How and Why Vaccines are Made

Stanley A. Plotkin

Vaccinology

A combination of:

- Microbiology
- Immunology
- Epidemiology
- Public Health and
- Pharmacy

"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, A Short History of Vaccination, in *Vaccines* 1st Edition, 1988

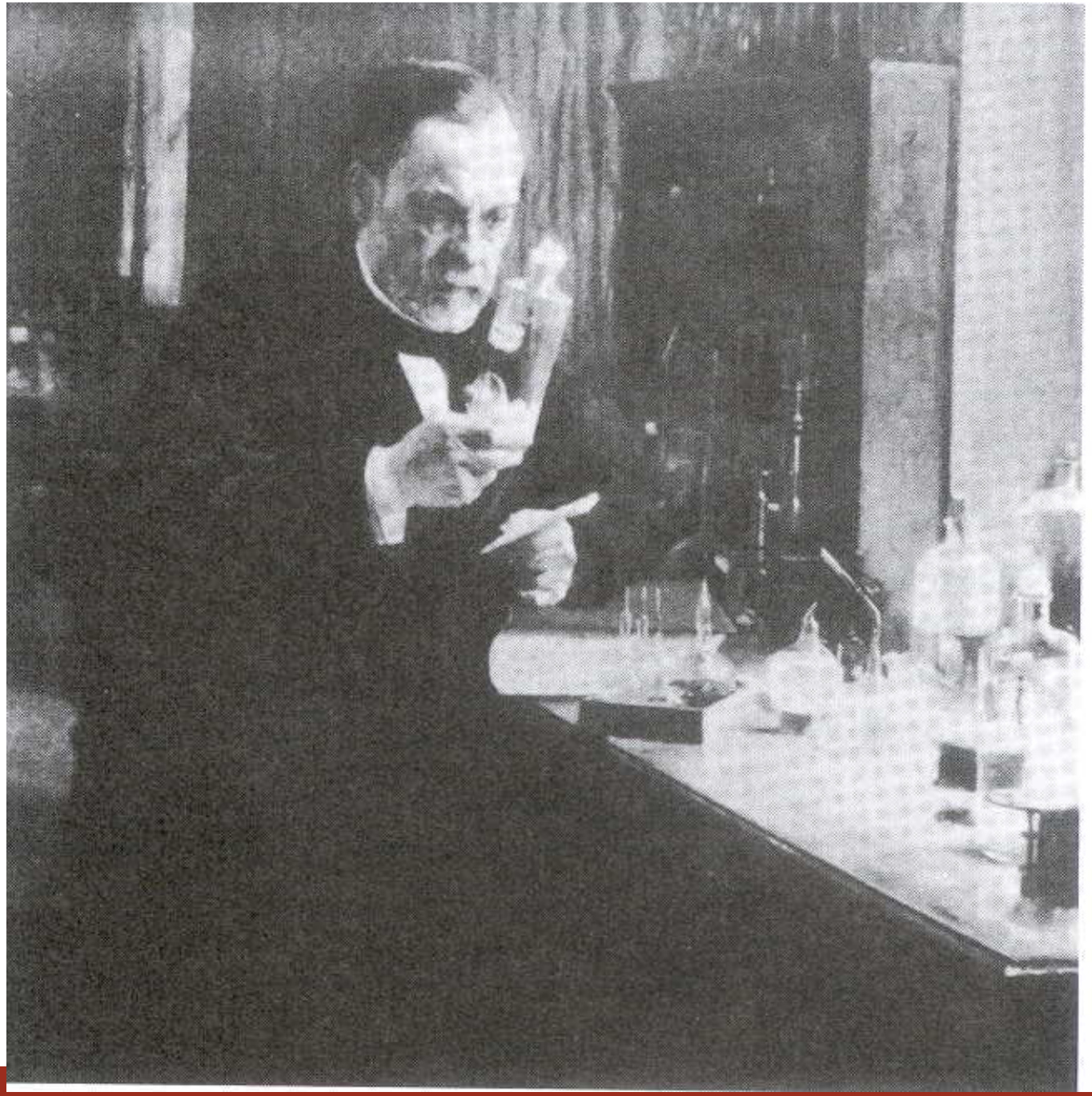
What is a Vaccine?

An inactivated or attenuated pathogen or a component of a pathogen (nucleic acid, protein) that when administered to the host, stimulates a protective response of the cells in the immune system

Vaccines

1) History of vaccination
2) The vaccine industry
3) Why vaccines are developed
4) The current problems of vaccinology

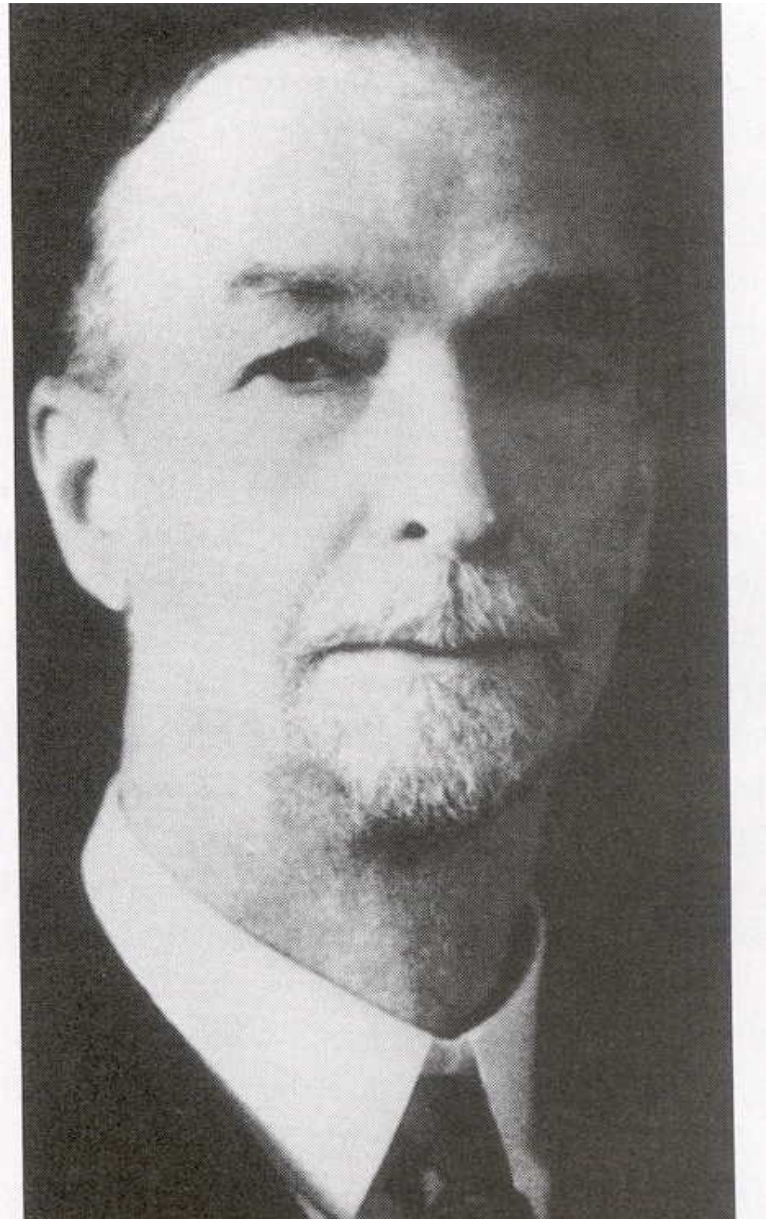
Edward **JENNER**



LOUIS **PASTEUR**

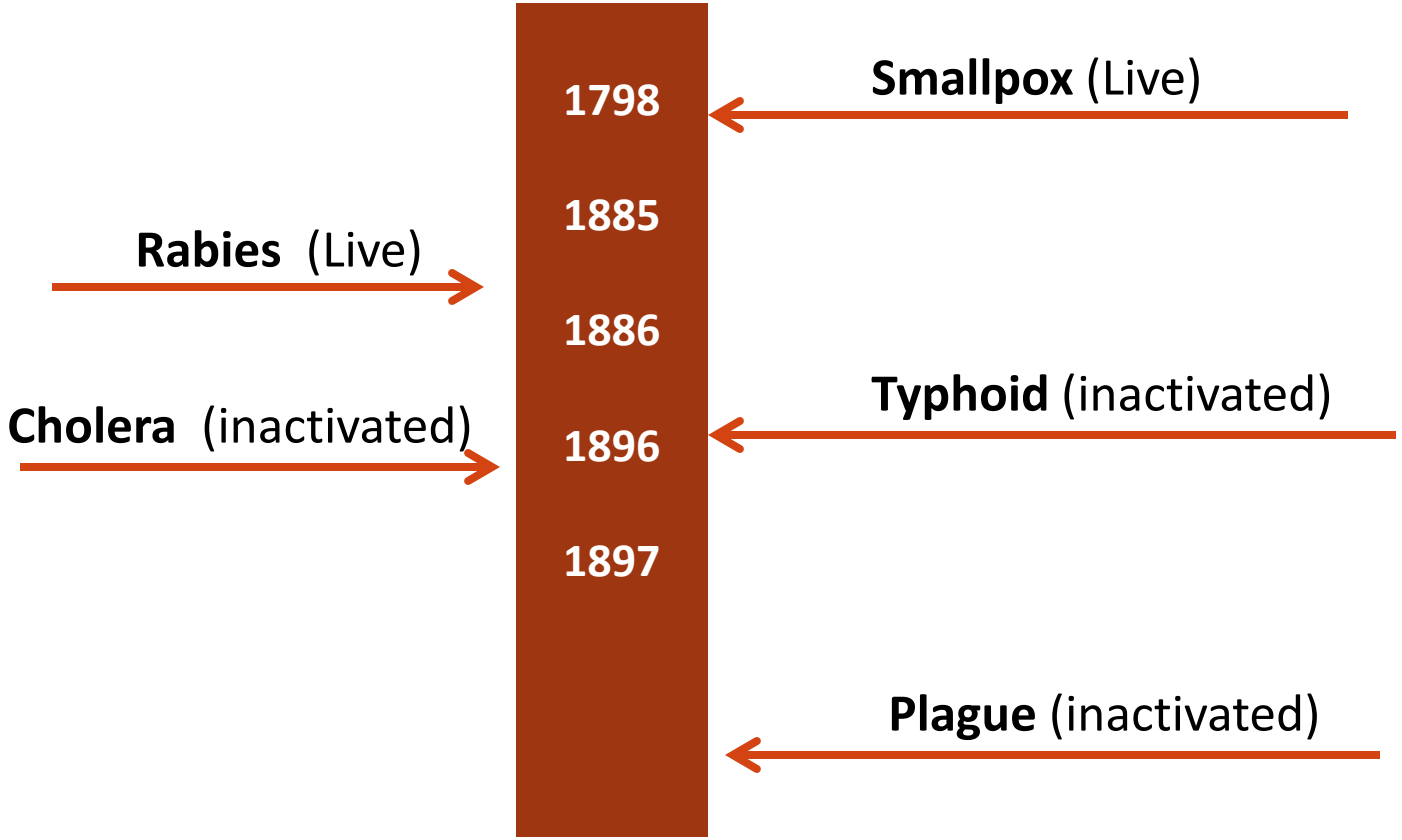
Daniel Elmer Salmon

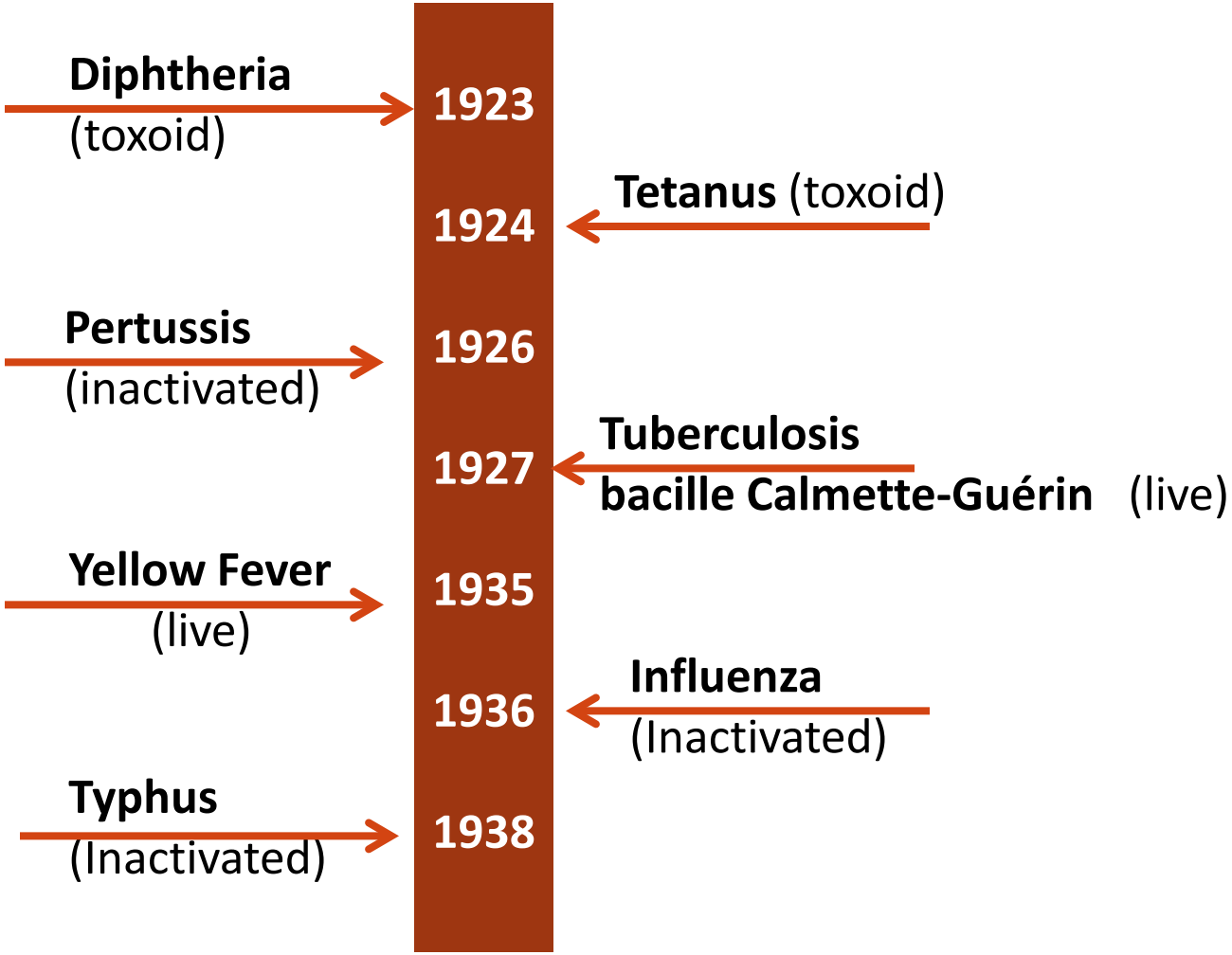
(1850 - 1914)

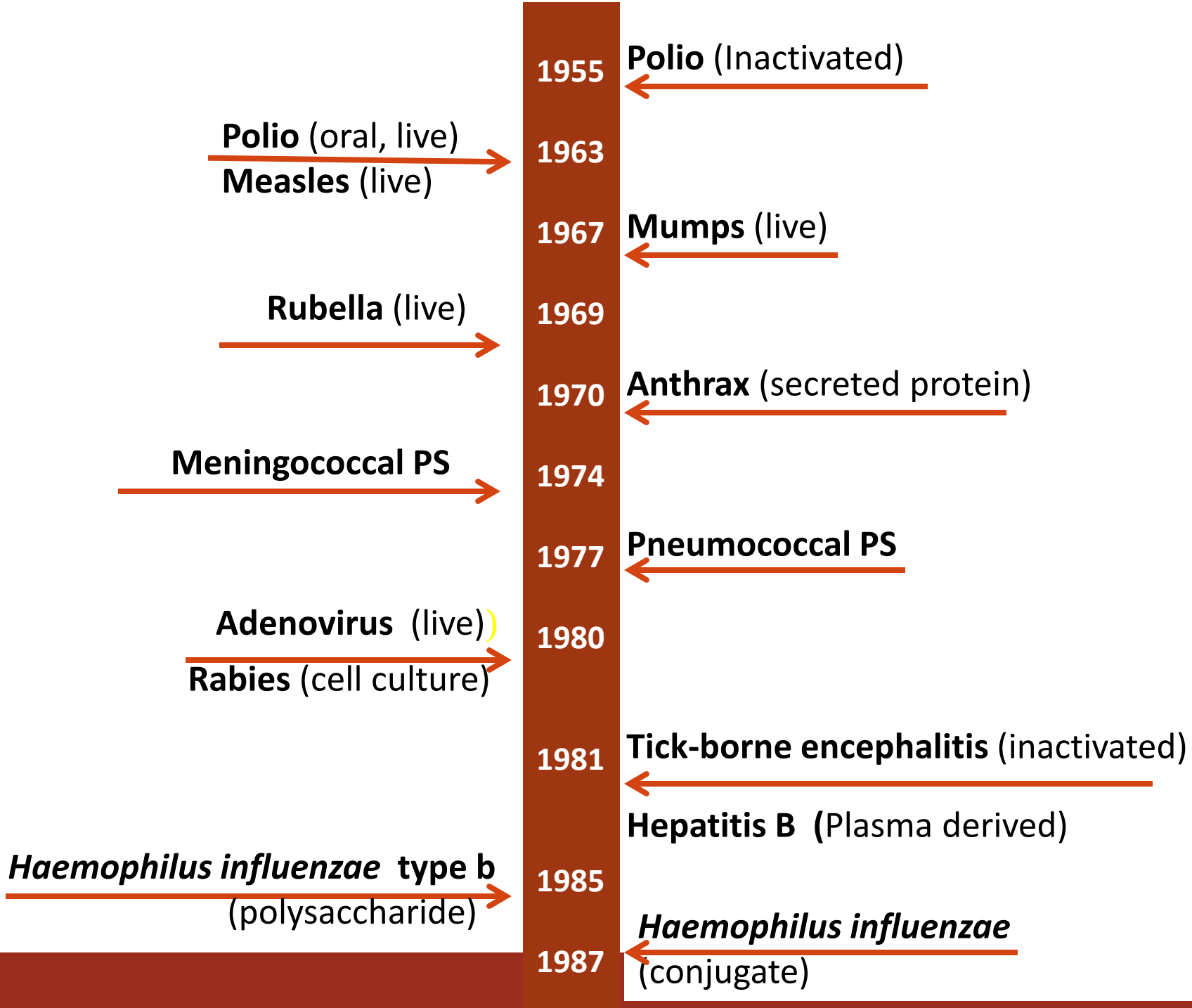


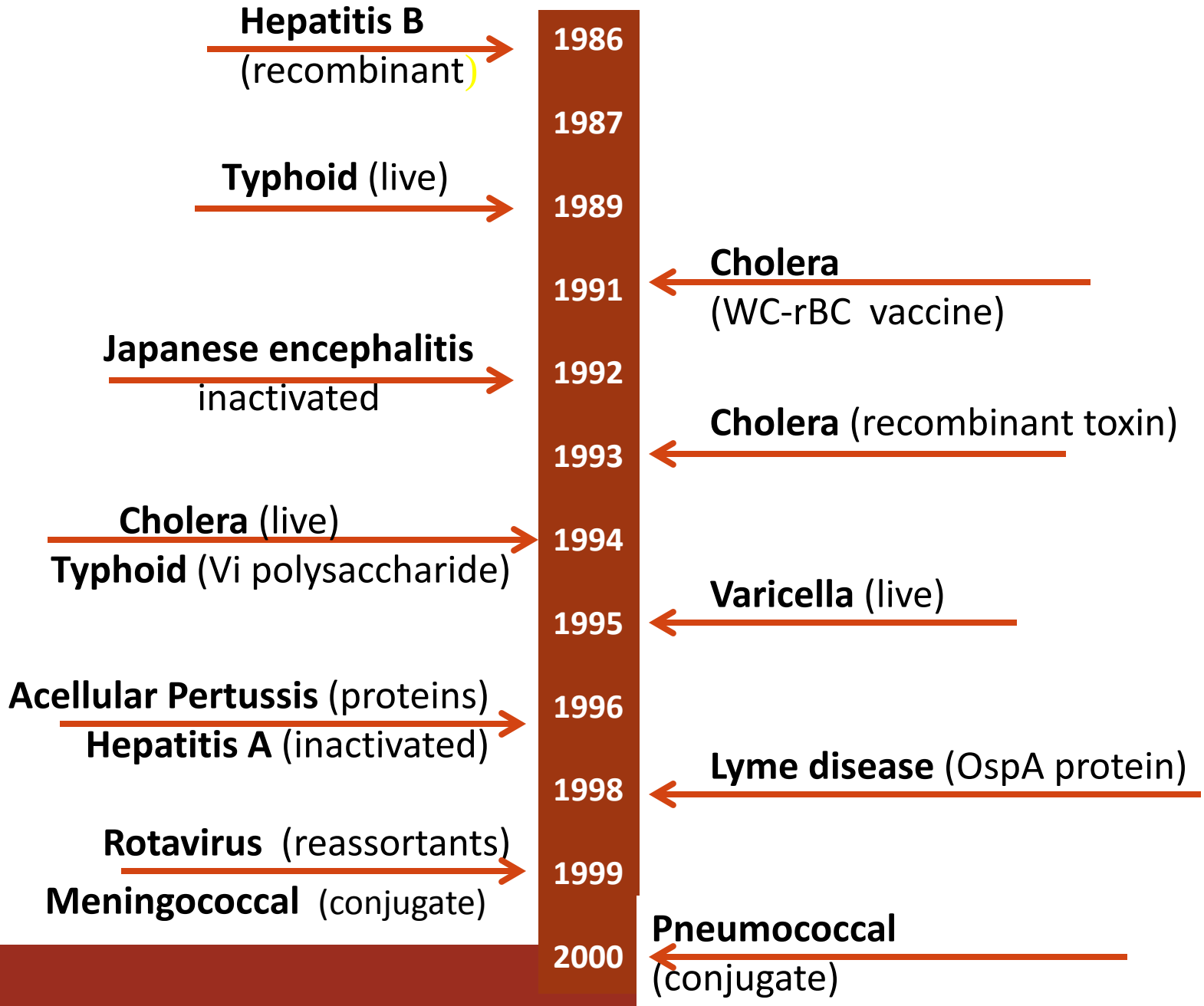
Theobald Smith

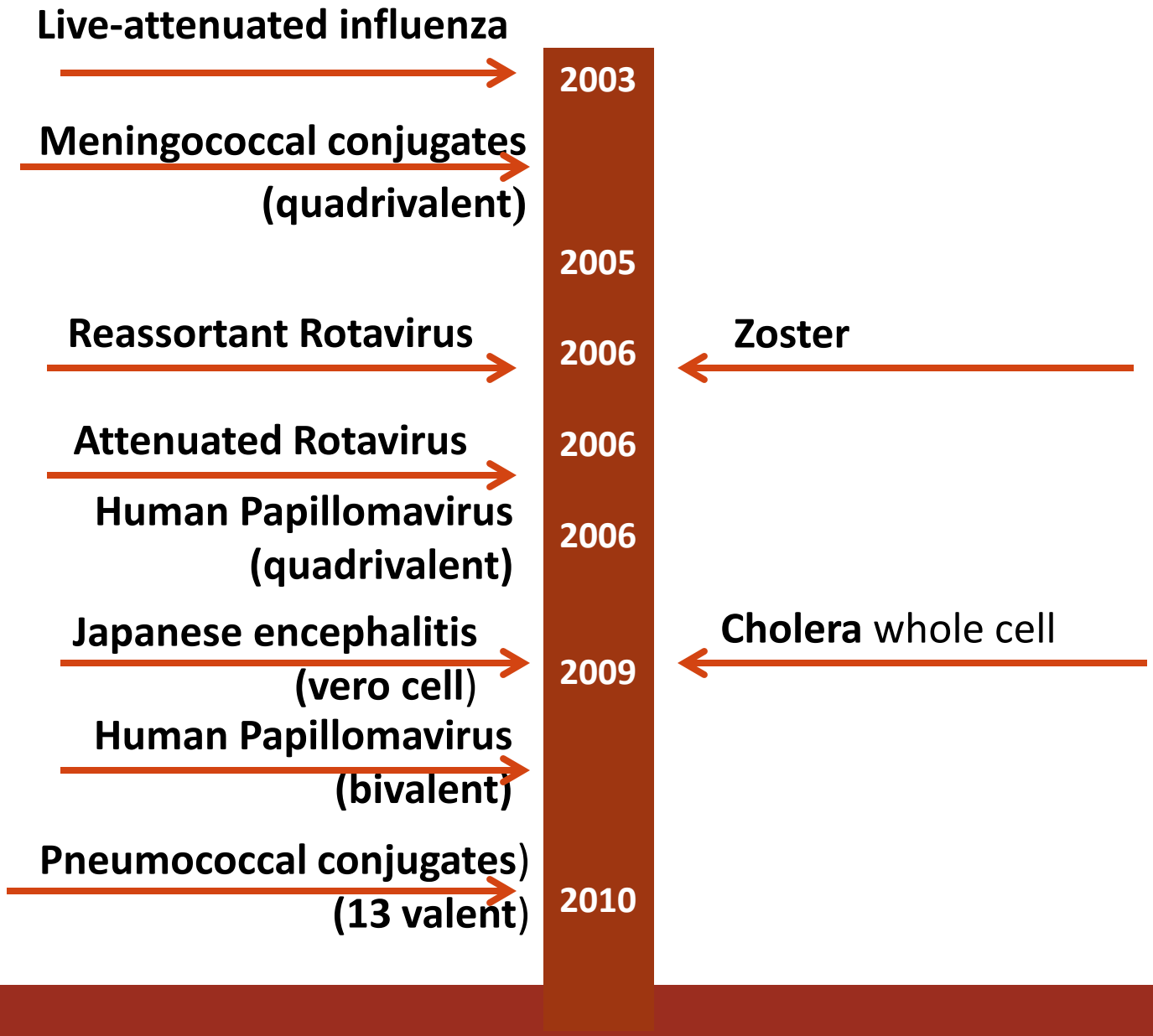
(1859-1934)


1798
1885
1886
1896
1897
Smallpox (Live)
Rabies (Live)
Typhoid (inactivated)
Cholera (inactivated)
Plague (inactivated)


Diphtheria
(toxoid)
1923
Tetanus (toxoid)
1924
Pertussis
(inactivated)
1926
Tuberculosis
1927
bacille Calmette-Guérin (live)
Yellow Fever
(live)
1935
Influenza
1936
(Inactivated)
Typhus
(Inactivated)
1938


1955
Polio (Inactivated)
Polio (oral, live)
1963
Measles (live)
1967
Mumps (live)
Rubella (live)
1969
1970
Anthrax (secreted protein)
Meningococcal PS
1974
1977
Pneumococcal PS
Adenovirus (live)
1980
Rabies (cell culture)
1981
Tick-borne encephalitis (inactivated)
Hepatitis B (Plasma derived)
Haemophilus influenzae type b
(polysaccharide)
1985
Haemophilus influenzae
1987
(conjugate)


Hepatitis B
(recombinant)
1986
1987
Typhoid (live)
1989
Cholera
(WC-rBC vaccine)
1991
Japanese encephalitis
inactivated
1992
Cholera (recombinant toxin)
1993
Cholera (live)
Typhoid (Vi polysaccharide)
1994
Varicella (live)
1995
Acellular Pertussis (proteins)
Hepatitis A (inactivated)
1996
Lyme disease (OspA protein)
1998
Rotavirus (reassortants)
Meningococcal (conjugate)
1999
Pneumococcal
(conjugate)
2000


Live-attenuated influenza
2003
Meningococcal conjugates
(quadrivalent)
2005
Reassortant Rotavirus
2006
Zoster
Attenuated Rotavirus
2006
Human Papillomavirus
(quadrivalent)
2006
Japanese encephalitis
(vero cell)
Cholera whole cell
2009
Human Papillomavirus
(bivalent)
Pneumococcal conjugates)
(13 valent)
2010

The Vaccine Industry

Why Vaccines are Different than Drugs

1) Given to healthy people, high safety required
2) Larger governmental role
3) Low efficacy unacceptable
4) Often used in infants
5) Given once or a few times
6) Manufacturing larger part of cost
7) High regulatory and quality control burden
8) Supposed to be cheap

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

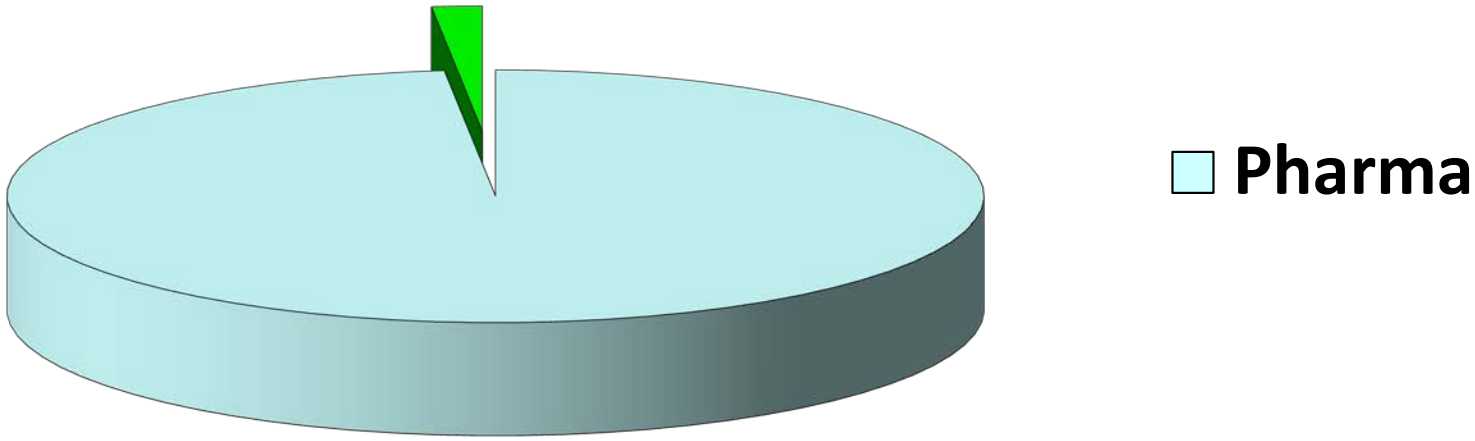
Producers Outside North America and Europe

- 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]

The Growing Chinese Vaccine Industry

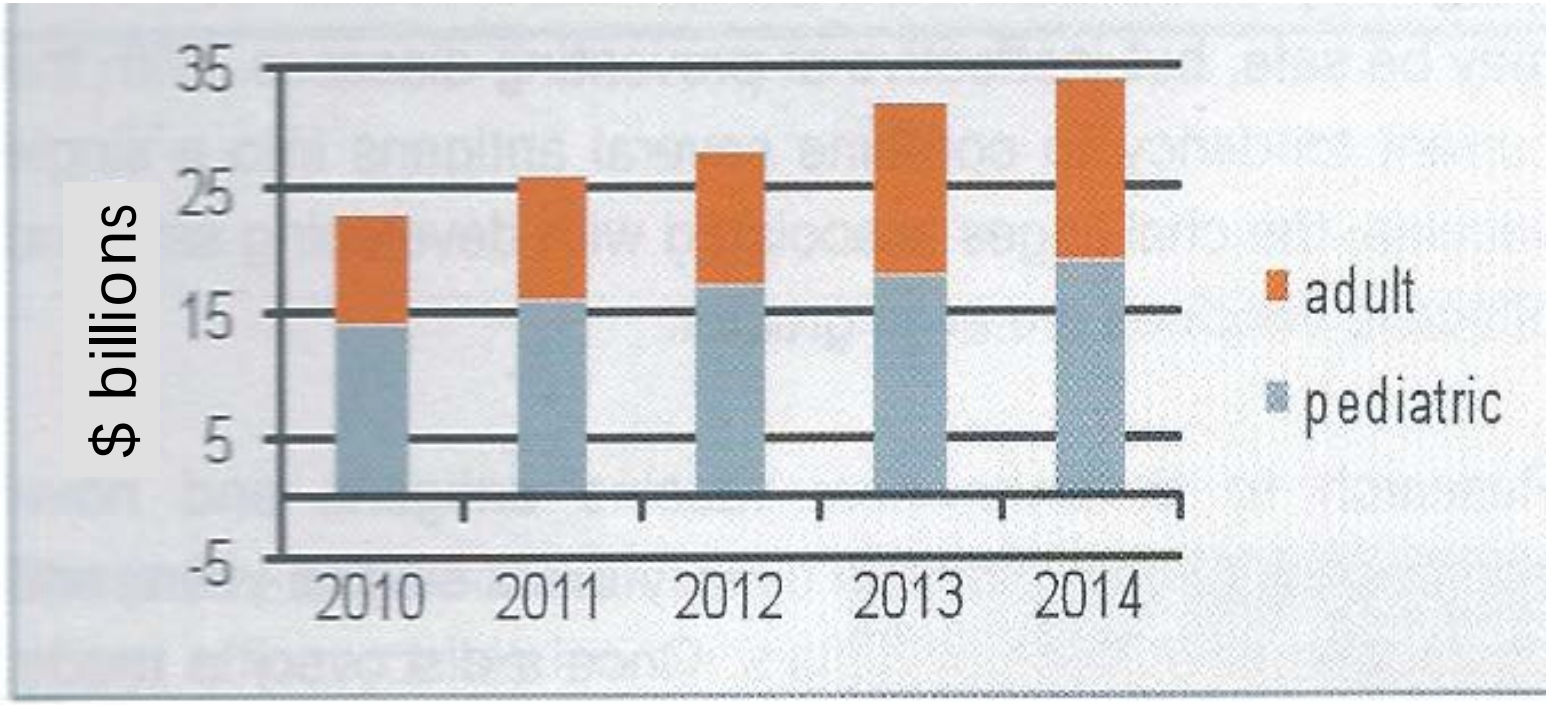
- 46 different companies producing 24 vaccines
- Many recently consolidated as “Sinovac”
- Most important producers are LanZhou, Chengdu, Wuhan, Changchun, Hualan
- Joint ventures with GSK, Novartis, Sanofi
- Already world’s largest producers

Vaccines 22 B$ = 2.9 %



TOTAL Pharma : 717 B$ in 2010

Projected Growth of the Vaccine Market by Adult And Pediatric Segments



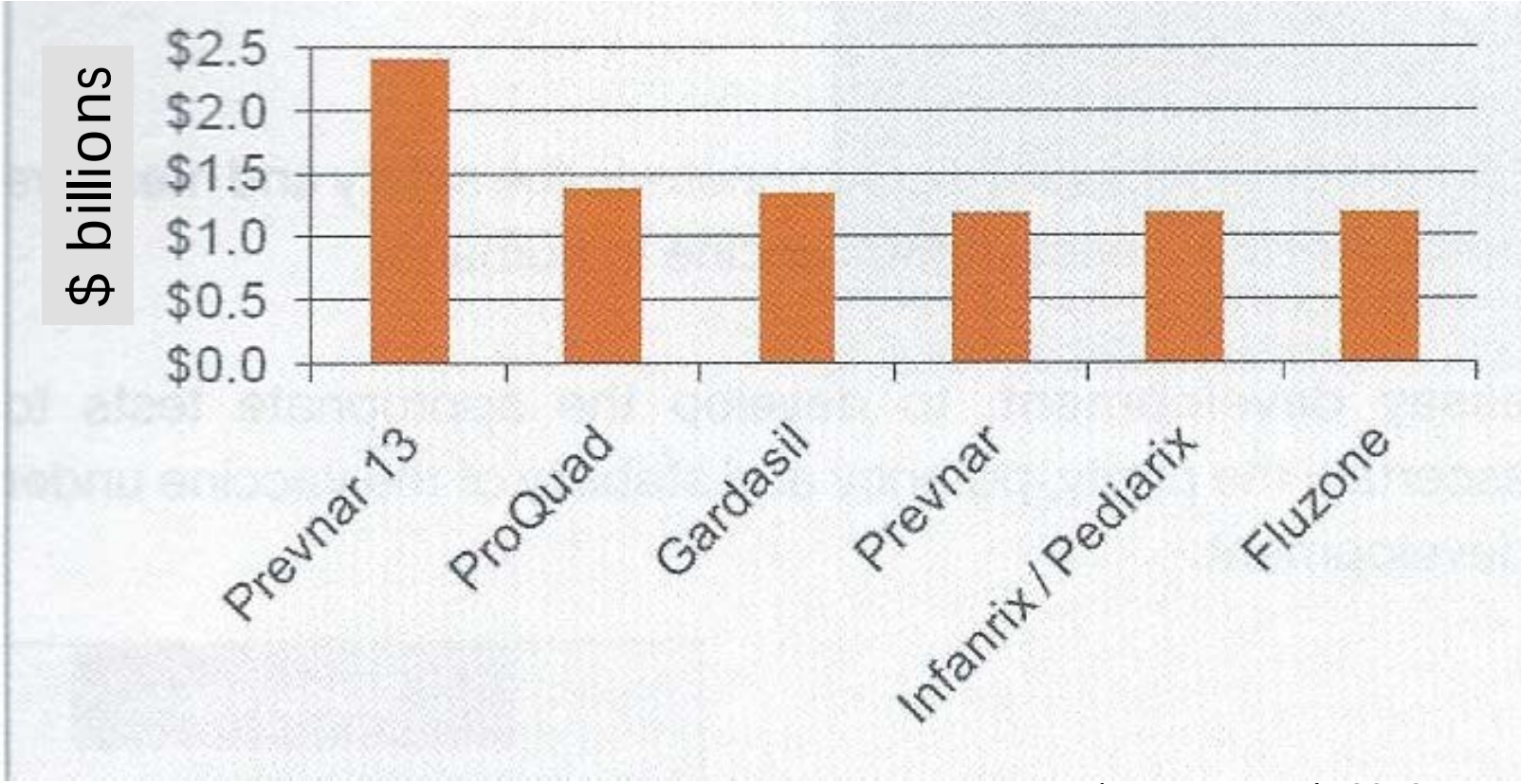
Vaccine Fact Book, 2012
Pharma, page 53

Why is There an Increase in the Vaccine Market?

- New vaccines give higher profits

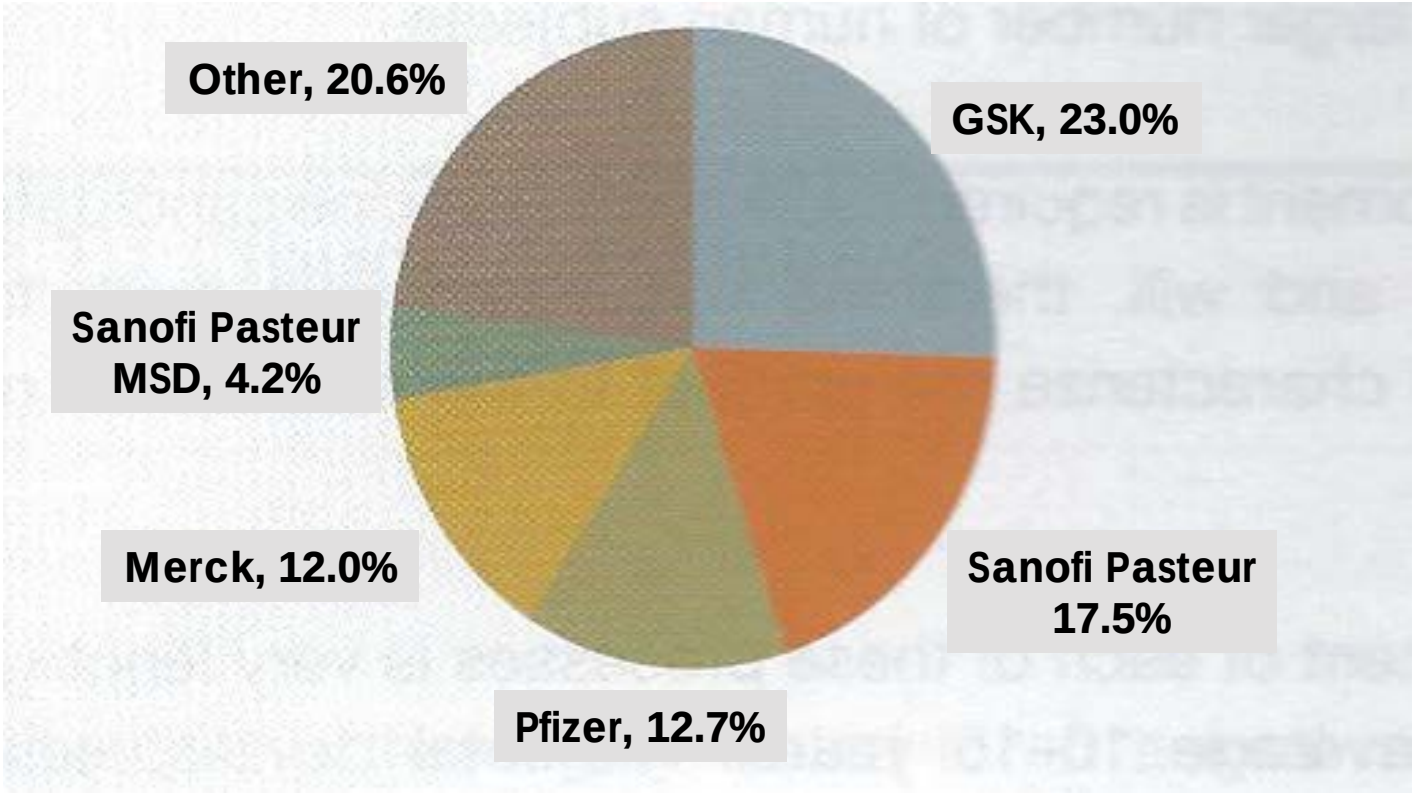
- Hib, Hepatitis B and Pneumococcal vaccines changed the paradigm of a “cheap” vaccine

Brand Name Vaccines
Sales Over $1 billion in 2010



Vaccine Fact Book, 2012
Pharma, page 53

Vaccine Market Share 2010

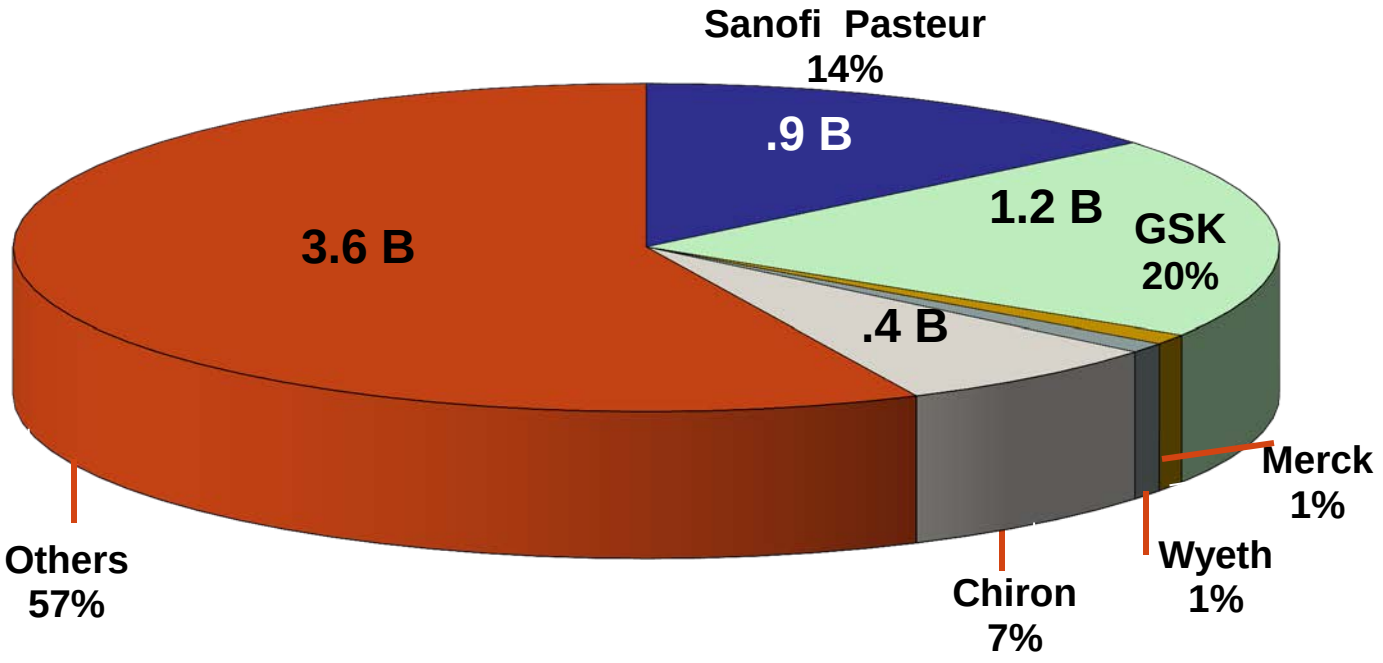


Vaccine Fact Book, 2012
Pharma, page 53

Worldwide Vaccine Market Share

(Doses)

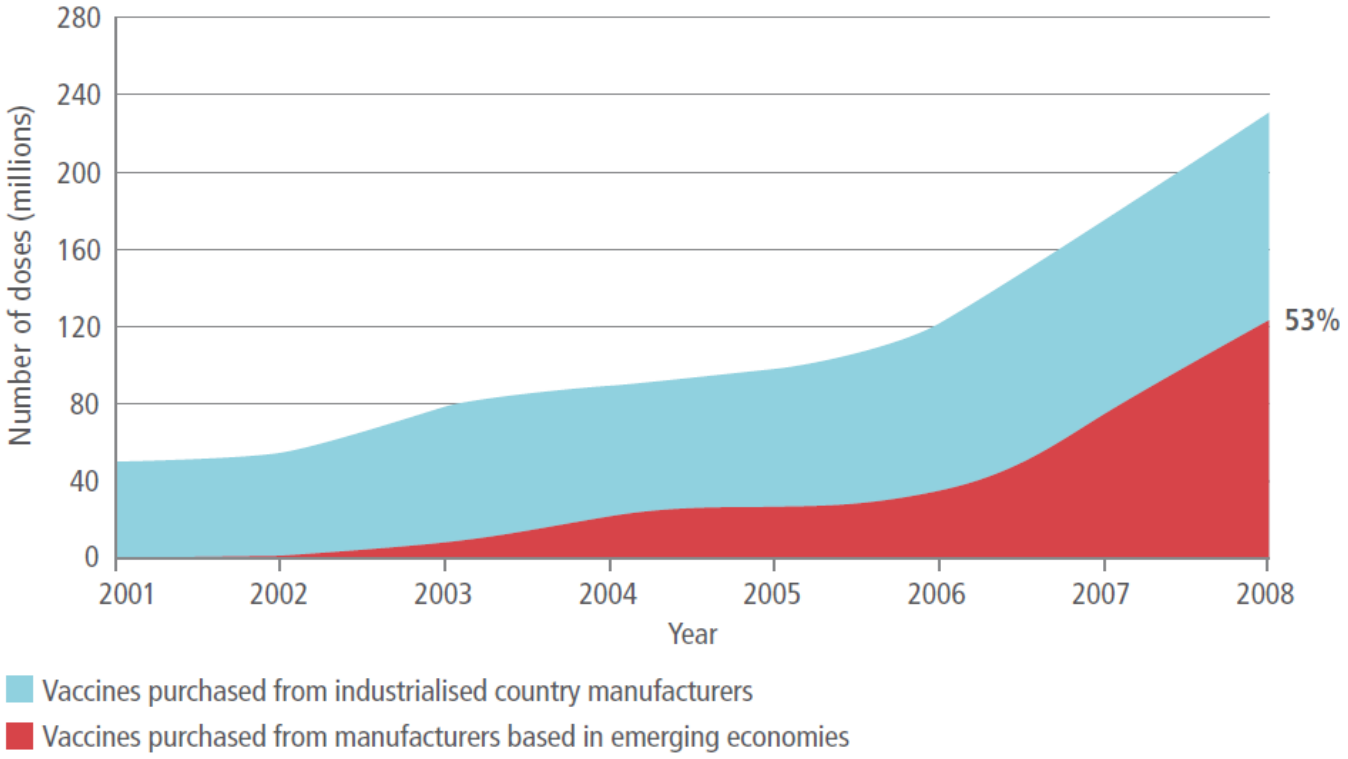
6.3 Billion Dose Global Market



Source: WMA 2004, SP Internal
Note: SP MSD sales split by origin

The Free market has allowed rapid growth in Emerging Economy producers (DCVMs).

Figure 16: Origin and volume of GAVI-funded vaccines – growing proportion of manufacturers based in emerging economies



Source: UNICEF Supply Division, 2009

Reasons Why Vaccine Manufacturers Launch a Development Program

1) Market

2) Market

3) Market

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

Public Health Interest

Development programs for HIV vaccines based more on this than on expectation of profit

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** (e.g. DNA)

Intellectual Property

A quagmire

May block development or sale

e.g. Hepatitis B
Lyme

Fit with Other Vaccines

Combinations

Travel Vaccines

Syndrome Coverage

e.g. Meningitis

How Successful Vaccines Have Been Discovered

- Inference from natural immunity
- Studies in animals
- Inference from passive immunization studies
- Search for protective antigens
- Identification of Correlate of protection

New Strategies for Vaccine Discovery

Attenuated vaccines:

- Attenuated vectors
- Reverse genetics, temperature-sensitive mutations, and reassortment
- Viral recombinants and deletion mutants
- Codon de-optimization
- Control of replication fidelity
- MicroRNA insertion
- Replication vectors that contain genes from pathogens
- Gene delivery by invasive bacteria

Plotkin S, Plotkin S, *Nature Rev Micro*, 2011

New Strategies for Vaccine Discovery

Inactivated vaccines:

- DNA plasmids and DNA shuffling
- Self-amplifying RNA
- Reverse vaccinology
- Antigen identification by transcriptomics and proteomics
- Development of fusion proteins
- Development of new adjuvants (including cytokines)
- Induction of innate immunity

The Road to Vaccine Development

Academic and Biotech

1) Identify the mechanism of natural protection
2) Isolate the antigen(s) responsible for the protection
3) Show in animals that the vaccine protects
4) Find the best formulation of the antigen

Industry

5) Increase yield and purity of vaccine
6) Show the safety of the vaccine in animals
7) Produce a lot under GMP
8) Perform Phase 1, 2, 3, 4 clinical trials

What Does "Preclinical Development" Mean?

- How to formulate antigen?
- Is adjuvant needed?
- Compatibility of antigen and adjuvant?
- How to measure antigen?
- How long is antigen stable?
- Can yield be increased?
- Toxicology and safety in animals
- Standardization of immunological assays
- What animal species is surrogate for immunogenicity?
- Consistency of manufacture?

Phases of Vaccine Development

Preclinical	Yield, Animal safety and Immunogenicity
Phase 1	Safety and Immunogenicity (10-100)
Phase 2	Dose, Schedule, Safety, Immunogenicity (100-1000)
Phase 3	Efficacy, Safety, Consistency (10,000 – 70,000)
Phase 4	Safety (100,000 -1,000,000)

Estimates of Clinical Development and Approval Times

Mean Time Duration in Months

Study Phase	Time (months)
Preclinical	NA
Phase I	19.5
Phase II	29.3
Phase III	32.9
Registration, Review and Launch	16.0
Total Excluding Preclinical	97.7 (8+ Yrs.)

Estimates of Transitional and Cumulative Success Probabilities for Vaccines

Transition Probability	
Preclinical to Phase 1	0.57
Phase 1 to Phase II	0.72
Phase II to Phase III	0.79
Phase III to Registration	0.71
Registration to Launch	0.96
Cumulative Launch Probability	
Preclinical to Launch	0.22
Phase I to Launch	0.39
Phase II to Launch	0.64
Phase III to Launch	0.68
Registration to Launch	0.96

Social Problems for the 21st Century

- Safety and Acceptance
- Cost and Availability
- Sufficient Production

Safety Issues

- Less and less tolerance of reactions
- Higher and higher levels of regulation
- False issues may be as costly as true issues

Critical Needs for Vaccinovigilance

- More epidemiologic studies of background incidence of serious events (e.g. Guillain-Barré, myocarditis)
- Better vaccinovigilance in low income countries
- Phase IV studies including 1 million vaccinees

For New Vaccines, Prices Can Only be Higher

↑ R&D Costs ↑ Risks ↑ Length of Development

↑ Cost of Patents

↑ Regulatory Requirements / Quality impacts

Current estimate per vaccine: $500-800 million

Vaccines for Poor Countries

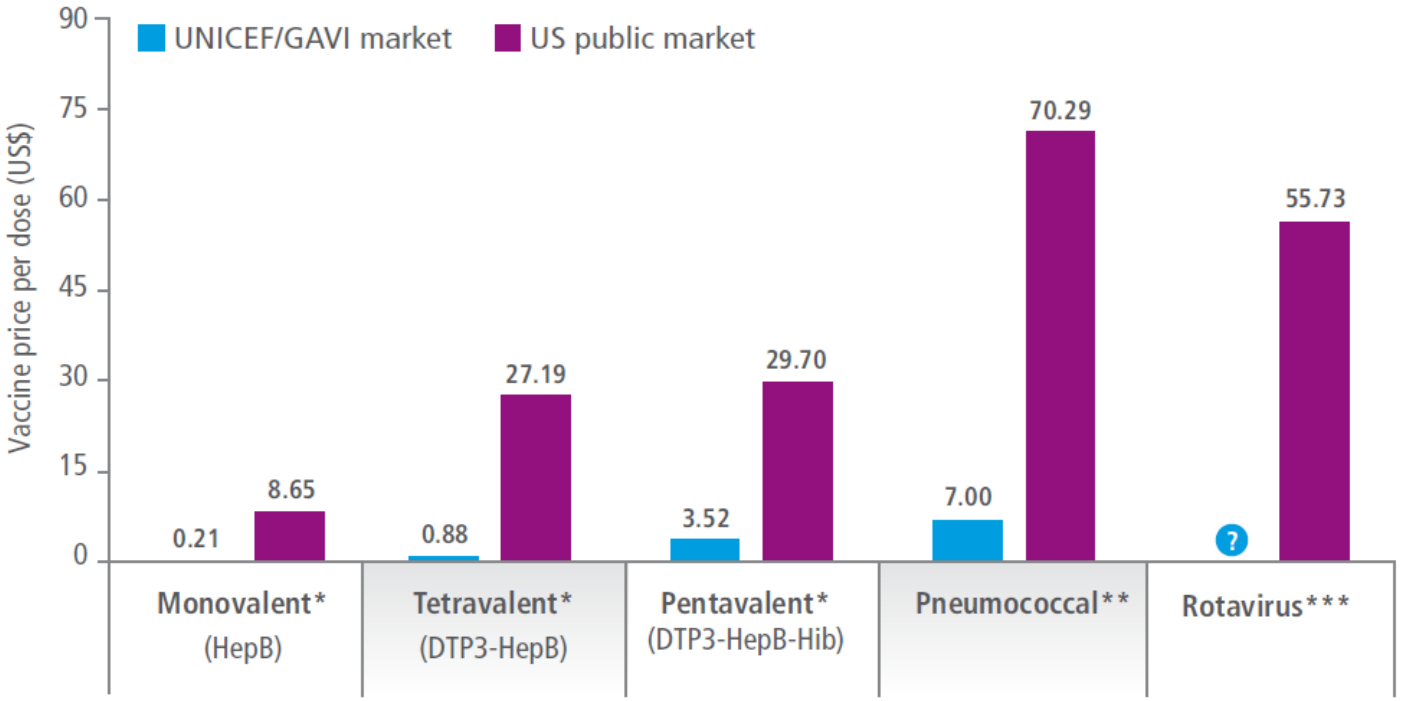
1) Tiered pricing

2) Local manufacture

3) Donations by rich countries or philanthropists

4) More investment by governments

The Free Market has Given Rise to Tiered Pricing



* Average price per dose for 3-dose vaccines between 2006-2009

** 2010 price for 7-valent vaccines (US public market) and price for AMC vaccines (UNICEF/GAVI market)

*** 2010 average price per dose assuming 3-dose equivalence among available products (US public market)

Source: UNICEF Supply Division, CDC Vaccine Price List[137]

Vaccine Supply

- Limited production facilities
- Large capital investment needed
- Need for new factories/producers in developing countries or pharmaceutical alliances

The Technical Problems in Vaccine Development

Problem	Example
Pathogen variability	Influenza
Short effector memory	Pertussis
Functional Response	HIV
Microbiome	Rotavirus
Unknown CoP	Dengue
Complex antigens	CMV
Unknown structure	RSV
Mucosal immunity	Many
T-Cell immunity	Malaria, TB

Coalition for Epidemic Preparedness Innovations

Norwegian Ministry of Foreign Affairs

BILL & MELINDA GATES foundation

wellcome trust

WORLD ECONOMIC FORUM

DEPARTMENT OF BIOTECHNOLOGY
Ministry of Science & Technology

“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

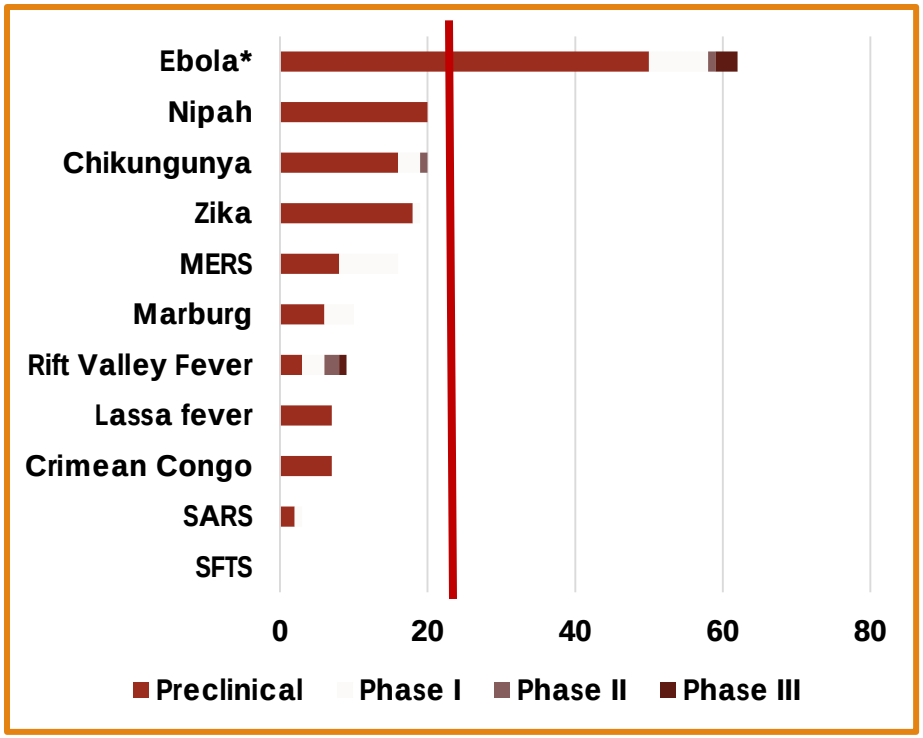
- Unilateral, uncoordinated government efforts to fund R&D preparedness are inefficient and unsustainable in addressing global epidemic risks

3

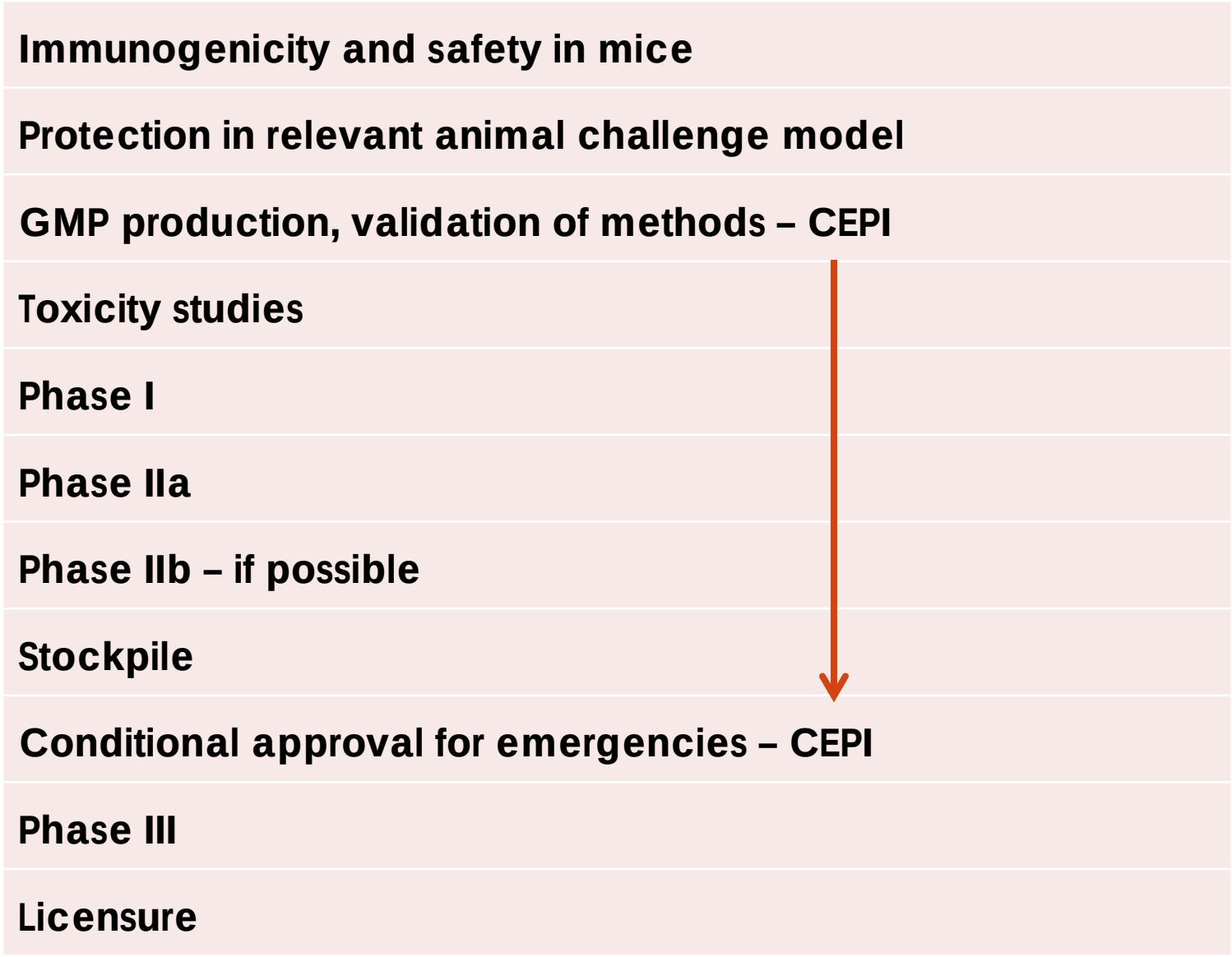
- Clinical & regulatory pathways are not easily adaptable to epidemic contexts

4

- Incentives are lacking to motivate greater industry engagement



Stages of Development



Most Important Criteria

Criteria	Comment to interpretation
Protection in a relevant animal model	Protection in mice also scored but rated lower than protection in models closer to humans.
Evidence for a correlate of protection	Preferably inferred from data in humans, but also counted if inferred from animal or natural history data.
A viable platform for vaccine manufacture exists	Preferably more than one. If the proposed vaccine was accomplished by an important technological advance in vaccinology that could be applied to other vaccines its score was increased.

CEPI Subgroup Recommendations

Immediate Funding

Chikungunya
Coronaviruses (MERS and SARS)
Filoviruses (Ebola strains and Marburg)
Rift Valley Fever
West Nile

Later Funding

Lassa
Nipa
Paratyphoid A
Plague

Not Yet

Crimean-Congo Hemorrhagic Fever
Severe Fever with Thrombocytopenia
Zika (but moving fast)

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)
- Securing initial commitments and contributions for CEPI launch
- Davos, January 2017
- G7 Summit, May 2017
- G20 Summit, July 2017