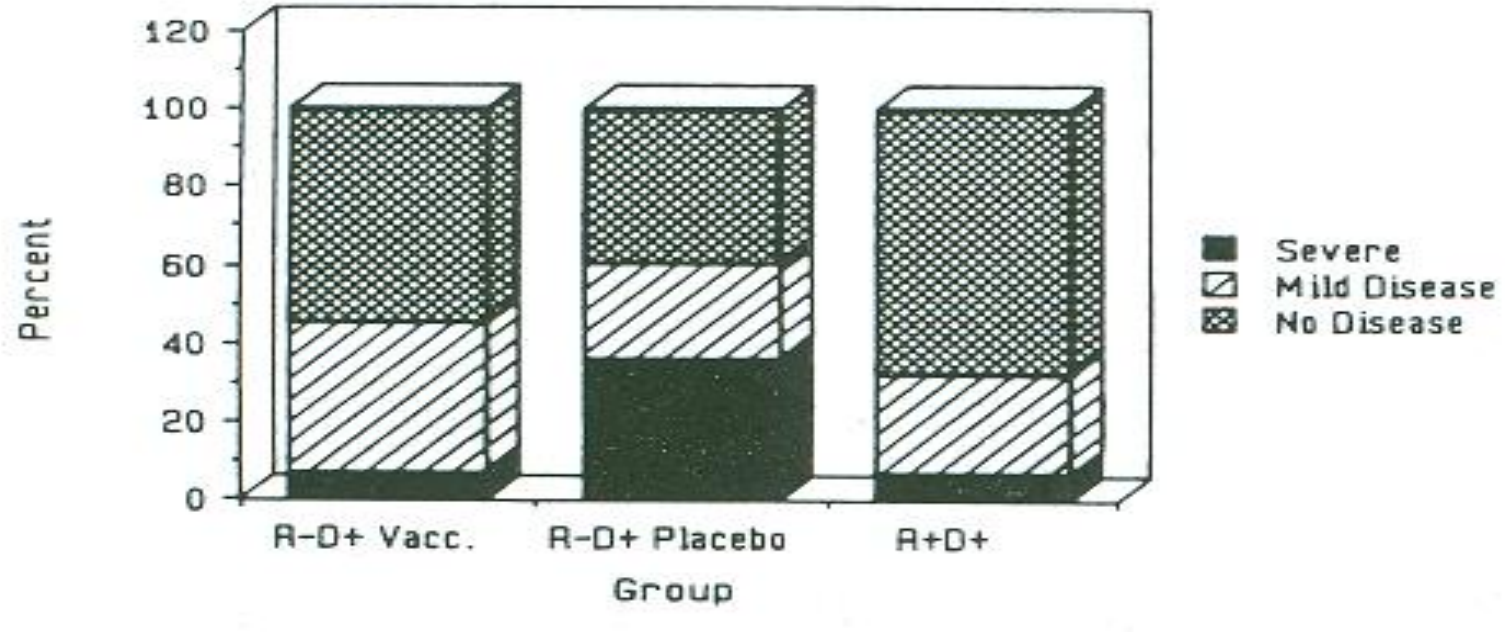
- Higher challenge dose of type 2, or strain variation therefore more antibodies needed
- Dengue Type 2 infects monocytes rapidly and antibody thus not effective
- T cell response also needed
- Type 2 replicates poorly and antibodies were heterotypic, not homotypic
- Envelope protein in chimora has different conformation than in virus (de Alwis et al, J Virol)
- Structure of virus produced at 37°C different from virus injected by the mosquito

(Rey et al, Nature 2013)

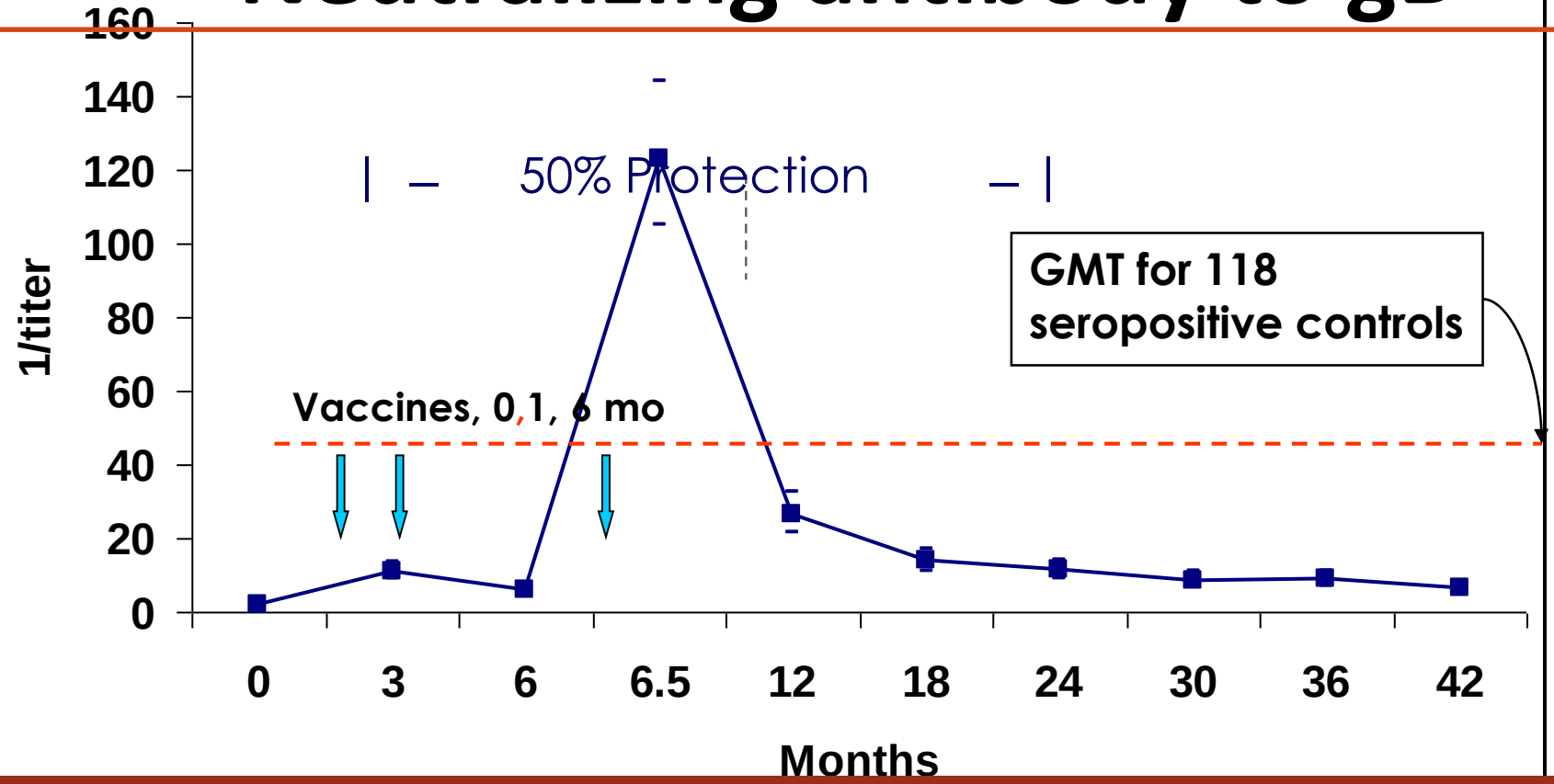
Antigens Needed for Protection Uncertain:

Cytomegalovirus

Outcome of Exposure to Transplanted Kidney from a CMV-seropositive donor (D+) in Renal Transplant Recipients

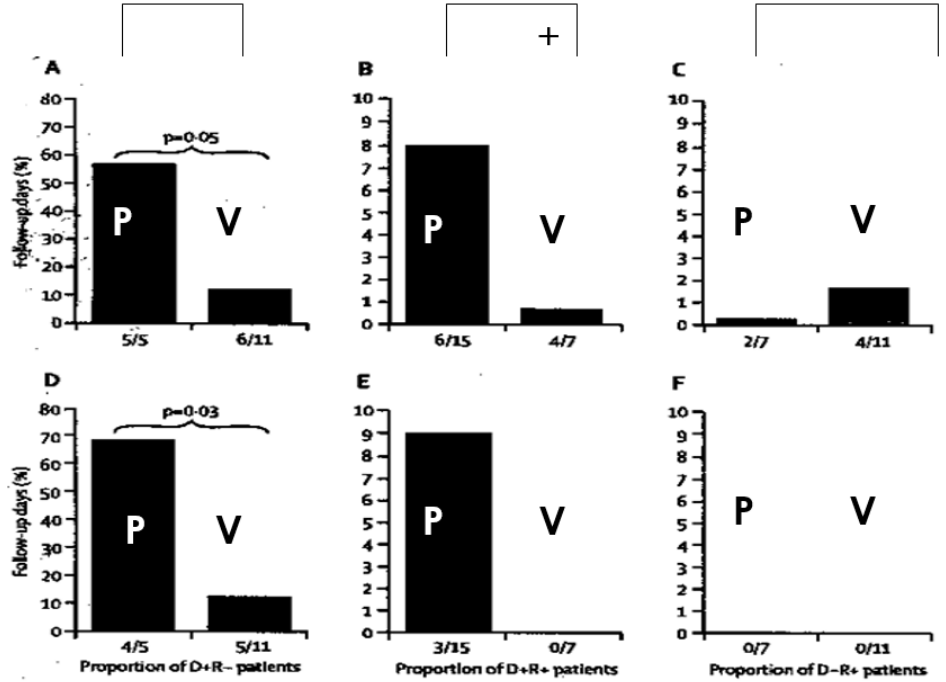


Neutralizing antibody to gB



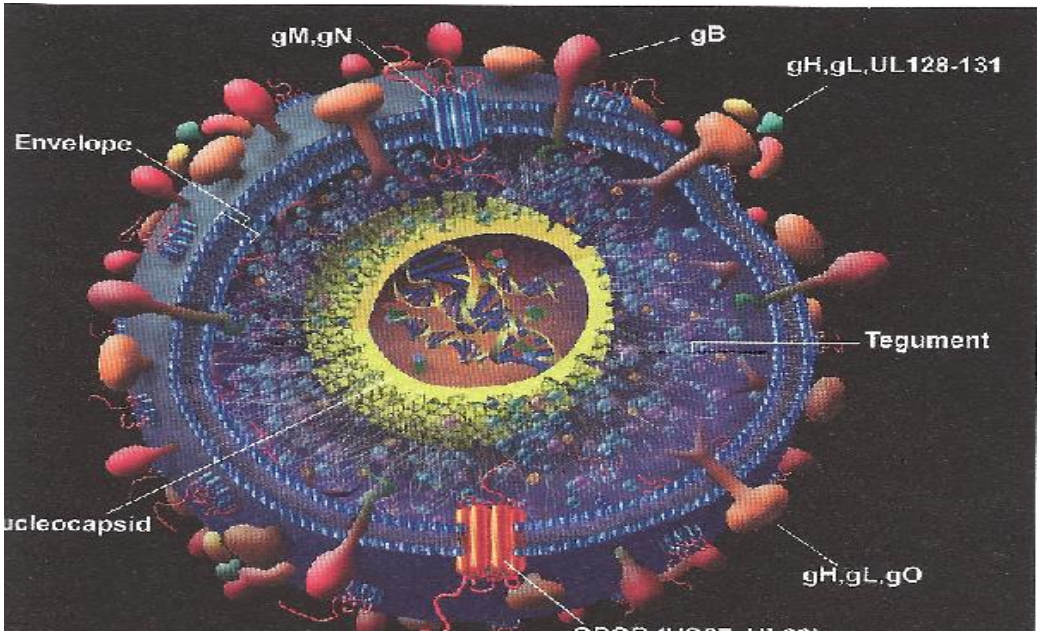
Sanofi-Pasteur gB/MF59 in Kidney or Liver Transplant Patients

Proportion of days that patients in the three subgroups at risk of CMV infection



Griffiths PD, et al. Lancet 2011;377:1256.

HCMV Structure, HCMV Virions are Comprised of Three Major Layers



Caposio P, Stgeblow DN, Nelson JA. Cytomegalovirus Proteomics Chapter 1.6 in Cytomegalovirus,from Molecular Pathogenesis to Intervention, Voll. ! Reddehase MJ, Lemmermann NA (eds) Caister AcademicPress, 2013, Page 87.

Antibodies Against the CMV gH/gL/UL128-131 Pentamer

- Comprise majority of neutralizing antibody in convalescent serum

- Early appearance in maternal infection correlates with protection against transmission to fetus

Ways Being Tried to Generate Responses to CMV Pentamer

- Replication – Defective Virus
- VLPs
- Soluble pentamer proteins
- Self-Amplifying RNA
- DNA - Plasmids

Value of Structural Biology:

RSV

Respiratory Syncytial Virus

- Number one respiratory infection of infants (0-2 yrs)
- Also, important in elderly
- Prior inactivated vaccine worsened disease because Fusion antigen was altered, leading to formation of immune complexes
- ? Need for “just right” antibody and CD8+ T cell responses
- Live viruses insufficiently attenuated

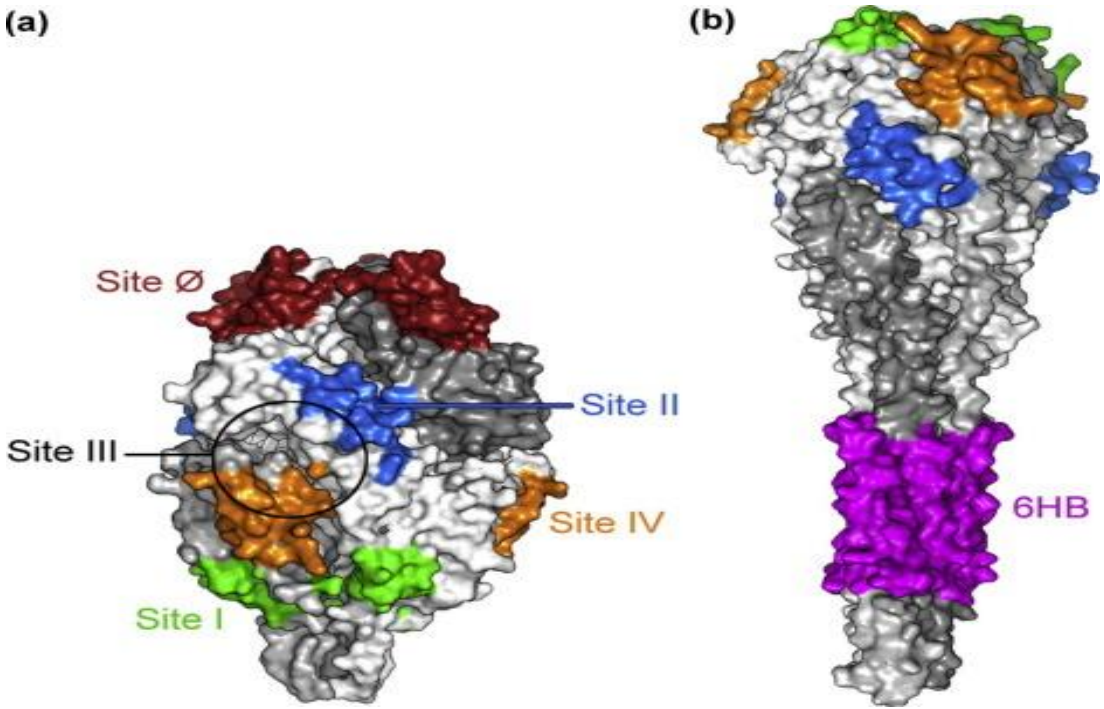


Fig. 4. Antigenic sites of hRSV F glycoprotein. The location of the different antigenic sites is shown in both the prefusion (a) and postfusion (b) conformation of hRSV F. Antigenic site III is delineated by a circle which includes residues identified by mutag...

Vaccine. 2017 Jan 11;35(3):461-468. doi: 10.1016/j.vaccine.2016.09.045. Epub 2016 Sep 28.

Structural, antigenic and immunogenic features of respiratory syncytial virus glycoproteins relevant for vaccine development.

Melero JA[1], Mas V[2], McLellan JS[3].

The Right T Cell Responses

T Cell Stimulating Vaccines

TB – Needed T cell response is polyfunctional and cytotoxic, such that it will kill infected macrophages

Malaria – Antibodies to circumsporozoite protein important, but T cell response needed to kill infected cells in the liver. May need other antigens

The Vaccine Industry

The BIG 4 Vaccine Manufacturers

GlaxoSmithKline
Merck
Pfizer-Wyeth
Sanofi Pasteur

Smaller Market Share or Limited Range

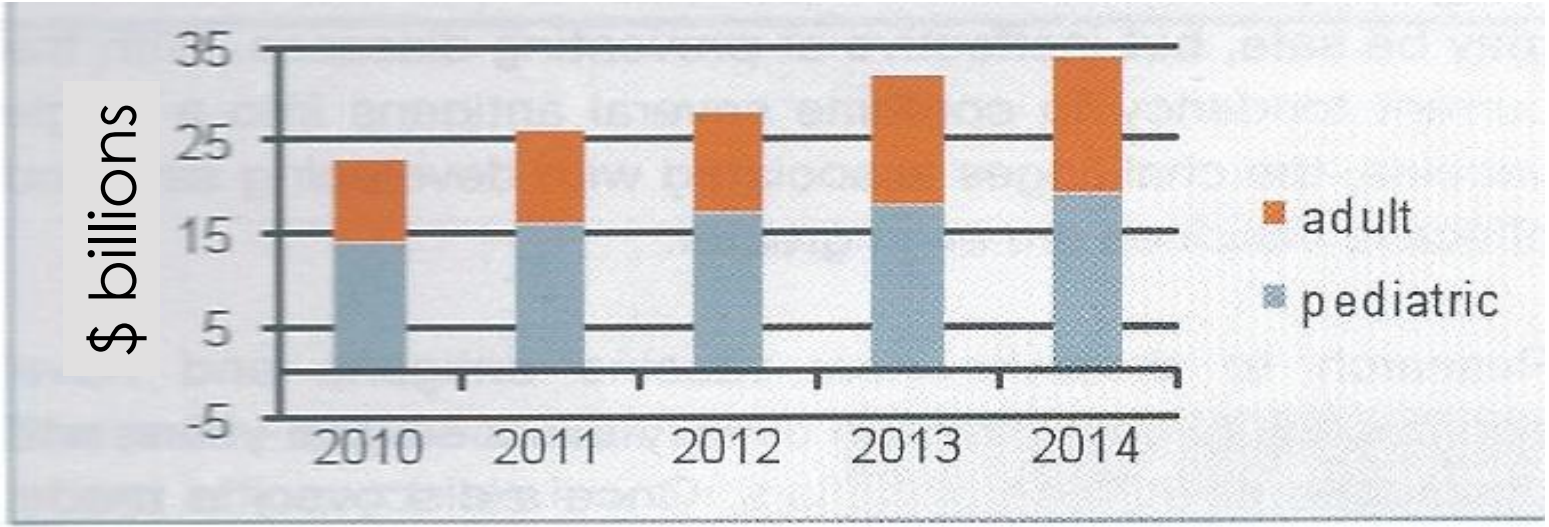
CSL	Astellas
Johnson & Johnson	Avant
MedImmune-AstraZeneca	Bioport
Serum Institute of India	Emergent
	ID Biomedical
	Solvay
	Statens Serum Inst.
	Takeda

Producers Outside North America and Europe

- Japanese Local Producers: Biken, Takeda, Kitasato, Kaketsuken, Japan BCG
- Indian Local Producers: Panacea, Bharat, Shanta, Biological E., Indian Immunologicals, Zydus
- Korean Local Producers: Green Cross, LG
- Latin American Local Producers: Butantan, Fiocruz, Birmex, Bio-Manguinhos, Finlay Inst.

- Biofarma [Indonesia]
- Saovabha [Thailand]
- Razi [Iran]
- IVAC, Vabiotech [Viet Nam]
- Microgen [Russia]
- Sinovac + 46 different producers (China)

Projected Growth of the Vaccine Market by Adult And Pediatric Segments



$ Billions
Adult: 2010 23% , 2011 26% , 2012 27% , 2013 31% , 2014 34%
Pediatric: 2010 14% , 2011 16% , 2012 17% , 2013 20% , 2014 21%

Vaccine Fact Book, 2012
Pharma, page 53

Why is There an Increase in the Vaccine Market?

- New vaccines give higher profits
- Hib, Hepatitis B and Pneumococcal vaccines changed the paradigm of a “cheap” vaccine

Reasons Why Vaccine Manufacturers Launch a Development Program

1) Market

2) Market

3) Market

> 500 M $

How Market is Determined

1) **Epidemiologic data**

   e.g. Pneumococcal conjugate

2) **Demand from consumers in developed countries**

   e.g. Lyme Disease, Acellular Pertussis

3) **Demand from authorities in developed countries**

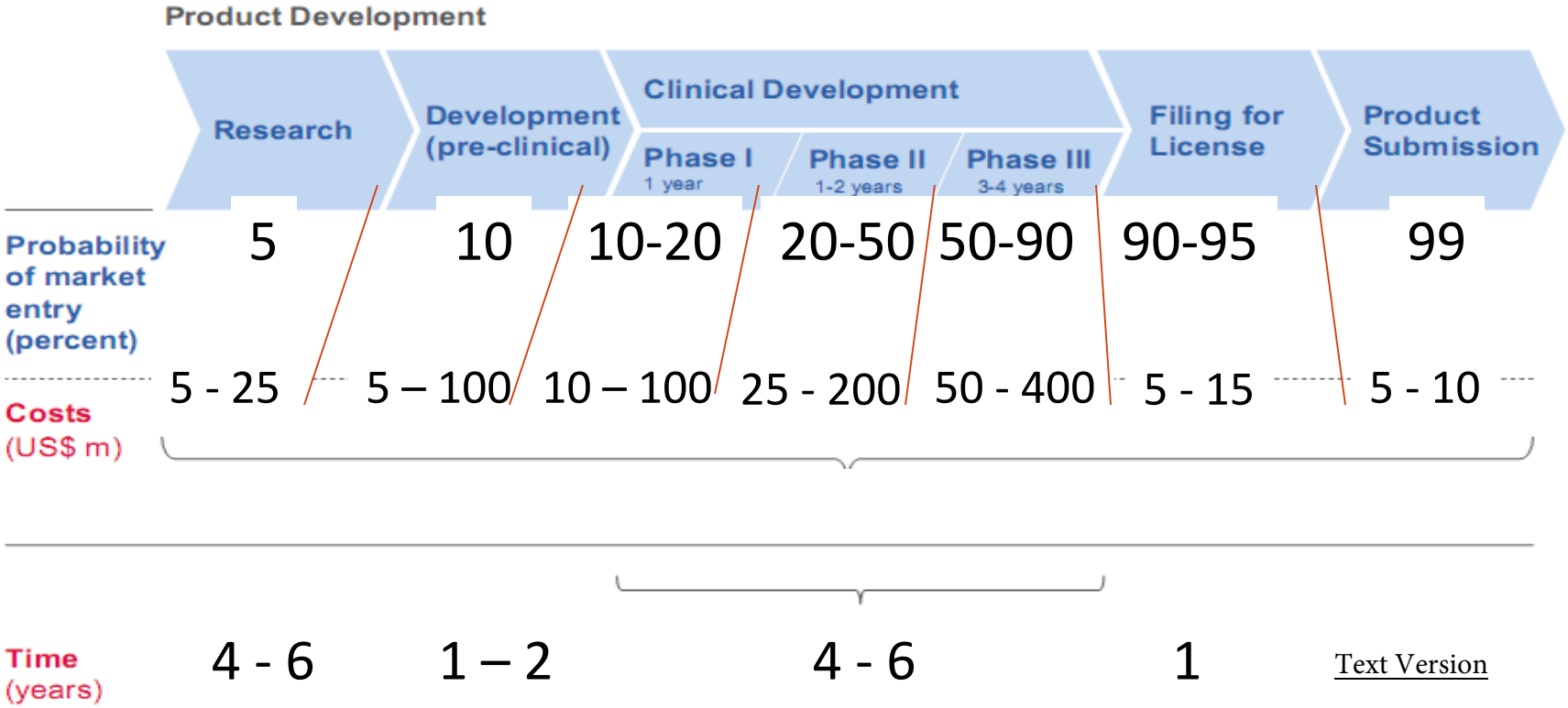
   e.g. Mening C

4) **Expert opinion**

   e.g. Mumps

5) **Guesses, buttressed by precise but inaccurate data.** e.g. Hepatitis B

Vaccine Development: a Long and Risky Journey
Technological, Resources and Regulatory Challenges



Text Version

Meningococcal B Vaccine

- In 1990s, it appeared to be necessary to complement Mening A/C/W/Y
- In 1995, Novartis started project
- Conjugation of B capsule non-starter
- In 2000, Novartis discovered reverse vaccinology
- Mening B vaccine licensed in 2015
- Interest of ACIP had declined

Technical Feasibility

- **Breakthroughs come from academia and government, and now biotech**
- **Importance of "proof of concept"**
- **An approach is useless unless it can be scaled up** (e.g. vectors)
- **Mice lie, or at least exaggerate**

Coalition for Epidemic Preparedness Innovations

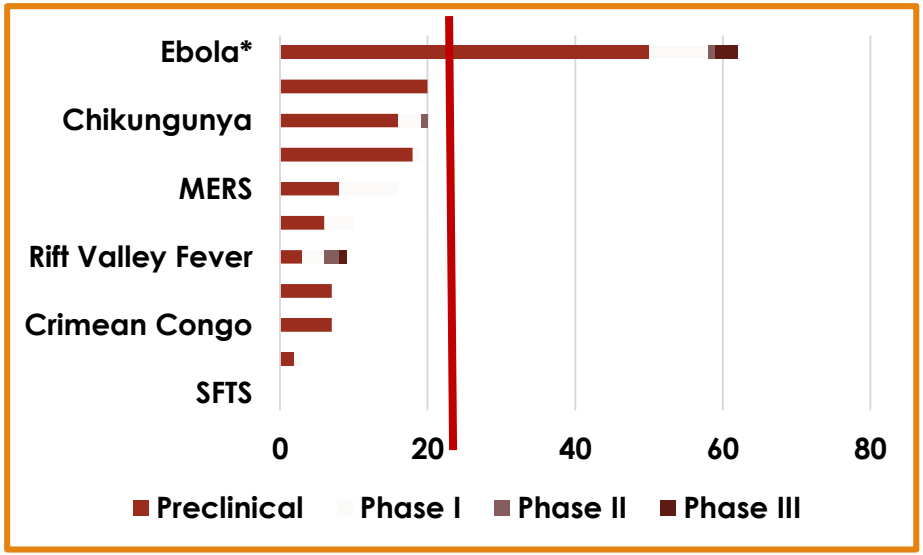
"We consider an international vaccine-development fund to be urgently needed to provide the resources and the momentum to carry vaccines from their conception in academic and government laboratories and small biotechnology firms to development and licensure by industry.

This support would permit efficacy assessment to begin – and thereby avert a repetition of the Ebola crisis."

N Engl J Med. 2015 Jul 23;373(4):297-300. doi: 10.1056/NEJMp1506820.
Establishing a Global Vaccine-Development Fund.
Plotkin SA[1], Mahmoud AA, Farrar J.

Challenges

1. The pipeline is weak for most EIDs characterized by market failure
2. Unilateral, uncoordinated government efforts to fund R&D preparedness are inefficient and unsustainable in addressing global epidemic risks
3. Clinical & regulatory pathways are not easily adaptable to epidemic contexts
4. Incentives are lacking to motivate greater industry engagement



Stages of Development

- Immunogenicity and safety in mice
- Protection in relevant animal challenge model
- GMP production, validation of methods – CEPI
- Toxicity studies
- Phase I
- Phase IIa
- Phase IIb – if possible
- Stockpile
- Conditional approval for emergencies – CEPI
- Phase III
- Licensure

CEPI process to date

CEPI startup phase: June 2016 – July 2017

- Adopted interim entity, CEO and secretariat
- Finalized strategic plan
- Finalized interim governance arrangements, including selection of BoD and SAC members
- Drafted CEPI preliminary business plan for first five years of operation (subject to revision)
- Chose targets: MERS, Lassa, Nipah
- Securing initial commitments and contributions for CEPI launch
- Davos, January 2017
- G7 Summit, May 2017
- G20 Summit, July 2017

What Should NVAC do for the Future of Vaccinology?

- Select and name important targets for vaccine development in the U.S.
- Promote development of new delivery systems such as intradermal, sublingual, electroporation
- Study personalized medicine: vaccinomics
- Urge USG support of CEPI for vaccine development against emerging diseases

Product Development

	Research	**Development (pre-clinical)**
Probability of market entry (percent)	5	10
Cost (UW$m)	5-25	5-100
Time	4-6	1-2

Clinical Development

	Phrase 1 1Year	**Phrase 2 1-2 Years**	**Phrase 3 3-4 Years**
Probability of market entry (percent)	10-20	20-50	50-90
Cost (UW$m)	10-100	23-200	50-400
Time	4-6	4-6	4-6

	Filling For License	**Product Submission**
Probability of market entry (percent)	90-95	10
Cost (UW$m)	5-15	5-10
Time	1	1