

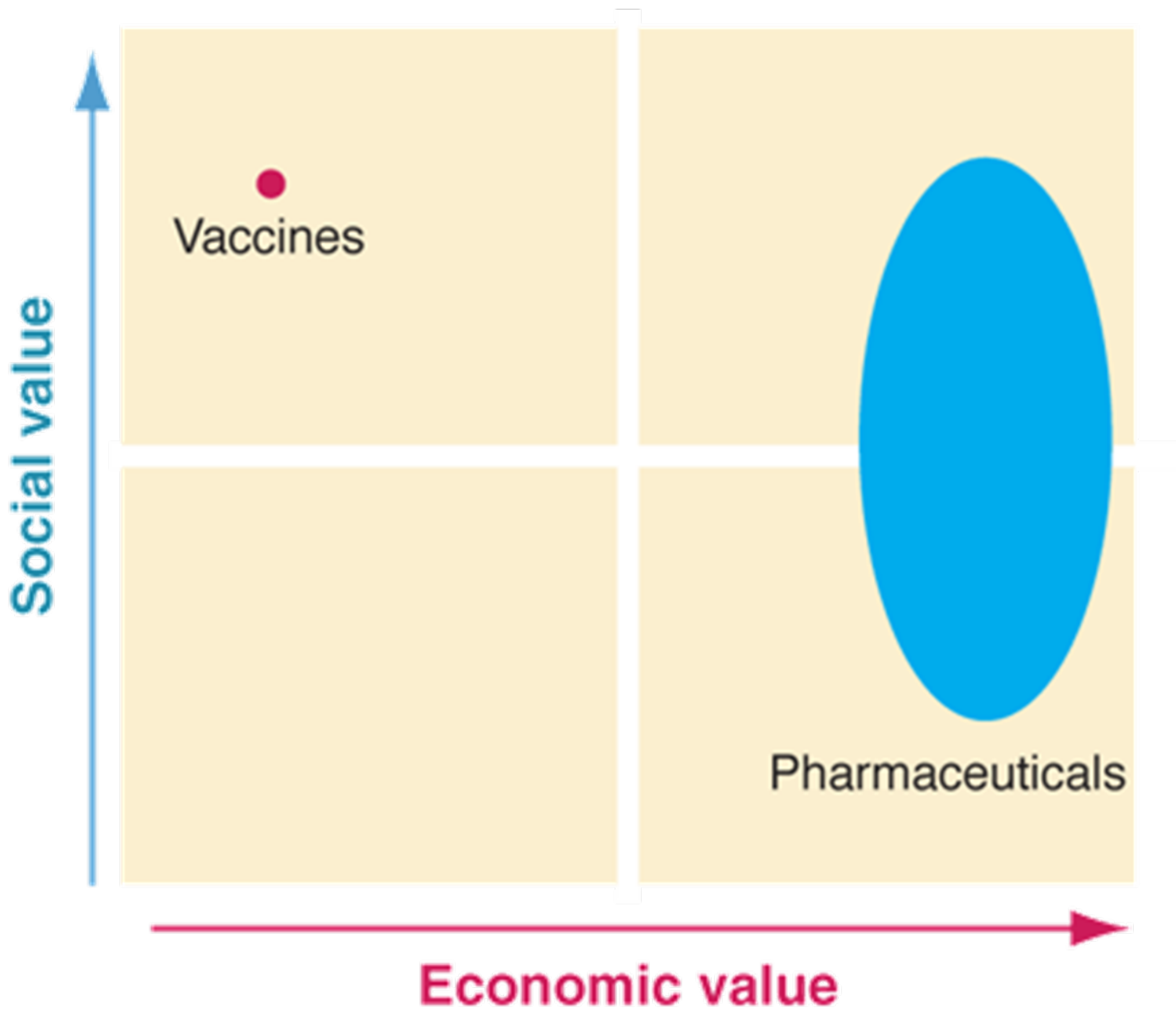
Vaccines



Learning outcomes

You should be able to:

- (1) List and give examples of different types of vaccines
- (2) List and give examples of new approaches being used in current vaccine development



What is a vaccine?

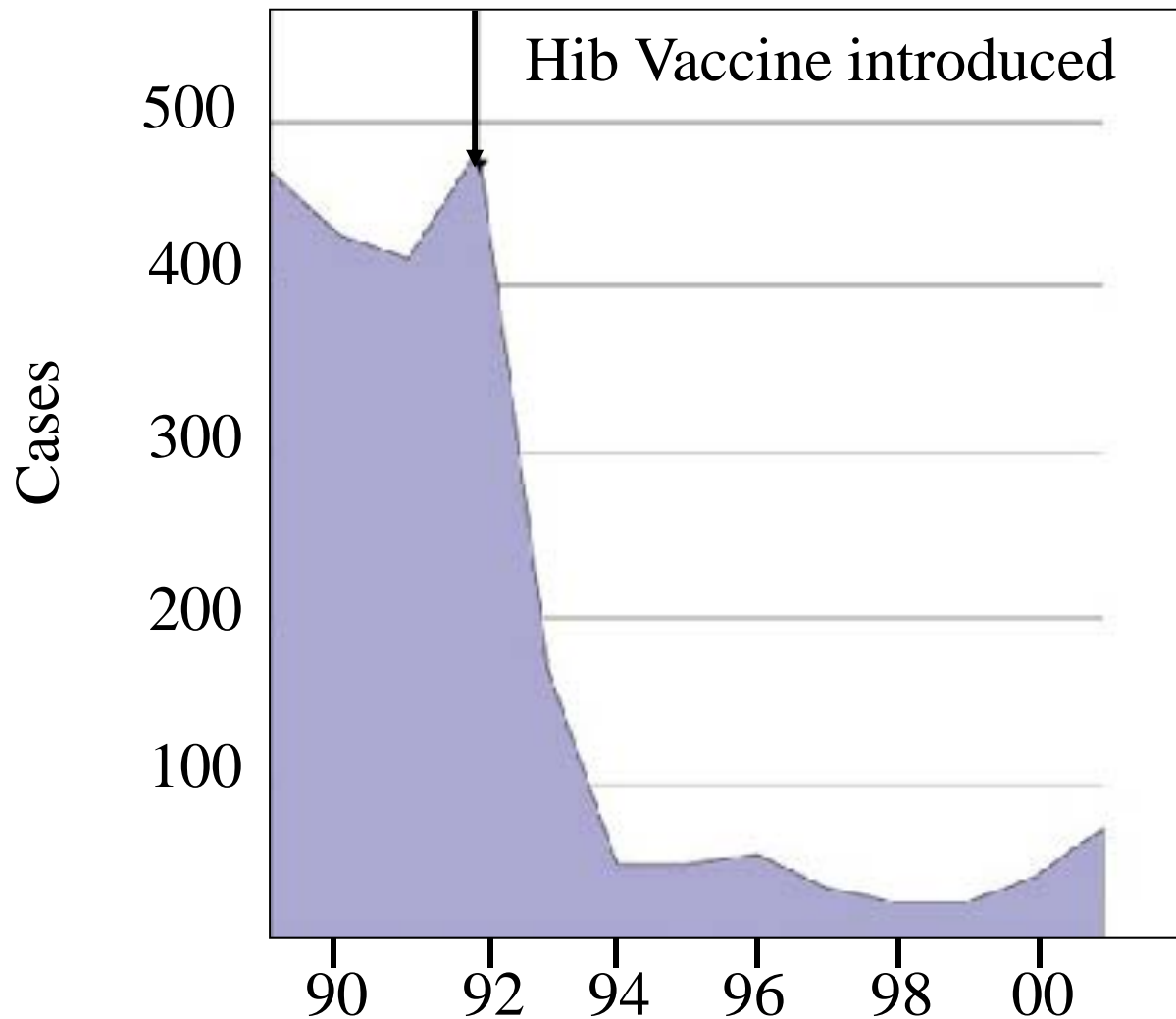
- a preparation, consisting of killed, pretreated, or living microorganisms or molecules derived from them, that is used in vaccination
- Latin *vaccinus*
= 'of or from cows'.
(Edward Jenner in 1796)



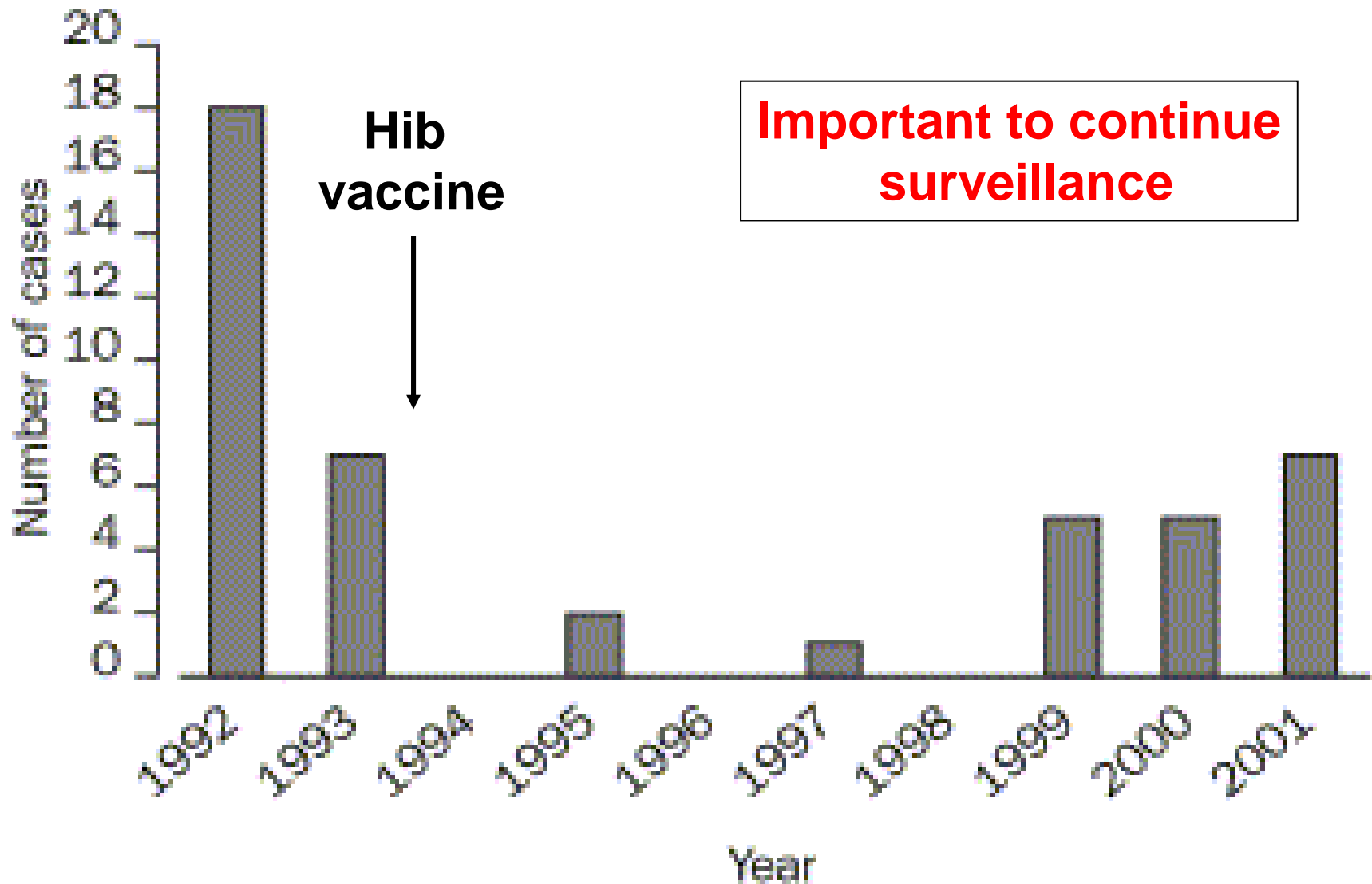
Ideal characteristics

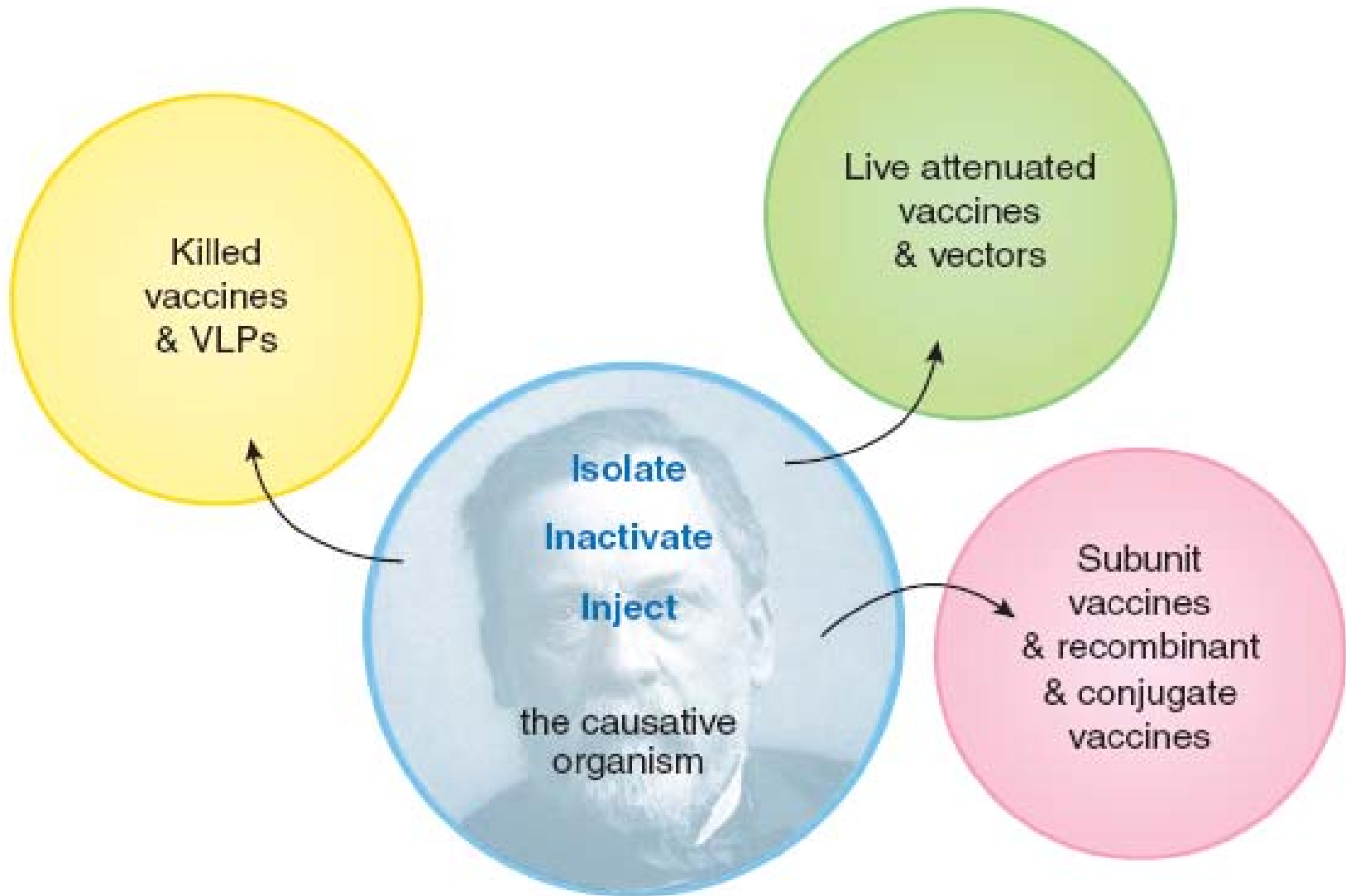
- One dose
- Life long immunity
- Protective against all variants of a target MO
- Prevents disease transmission
- Induces rapid immunity
- Effective in all (kids vs elderly)
- Transmits maternal protection to foetus
- Not administered by injection
- Cheap, stable and safe

Reported cases of *Haemophilus influenzae* meningitis
(England and Wales 1989-2001)



Hib cases in Nottingham





- Rappuoli R (2007) Nat Biotechnol 25:1361-6

Passive vs active immunisation

Passive immunotherapy

	Horse	Human	Use
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Tetanus	+	+	Prophylaxis
Varicella	-	+	Immunodeficiency
Kawasaki	-	+	Treatment

Sheep better than horse

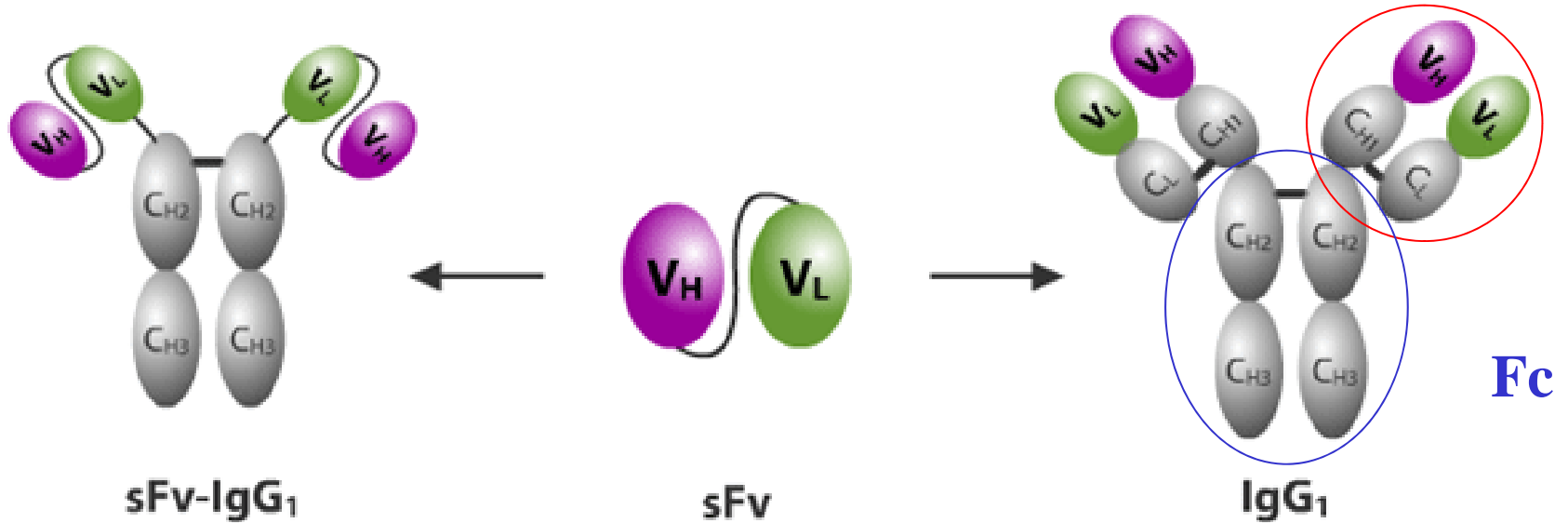
The “Future”

- Cultured antibodies made to order
 - Fab and ScFv (V_H - V_L) ----- Fc portion?
 - expression in plants e.g. *Strep mutans*

(Anthrax, botulinum, Q fever, plague, smallpox, tularaemia)

e.g. Symphogen smallpox vaccine)
26 Abs vs 12 antigens (all humanised)

Rebuilding a Human IgG₁ or sFv-IgG₁ from a Selected sFv Molecule



Types of vaccines

Killed (bacterins)

- Polio (Salk) virus
- low immunogenicity
& need several doses
- formalin (Salk)
b-propiolactone (rabies)
cholera (heat)



Live attenuated

- modified organism which does not cause disease → immune response

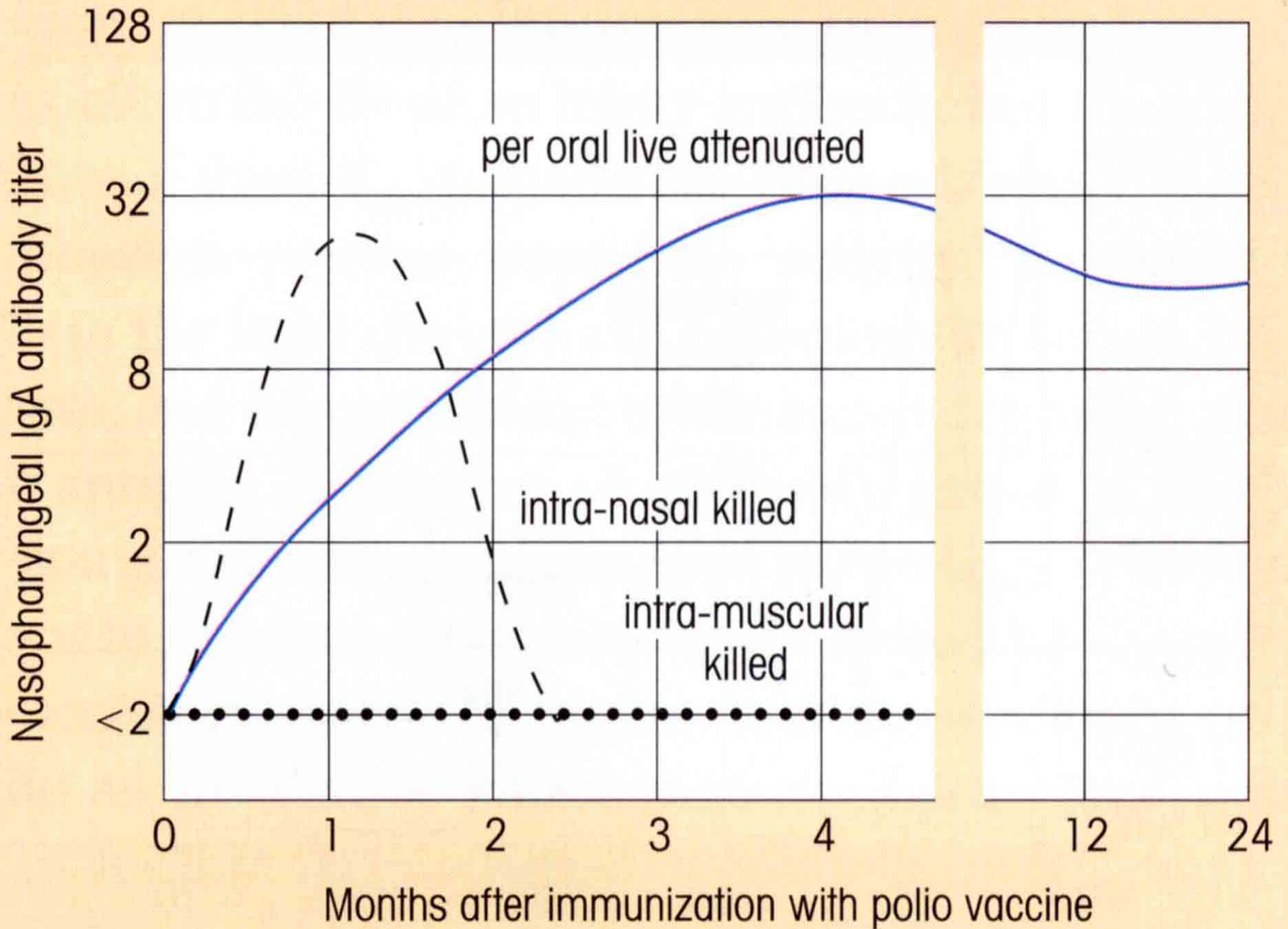
Advantages

- replication → more sustained Ag dose
- response at natural site of infection
- potential to protect against many diseases (heterologous expression)

Sabin live attenuated Polio vaccine

- culture in cell line at sub-physiological temperature





Other methods of attenuation

- BCG Albert Calmette and Camille Guerin
 - *M. bovis* (first human experiments 1921)
 - glycerine potato medium containing ox bile
 - 231 subcultures over 13 years
- Salmonella Ty21a (typhoid fever)
 - chemical mutagenesis
- Targeted genetic approaches

Constraints of live attenuated vaccines

- Reversion to virulent form
- Inadequate inactivation (Polio)
- Cold chain requirements – but freeze dry
- Complications esp:
 - pregnancy
 - immunocompromised

Subunit vaccines

Subcellular fractions (carbohydrate or protein)

- Hib, MenC, *Strep pneumoniae* (carbohydrate)
- Hepatitis B surface antigen (protein)
- Many experimental in progress
e.g. pili, fimbriae, OMPs etc (usually recombinant)
- Peptide vaccines

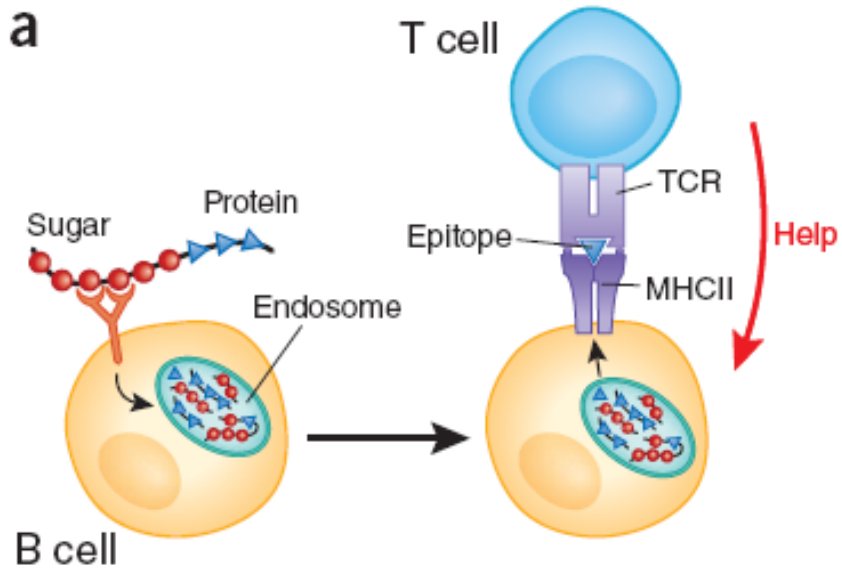
Carbohydrate



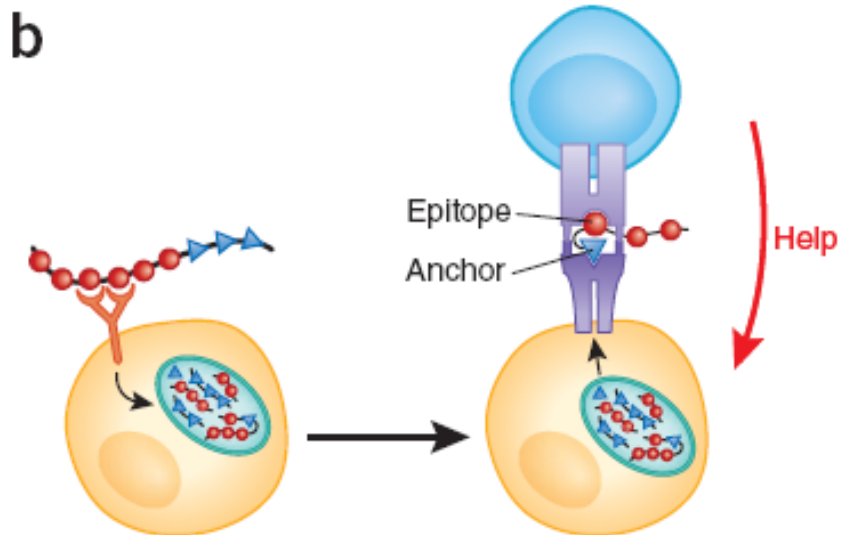
Conjugate vaccines

- Hib, meningococcal C, pneumococcal
- capsule-protein
- CRM197, a non-toxic mutant of DT
- Induce memory (cf capsule alone)

Carbohydrate  **Protein** = conjugate



Rappuoli R and De Gregorio E (2011)
 A sweet T cell response.
 Nat Med 17:1551-2



Living vs non-living vaccines

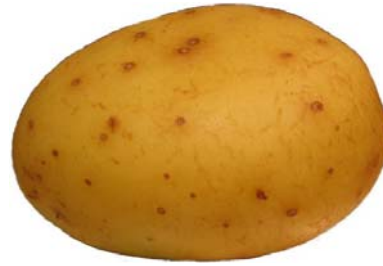
	Living	Dead
Administration	Natural route Single dose	Injection Multiple dose
Adjuvant	No	Yes
Safety	May revert	Local reactions
Heat labile	Cold chain	OK
Cost	Low	High
Immunity	Long	Long/short
Response	IgA, IgG, CMI	IgG

New approaches

- Edible vaccines
- DNA vaccines and prime boost
- Adjuvants
- Delivery
 - devices
 - intranasal

Edible vaccines

- Tobacco
- Potato
- Tomato
- Banana
- Lettuce



Advantages

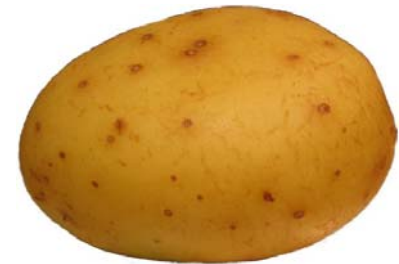
- Cheap
- Stable e.g hot countries
- Mucosal immunity
- Protect against many diseases

Human trials

(1) Hepatitis B surface antigen
in lettuce (1mg)



(2) Norwalk virus capsid
protein in potato
- 150g raw potato
= 250-750 mg



Problems

- Variability in dose between plants
- Induction of tolerance
- Th1 vs Th2
- Regulatory aspects (environmental)
 - contamination of food supplies

Current thinking

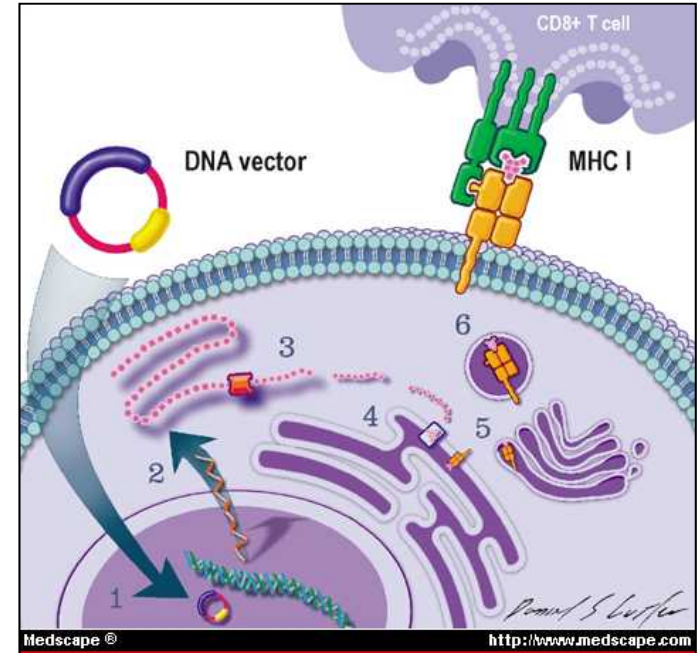
Freeze drying products for oral dosing

Lactic acid bacteria

- *Lactobacillus lactis* (commensal)
- Colonise mucosal surfaces → immune response
- Generally regarded as safe (GRAS)
- Persist/replicate (typically weeks)
- Whole cells expressing Ag (typically cytoplasm)
- Good results in mice (nasal, oral, ± cytokines)
- Even express capsule Ags!

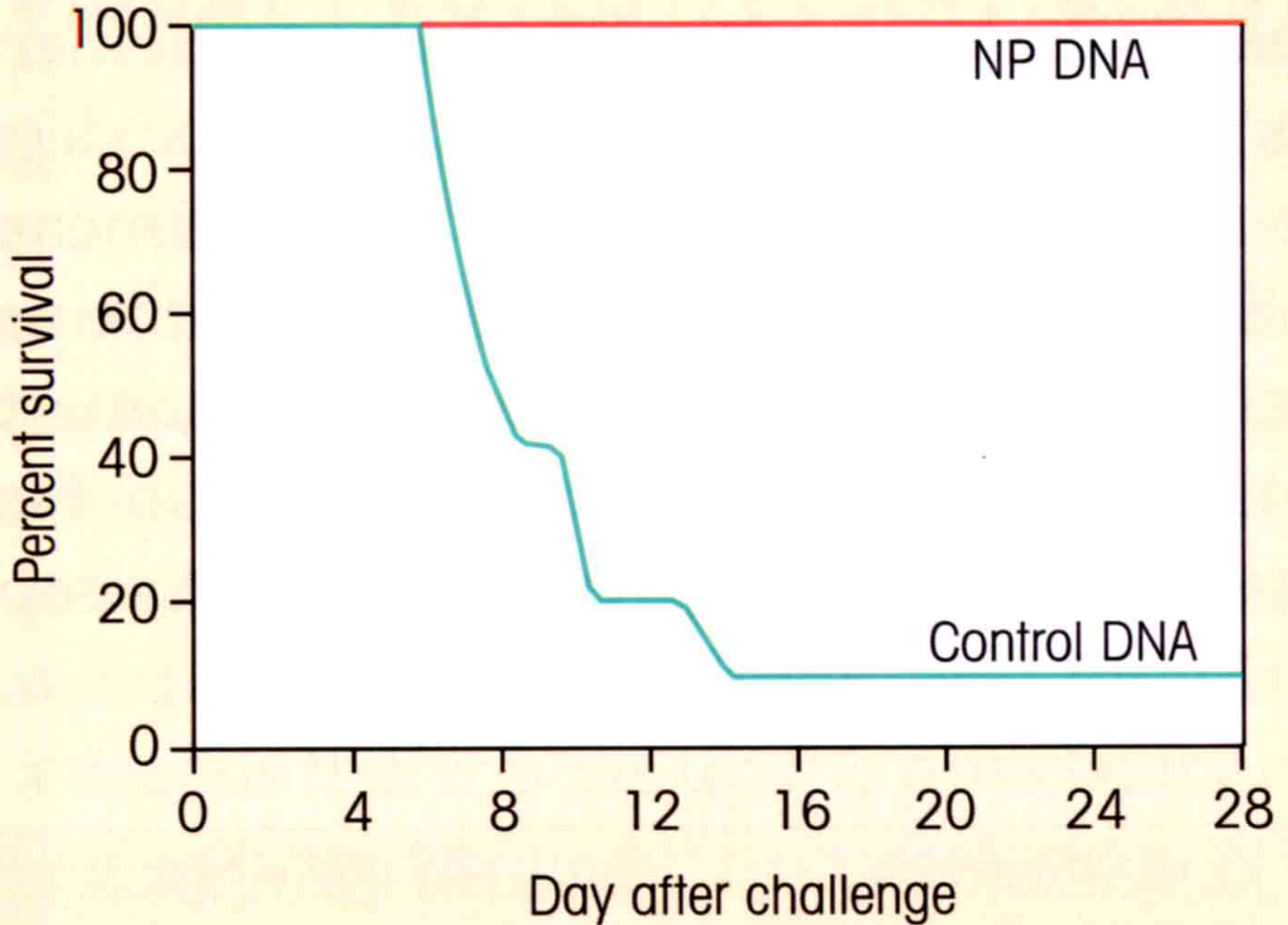
Plasmid DNA

- Bacterial vector + insert
- Intramuscular injection → Ag → immune response



- Bacterial DNA GTcgTT (unmethylated CpG)
 - Th1 and Th2 responses possible

Protection against influenzae (nucleoprotein)



Advantages

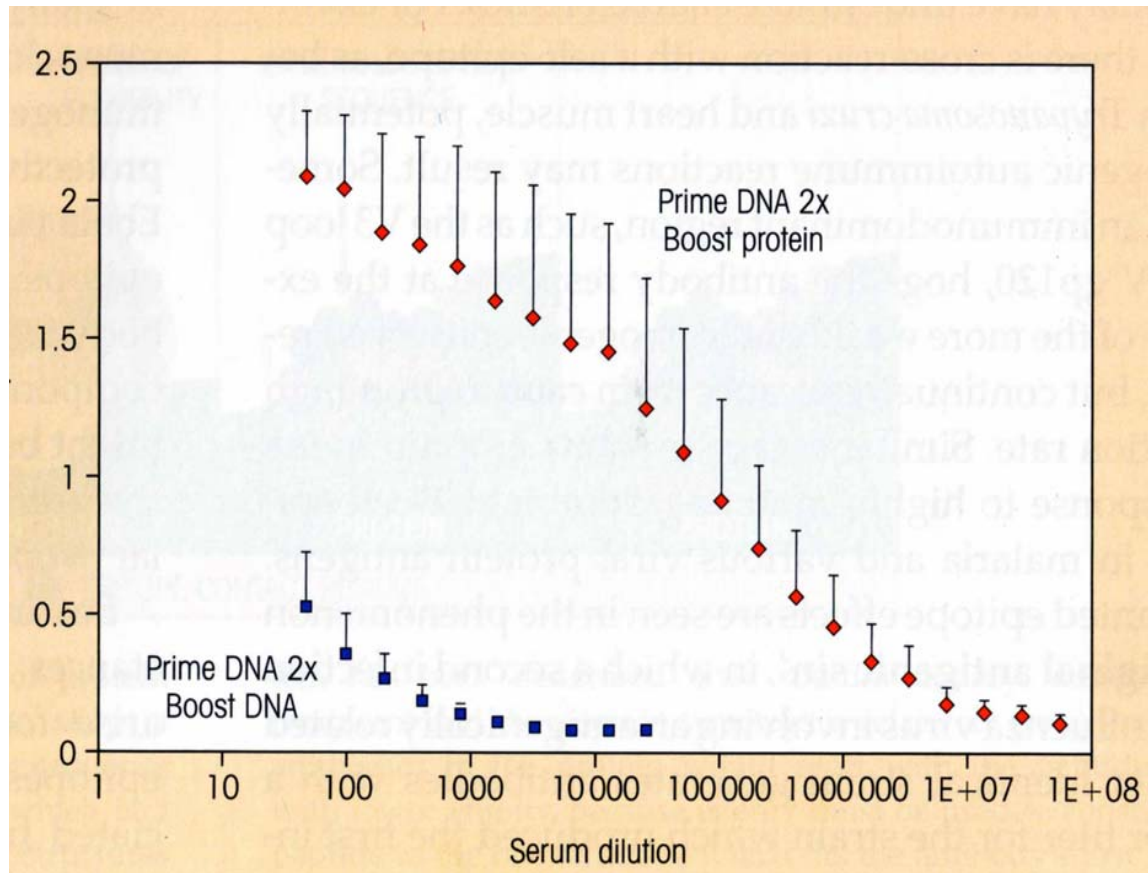
- cheap
- stable
- absence of infectivity

Disadvantages

- integration of DNA into genome
- anti-DNA antibodies

Prime boost strategy

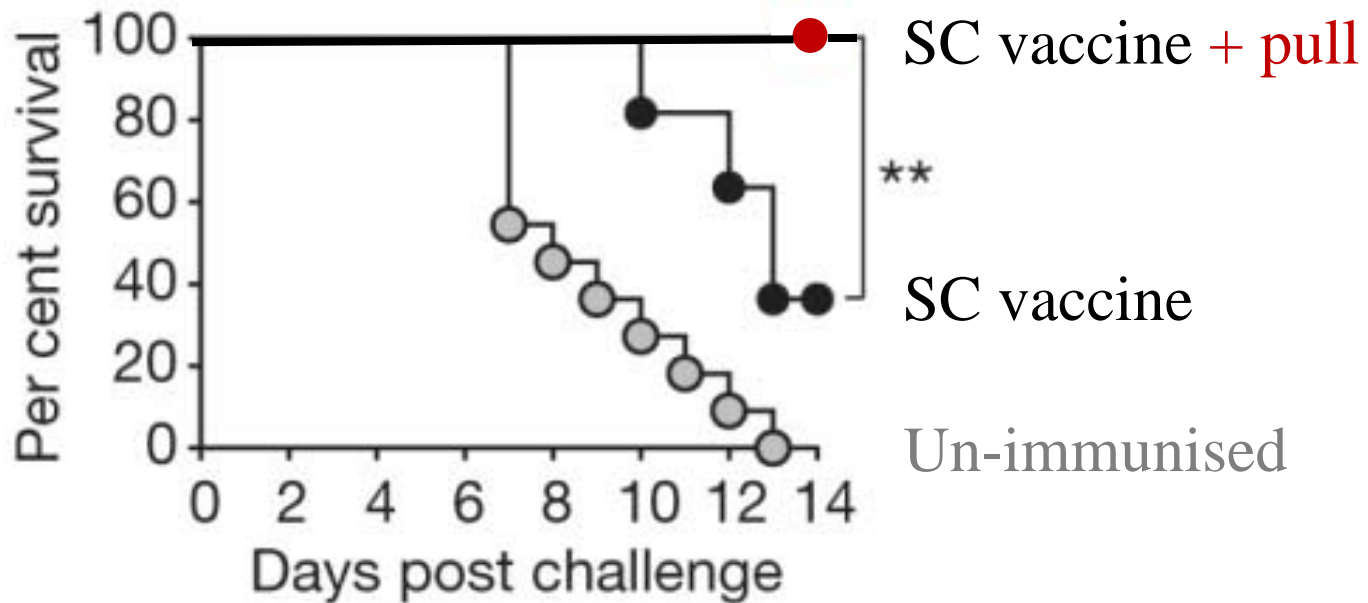
- Malaria, TB, Leishmania



Prime and pull protects mice from lethal genital HSV-2 challenge

Prime = live attenuated HSV-2 vaccine

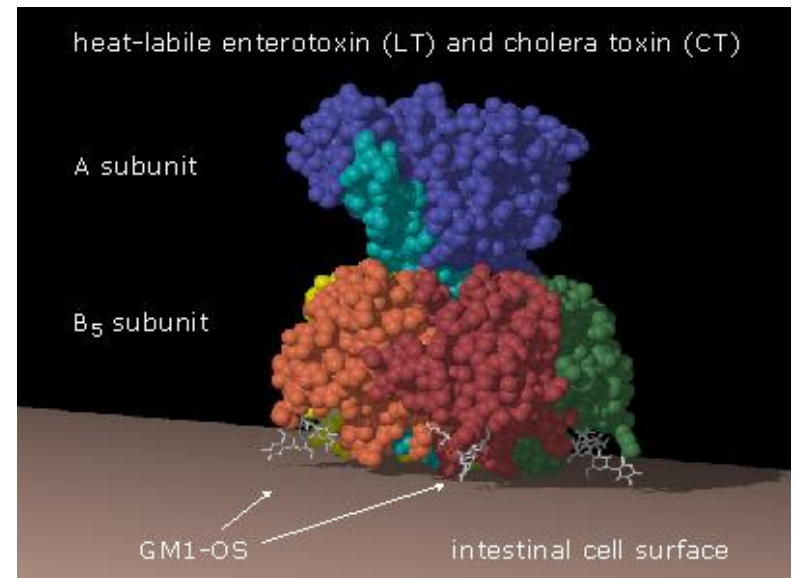
Pull = topical chemokine (CXCL9 and CXCL10) application



Shin & Iwasaki (2012) Nature 491:463-7

Adjuvants evaluated in man

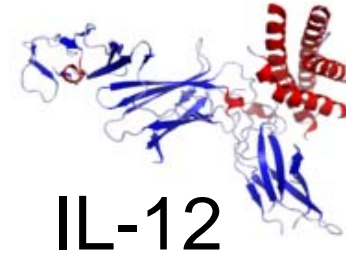
- Inorganic salts
 - aluminium hydroxide (alhydrogel)
- Bacterial products
 - BCG
- Holotoxins (subunits or inactivated)
 - Cholera toxin (CT)



- CpG oligonucleotides

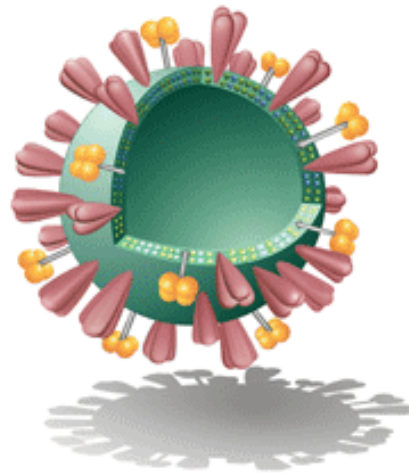






- Immunoadjuvants



- Particulate formulations

e.g. liposomes/influenzae A (virosome)



-  Hemagglutinin
-  Neuraminidase
-  Phosphadidylcholine
-  Phosphadidylethanolamine

Delivery devices

- Needle free or modified needles
- Increased safety
- Self administration
- Smaller doses of antigen/adjuvant
- High throughput

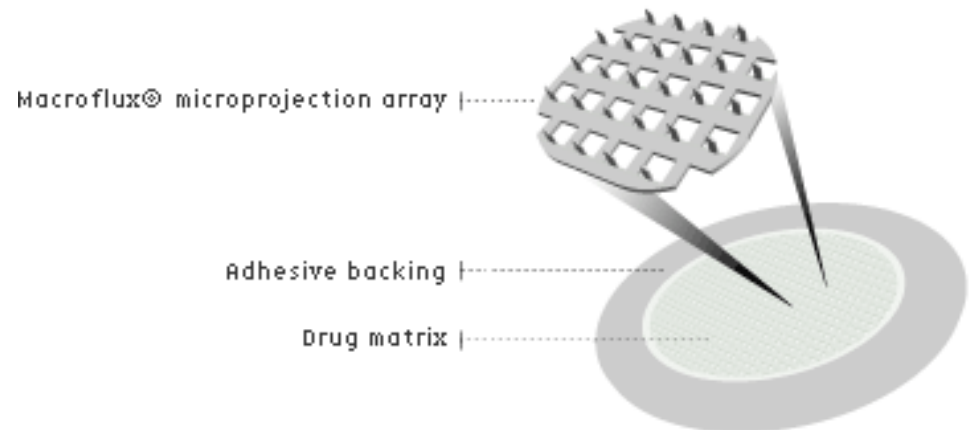
Devices being tested in humans

Patches (Transcutaneous immunisation)

- in combination with adjuvant (CT, LT)
- Shigella, Salmonella

e.g. Macroflux microneedle (various Ags)

- a thin titanium screen with precision microprojections

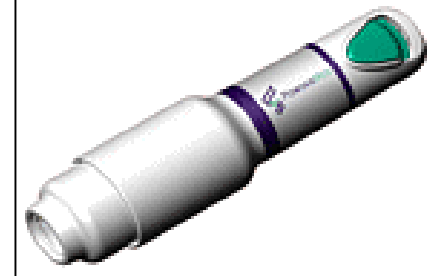


Needle-free injection

Spring powered
(Advantajet, Injex,
Medi-jector, Vitajet 3)



Gas powered
(J-tip, PowderMed)



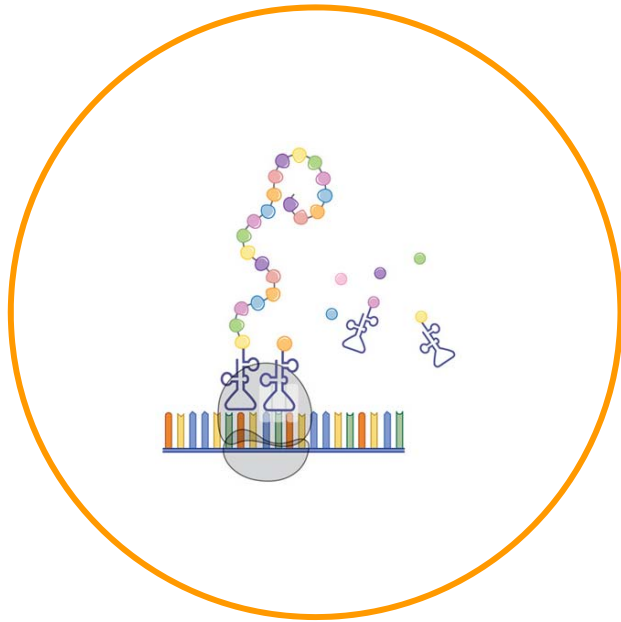
Aerosol

- for delivery of powder vaccines
- live attenuated measles virus (1-5 mm)



Influenzae
vaccines

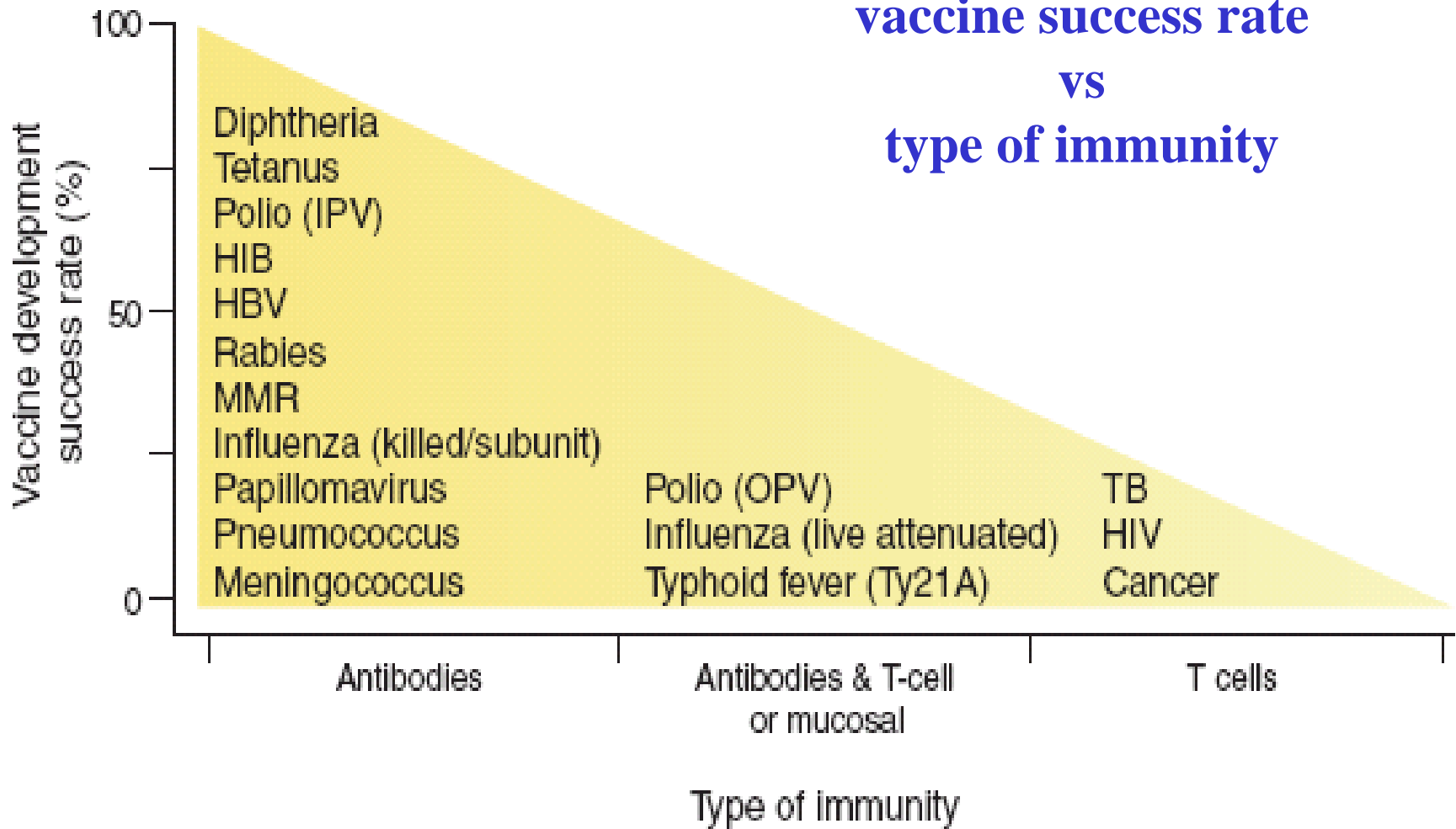
Synthetic biology approaches?



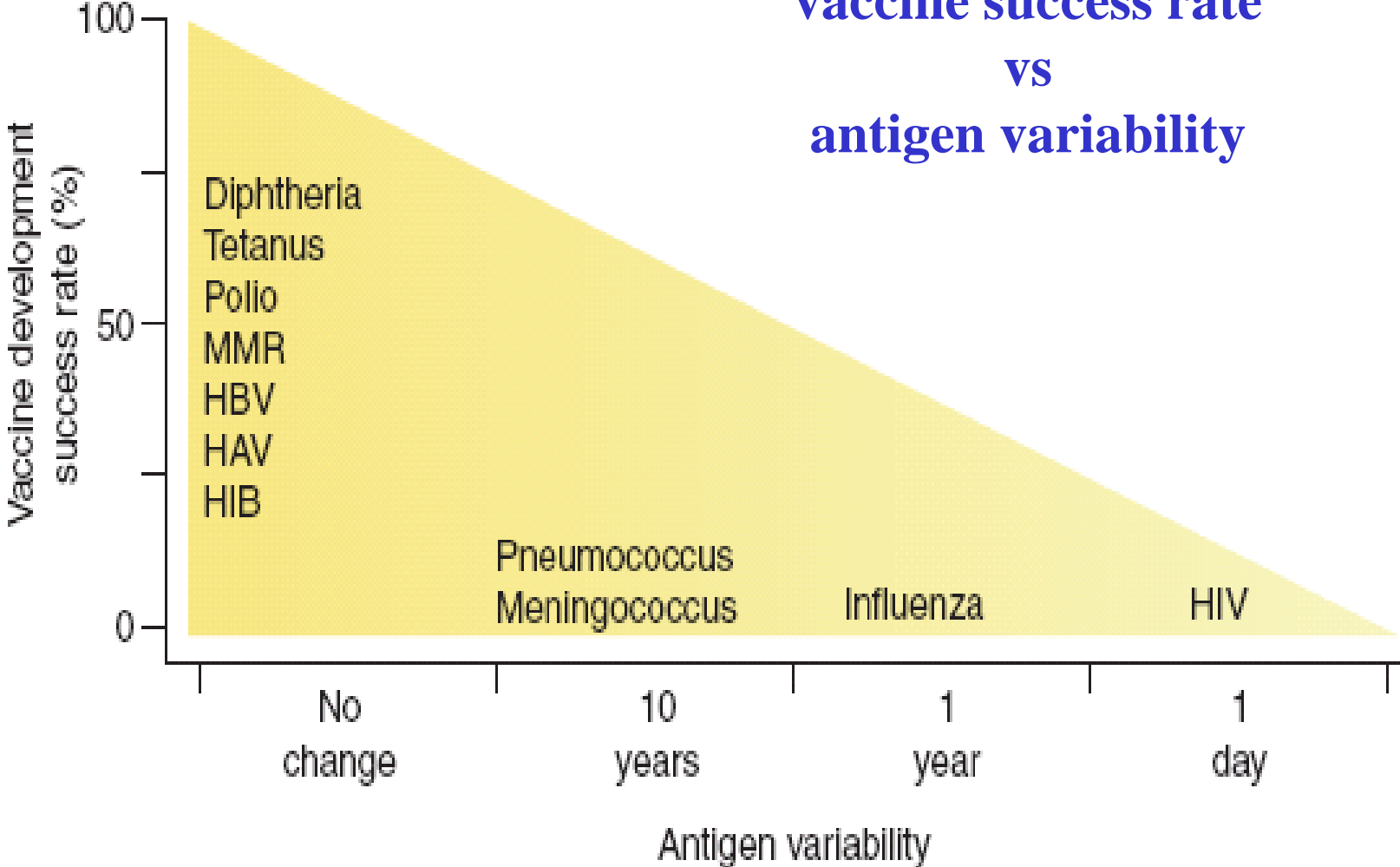
- Combination of Ags
- Ag + adjuvant
- Target to DCs
- Synthetic circuits

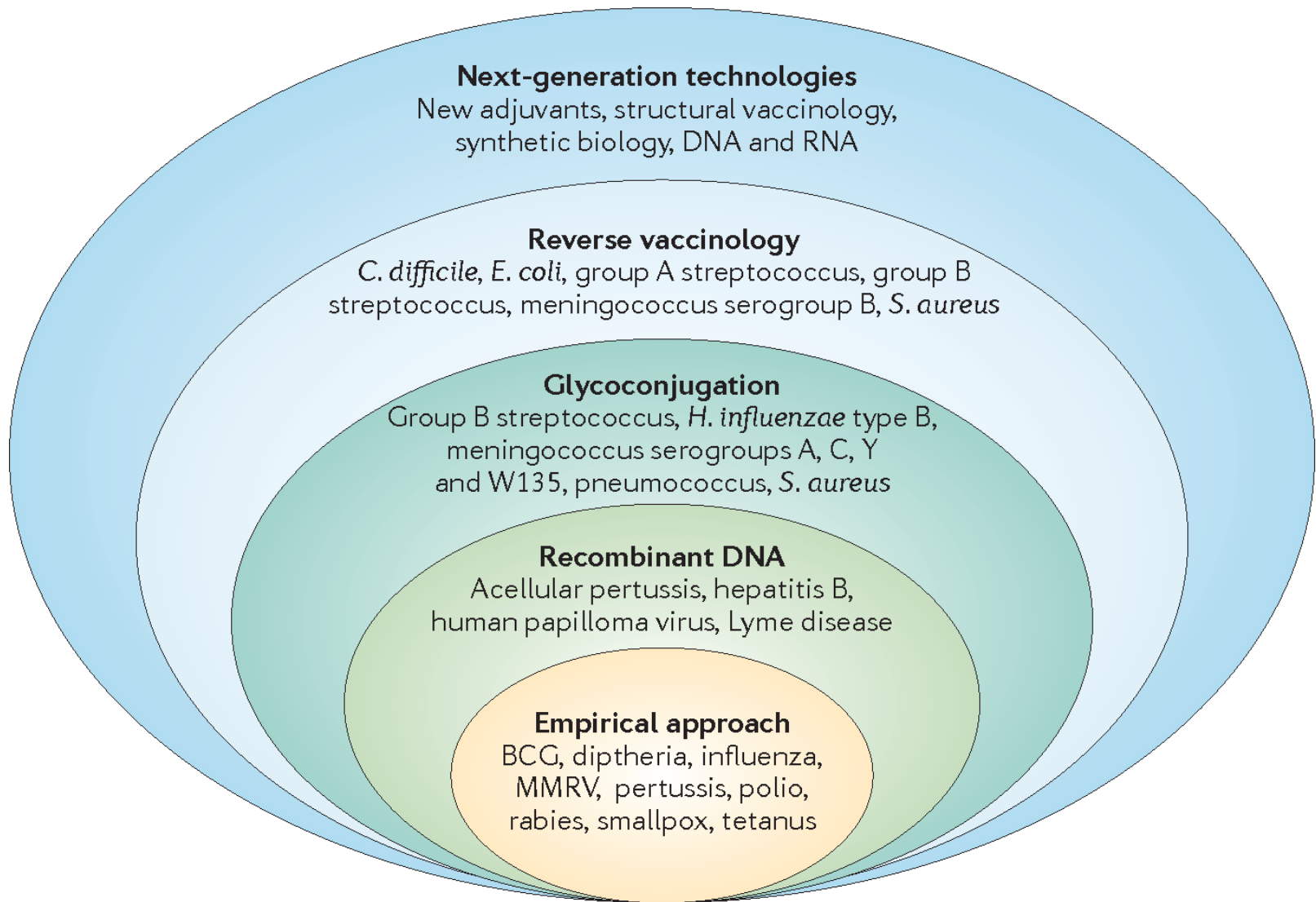
Ribosome complex + DNA template
encoding vaccine antigen

**vaccine success rate
vs
type of immunity**



**vaccine success rate
vs
antigen variability**





Rappuoli R et al. (2011) Vaccines for the twenty-first century society. Nat Rev Immunol 11:865-72.

Paediatric labs?

- Antigen discovery (but compete with Pharma) esp. immune responses (*human* convalescent sera + matched controls)
- Suitability of Ag for a vaccine (bactericidal assays, epitope variability in isolates etc)
- ID of live vaccine candidates
- Novel adjuvants, delivery methods, edibles
- Phase II, III and IV trials
- Continuing surveillance
- (Serendipity)

Lots!