

# Viruses in May 2009

*Developing Vaccines – it is harder  
than you think*

Dick Strugnell  
Microbiology & Immunology  
University of Melbourne

# Me

- PhD in *Treponema pallidum* 1985
- Post-doc in UK inc. Wellcome Biotech
- Monash then Melbourne Universities
- CRC for Vaccine Technology inc. CSL (13 years)
- Editor of VACCINE
- VacTX
- SingVax
- Research bacterial pathogenesis

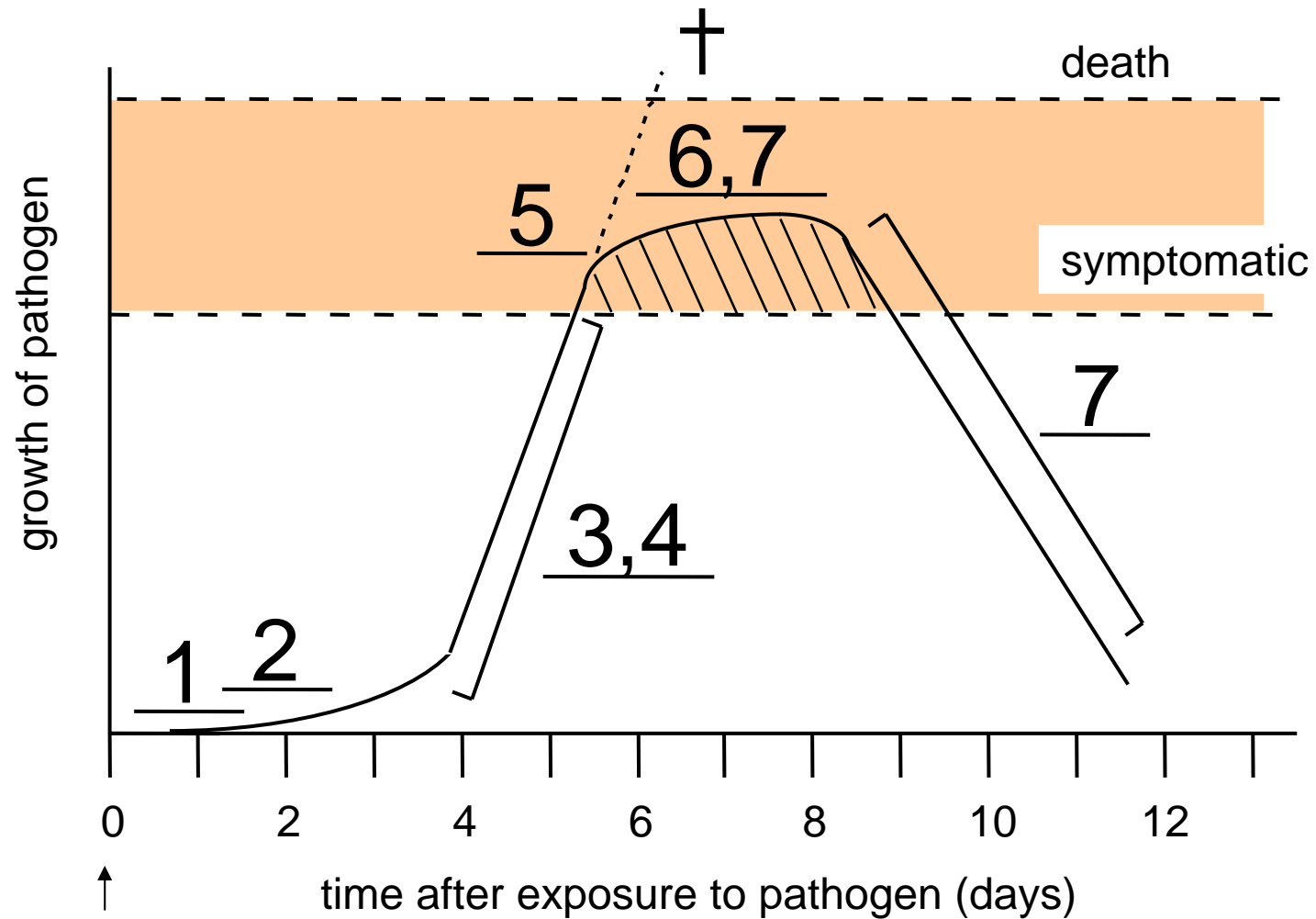
# Outline

- What vaccines do
- What vaccines might do
- Value of vaccines and who makes them
- Vaccine development process
- Drivers for selecting vaccines over drugs
- The vaccines market
- Influenza vaccines

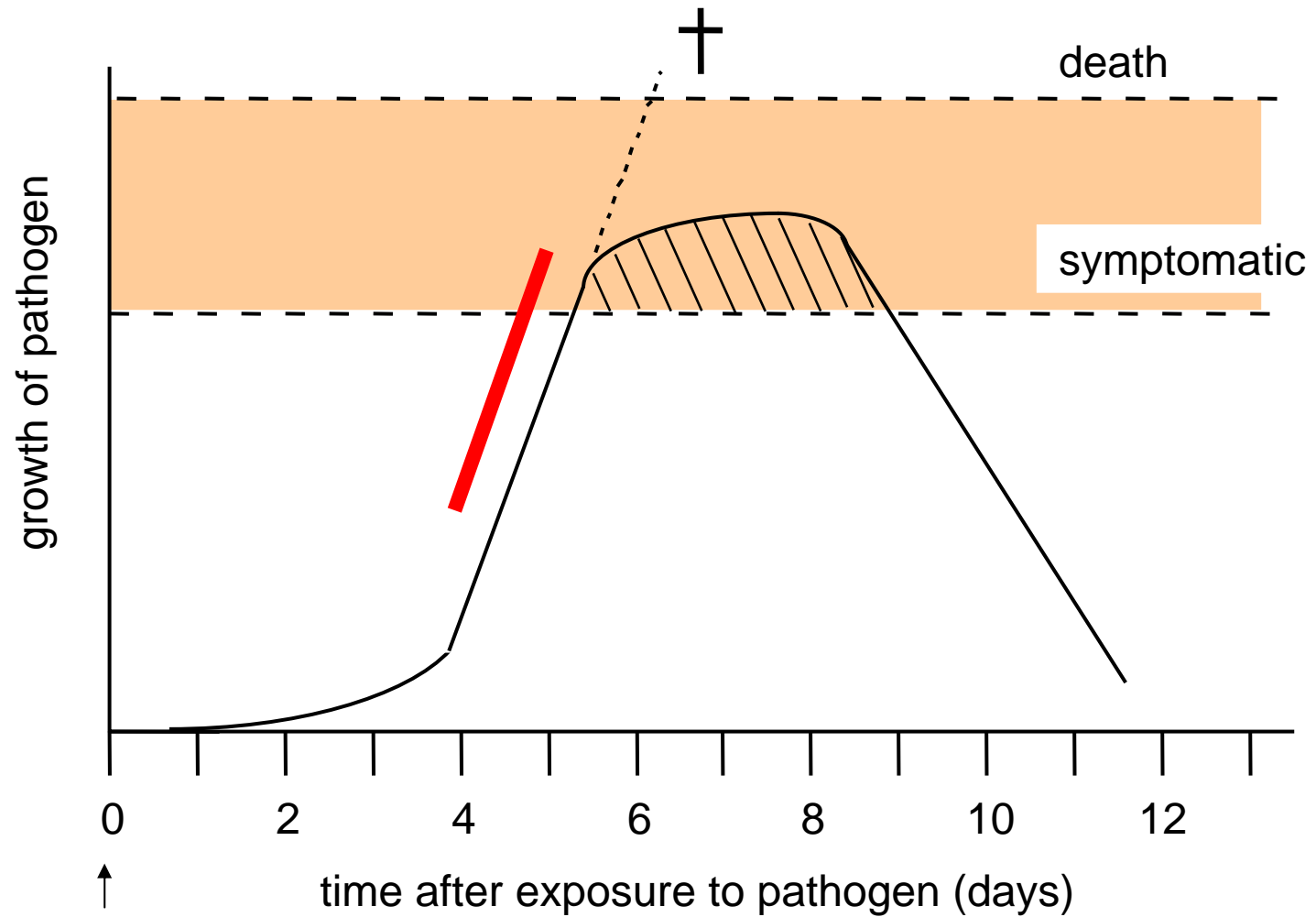
# What vaccines do

- Prevent disease (rarely infection) by antibodies and CTLs in some viral infections (e.g. Herpes)
  - usually no mucosal immunity (? Sabin)
- Usually given to the very young (consent?)
- Given multiple times, in combinations
- Protect humans against viral and bacterial infections
- Inhibit transmission
- Individual and population health roles

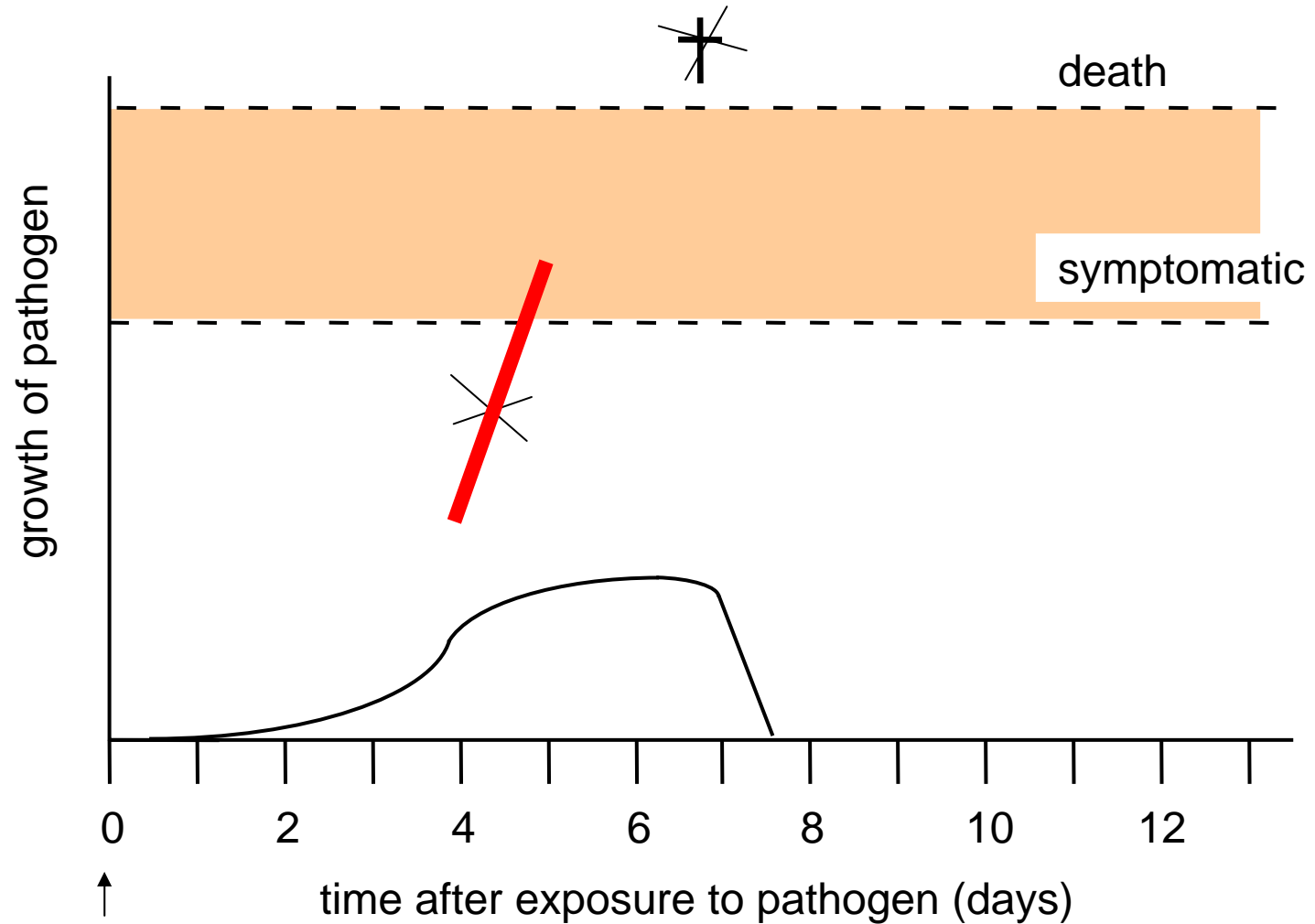
# The Pathogenic Process



# Transmission



# Vaccination inhibits transmission



## What vaccines might do

- Desensitization (IgE to IgG)
- Therapeutic vaccines
- Provenge – patients DCs are loaded with a protein from prostate cancer, returned to patient
- Immunocastration (Boar Taint, anti-GnRH)
- Control hormone-dependent cancers (anti-GnRH, anti-gastrin)
- Anti-EBV CTL in NPC.....





Boar taint is the contamination of male pig meat by two naturally occurring compounds - androstenone and skatole that are detected in pig meat by some people.

One of these pigs was vaccinated!

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# Vaccines are usually classed as “biologicals”

- New chemical entities are defined by formula (eg. mass spec) and are strictly controlled (exc. chiral forms)
- A biological cannot be subject to the same analysis – folding as important as mass
- Biological regulation is typically about the manufacturing process and the validated assays

# Vaccine Development Process

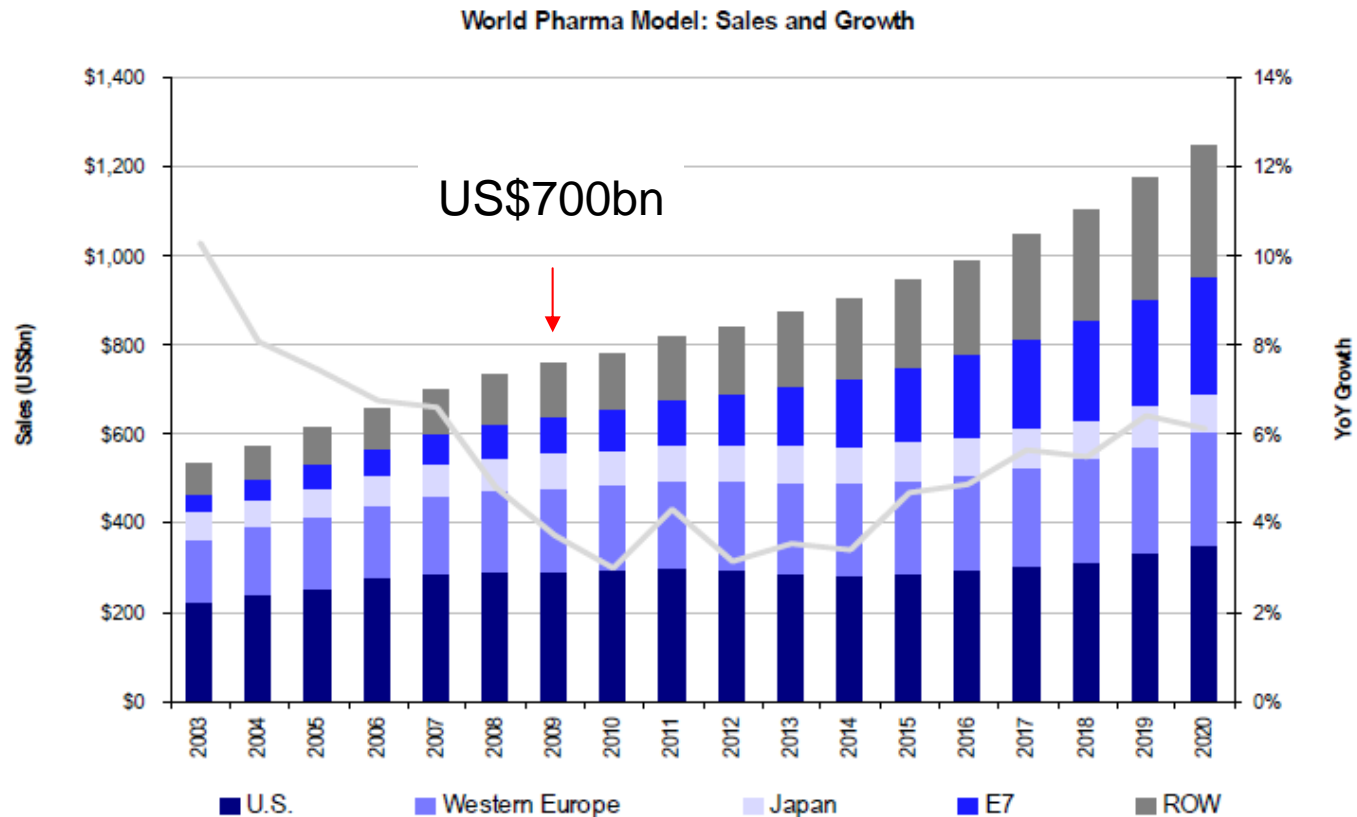
- Discovery phase – often @ University, MRI, IP?  
(antigen, delivery, adjuvant, combination)
- Project selection by Pharma/Biotech
- Preclinical development inc. release assays
- Clinical Development
  - Phase I (immunogenicity, safety)
  - Phase II (proof of concept)
  - Phase III (safety, efficacy)
- Registration, then post-registration trials

## Recent Phase III Trials

- Velcade, multiple myeloma 300 vs 300
  - Lipitor, high cholesterol 1,800 vs 250
- 
- HIV Ad5 (Merck) Phase II 1,500 vs 1,500
  - HPV (Merck) 5,200 vs 5,200
  - Hepatitis A 20,000 vs. 20,000  
*then cross over @ 18mo*
  - Rotavirus (Merck) 34,000 vs 34,000
  - Size of Phase III reflects disease incidence, seasonal differences major problem

# World Pharma Market

UBS World Pharma Model – absolute world pharma sales and YoY growth, 2003-2020



Source: IMS Health, IMF, US Census Bureau, BLS, US PTO, UBS estimates

# “Optimal” Pharmaceutical

- Chronic disease
- High penetration
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- Vaccine given once (+ boosters)
- Patients are “well”
- Incidence can vary and decrease



# Vaccines are a growing business

- Small part of global Pharma market
- Were viewed as low cost, commodity products
- Long development cycle
- Very large Phase III trials

BUT

- ‘Protected’ against generics
- Pricing more favourable – Pevnar, then Gardasil
- Preventative medicine numbers are favourable

## What do they cost? (Tufts 2006)

- **Average Cost to Develop a New Biotechnology Product Is \$1.2 Billion**
- Average out-of-pocket cost (cash outlays) per approved biopharmaceutical for the **preclinical** period totalled **\$198 million** (capitalized @ \$615 million).
- Average out-of-pocket **clinical** period cost per approved biopharmaceutical was **\$361 million** (capitalized @ \$626 million).
- Biotech products take **97.7** months for clinical development and regulatory review (8% longer than for pharmaceuticals) – **what is the life of a patent?**
- Biopharmaceuticals had an overall clinical approval success rate of **30.2%** vs. 21.5% for traditional Pharma firm pipelines.

<http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69>

# Who makes vaccines?

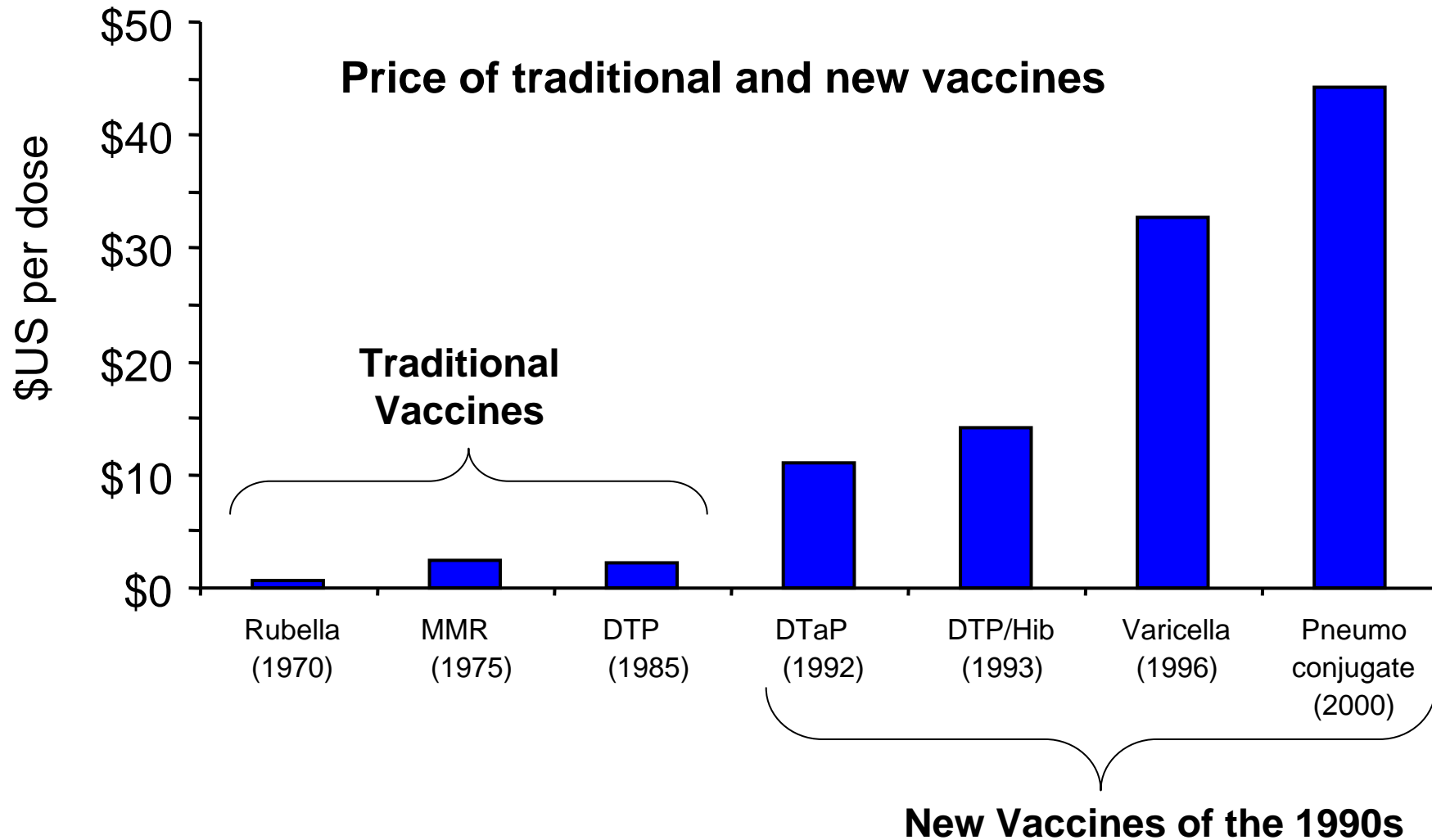
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- Sanofi  
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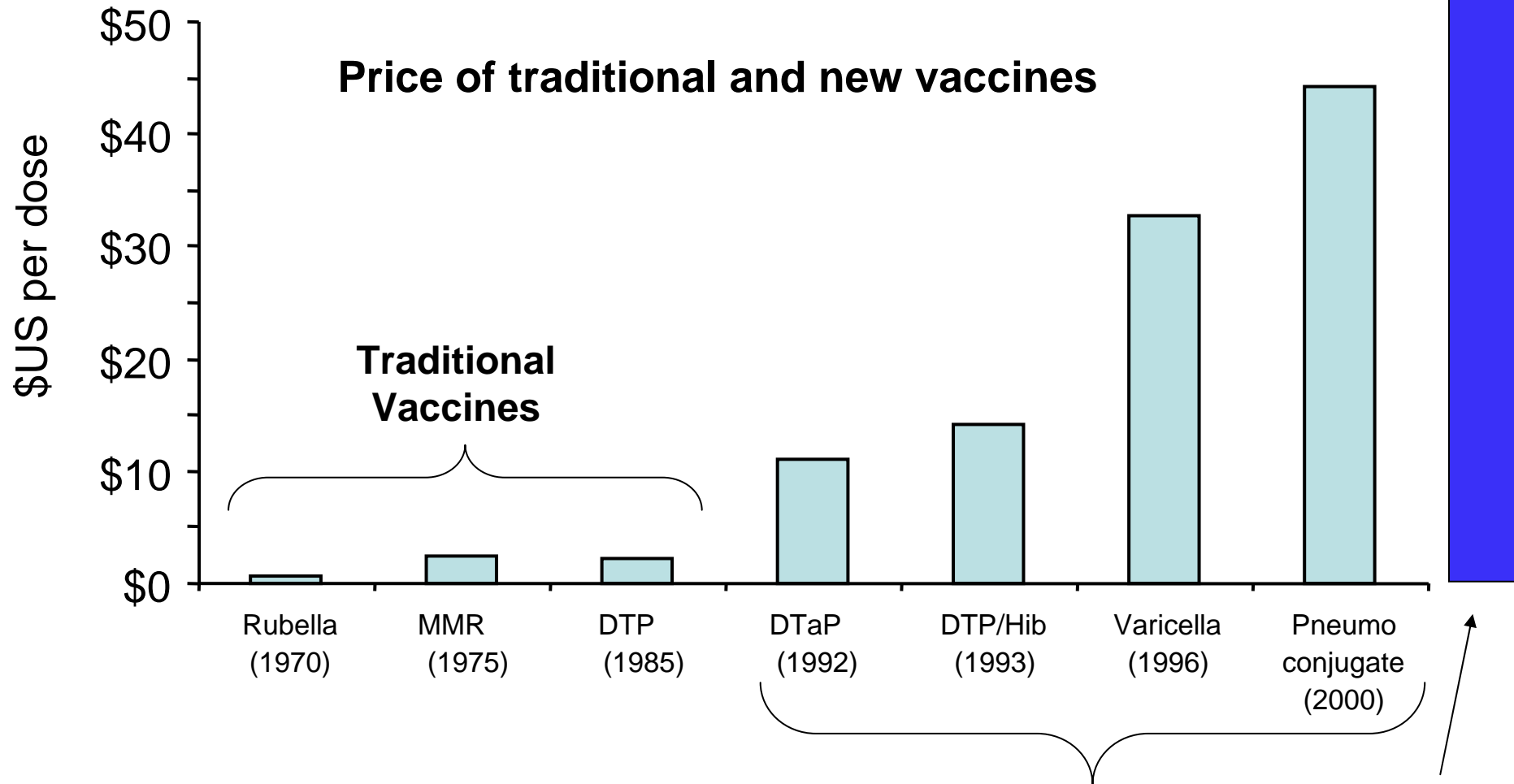
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less  
fractionated  
markets are  
“more efficient”

# Prices for newer vaccines are more than for traditional vaccines



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	2004A	2009E
<b>AstraZeneca (\$ mm)</b>		
FluMist	0	124
<b>GlaxoSmithKline (\$ mm)</b>		
Cervarix	-	518
Therapeutic cancer vaccines	-	-
Flu vaccines (Fluarix, flu improved, pandemic)	-	468
Synflorix (formerly Streptorix)	-	136
Hepatitis	755	1,152
Kinrix, Infanrix, Pediarix, Boostrix	660	1,410
Rotarix	-	422
Other	798	1,102
<b>Total</b>	<b>2,213</b>	<b>5,208</b>
<b>MERCK/Schering-Plough (\$ mm)</b>		
Hepatitis Vaccines	196	270
Viral Vaccines	555	1,550
Gardasil (HPV vaccine) ex. EU	-	1,740
Rotateq (rotavirus vaccine) ex. EU	-	620
Zostavax (shingles vaccine) ex. EU	-	500
Other Vaccines	283	465
<b>Total</b>	<b>1,034</b>	<b>5,145</b>
<b>Novartis (Chiron) (\$ mm)</b>		
Menveo	0	281
MenB	0	0
Other	468	1,873
<b>Total</b>	<b>468</b>	<b>2,155</b>
<b>Sanofi-Aventis (\$ mm)</b>		
Pediatric combination vaccines	646	1,112
Flu vaccines	650	980
Travel vaccines	183	419
Meningitis / pneumonia vaccines	107	702
Adult boosters	216	557
Trovax	-	-
All other	215	263
<b>Total</b>	<b>2,017</b>	<b>4,032</b>
<b>Pfizer-Wyeth (\$ mm)</b>		
Total Prevnar	1,054	2,940
<b>Other (\$ mm)</b>		
	1,357	3,142 10.0%
<b>Total (\$ mm)</b>	<b>8,143</b>	<b>22,746</b>

2004A  
US\$8.1bn

2009E  
US\$22.7bn

# Pharmacoeconomics

**Chart 36: Vaccines continue to prove exceptionally cost-effective**

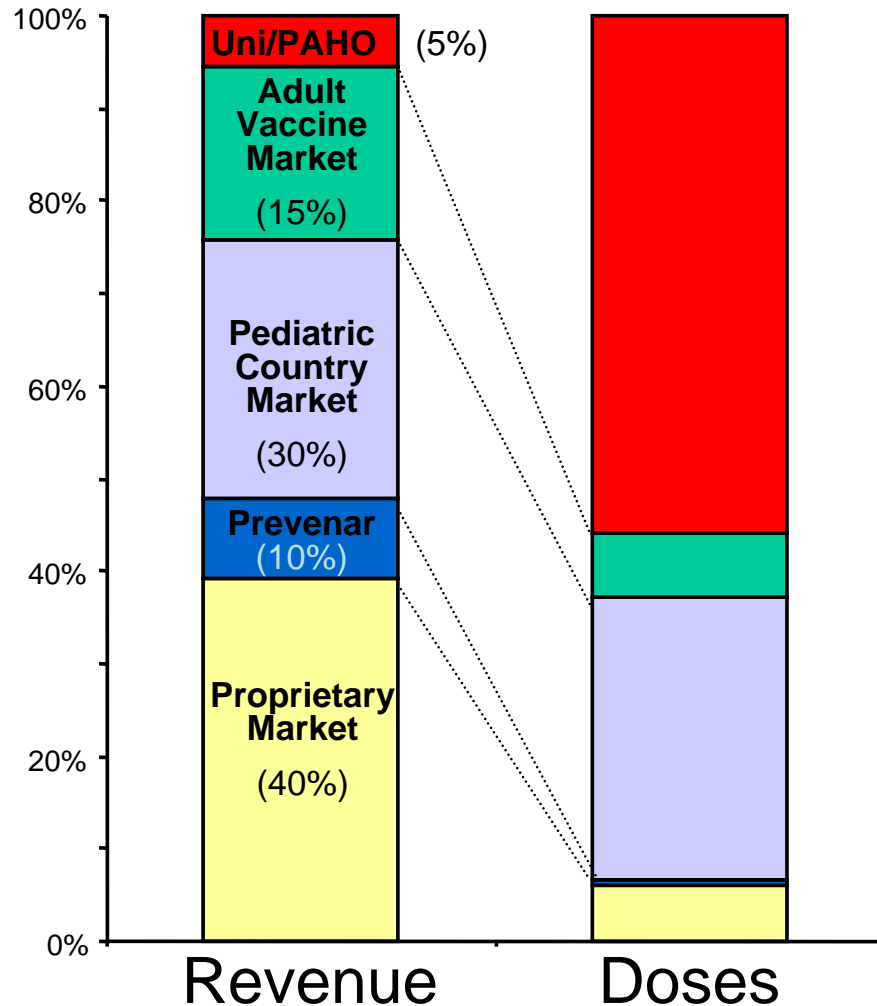
Vaccination program or other preventive service	Benefit-cost	Dollars per life	Dollars per QALY
Diphtheria, tetanus, pertussis, Haemophilus influenzae type B (Hib), polio, measles, mumps, rubella, and hepatitis B—combined program	17		
Varicella vaccination	5		
Pneumococcal conjugate vaccination		128,000	6,500
Influenza vaccination of children ages 6–23 months			13,000
Pertussis vaccination of adolescents			20,000
Mammography for women ages 50–69		29,000	
Pap screening with human papillomavirus testing for cervical cancer			80,000
Colorectal cancer screening for people age 50 or older using sigmoidoscopy		90,000	
Mammography for women ages 40–69		140,000	

Source: TA Lieu *et al.* *Health Affairs*, 2005; 24(3): 666-679



# The vaccine market is complex

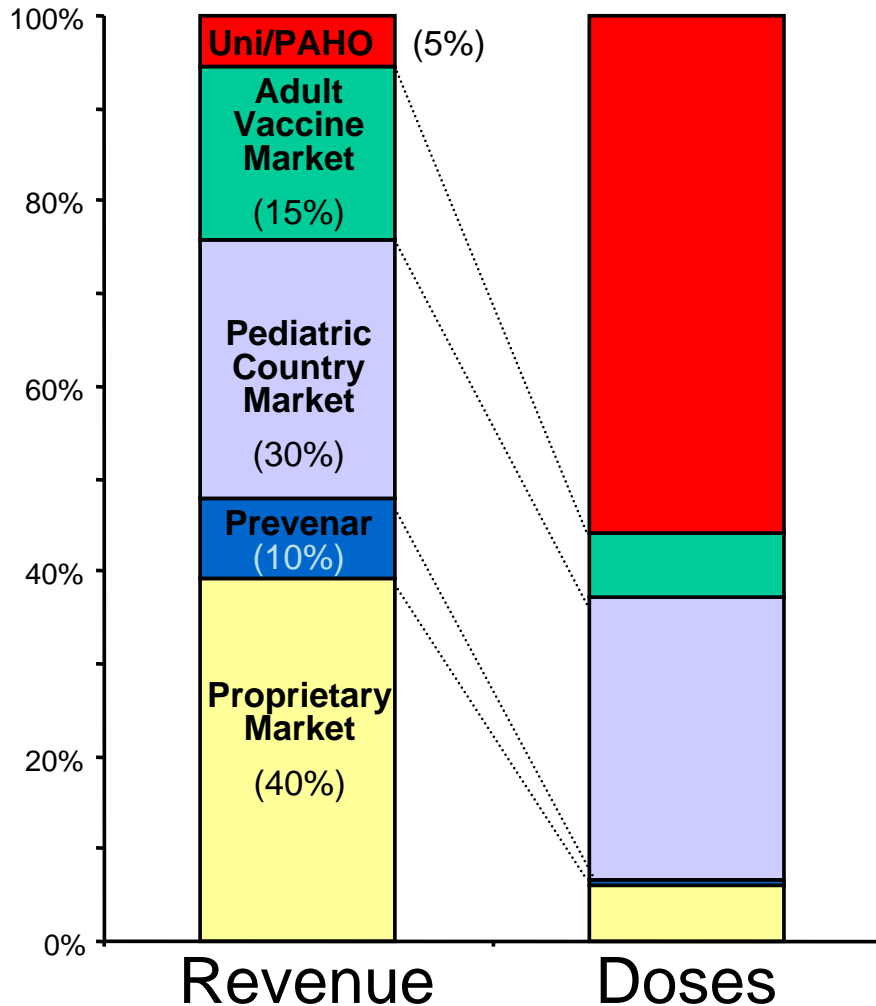
**Vaccine market**



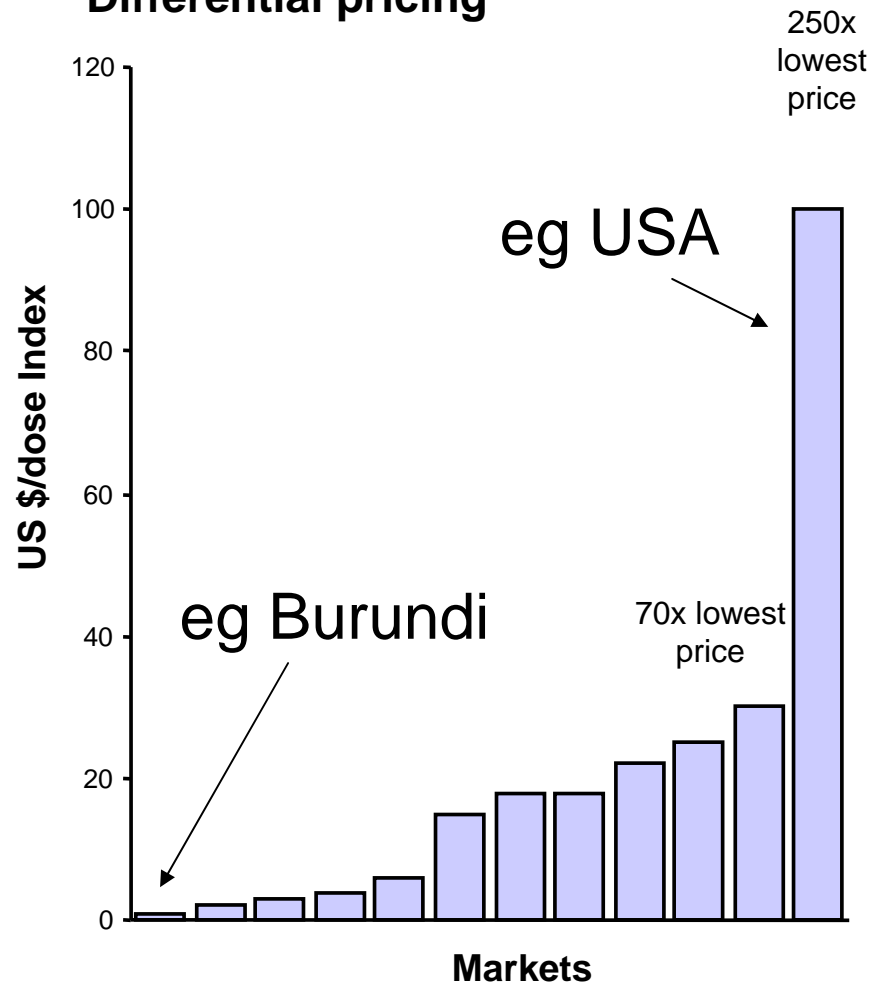
UNICEF and PAHO account for 5% of the revenues and roughly 50% of the volume

# Differential Pricing - paying for developing country vaccines

Vaccine market

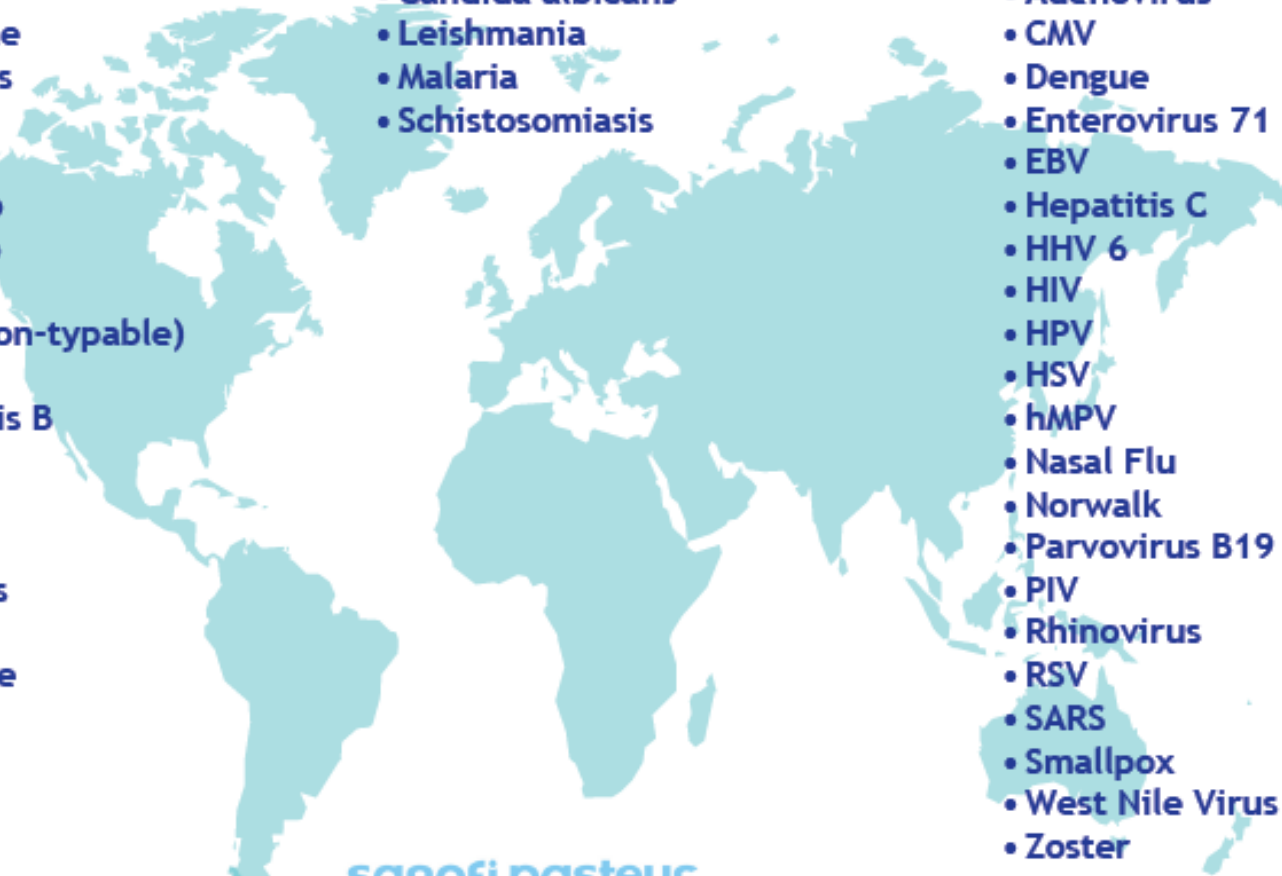


Differential pricing



# Pipeline

**There Remain Approximately 50 Targets Without a Vaccine  
(or Where Existing Vaccines Could be Improved)**

- 
- Anthrax
  - C. pneumoniae
  - C. trachomatis
  - E. coli (UTI)
  - ETEC
  - Group A Strep
  - Group B Strep
  - Haemophilus influenzae (Non-typable)
  - H. pylori
  - N. meningitidis B
  - P. acnes
  - P. aeruginosa
  - S. aureus
  - S. epidermidis
  - S. mutans
  - S. pneumoniae
  - Salmonella
  - Shigella
  - TB
  - V. cholerae
  - Candida albicans
  - Leishmania
  - Malaria
  - Schistosomiasis
  - Adenovirus
  - CMV
  - Dengue
  - Enterovirus 71
  - EBV
  - Hepatitis C
  - HHV 6
  - HIV
  - HPV
  - HSV
  - hMPV
  - Nasal Flu
  - Norwalk
  - Parvovirus B19
  - PIV
  - Rhinovirus
  - RSV
  - SARS
  - Smallpox
  - West Nile Virus
  - Zoster

April 15, 07

sanofi pasteur

The vaccines business of sanofi-aventis Group

# Outline

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- **Influenza vaccines**

# Influenza

- Method of manufacture regulated
- Product undergoes very limited testing
- Made in eggs (and cell culture)
- Given as a 'split' inactivated vaccine or live attenuated vaccine (nasal spray)
- Changed every year (antigenic drift)
- 4-5 month manufacturing process

# US Influenza Vaccine Production Timeline

Jan      Mar      May      Jul      Sep      Nov

\*eggs (production system)

\*strain selection

\*production of concentrates

\*formulation, testing, FDA release

\*filling, testing

\*distribution

\*administration

# Influenza – pressure points

- Predicting the strains
- Getting eggs (H5 pandemic?)
- Making a hi yield reassortant virus
- Immunogenicity (H5 low)
- Few manufacturers of scale
- Competing international/national interests

# Conclusions

- Pharma are rethinking their strategy
- Vaccines are becoming very popular targets
- They work at disease prevention
- ? Develop vaccines that prevent infection
- They are expensive to develop
- Pricing is now reflecting this
- Lot of viruses for which we need better/new vaccines