Vaccines

- **What is a Vaccine ?**
- **How do Vaccines work ?**
- **The economics of Vaccines ?**
- **Do Vaccines prevent disease ?**
- **Where are new Vaccines needed ?**
- **What is hot in vaccine development ?**

Vaccines

Vaccines elicit immune responses

These responses:

- **prevent infectious diseases (ie. prophylaxis)**
- **cure existing infectious diseases (ie. therapeutic)**
- **block physiology (eg. anti-hormone, fertility...)**
- **prevent and cure cancers (eg. antiviral, anti-cancer)**
- **block autoimmune, allergic reactions (eg. desensitize)**

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Vaccines

Vaccines elicit immune responses

- **Systemic antibody - neutralize infectivity**
- **Secretory antibody - block initial adhesion**
- **Killer T cells (CTL, CD8+) - kill infected cells**
- **Helper T cells (Th, CD4+) - help B cells and CTL**

- **Type of immune response depends on the 'formulation'**
- **Live attenuated vaccines (eg. Sabin polio) = broad**
- **Adjuvanted subunit vaccine = narrow, improving**

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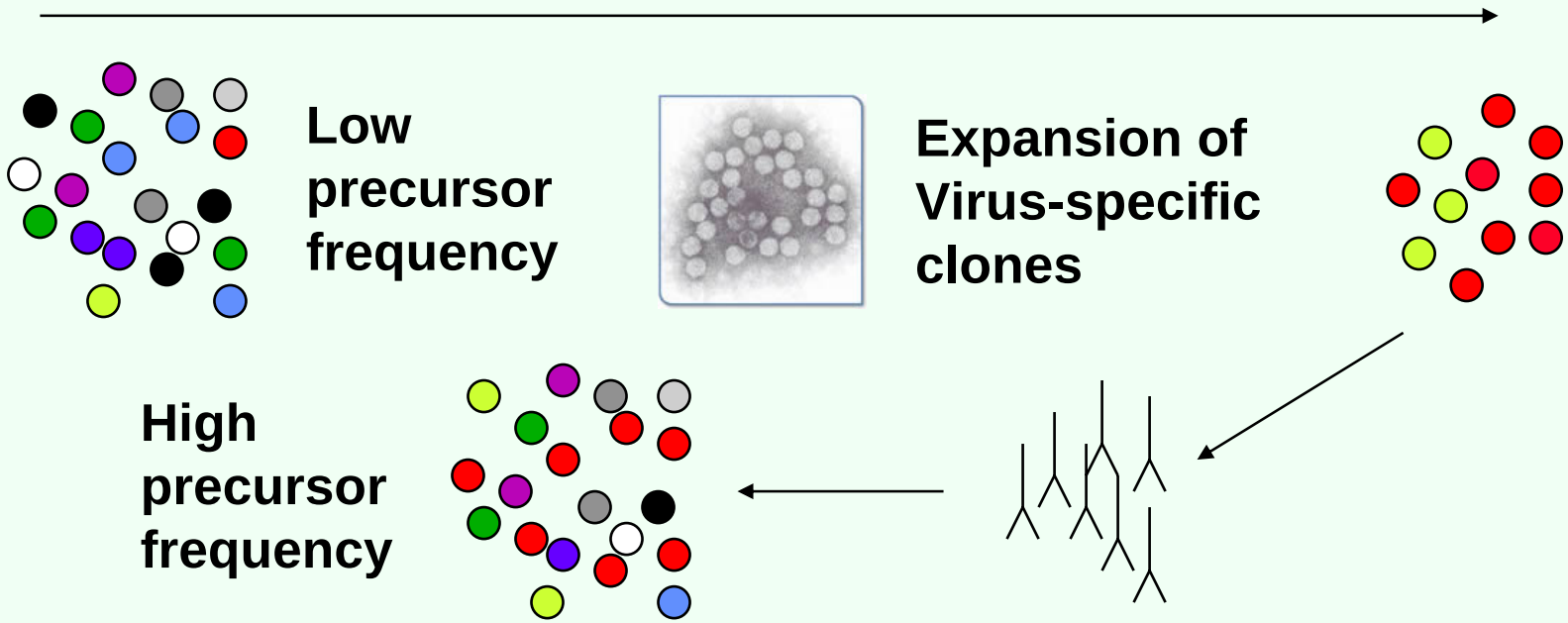
How do Vaccines work ?

Immunological Memory

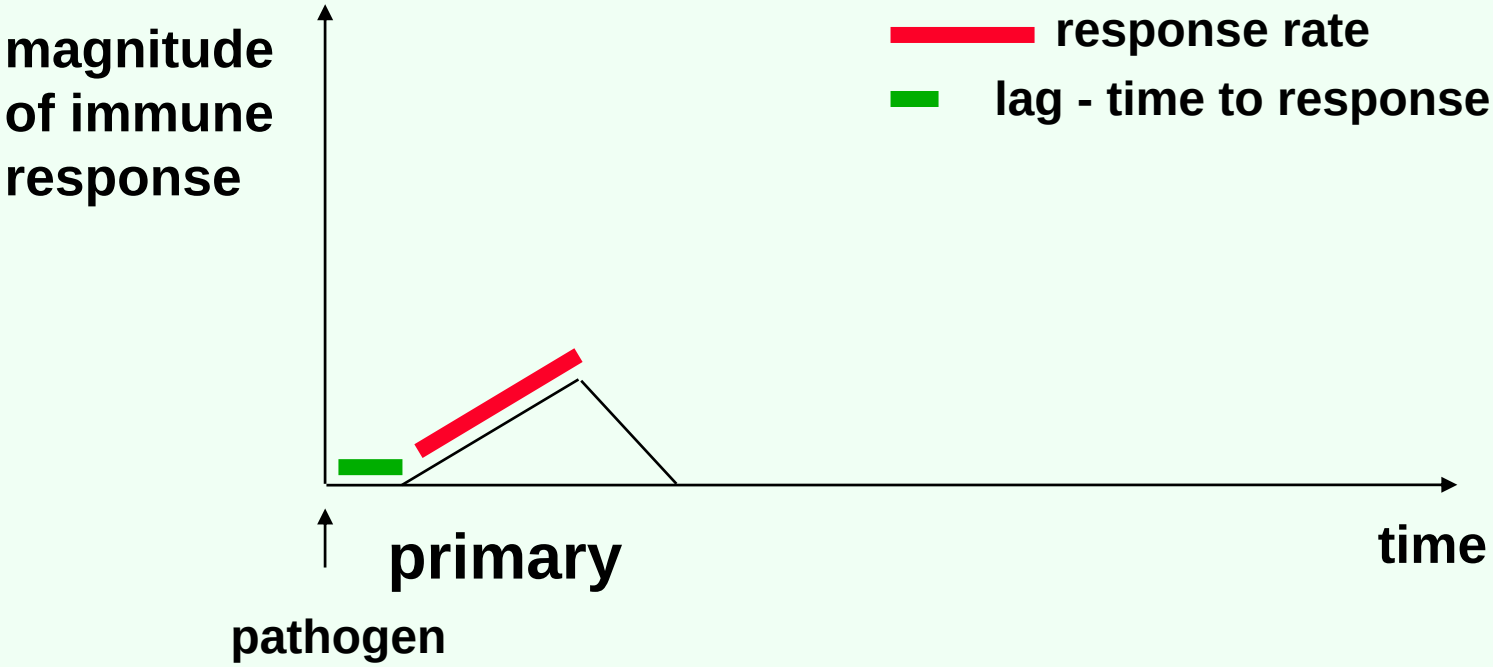


- **An immune response changes the pool of lymphocytes - increases frequency of some cells**

How do Vaccines work ?

Immunological memory (cont.)

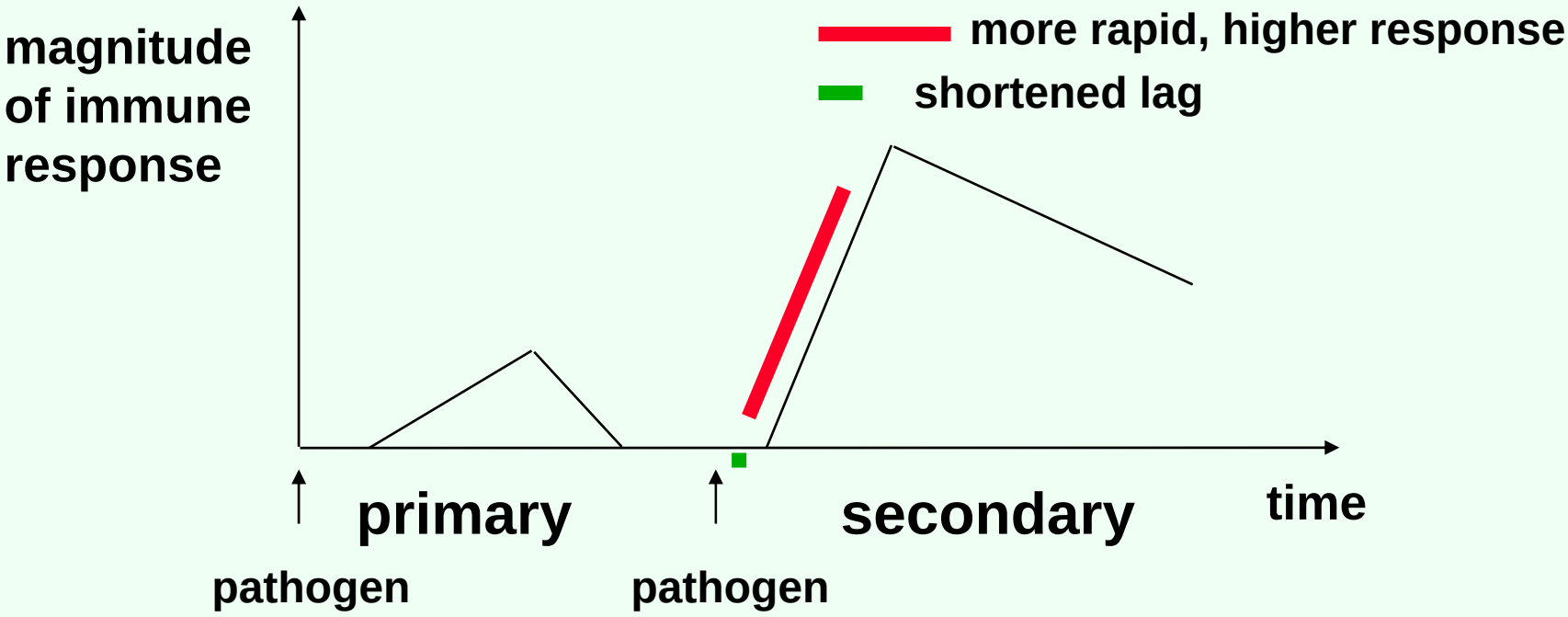
- The change in frequency of specific cells = change the kinetics of the immune response
- Organism seen for first time (= primary response)



How do Vaccines work ?

Immunological memory (cont.)

- **Organism seen for second time (secondary response)**
- **More rapid, higher immune response**



How do Vaccines work ?

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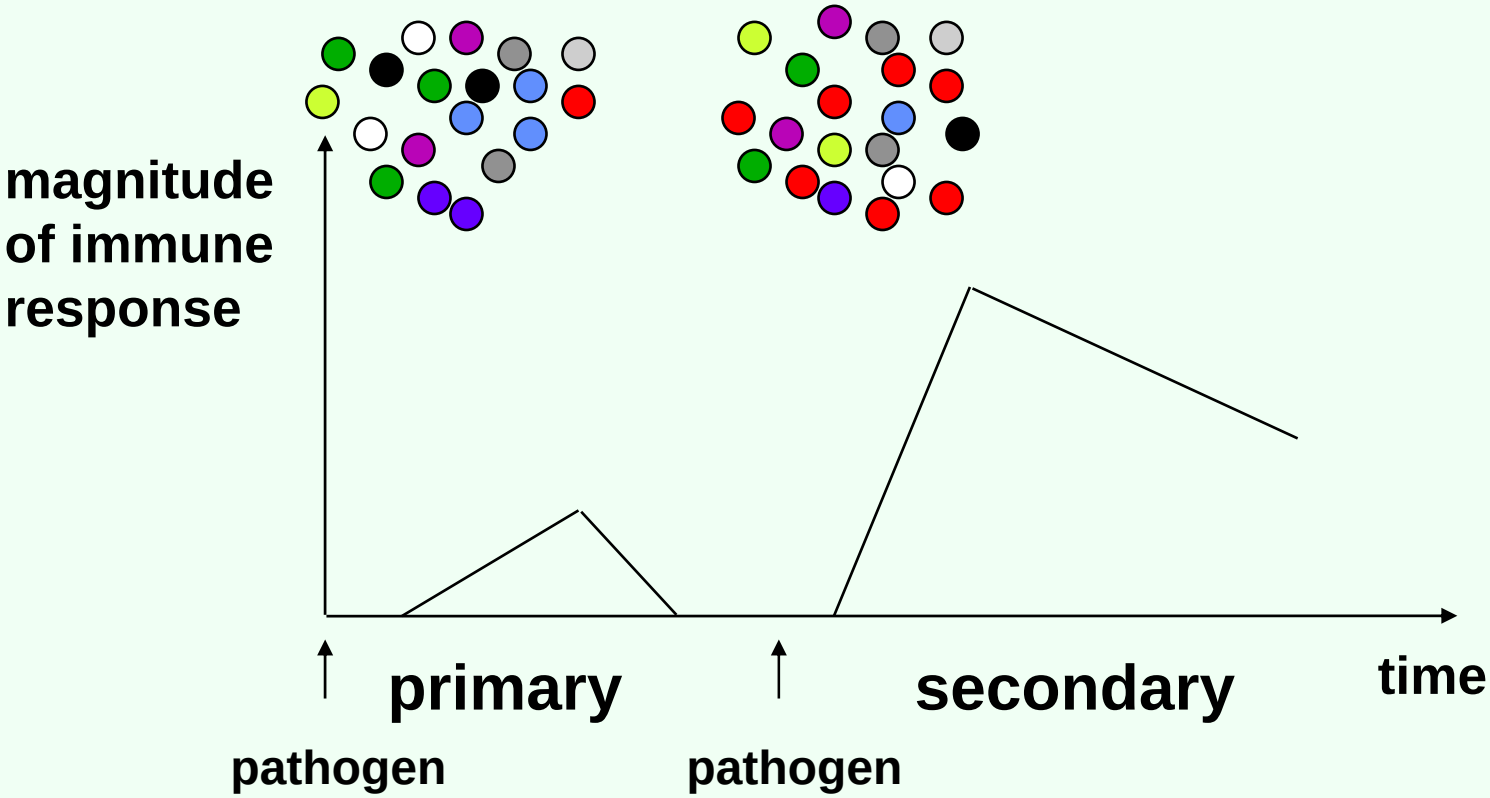
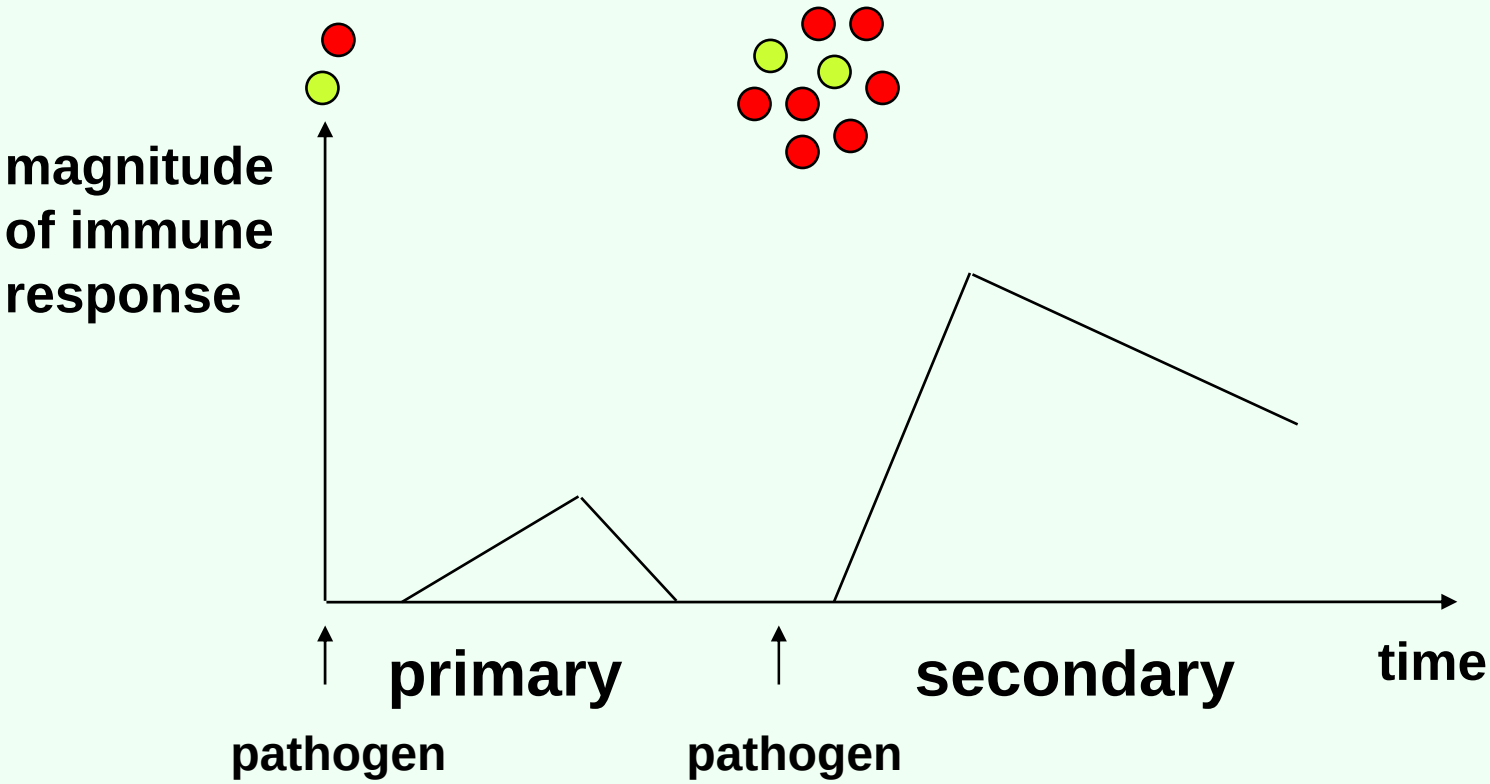


How do Vaccines work ?

Immunological memory (cont.)

- **Organised lymphoid tissues esp. lymph nodes**
- **Leads to increase in precursor frequency eg. pCTL**



How do Vaccines work ?

To increase the pCTL, specific B cell numbers..

4 strategies:

- ***a virus similar to the pathogen is used***
- ***a less virulent variant of the virus is used***
- ***only a part (subunit) of the pathogen is used***
- ***the virus is cultured, killed, then injected***

How do Vaccines work ?

To increase the pCTL, specific B cell numbers..

4 strategies:

- ***a virus similar to the pathogen is used***
- **eg. cowpox, vaccinia for smallpox, Sabin polio**
- ***a less virulent variant of the virus is used***
- **eg. measles, mumps, rubella**
- ***a part (subunit) of the virus is used***
- **eg. influenza split virus**
- ***the virus is cultured, killed, then injected***
- ***eg. Salk polio***

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The economics of vaccines

The 3 most effective health interventions are:

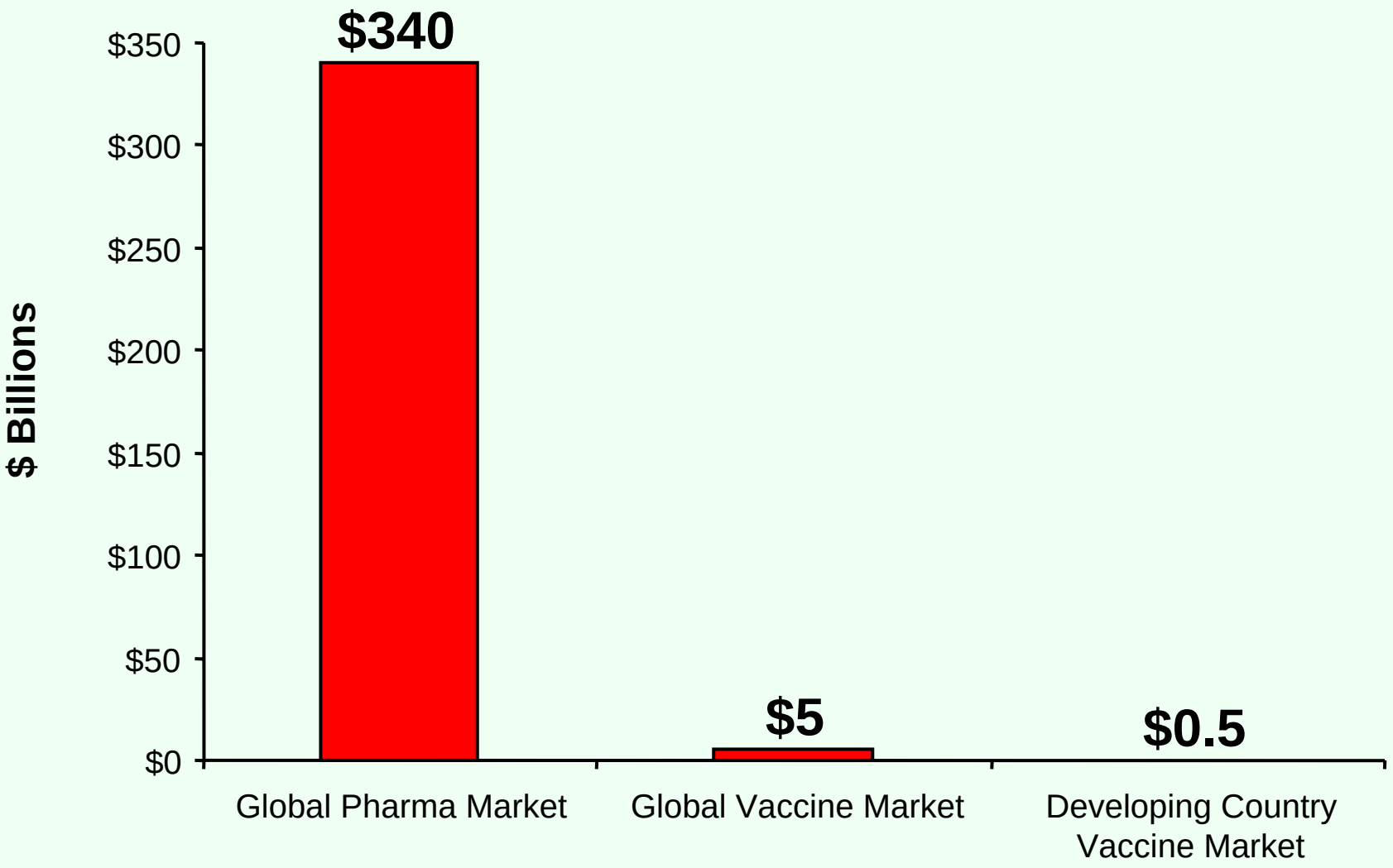
1. Provision of clean water
   (ie. preventing infectious diseases)

2. Anti-smoking campaigns
   (ie. preventing self harm)

3. Vaccination
   (ie. preventing infectious diseases)

BUT

Vaccines represent a VERY small percentage of global pharmaceutical sales

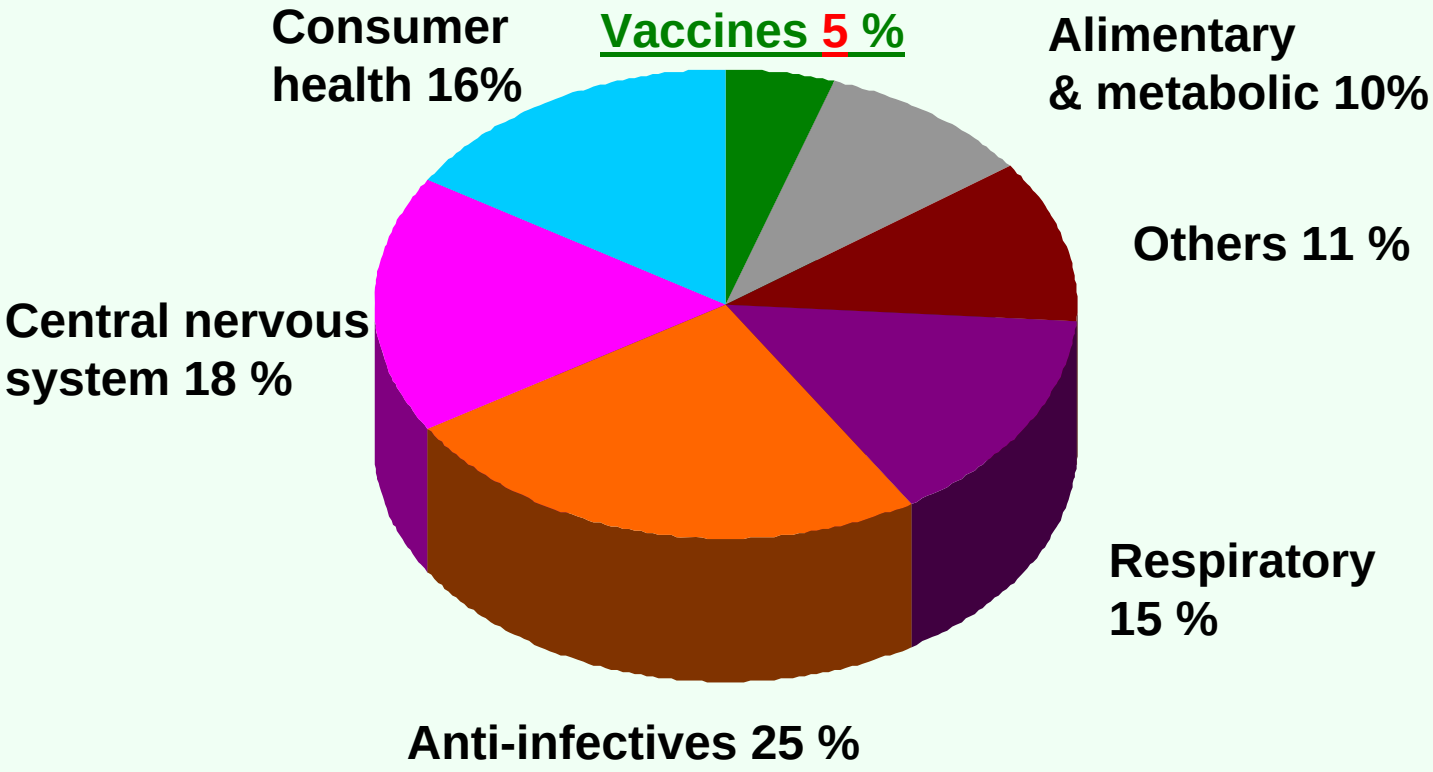


Amy Batson, Orphan Vaccines 2001

GlaxoSmithKline - breakdown of sales

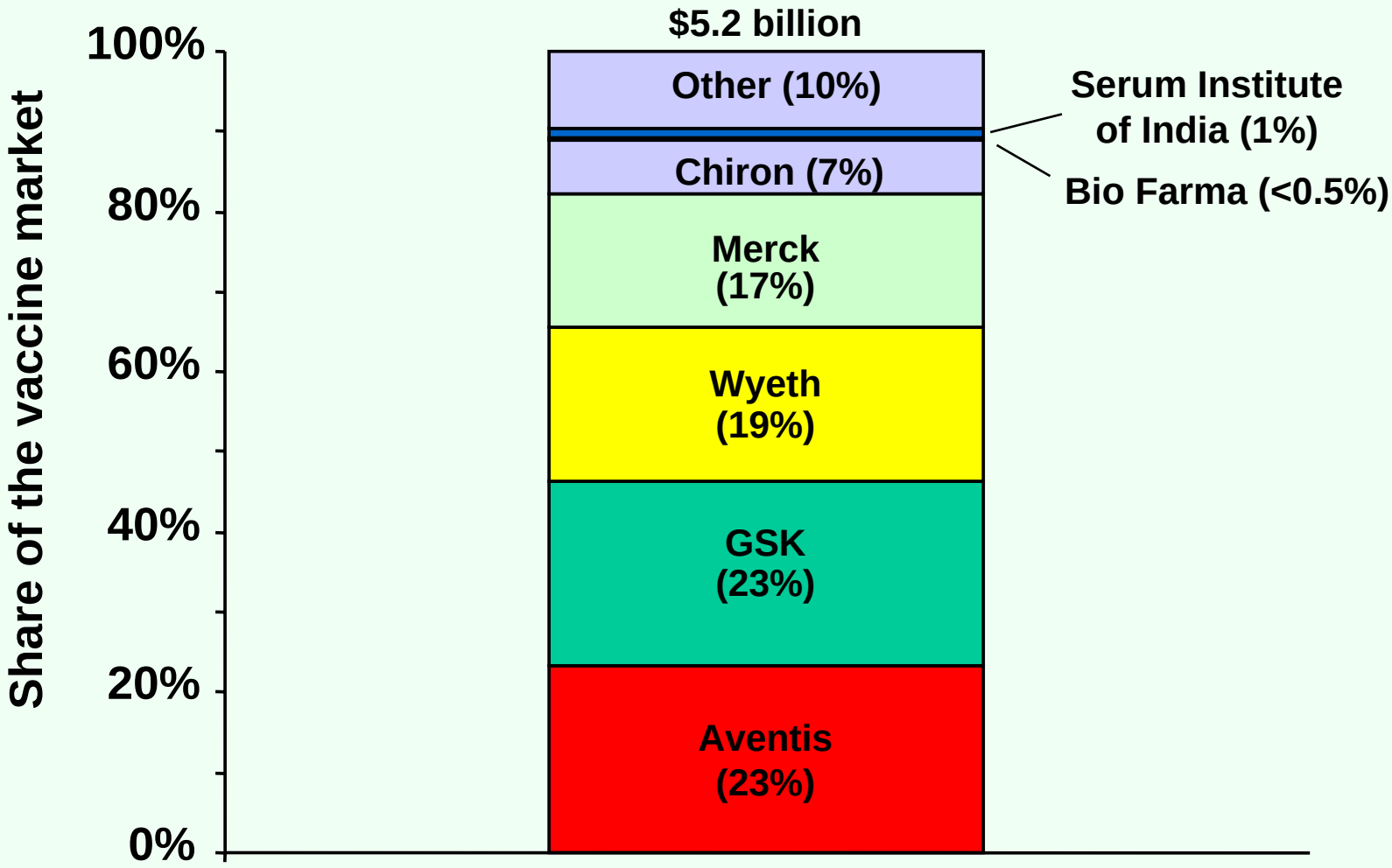
GSK Pharmaceuticals

Pro-forma sales: $27 billion (1999)



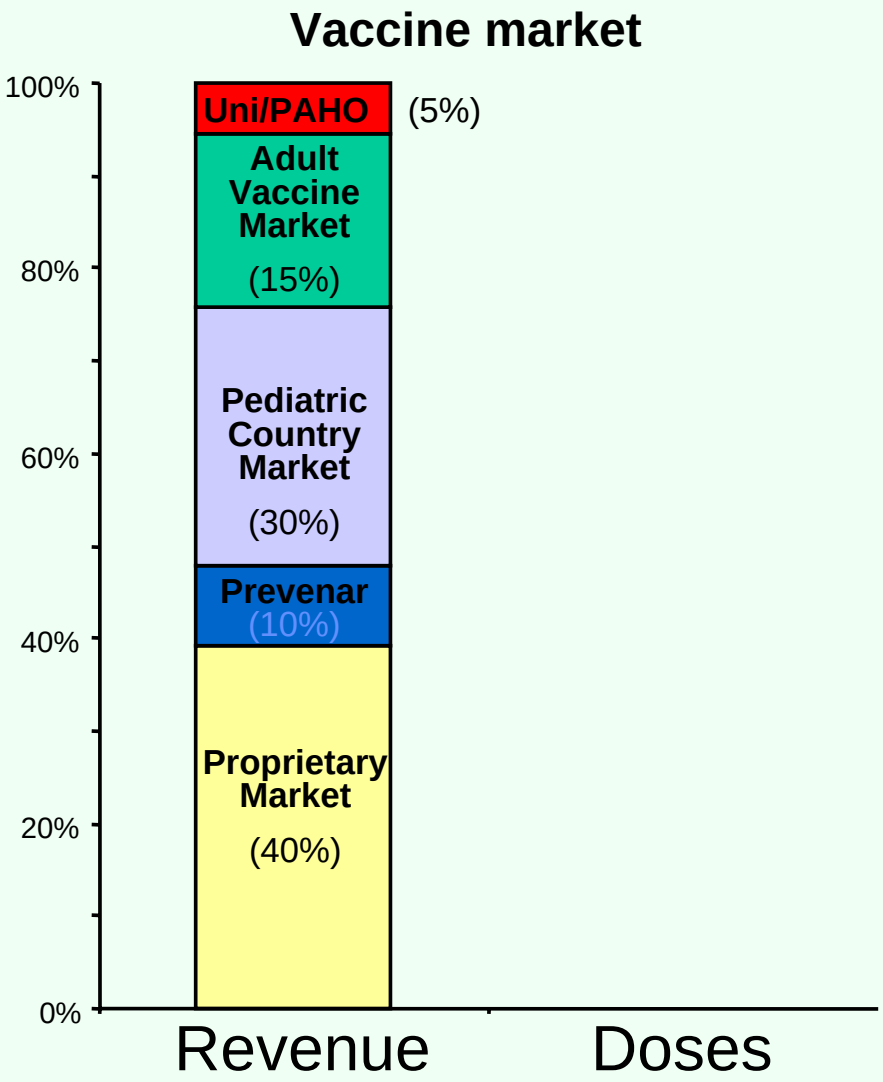
Amy Batson, Orphan Vaccines 2001

5 vaccine manufacturers control the vaccine market



Amy Batson, Orphan Vaccines 2001

The vaccine market is comprised of a number of distinct product and customer groups



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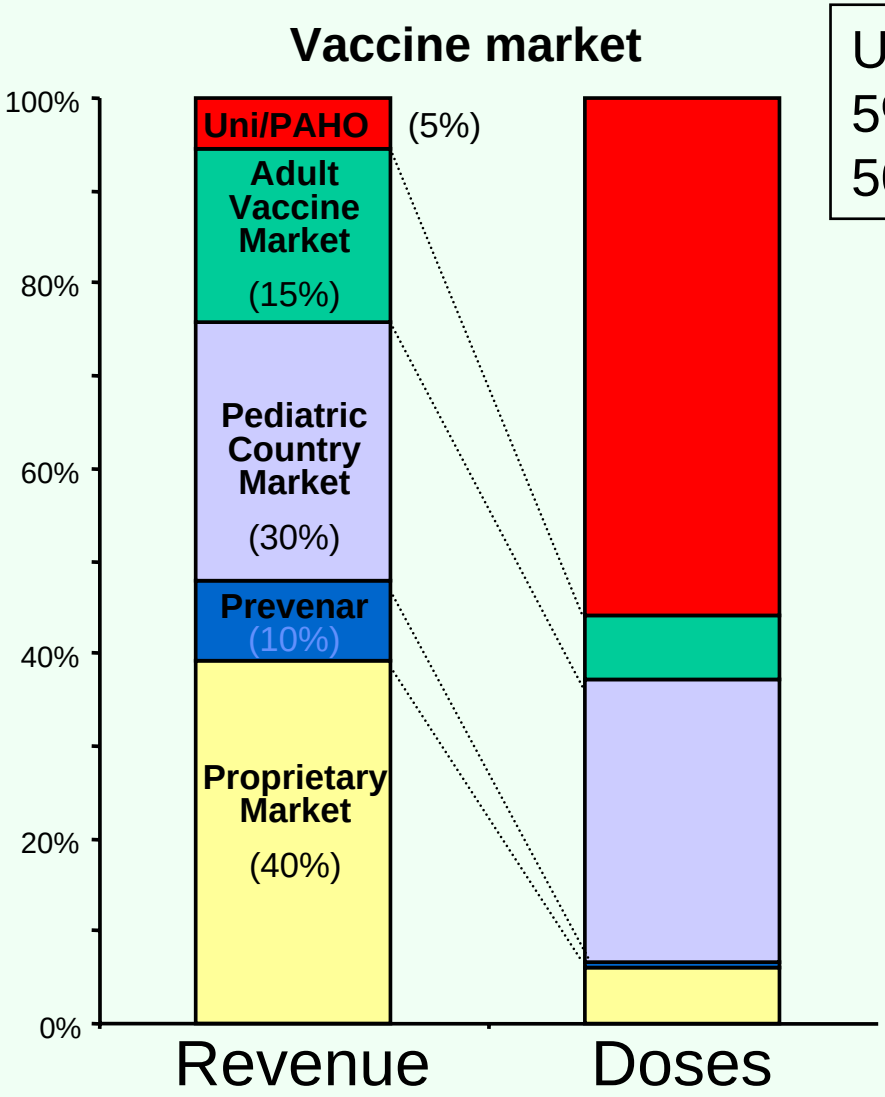

UNICEF and PAHO account for 5% of the revenues and roughly 50% of the volume

Amy Batson, Orphan Vaccines 2001

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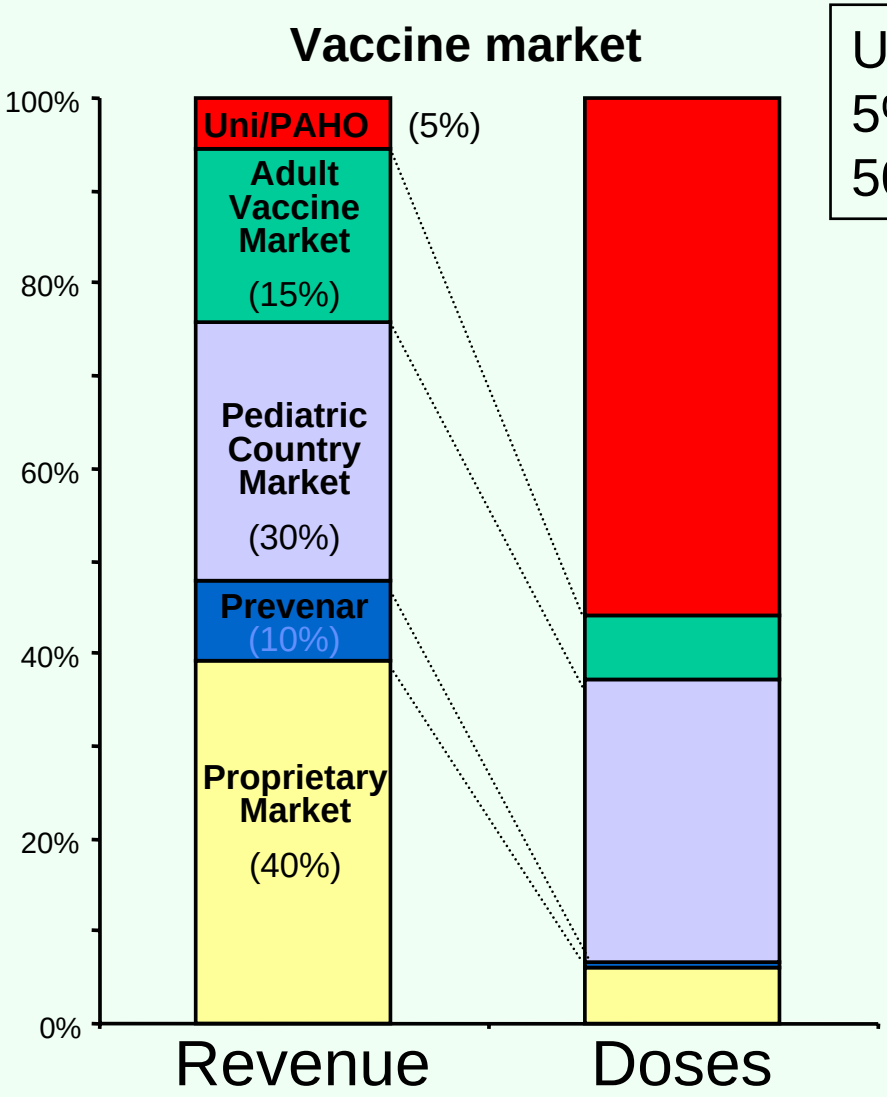

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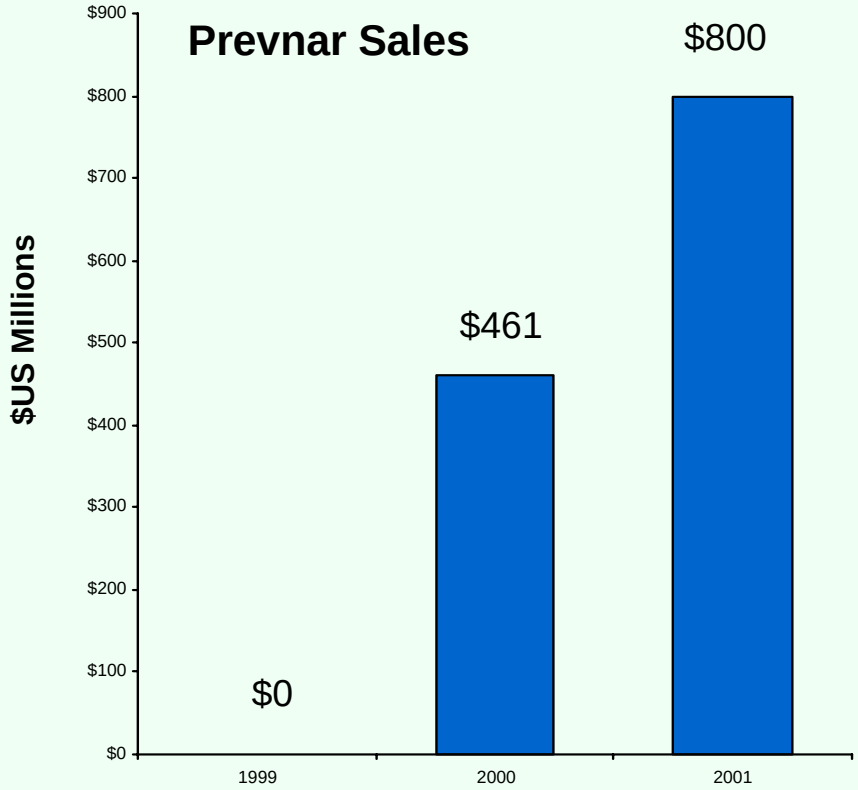
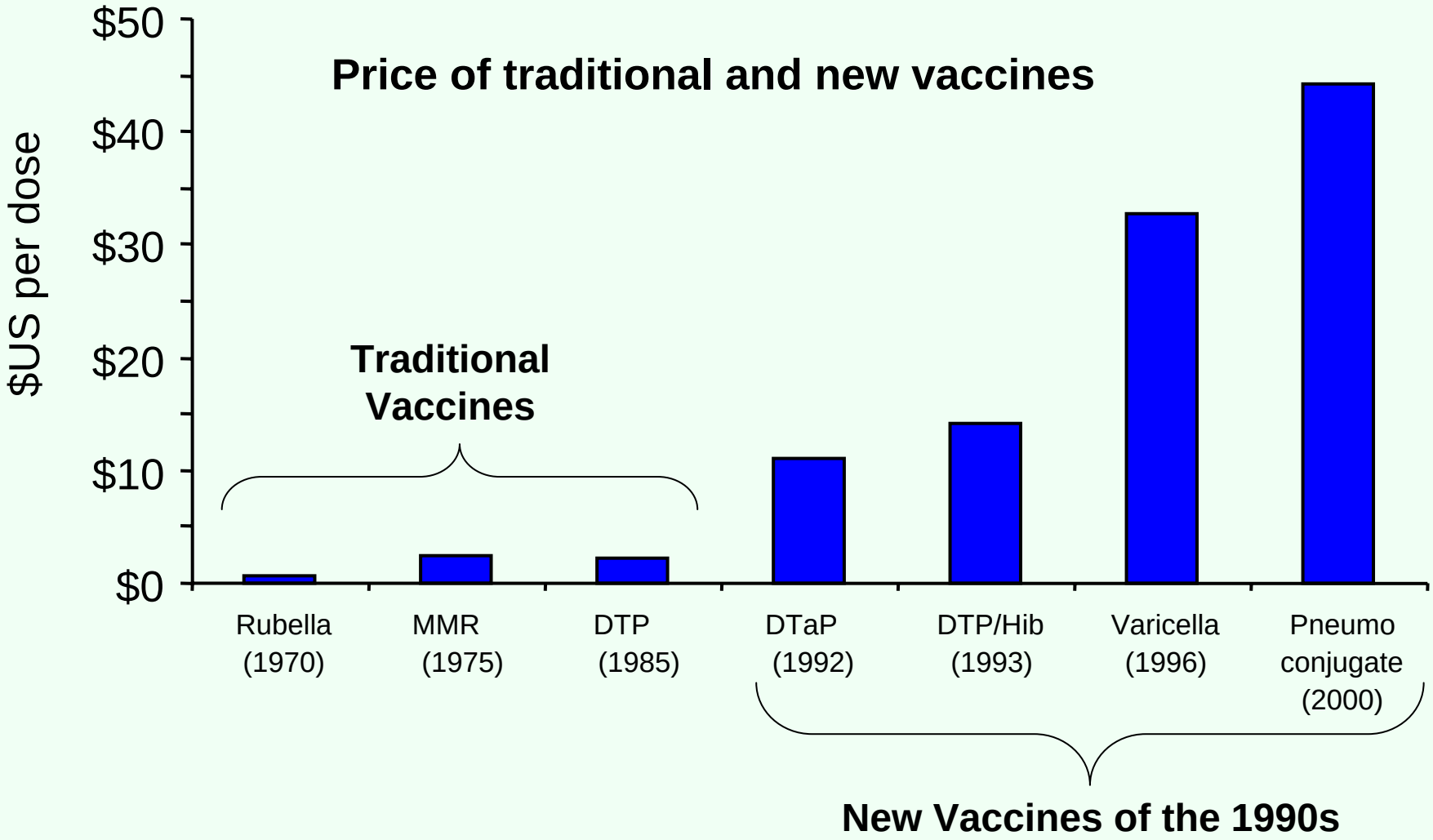


Amy Batson, Orphan Vaccines 2001

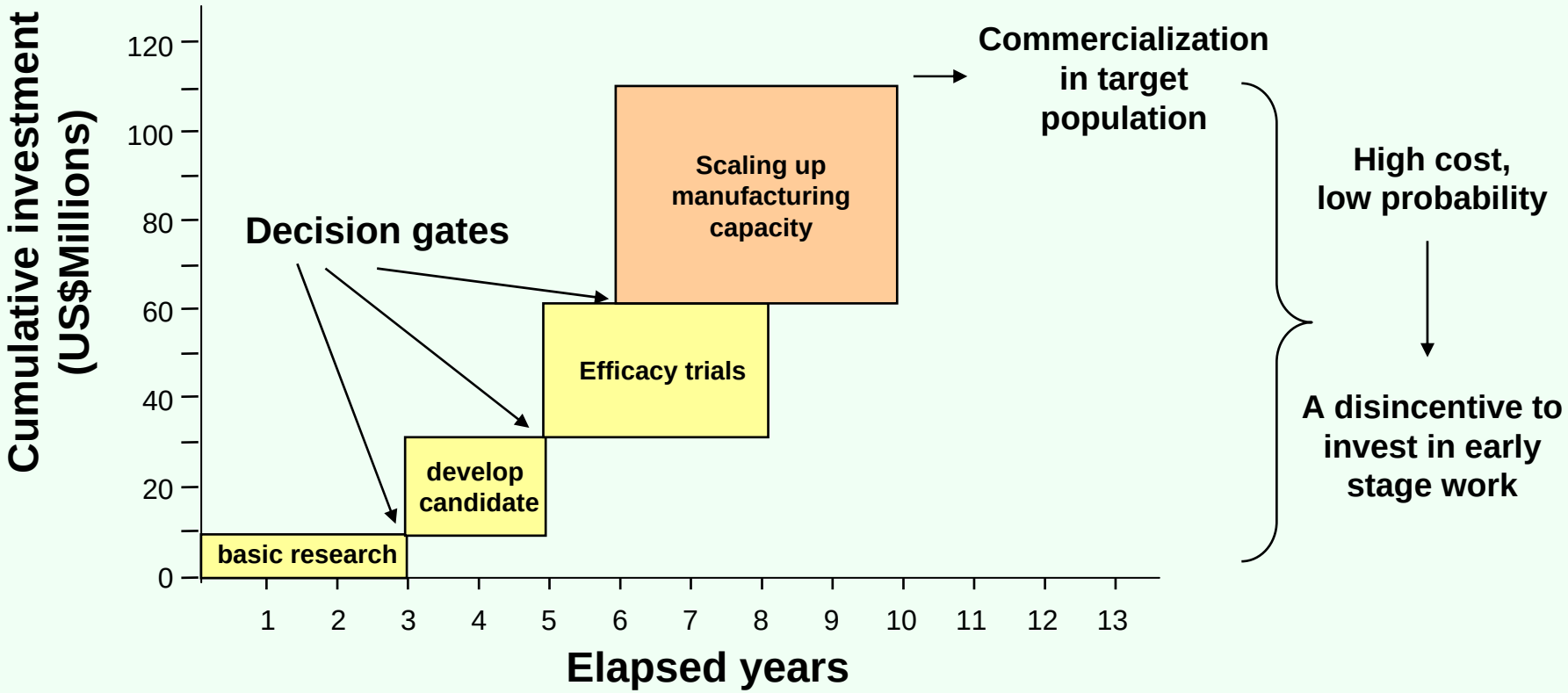
Prices for newer vaccines are more than for traditional vaccines



Amy Batson, Orphan Vaccines 2001

Source: CDC contract prices, 1970-2000

Baseline: Costs and decision gates in vaccine development



Amy Batson, Orphan Vaccines 2001

Source: Mercer Management Consultants

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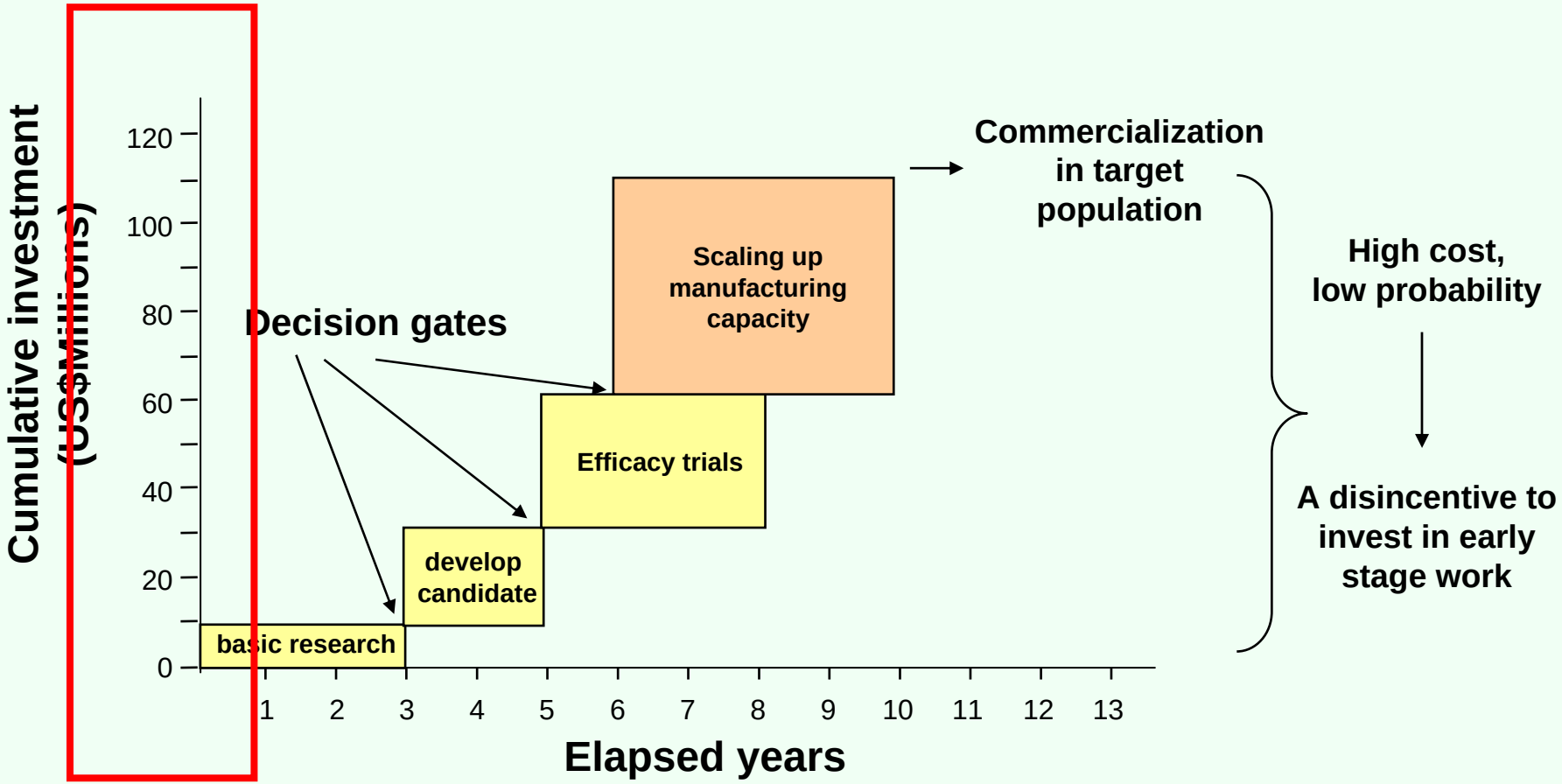

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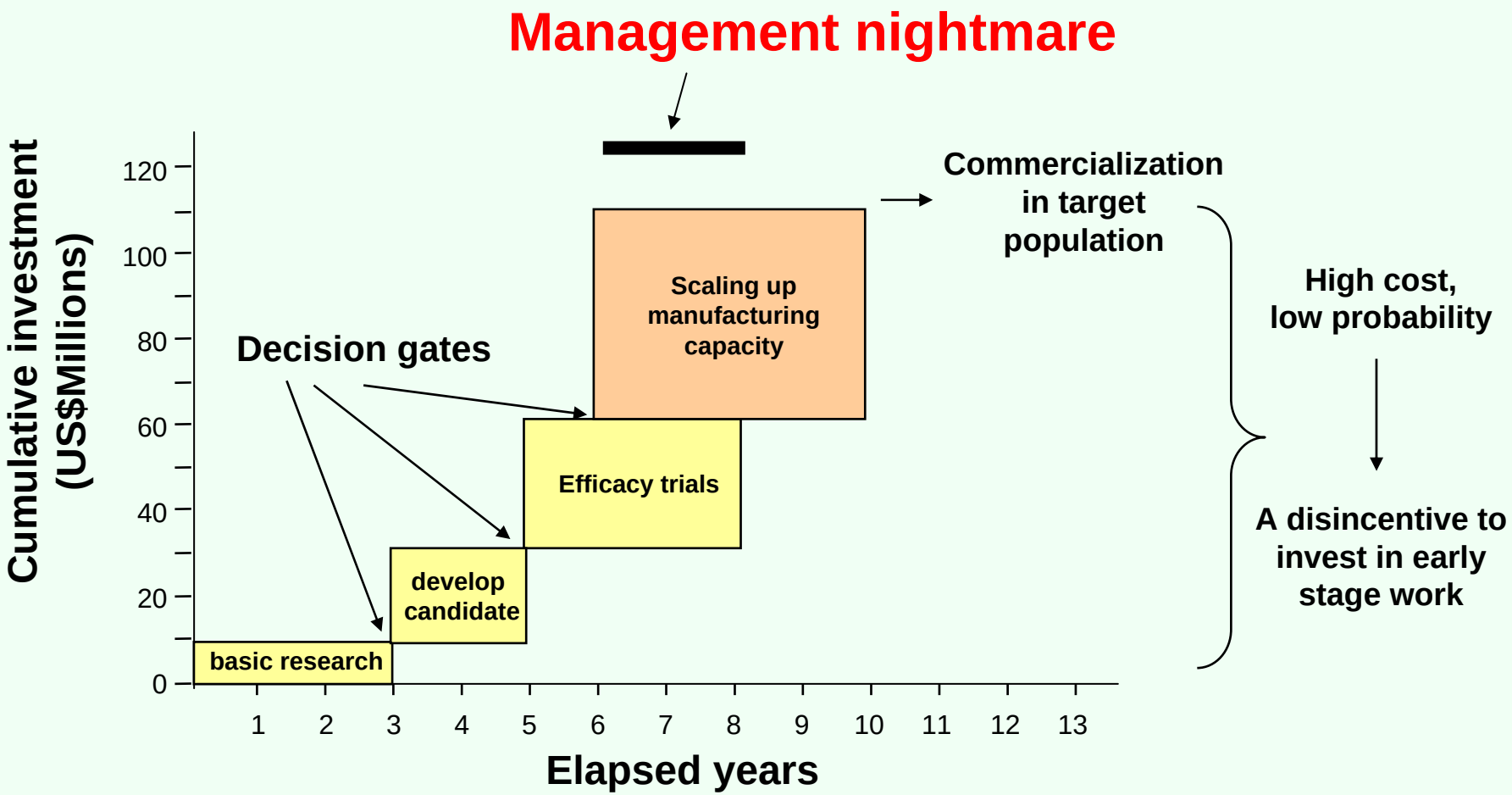
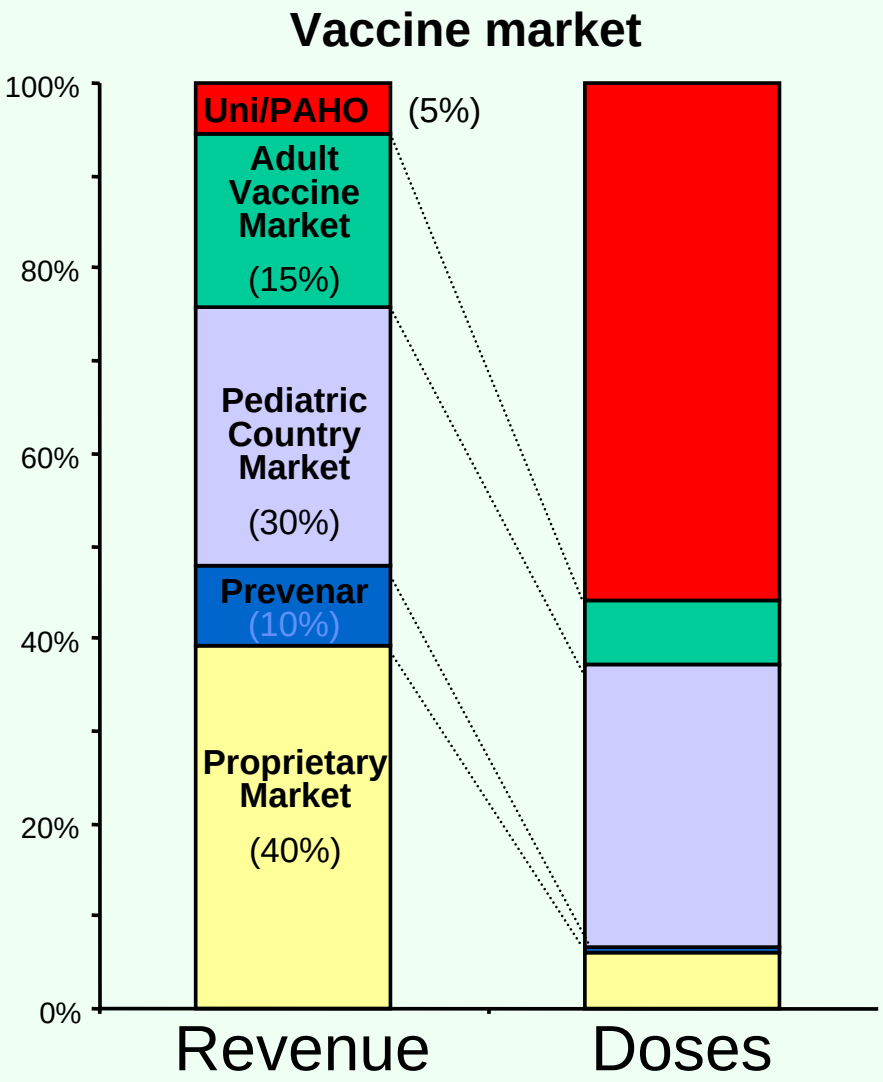
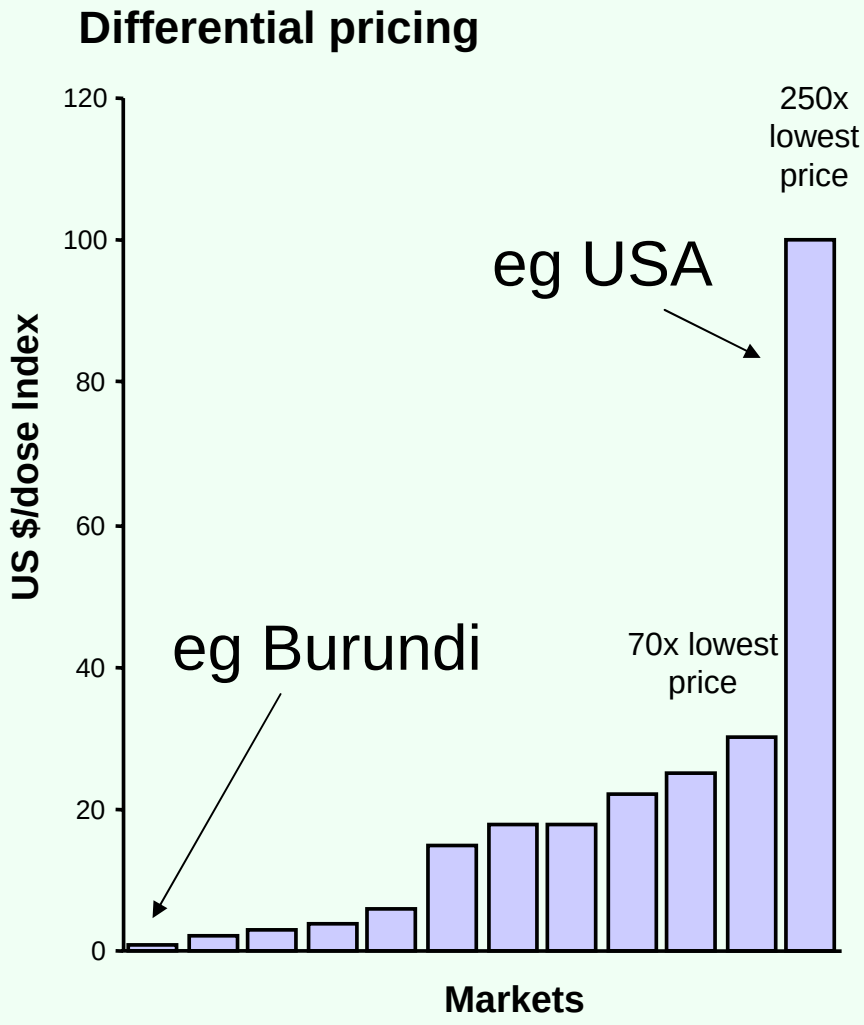


Amy Batson, Orphan Vaccines 2001

Source: Mercer Management Consultants

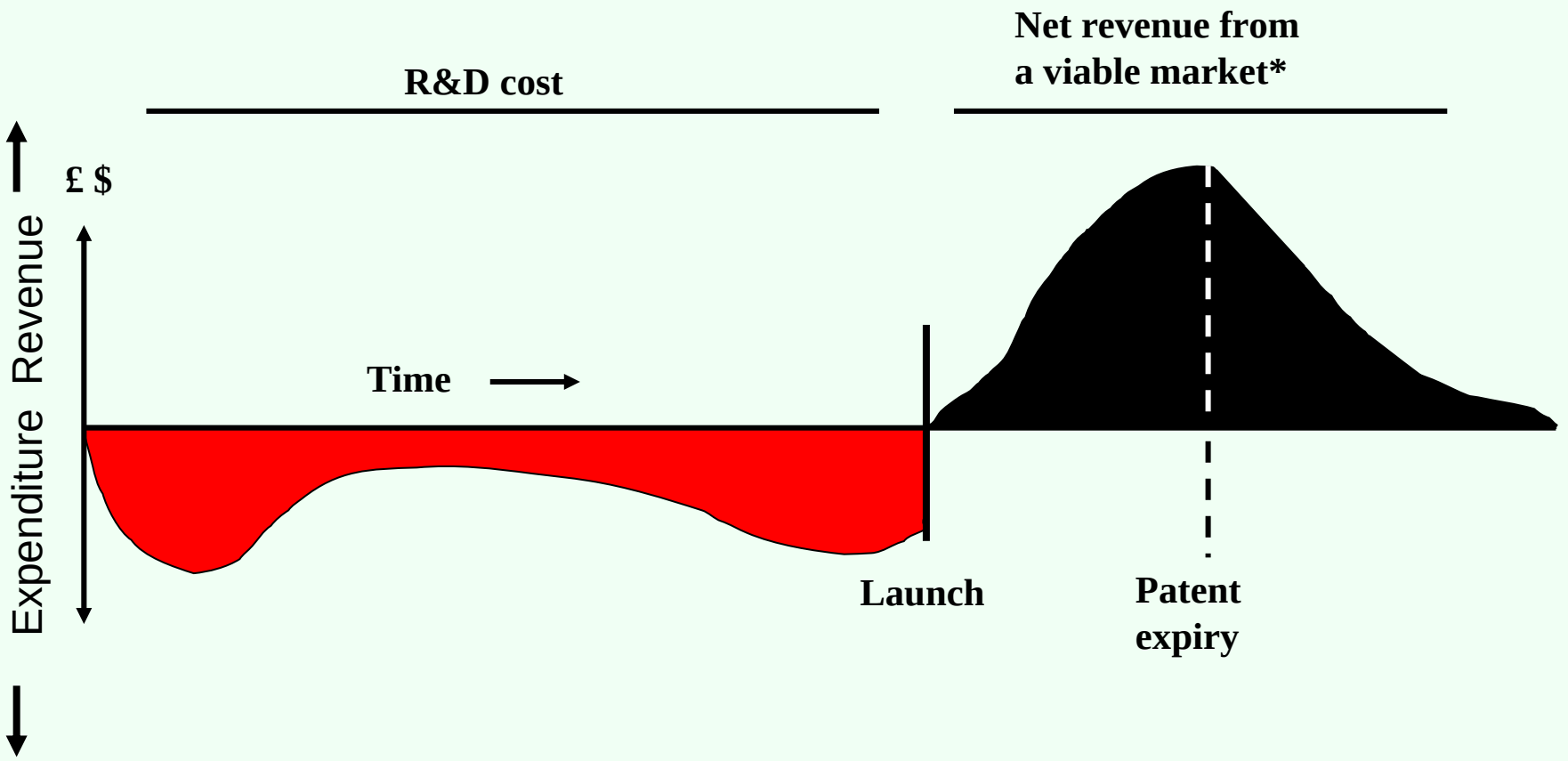
Commercial Strategy: Differential Pricing - paying for developing country vaccines





Amy Batson, Orphan Vaccines 2001

Schematic model of the cash flow of a new medicine



*NB expenditure on clinical studies, manufacturing, marketing etc continues after launch but for simplicity has been netted out.

The bottom line

- **Vaccines are expensive to develop (though cheaper than some drugs)**
- **Margins on vaccines are poor**
- **As vaccines improve, they are used less often**
- **cf. chronic disease drugs eg. Enbrel**

- **ROI drives R&D expenditure**
- **Reluctance by Pharma to invest on the most needed (ie. unmet medical need) vaccines**
- **Growing involvement of Big Philanthropy**

Vaccines

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Polio - 1954

“Boston has so many polio cases that parents drive their sick children to Children's Hospital and sit in their cars on the street while resident physicians decided who would go inside.

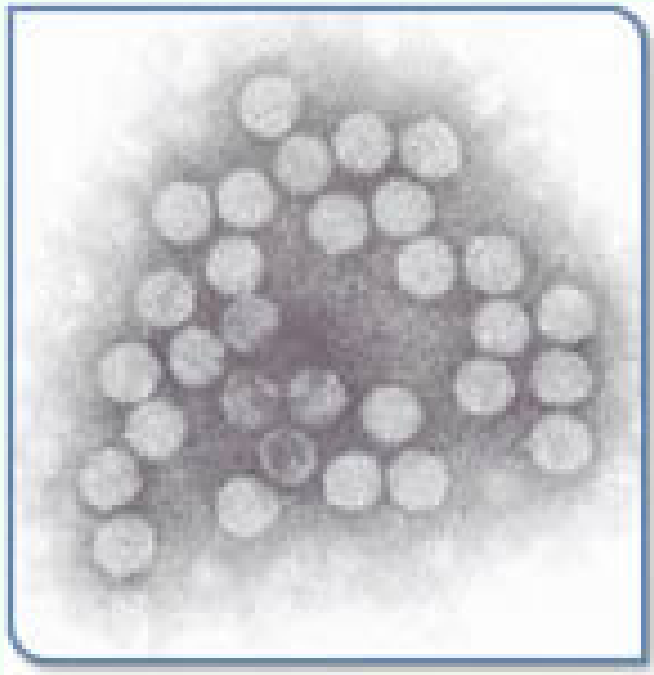
Polio had earlier crippled an American president, Franklin Delano Roosevelt, and had fearful parents keeping children out of public places.

The symptoms started with fever and, in severe cases, progressed to the point where only an iron lung could keep its victims alive.”

Do Vaccines prevent disease ?

Example Polio

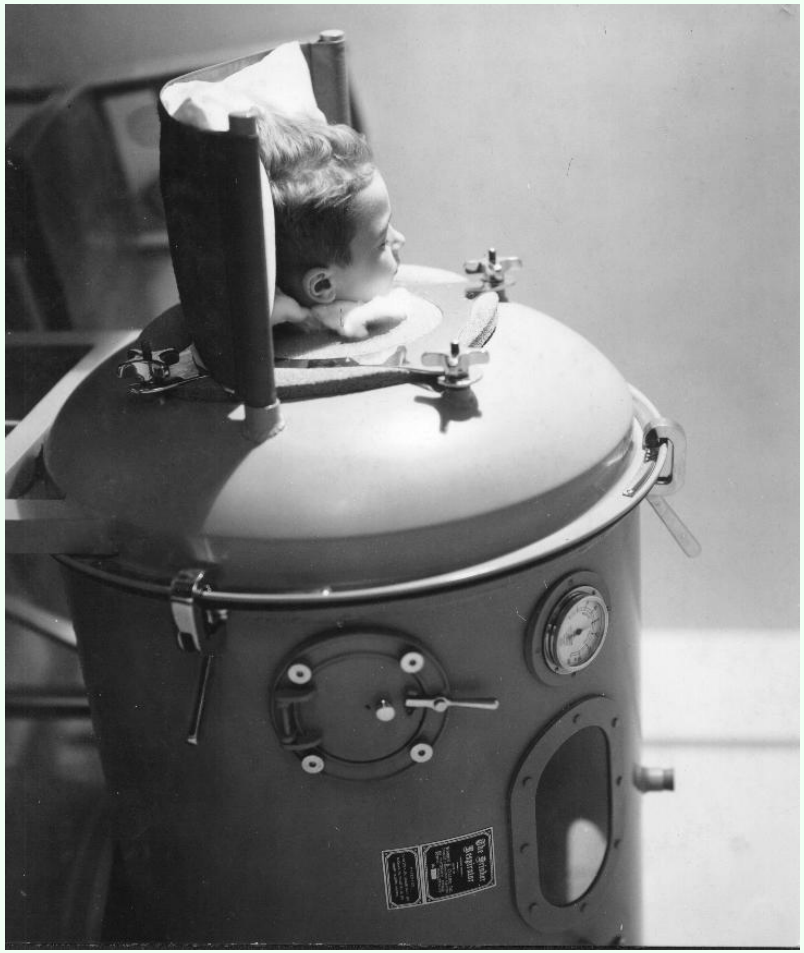
Weller Enders Robbins



grew poliovirus in 1950

Do Vaccines prevent disease ?

Example Polio



Do Vaccines prevent disease ?

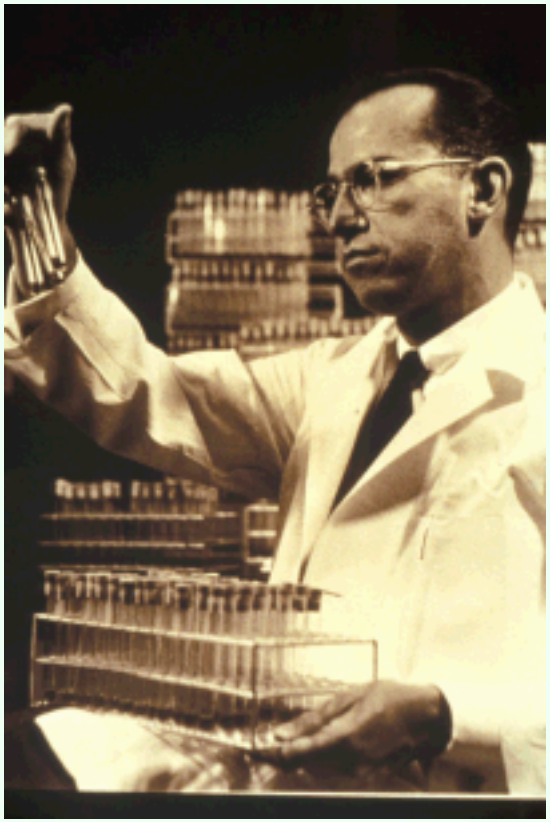
Example Polio

Rancho
Los Amigos
US, 1950s

Do Vaccines prevent disease ?

Example Polio

Killed vaccine



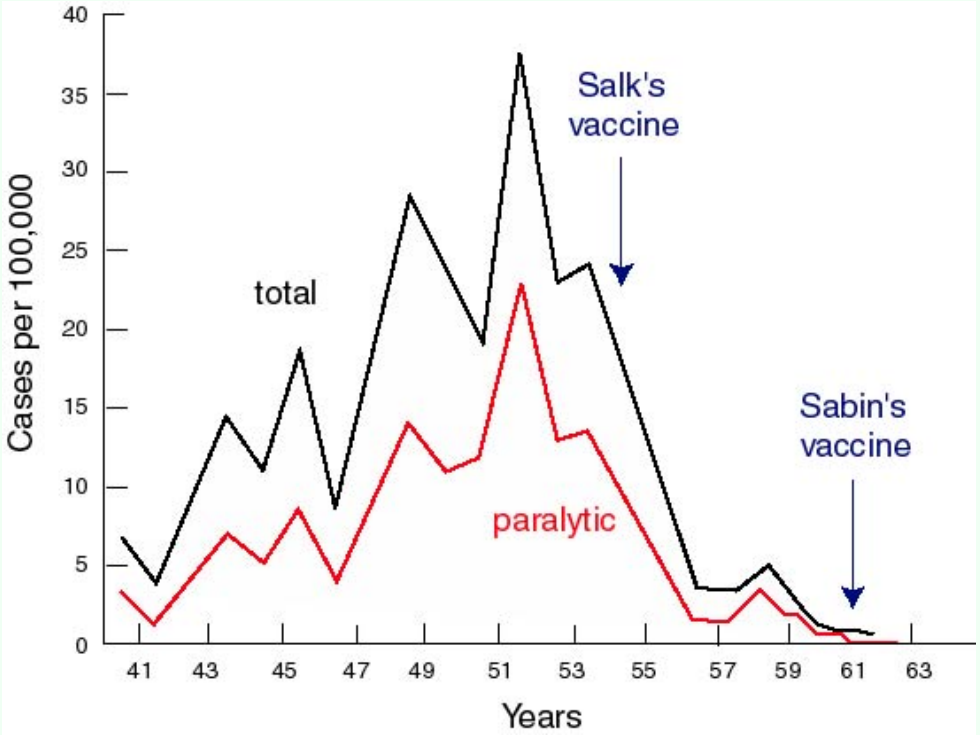
Salk - 1956

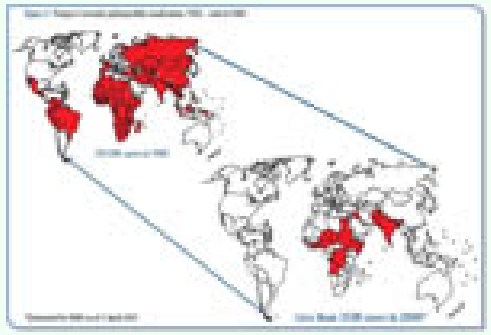
Live vaccine

Sabin - 1961

Do Vaccines prevent disease ?

Example Polio

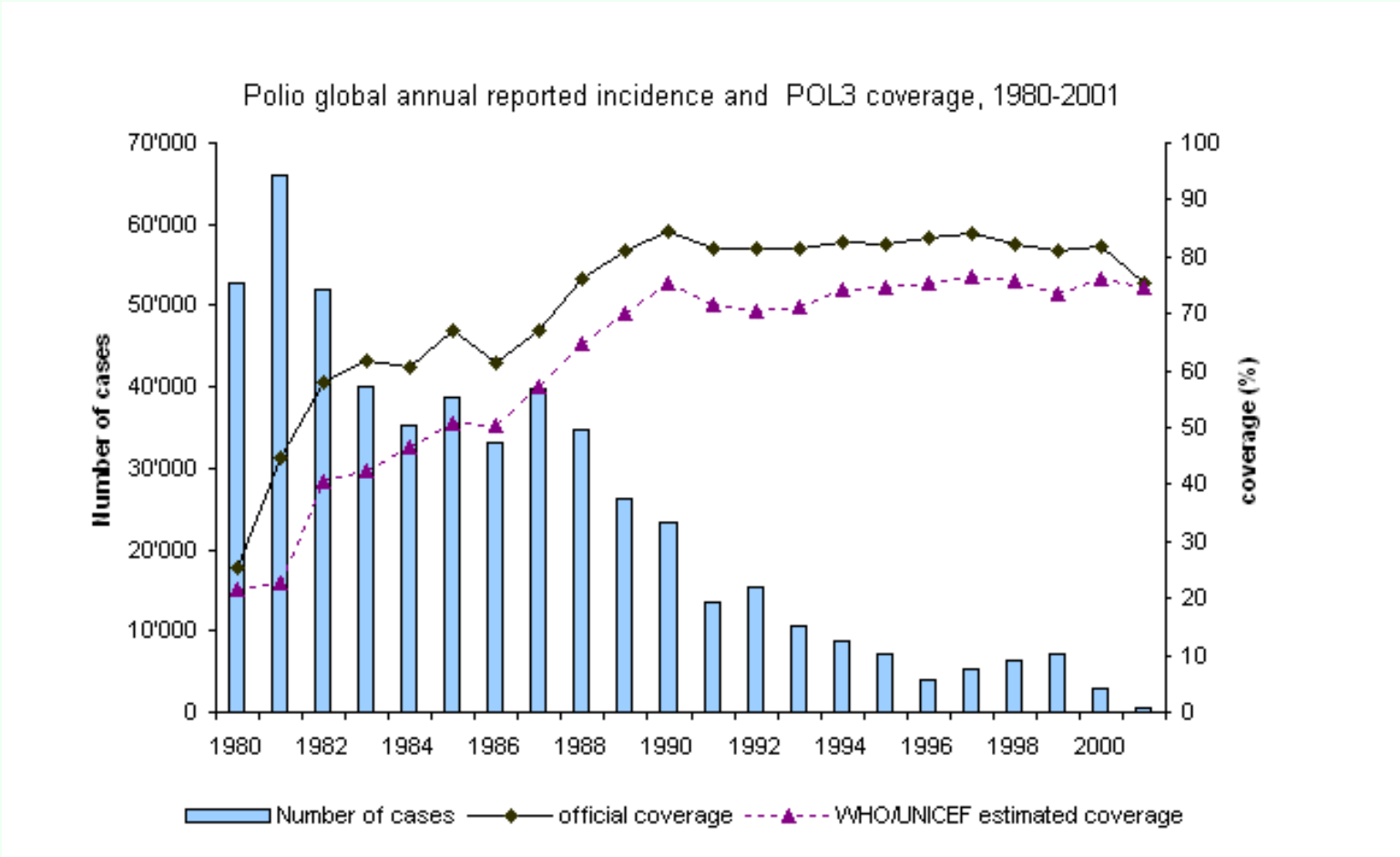




Last case of polio
In the Pacific

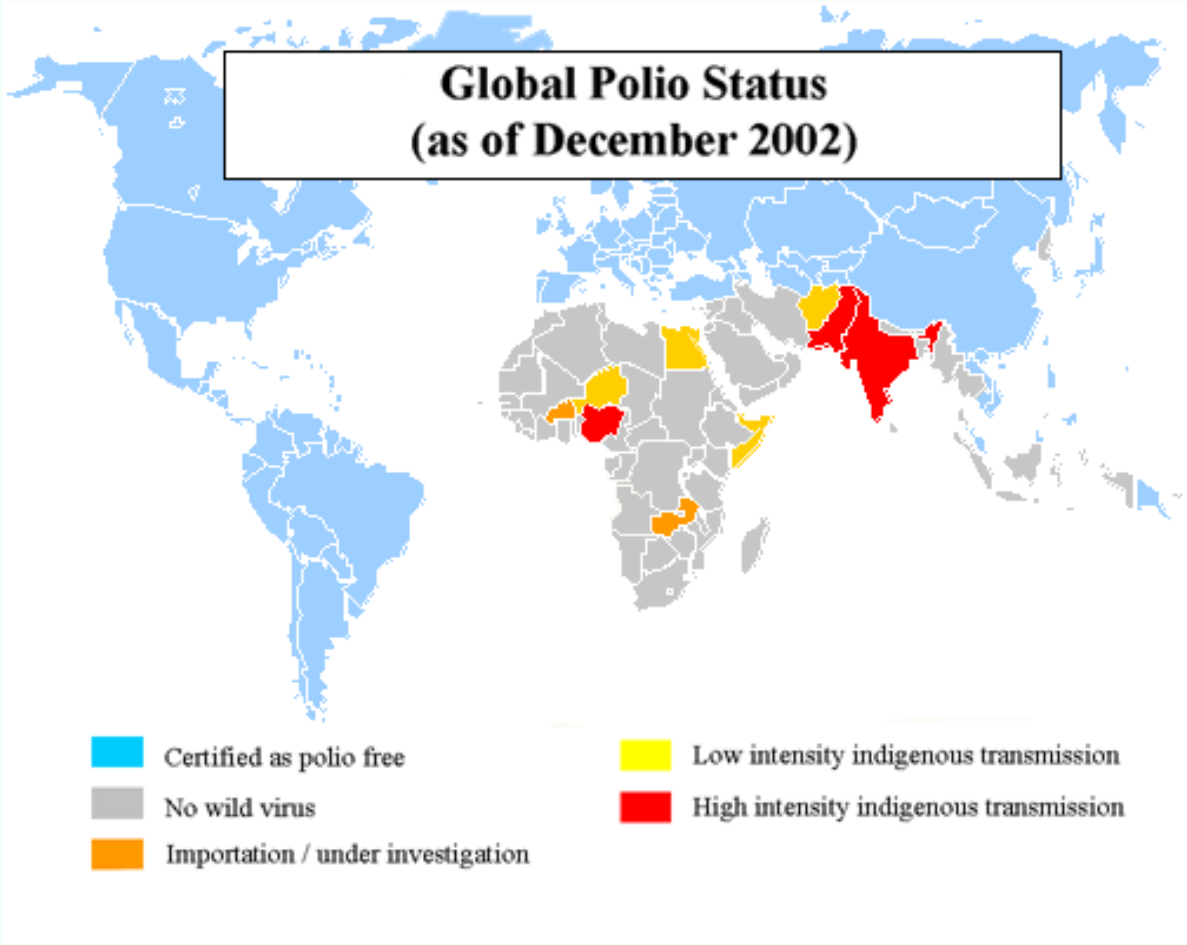
Do Vaccines prevent disease ?

Example Polio



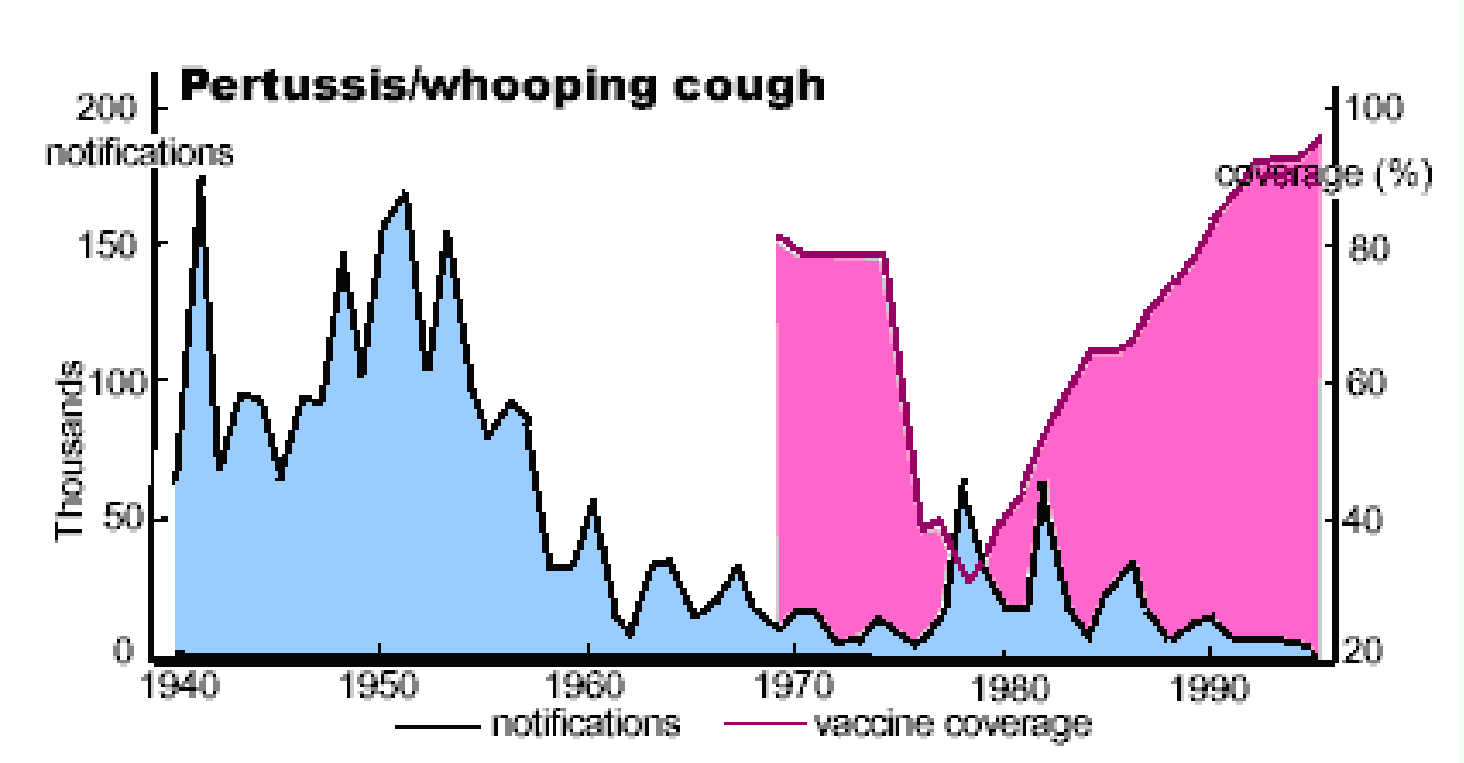
Do Vaccines prevent disease ?

Example Polio



Do Vaccines prevent disease ?

Example Pertussis (whooping cough)



Vaccines - impact on incidence

Vaccine-preventable disease incidence reductions

Data	c.1900	c.2000	% decrease
Smallpox	48,000	0	100
Diphtheria	175,000	1	100
Pertussis	147,000	6,279	95.7
Tetanus	1,300	34	97.4
Polio	16,300	0	100
Measles	503,000	89	100
Mumps	152,000	606	99.6
Rubella	47,745	345	99.3
Hib	20,000^	54	99.7

Do Vaccines prevent disease ?

Yes !

Cf. infection in the recipient and ‘herd’ immunity

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Infectious Disease Mortality 1995 (World Health Rep 1996)

	Deaths (1,000s)
ALRI	4416*
Diarrhea	3115*
Tuberculosis complex	3072*
Malaria	2100
HBV	1156
Measles	1066*
HIV/AIDS	1063
Tetanus	459
Pertussis	355
Leishmaniasis	80
Hookworm	65
Ascariasis	60
Onchocerciasis	47
Chagas disease, dengue etc	c.120
Total	17312 (= 17million)
All causes	51882 (= 51 million)
Vaccine preventable (*some)	10000 (= 10million)

Where are new Vaccines needed ?

- **Malaria**
- **HIV/AIDS**
- **Gastrointestinal diseases (eg. rotavirus)**
- **Respiratory diseases (eg. RSV (croup))**
- **Better TB**
- **Parasitic infections…..**

- **Who will fund these vaccines ?**
- **Each cost >$500M to develop, then much more to implement**

What does it take to make a vaccine ?

1. Understanding of the disease
2. Understanding of the pathogen
3. Pre-genetic era - growth of the pathogen or part of the pathogen, attenuation (reduction in potency of the pathogen)
4. Post-genetic era - recombinant subunit
5. Testing of the vaccine = safe + effective (= $$)
6. Use of the vaccine (=$)
7. Use of the vaccine (=$)
8. Use of the vaccine (=$)

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What is hot in Vaccine development ?

- Harmonisation of regulatory environments
- Move towards greater characterisation, purity
- Safety paramount eg. rotavirus

= longer lead times to deployment

- Polio = 6 years
- HAV, HZV, rotavirus > 25 years
- HIV, first pivotal trial reported 2003 (>15 years)

Vaccines – what is hot ?

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These responses:

- **prevent infectious diseases (ie. prophylaxis)**
- **cure existing infectious diseases (ie. therapeutic)**
- **block physiology (eg. anti-hormone, fertility...)**
- **prevent and cure cancers (eg. antiviral, anti-cancer)**
- **block autoimmune, allergic reactions (eg. desensitize)**

Therapeutic Vaccines

- **Vaccines in advanced development for:**

- **HPV-induced cancers, pre-cancerous conditions eg. anal dysplasia, cervical dysplasia (eg. CSL)**

- **Therapy for HIV (eg. Virax)**

- **Chronic HBV, HCV infections (CTL-based, CSL)**

……..

Greater purity – better adjuvants

- **Toll-like receptors – the basis of adjuvants ("immunology's dirty little secret")**
- **TLRs stimulate innate responses, activate acquired immune responses**
- **TLRs are a series of cell surface receptors which act through common signalling pathways (eg. MyD88) -> cytokines eg. TNF-α**
- **Recognise bacterial products eg. flagella (TLR5), LPS (TLR4), Lipoproteins (TLR2), bacterial ie. methylated DNA (CpG TLR9)**
- **Basis of immunostimulation by Mtb in FCA ?**

Greater purity – better antigens

- **CTL determinants – peptides (9-11, 14+ aa)**
- **Force dominance of the immune response**
- **String minimal epitopes together = Polytope**
- **Deliver from live vectors (adenovirus, MVA**
- **Combine with DNA vaccine prime (prime-boost)**
- **Tested in HIV *et al.***

- **HPV – Ian Frazer, VLPs with CSL/Merck**
- **$US300m+ Phase III (highly protective in PII)**

Vaccines Summary

- Vaccines are important public/individual health tools
- Work through the immune system
- Expensive to develop
- Usually effective
- New vaccines are needed, but understanding of basic disease biology equally important
- Vaccines entering new fields such as therapy
- Exciting and challenging area