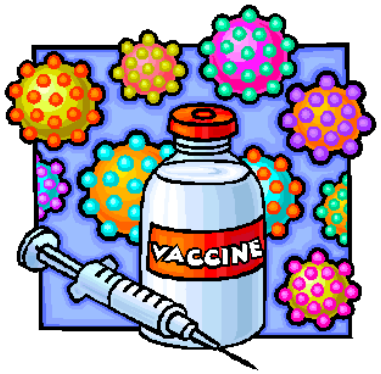
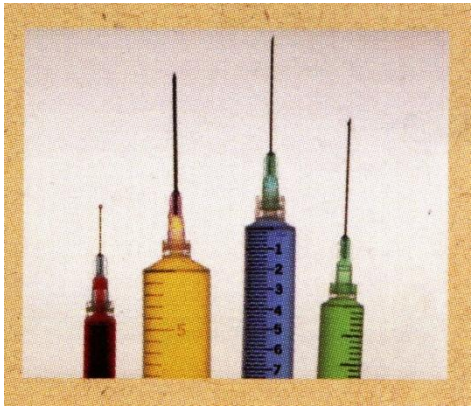
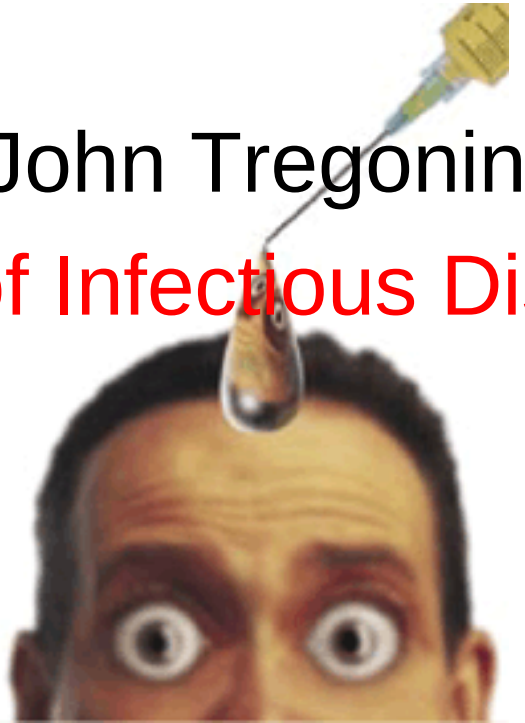




Vaccines

Dr John Tregoning

Section of Infectious Diseases



Name The Scientist

Almroth Wright
(Wright of Wright Fleming)
Made anti-typhoid vaccine
Predicted rise of antibiotic resistant bacteria

Outline of Week

Introduction to Key Concepts

New Vaccine Development

Challenges in Vaccine Development

Case studies of specific diseases

Vaccine Week Learning Objectives

By the end of this week you will be able to:

- Understand how vaccines control infectious diseases and some of the maths/epidemiology used to describe their efficacy.
- Describe the characteristics (incidence and symptoms) of vaccine preventable diseases.
- Describe the vaccines and vaccines schedules routinely used to control infectious diseases in the UK and globally.
- Understand the challenges to new vaccine development
- See how this applies to specific diseases including HPV, Influenza and Polio

A vaccine is…

Something that stimulates the immune system, without causing serious harm or side effects *(purified viral protein, killed bacteria…)*

Aim of immunisation: to provoke immunological memory to protect individual against a particular disease if you later encounter it

Vaccine comes from Vaccinia – originally believed to be Cow pox (Vaccination' and 'immunisation' mean roughly the same)

The ideal vaccine

- Completely safe
- Easy to administer
- Single dose, needle-free
- Cheap
- Stable
- Active against all variants
- Life-long protection

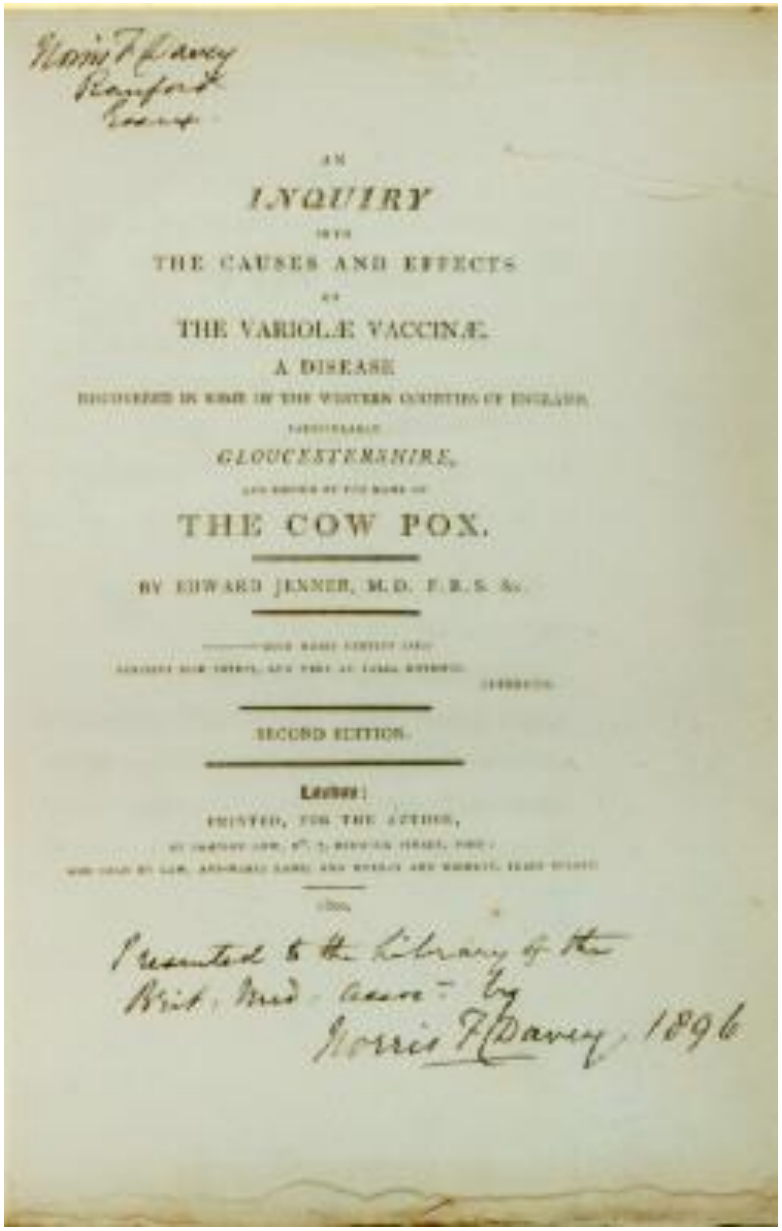
Vaccines are the single most cost-effective tool we have for improving health

Why Vaccinate?

EXHIBIT 1
Benefit-Cost And Cost-Effectiveness Ratios For Vaccines Compared With Other Commonly Used Preventive Services, 2003

Vaccination program or other preventive service	Benefit-cost ratio	Dollars per life year saved	Dollars per QALY saved
Diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B (Hib), polio, measles, mumps, rubella, and hepatitis B—combined program[1]	17		
Varicella vaccination[2]	5.4		
Pneumococcal conjugate vaccination[3]		128,000	6,500
Influenza vaccination of children ages 6–23 months[4]			13,000
Pertussis vaccination of adolescents[5]			20,000
Mammography for women ages 50–69[6]		29,000	
Pap screening with human papillomavirus testing for cervical cancer[7]			80,000
Colorectal cancer screening for people age 50 or older using sigmoidoscopy[8]		90,000	
Mammography for women ages 40–69[6]		140,000	

The early days…



AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ.

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

SECOND EDITION.

LONDON:

PRINTED, FOR THE AUTHOR,

Presented to the Library of the
Brit. Med. Assoc. by
Norris F. Davey, 1896

The Godfathers of vaccination

Edward Jenner

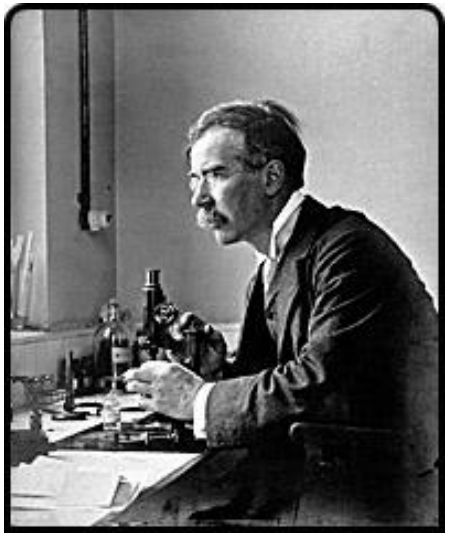
1749-1823

Small Pox

Louis Pasteur

1822-1895

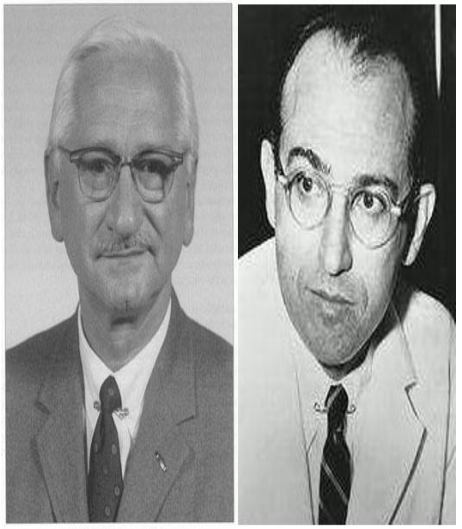
Rabies
(Cholera and Anthrax)



Almroth Wright

1861-1947

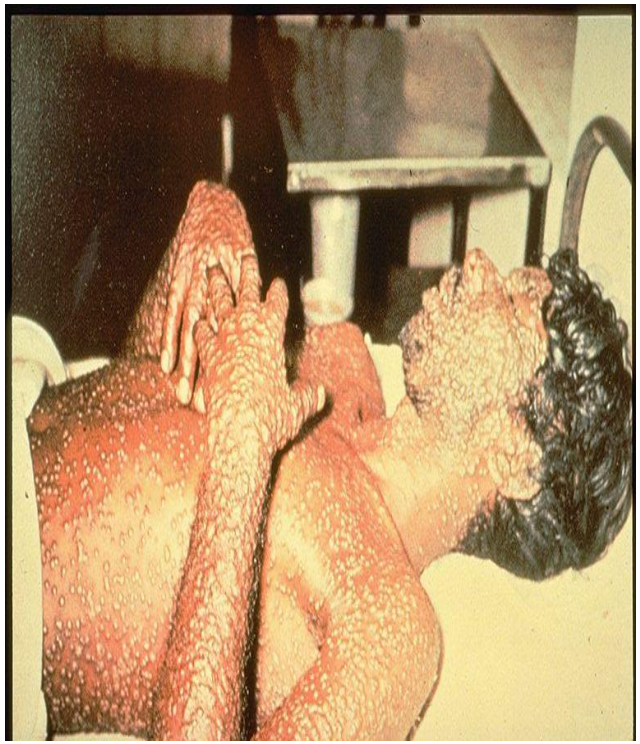
Typhoid

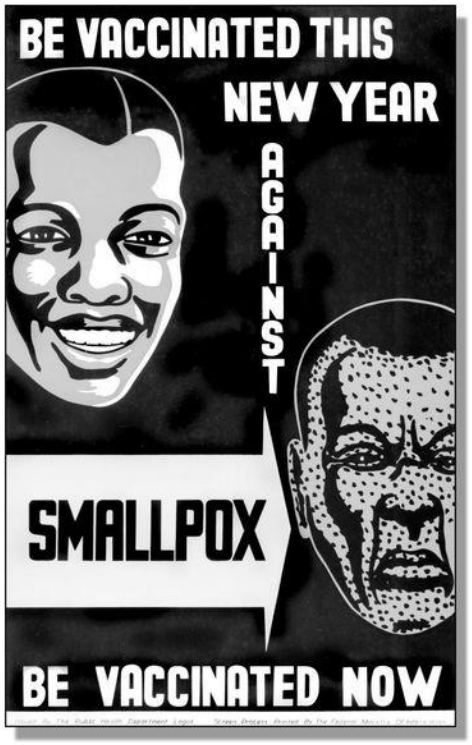


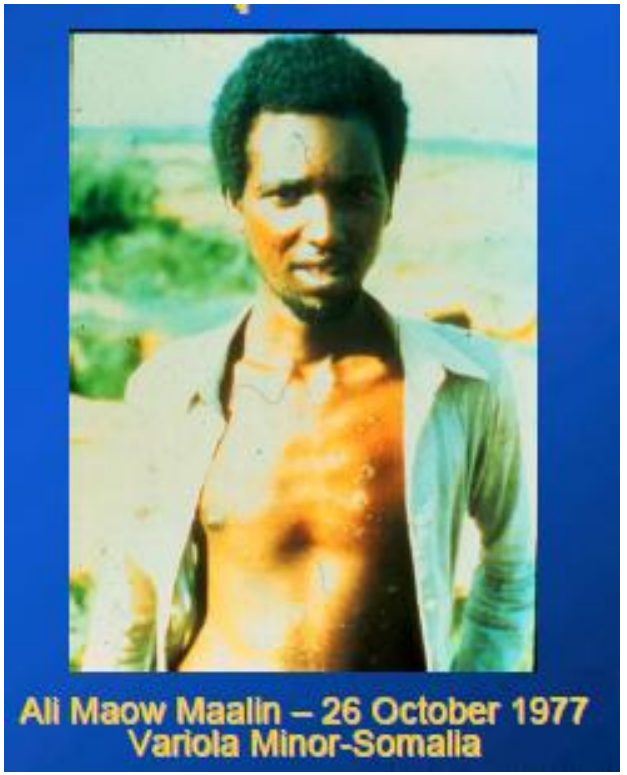
Sabin/ Salk

Polio
(Oral)

Smallpox in unvaccinated adult

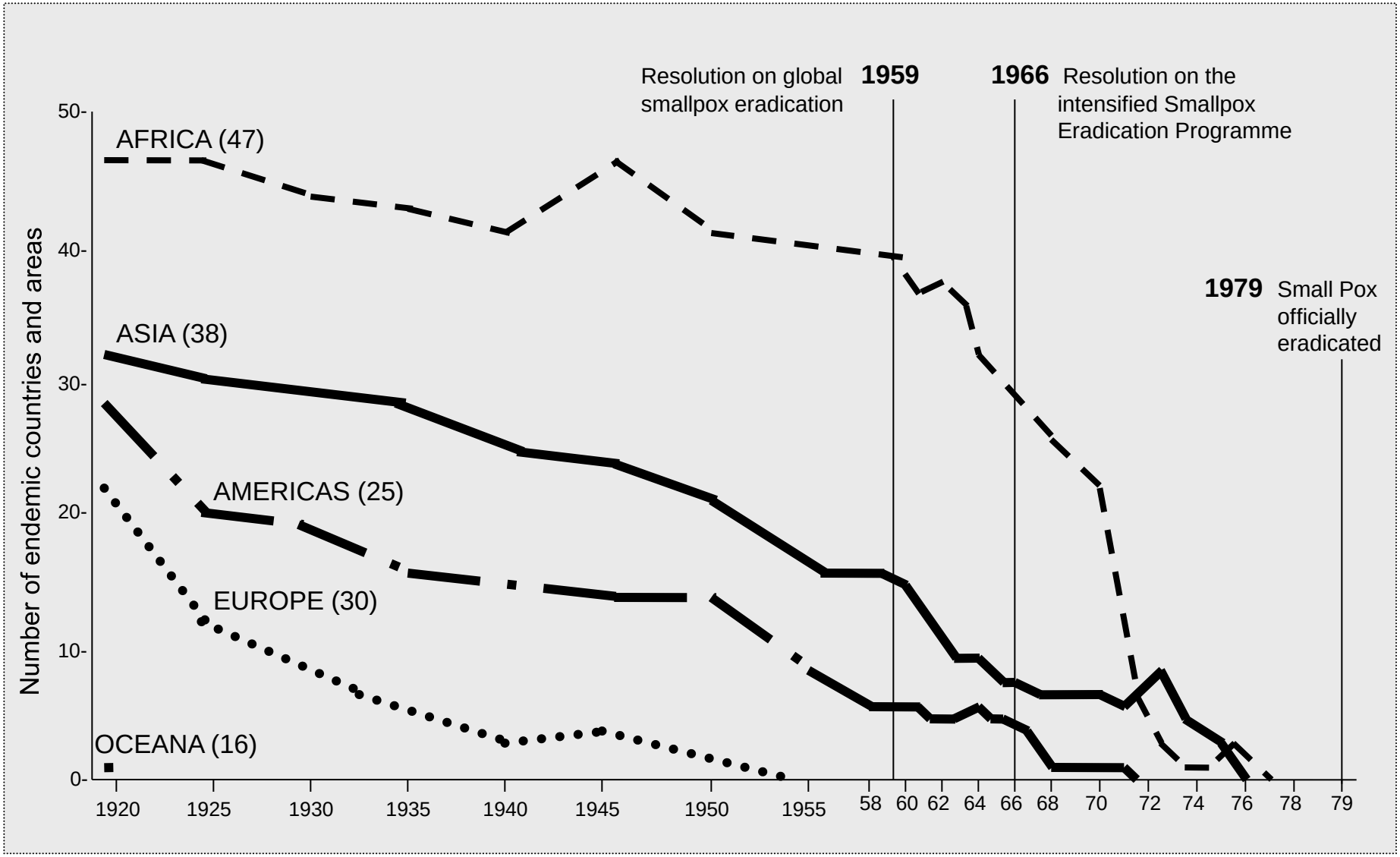






How many lives did Jenner and co save? **About 300 million**
USA recouped the $21m it contributed to eradicating smallpox in the ten years to 1978 in just 26 days

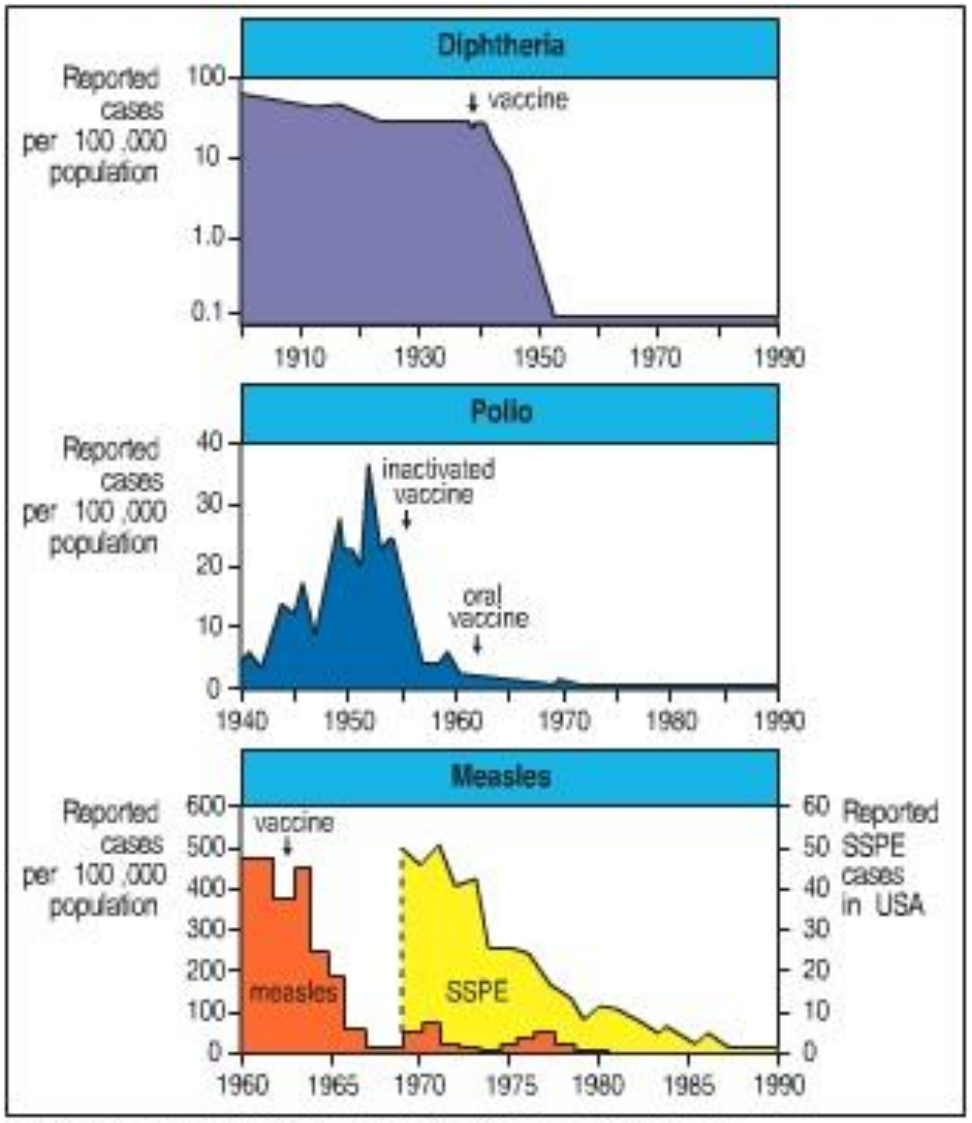
Global eradication of smallpox



Year

NB some accidental outbreaks later on

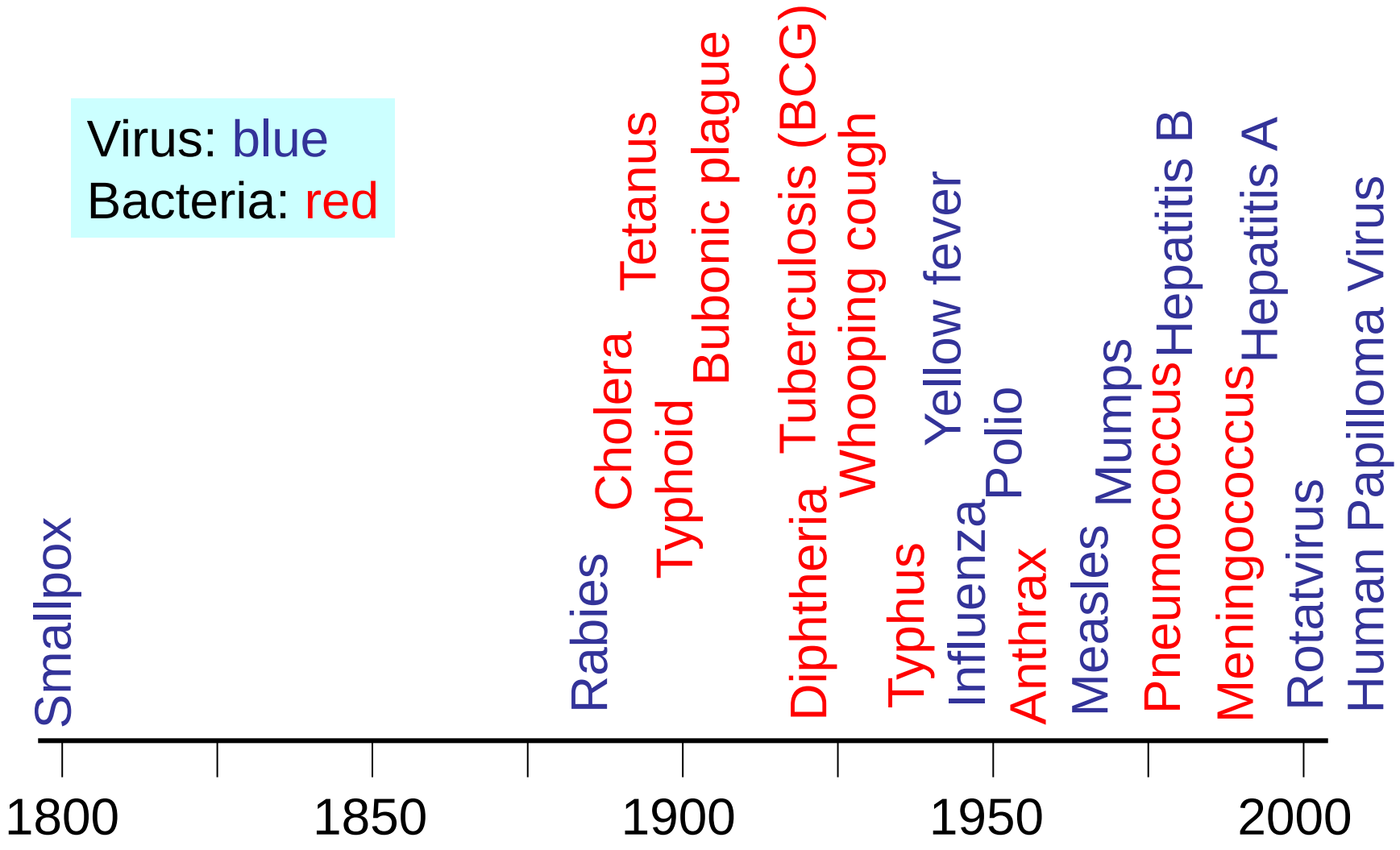
Other Vaccine Success stories



Characteristics of an eradicable infectious disease

- Safe and effective vaccine
- Genetically stable target
- No animal reservoir
- Eliminates persistent infection, or persistently infected host can't transmit
- Easy and reliable diagnostics

Vaccine timeline



Diseases for which improved or new vaccines are needed

HSV
TB
Malaria
HIV

EBV
RSV
Worms
Hep C

Medicine at the intersection

Big Pharma

The Media

NGOs

Basic Science

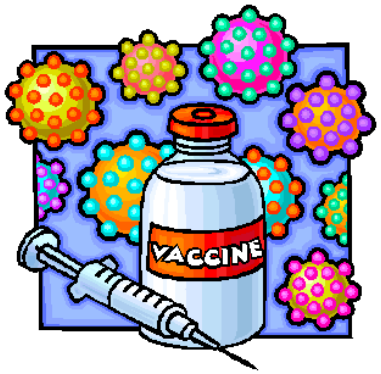
The public

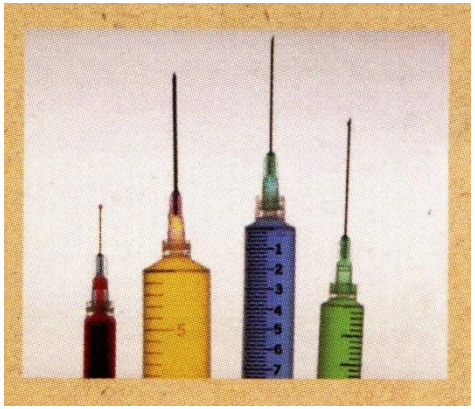
Public Health
NHS/HPA

Learning Objectives for this lecture

This lecture will focus on:

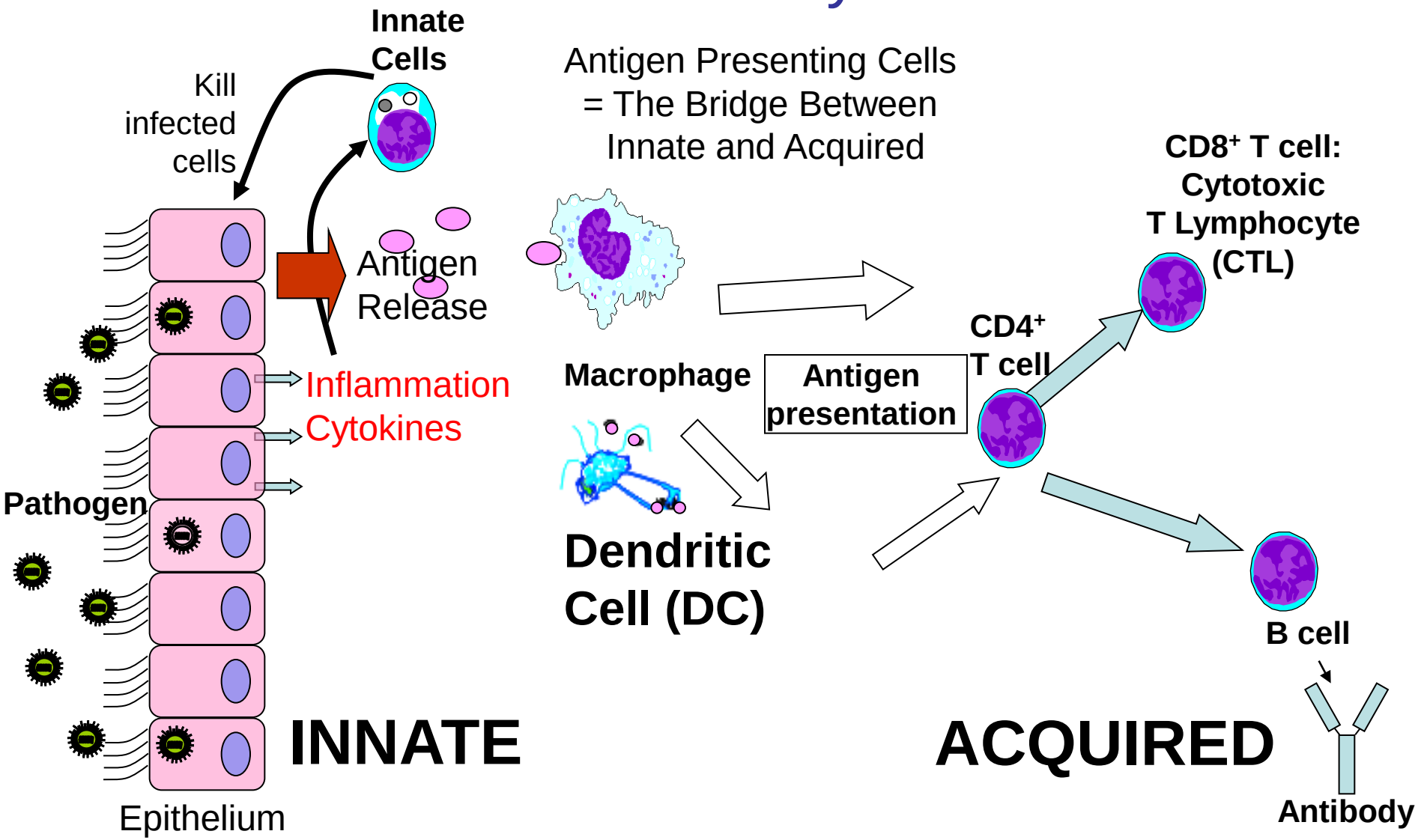
- An Introduction to the immunological principles of vaccines
- An Introduction to the epidemiological understanding of how vaccines prevent disease





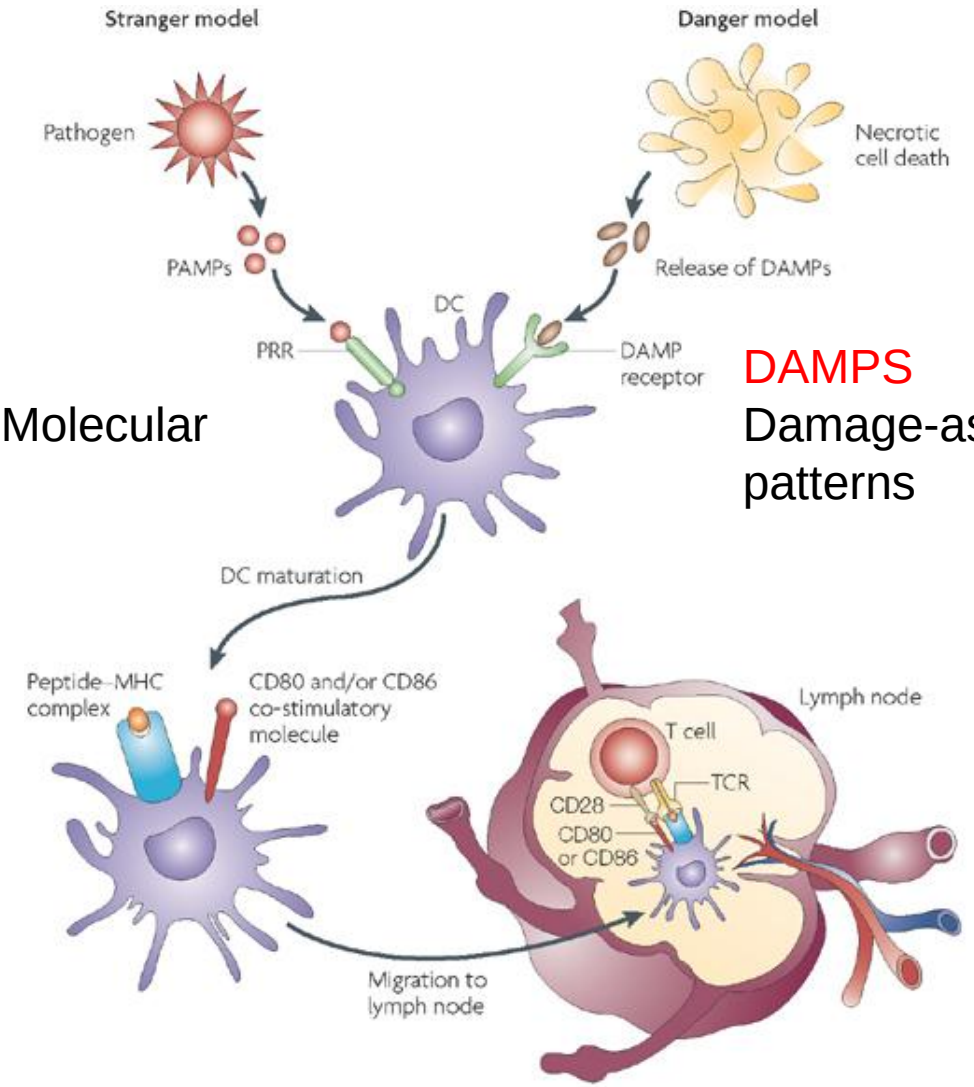
Vaccine Immunology

The Immune system



“Stranger Danger!” (Adjuvants)

PAMPS
Pathogen Associated Molecular Patterns



DAMPS
Damage-associated molecular patterns

Key Members:
Toll Like Receptors
Rig Like Receptors
C-type Lectins

Key Members:
Nod Like Receptors

Antigens and epitopes

- Proteins or molecules that act induce an adaptive immune response
- The region of an antigen which the receptor binds to is known as an **epitope**

T cells recognise linear epitopes

In the context of MHC

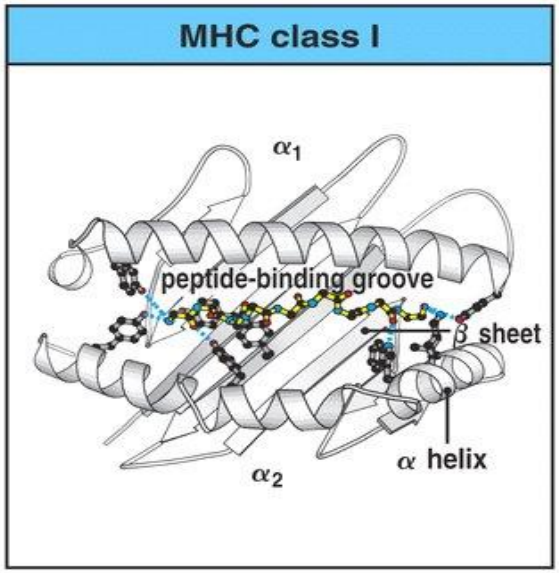
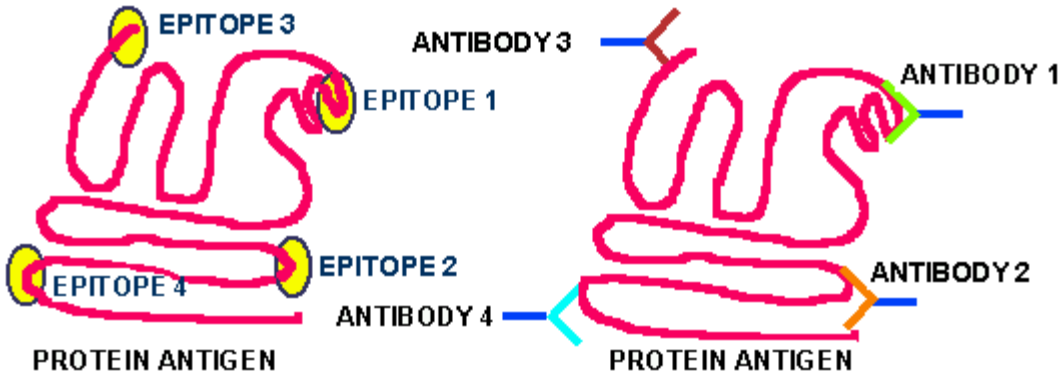


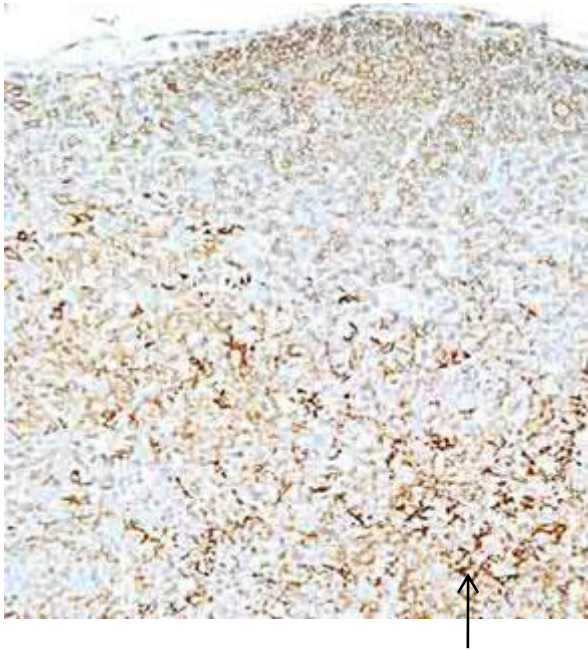
Figure 3-15 The Immune System, 2/e (© Garland Science 2005)

Antibodies recognise Structural Epitopes



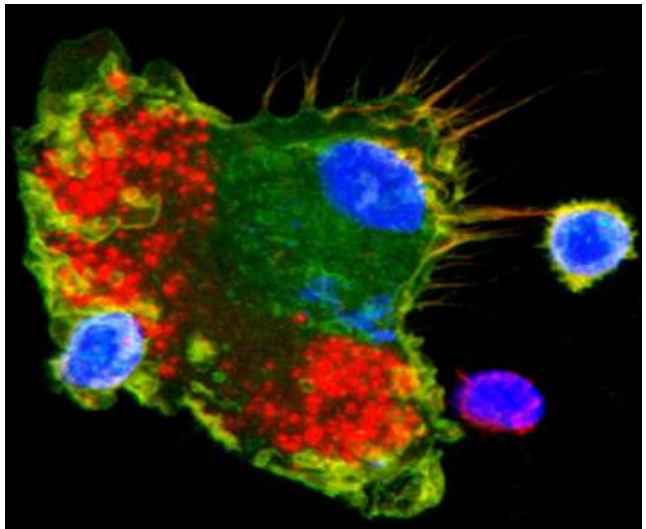
Dendritic cells

Surveillance

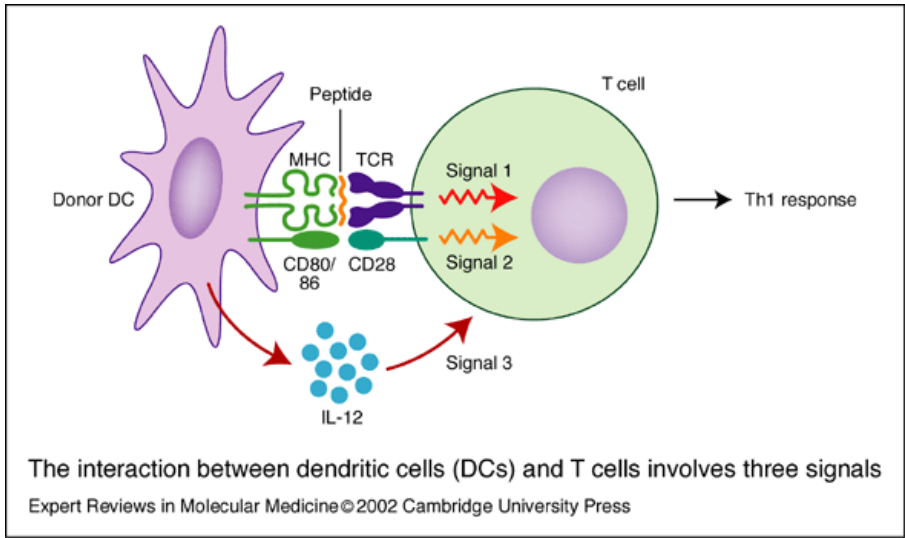


- Specialised antigen presenting cells, patrol tissues performing surveillance
  - Require activation by PRR activation
  - When immature dendritic cells capture Ag, they travel through the lymphatic system to LYMPHOID TISSUES where they mature
  - In lymph nodes, mature dendritic cells present the antigen they have encountered.

Capture

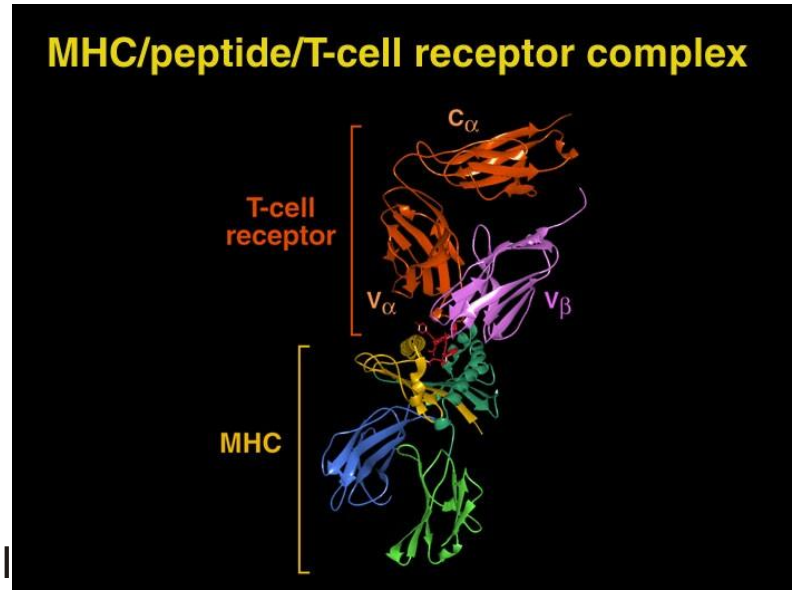


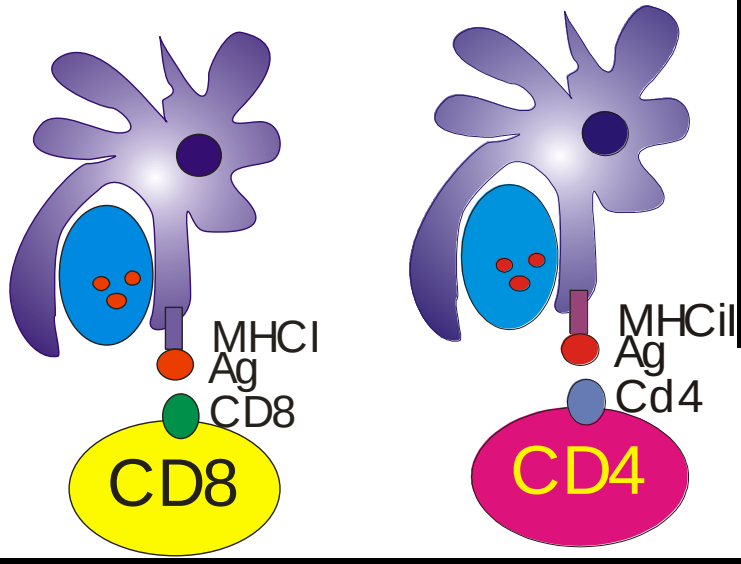
Presentation



The interaction between dendritic cells (DCs) and T cells involves three signals

MHC/ TCR Interactions



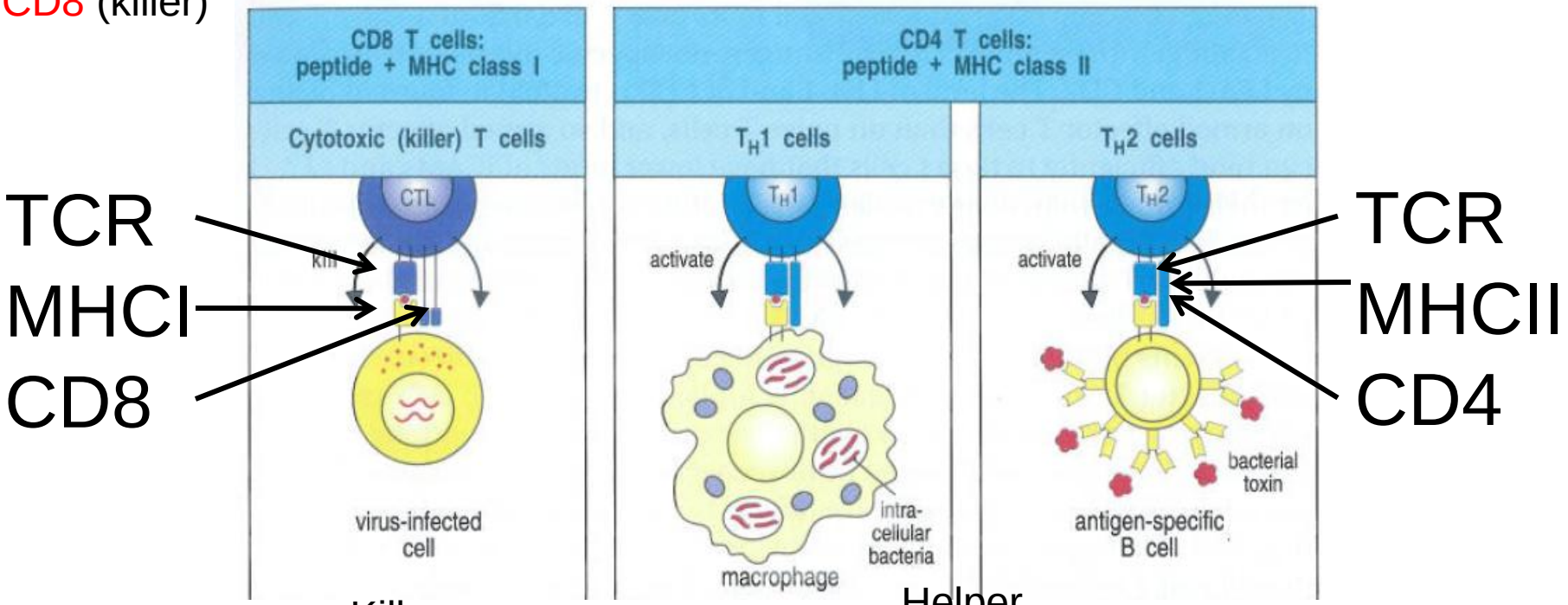


Type	Intracellular pathogen/antigen	Extracellular pathogen/ Antigen
Processed in	Cytosol	Endosomes
Presented on	MHCI	MHCII
Presented to	CD8 T cells	CD4 Cells

- MHC Stands for Major Histocompatibility Complex
- Presents the peptide epitopes to T cells
- MHCI peptides are intracellular
- MHCII peptides are extracellular
- In humans it is encoded by the HLA genes
- Important for disease susceptibility e.g. HLA-B57 is protective against HIV (since it presents an HIV epitope that alters viral fitness)

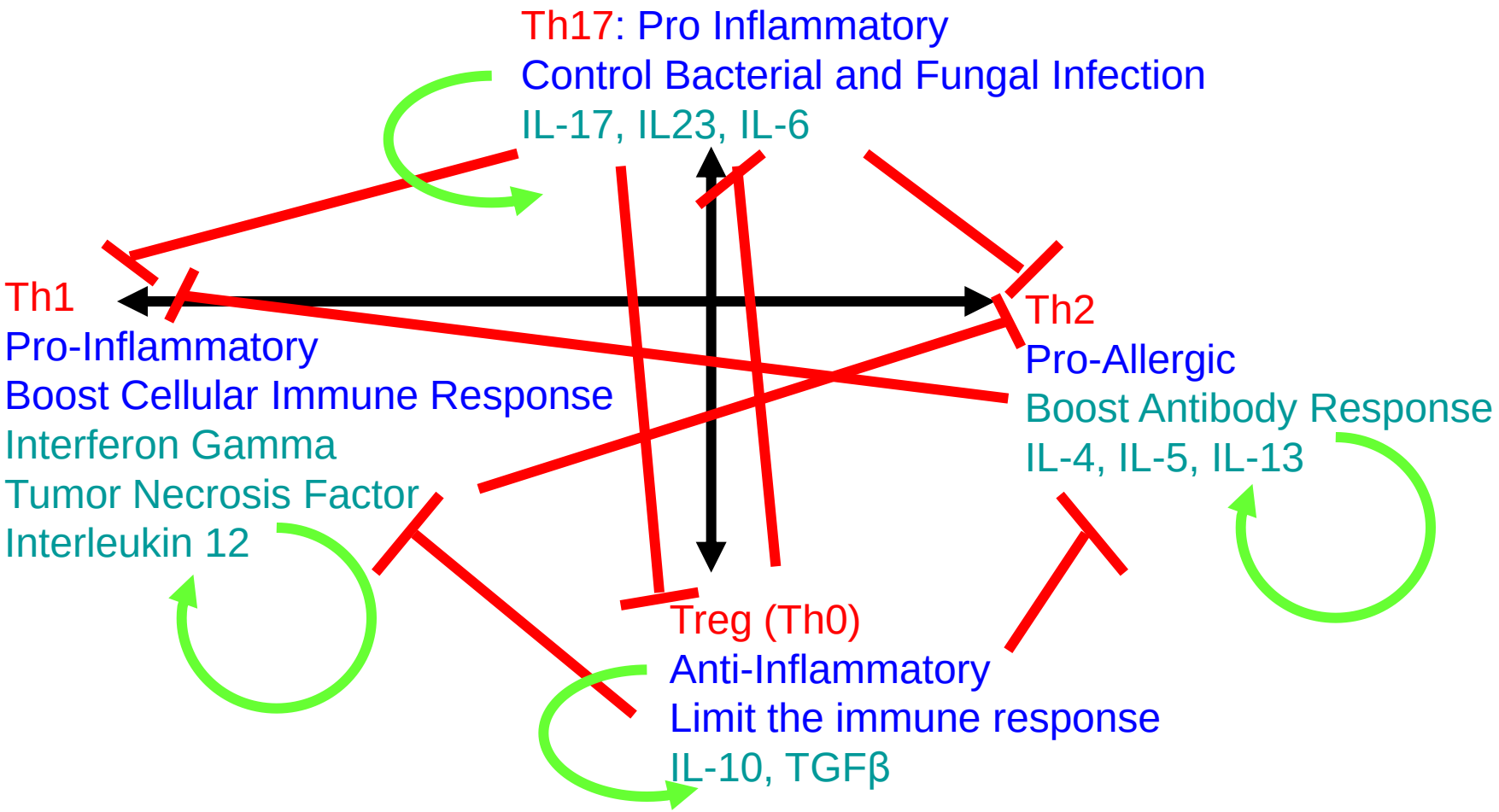
T Cells

- T cells mature in the thymus
- Their receptors (T cell receptor (CD3)) remains membrane bound
- Recognise specially processed fragments of protein which are presented to them by target cells. T cell receptor recognises combination of peptide and MHC
- Two families CD4 (helper) and CD8 (killer)



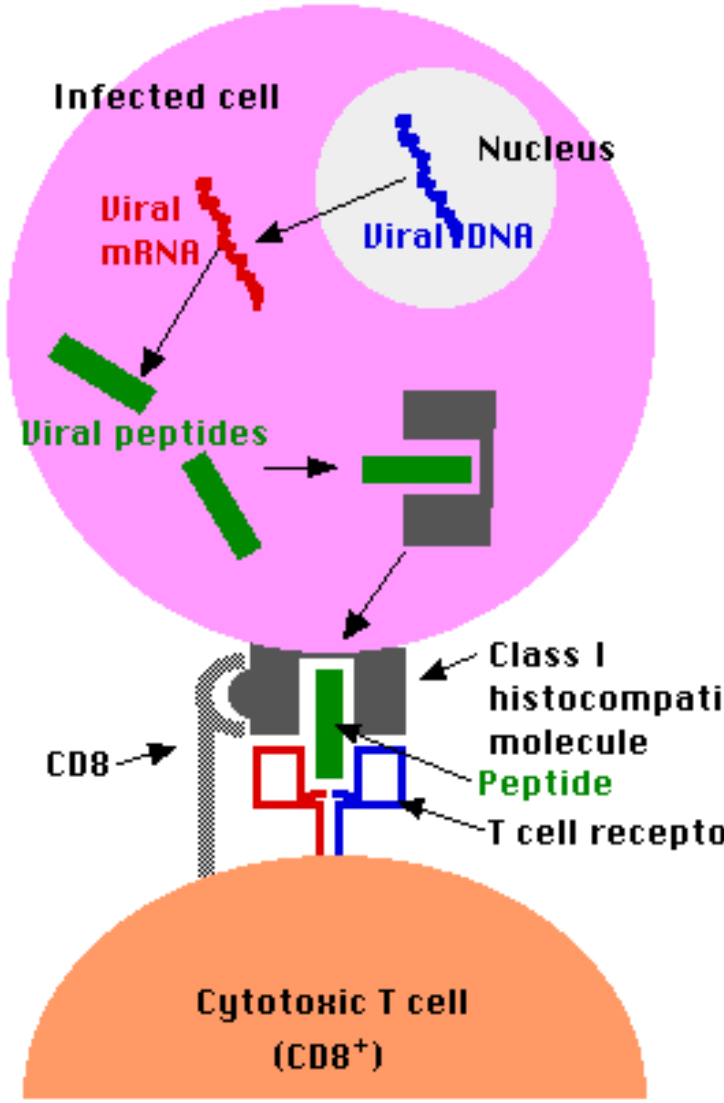
CD4 T Helper cells

- T Helper cells produce cytokines (a family of inflammatory mediators).
- Cytokines have diverse actions on a wide range of cells
- Cytokines influence the outcome of the immune response



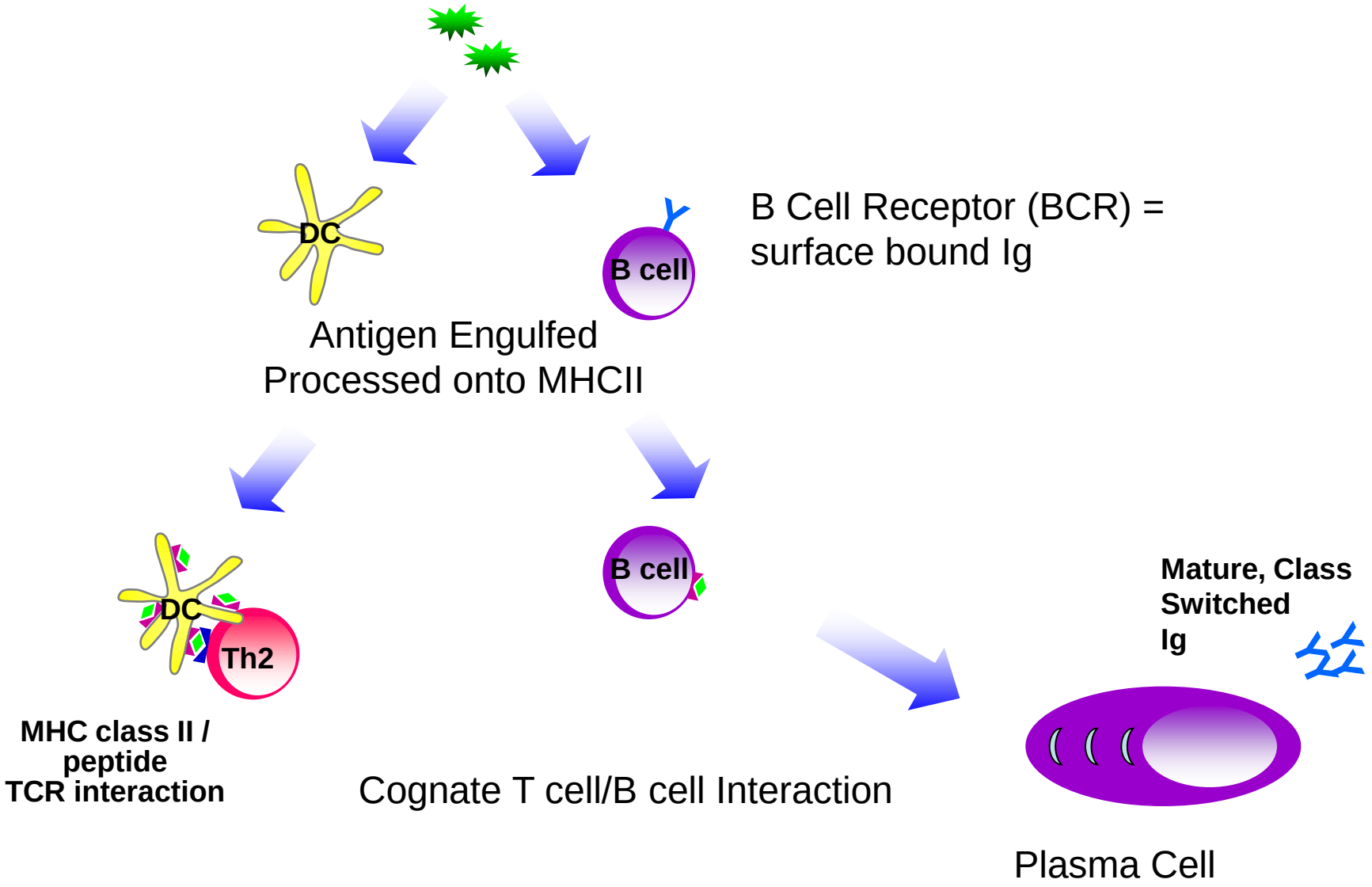
CD8 (Cytotoxic T lymphocytes/ CTL)

- Cytotoxic T cells (Killer) destroy target cells such as virus infected cells
- Recognise MHCI: Peptide Complexes
- Kill cells in 2 ways
  - punching holes in and injecting poison (Perforin/Granzyme)
  - Inducing Apoptosis (FasL/Fas)



http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/B/B_and_Tcells.html

B cell activation



Antibody Classes

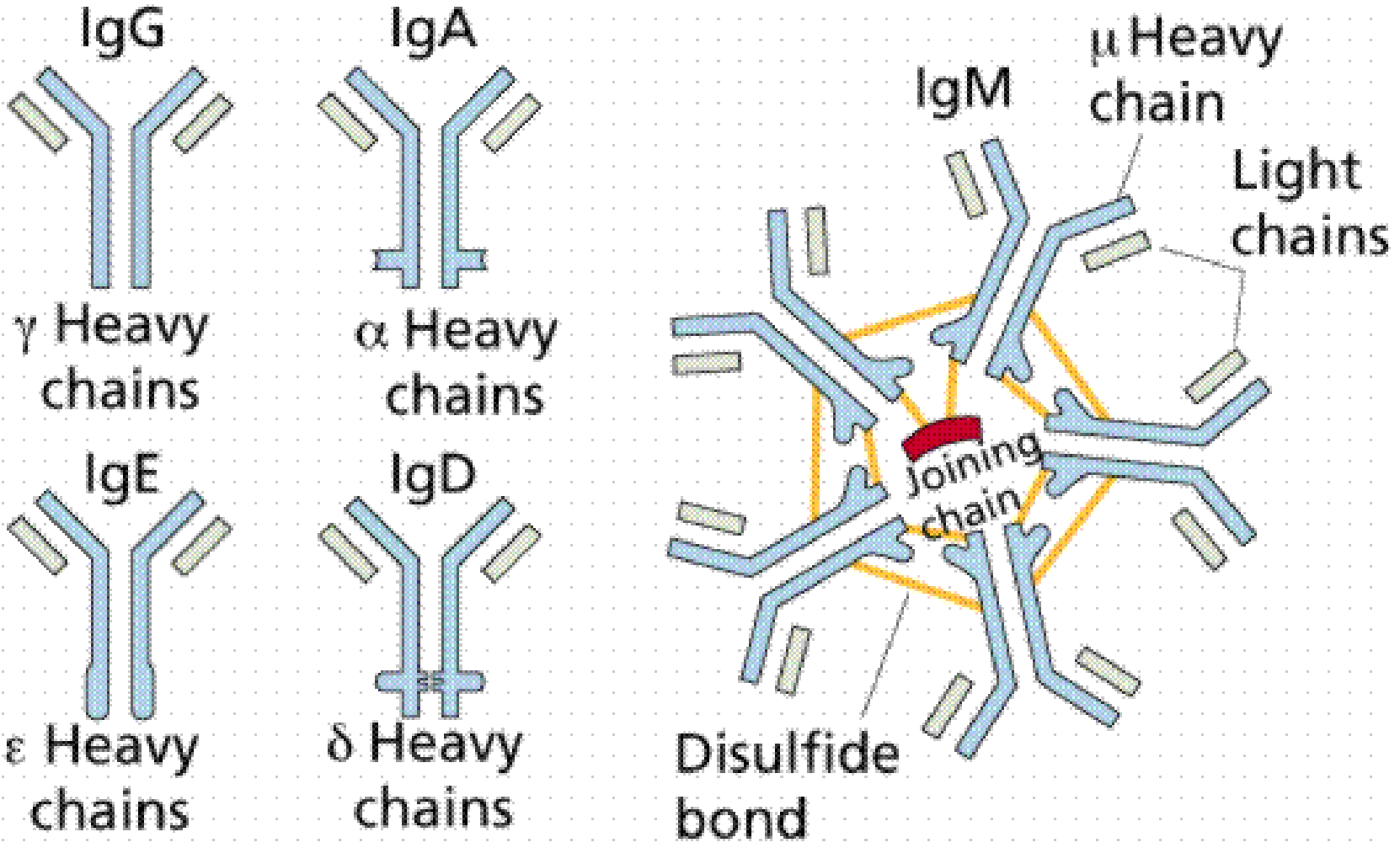


Image from Purves et al., Life: The Science of Biology, 4th Edition

Antibody Function

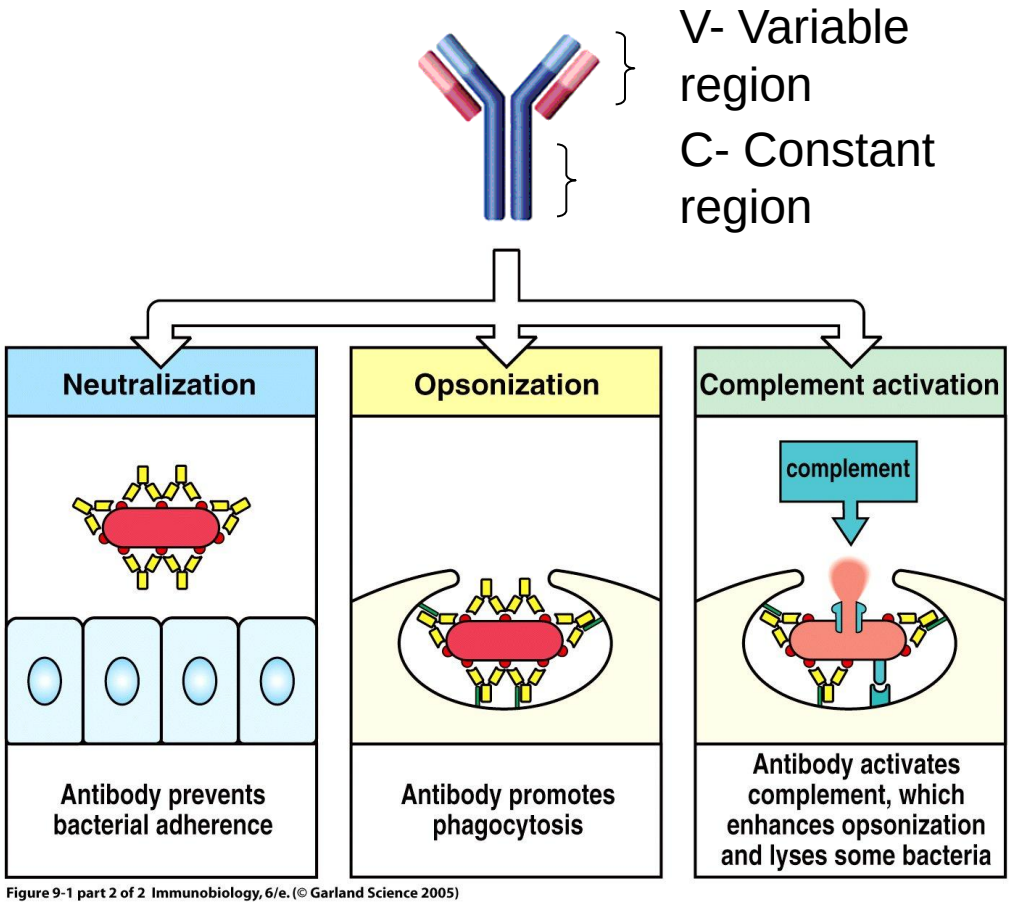


Figure 9-1 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Antibodies extremely important in protection against reinfection

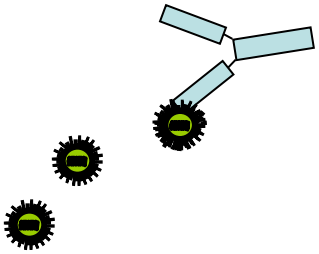
3 Core protective roles:

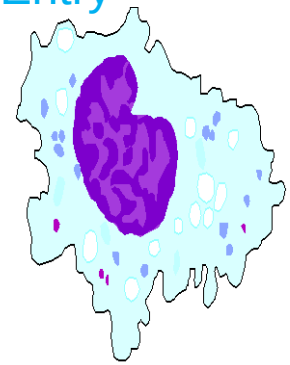
1. Neutralisation
2. Opsonisation
3. Complement activation

How Vaccines stop infection

Vaccination is the generation of
Immune Memory in the absence of harmful infection

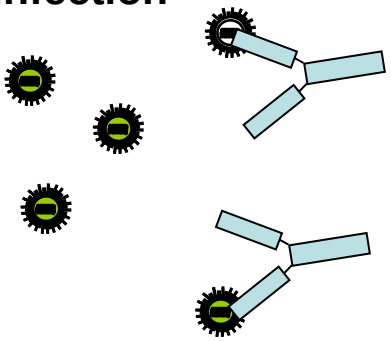
Prevention of Entry





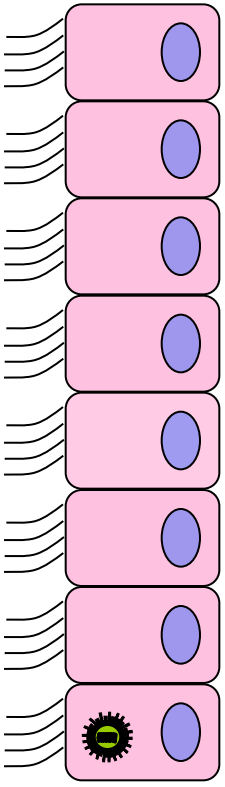
Macrophage:
Engulfs
Pathogen

Infection



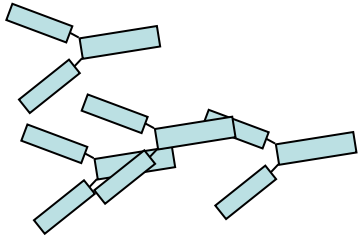
Antibody: Blocks Entry

Epithelium



CD8: Kills

Killing infected cells

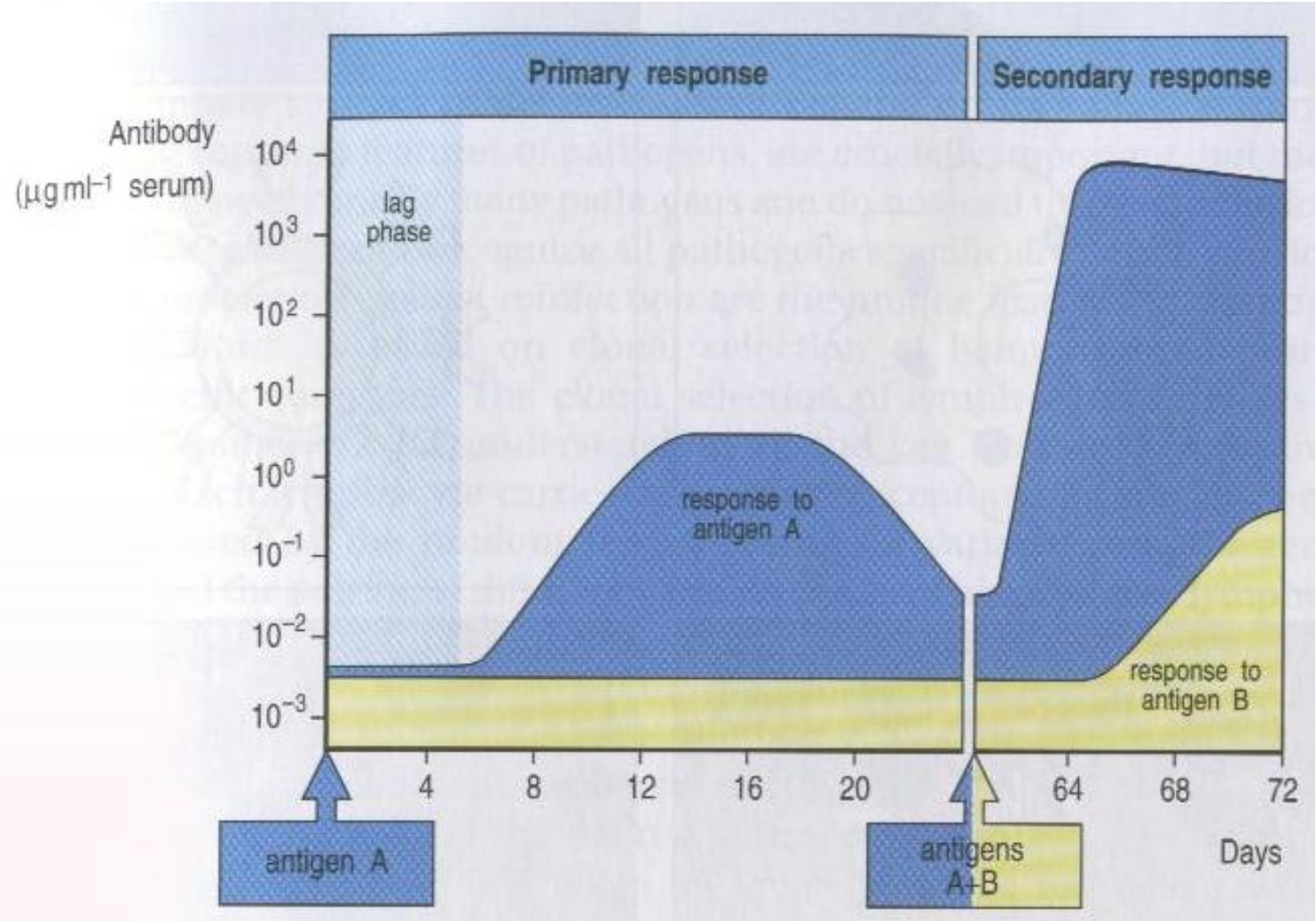


B Cell: Makes Ig

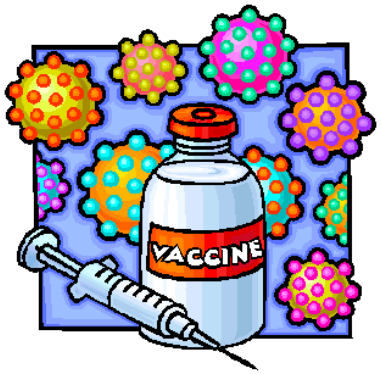
CD4 T Cell:
Helps

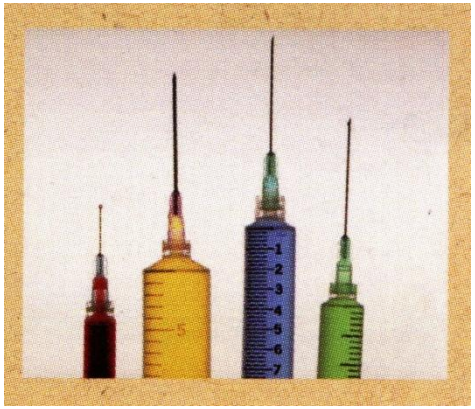
Boosting Immune Response

Immune Memory



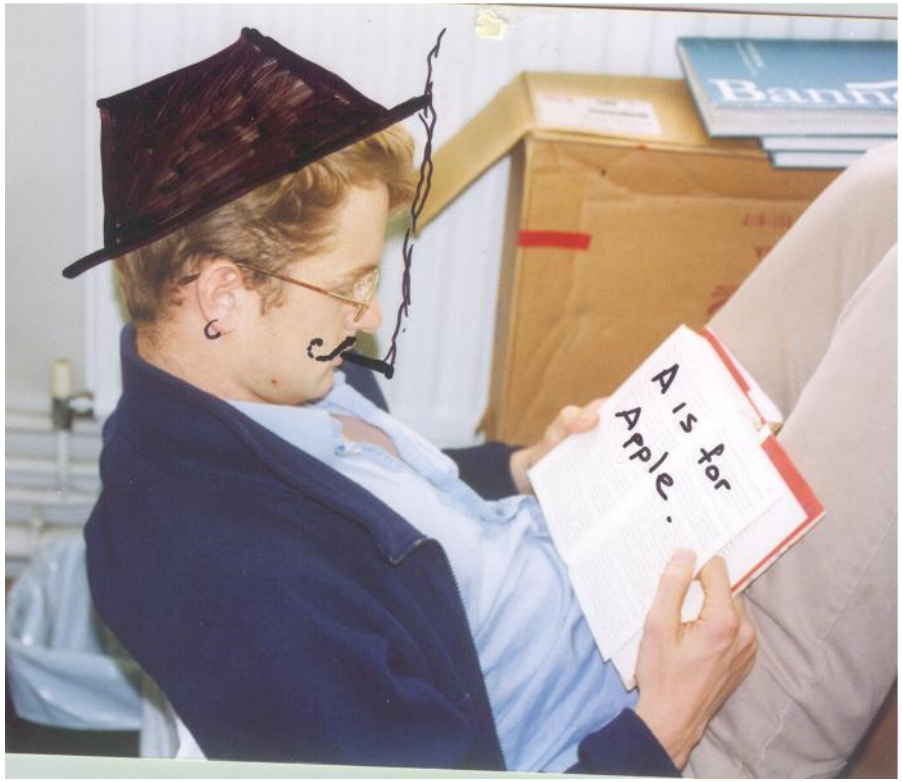
From Janeway et al





The epidemiology of vaccines

Epidemiology for Dummies



Basics

- **Eradication -** Disease and its causal agent have been removed worldwide e.g. small pox
- **Elimination -** Disease has disappeared from one WHO region but remains elsewhere e.g. polio
- **Containment -** The point at which the disease no longer constitutes a 'significant public health problem' e.g. Hib

R_0 - Basic reproduction number

The number of cases one case generates on average over the course of their infectious period

If $R_0 < 1$ the infection will die out in the long run.

If $R_0 > 1$ the infection will be able to spread in a population.

Disease	R_o
Diphtheria	6-7
Measles	12-18
Mumps	4-7
Pertussis	12-17
Polio	5-7
Rubella	6-7
Smallpox	5-7

† Modified from *Epid Rev* 1993;15: 265-302, *Am J Prev Med* 2001; 20 (4S): 88-153, *MMWR* 2000; 49 (SS-9); 27-38

From CDC website

Calculating the R

$$R_0 = D \cdot C \cdot \beta$$

Where

D Mean length of time infectious

C Rate at which contact occurs

β Likelihood of transmission on a contact

R_t – Effective reproduction number

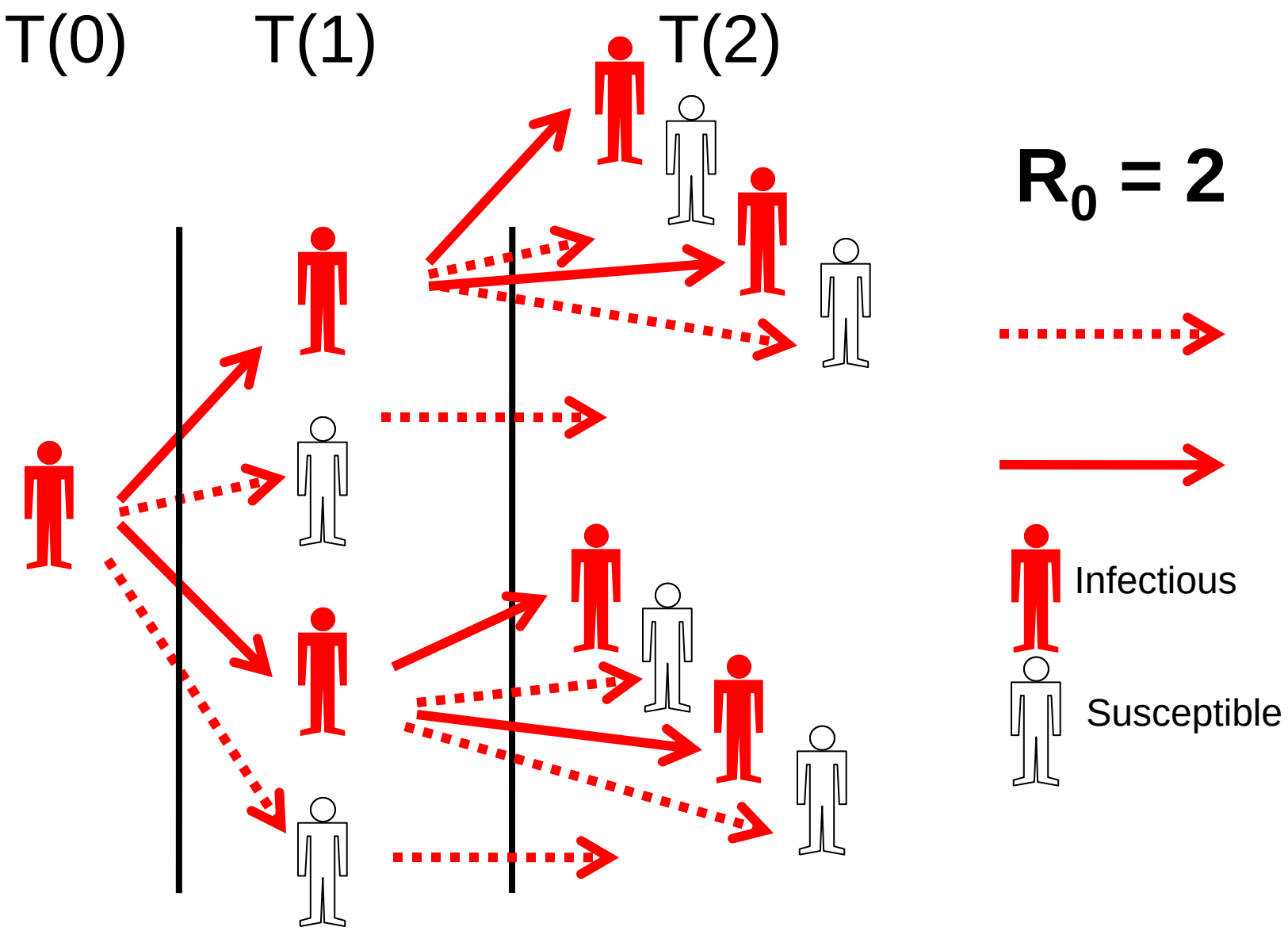
A population will rarely be totally susceptible to an infection in the real world.

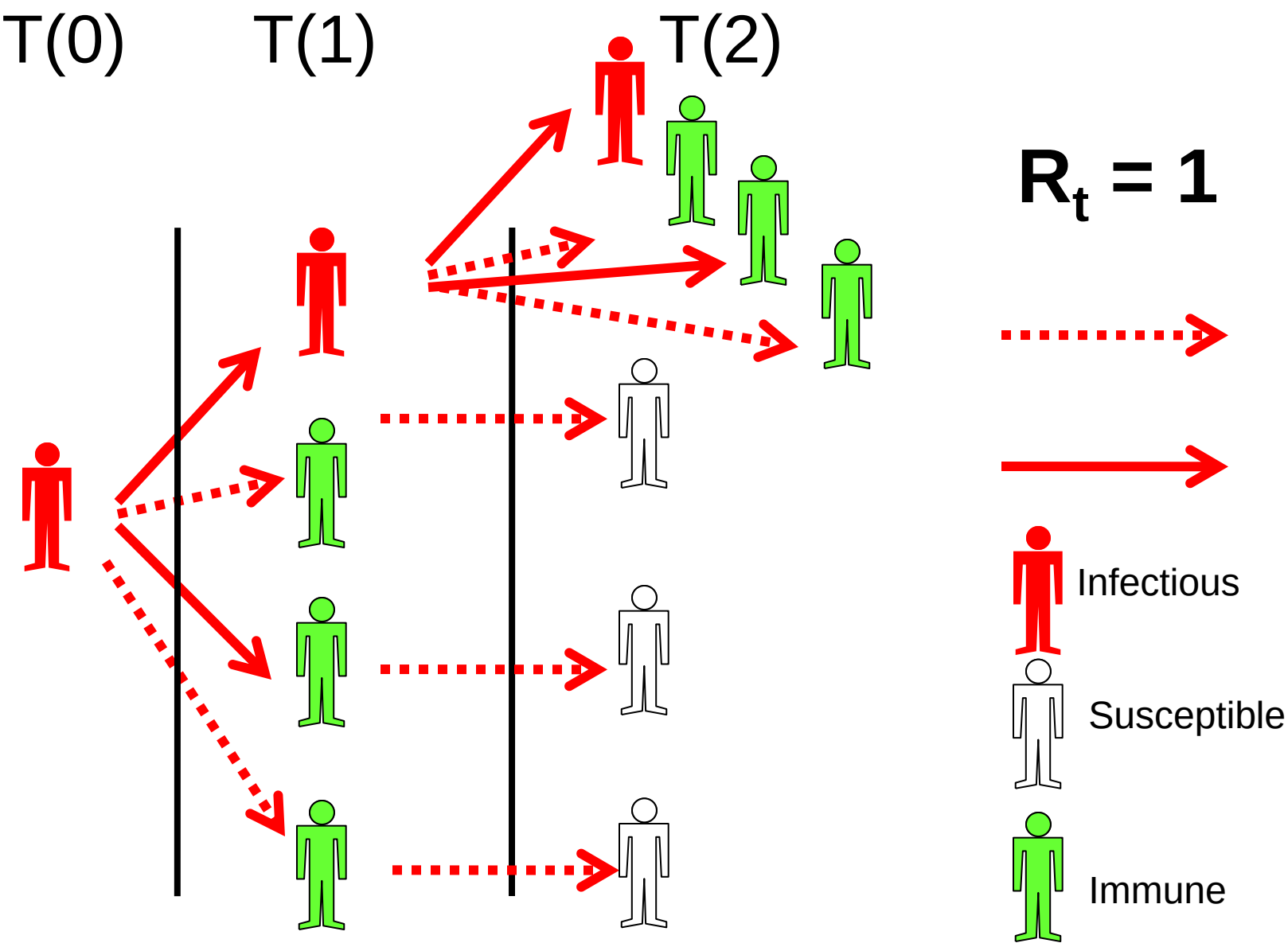
R_t reflects the number of susceptible cases

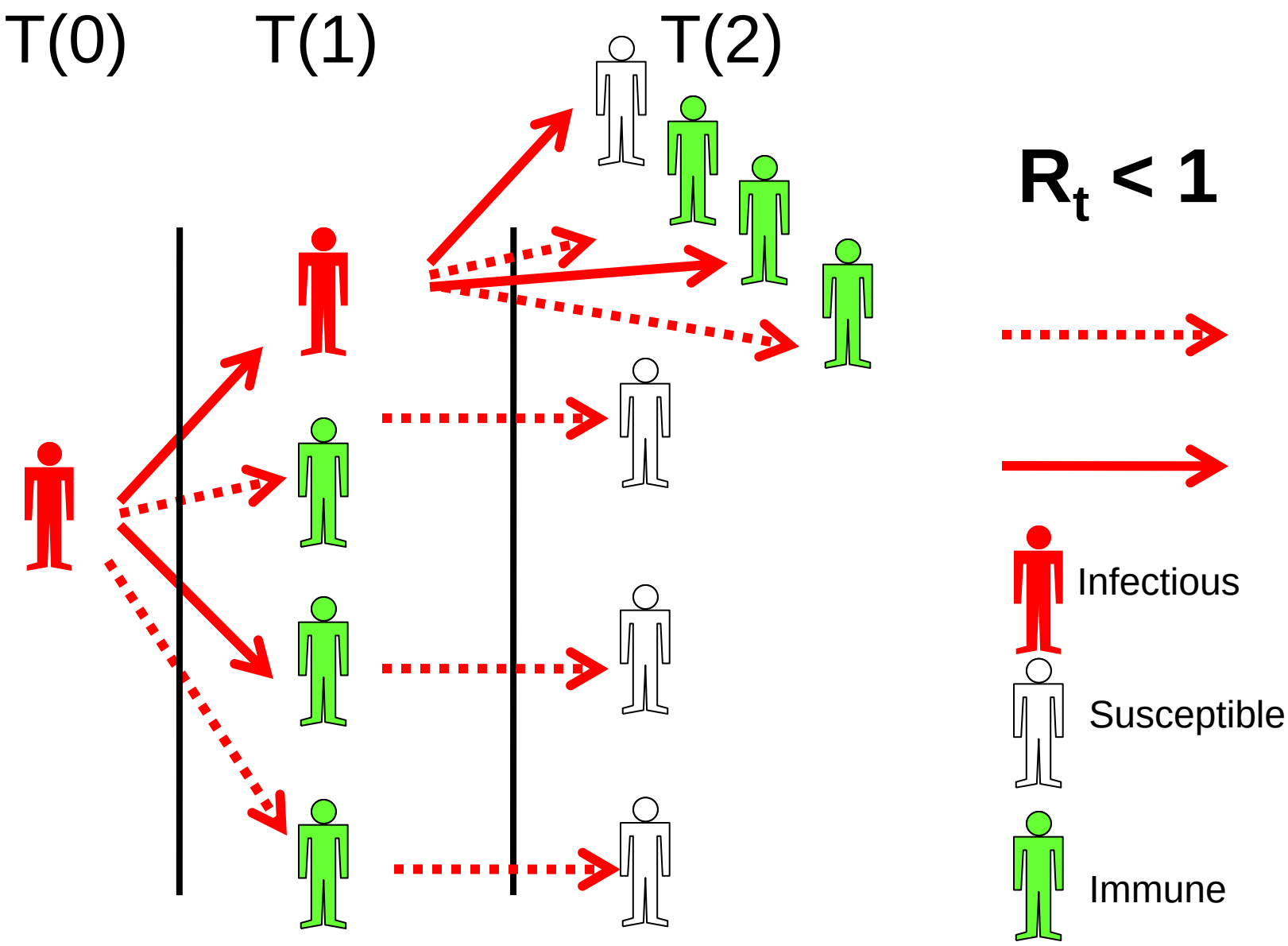
$$R_t = R_0 . x$$

Where x is the proportion of contacts susceptible

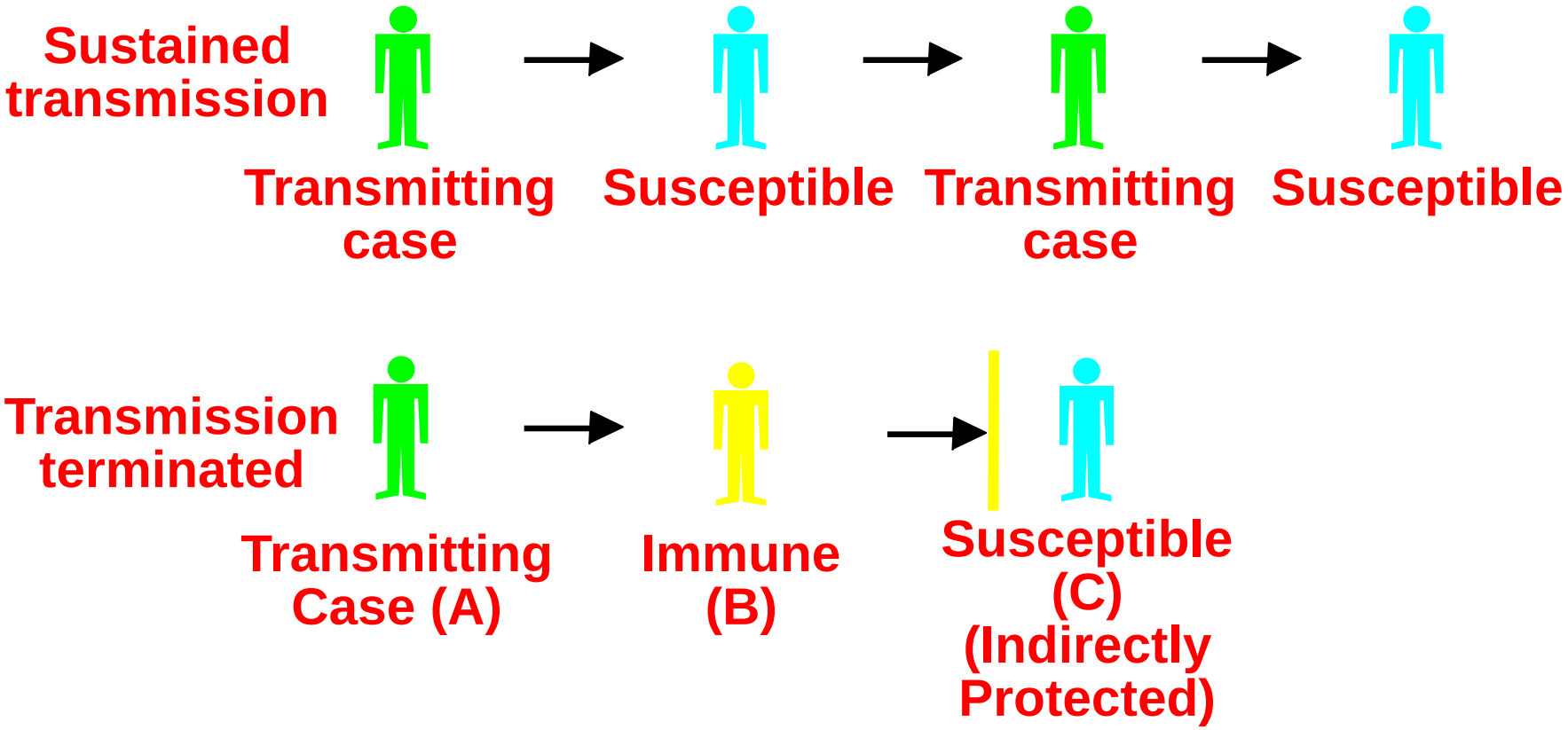
Effect of vaccination on R_0




T(0)
T(1)
T(2)
$R_t = 1$
Infectious
Susceptible
Immune


T(0)
T(1)
T(2)
$R_t < 1$
Infectious
Susceptible
Immune

Herd Immunity

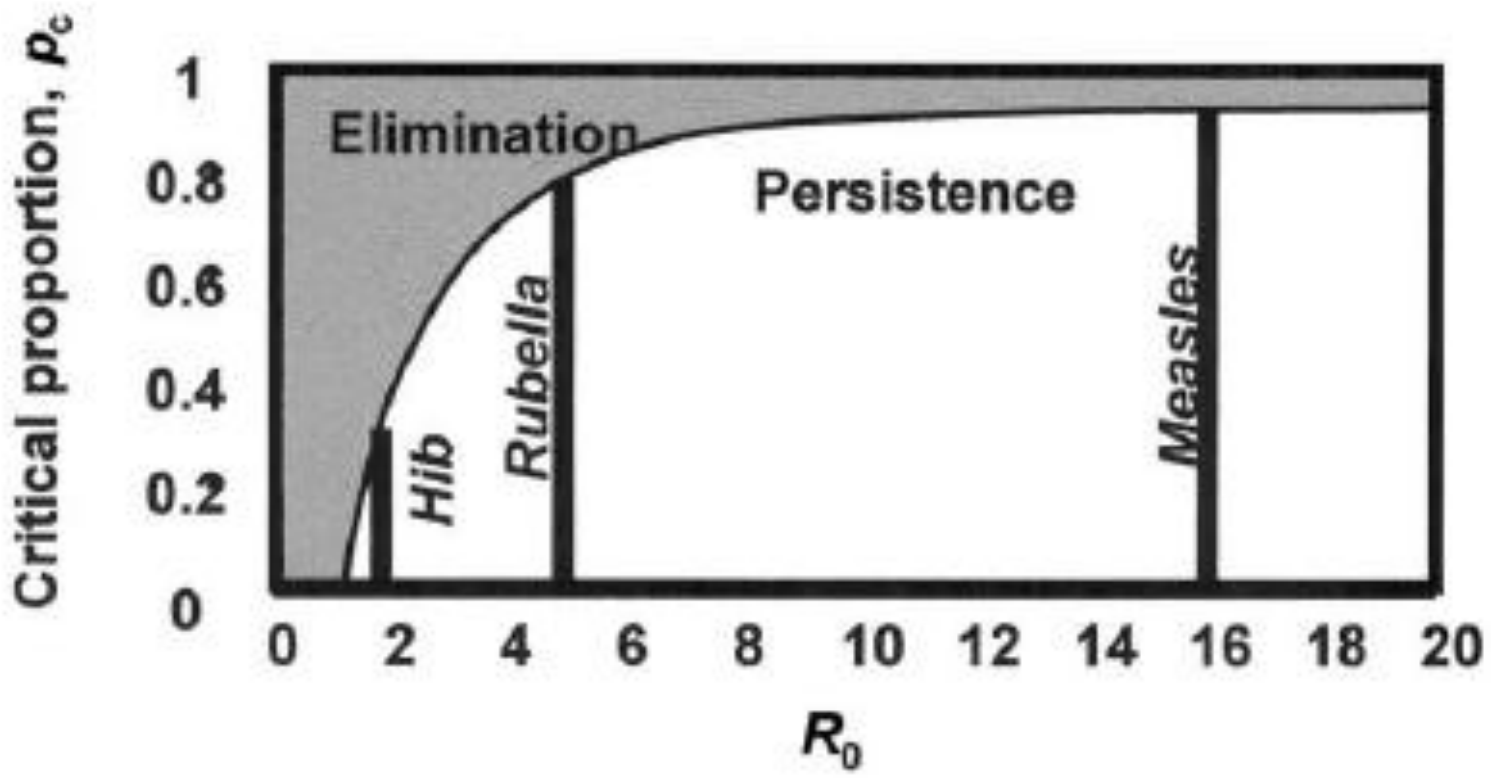


Herd Immunity Threshold: p_c

- The proportion of individuals that need to be vaccinated to control the incidence of infectious disease is called p_c
- p_c = **$1-(1/ R_t)$**
- **$R_t = R_0 . x$** (vaccination directly decreases x)
- where $R_t < 1$ for the elimination of infection)

NB this value seems to have as many different names as there are authors!

p_c increases as R_0 increases



From Garnett GP The Journal of Infectious Diseases 2005; 191(Suppl 1):S97–106

R0 and herd immunity

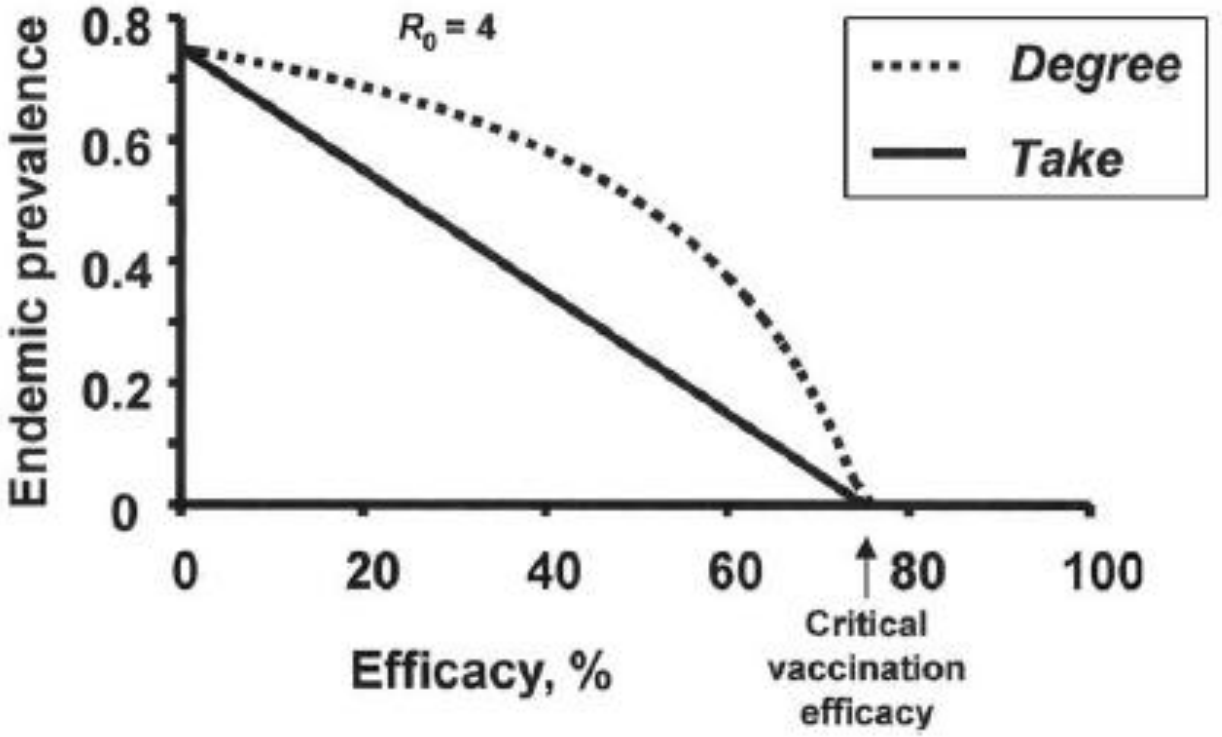
Disease	R_o	Herd Immunity
Diphtheria	6-7	85%*
Measles	12-18	83-94%
Mumps	4-7	75-86%
Pertussis	12-17	92-94%
Polio	5-7	80-86%
Rubella	6-7	83-85%
Smallpox	5-7	80-85%

Vaccine Efficacy

Two theoretical ways in which a vaccine fails

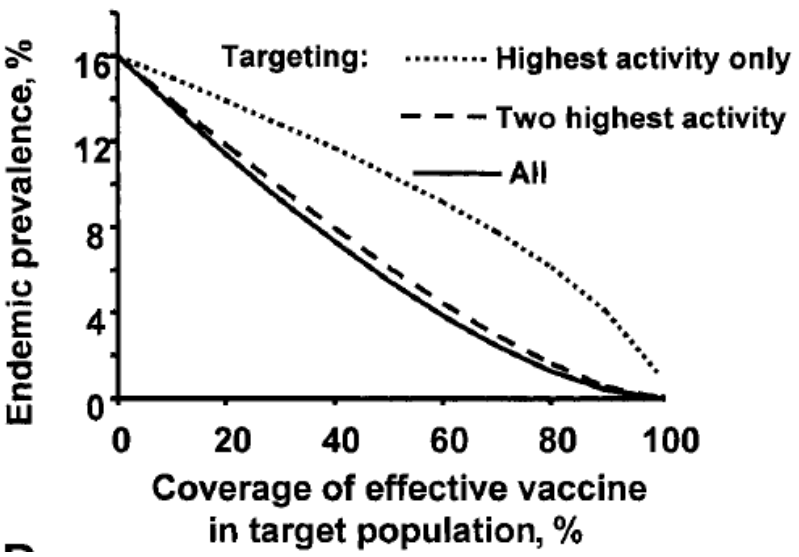
- **Failure to *Take* *failed sero-conversion/ immunogenicity. Efficacy = fraction fully protected.***
- **Failure against infectious challenge (infection) – challenge dose, cofactors, *Degree* –*Efficacy = number of challenges protected from.***
- ***This affects*** $p_c = \frac{(1 - 1/R_0)}{E}$

Modelling the different effects of efficacy



Take is a linear relationship
Degree is a proportional relationship

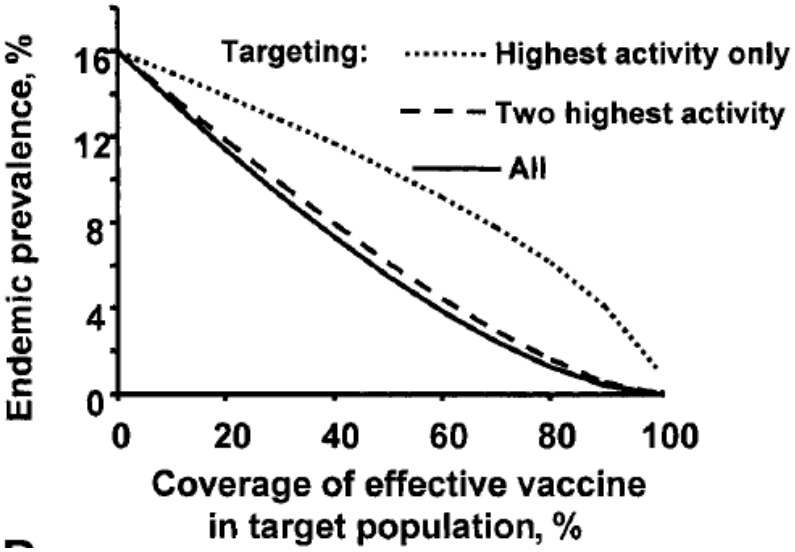
Targeted Vaccination



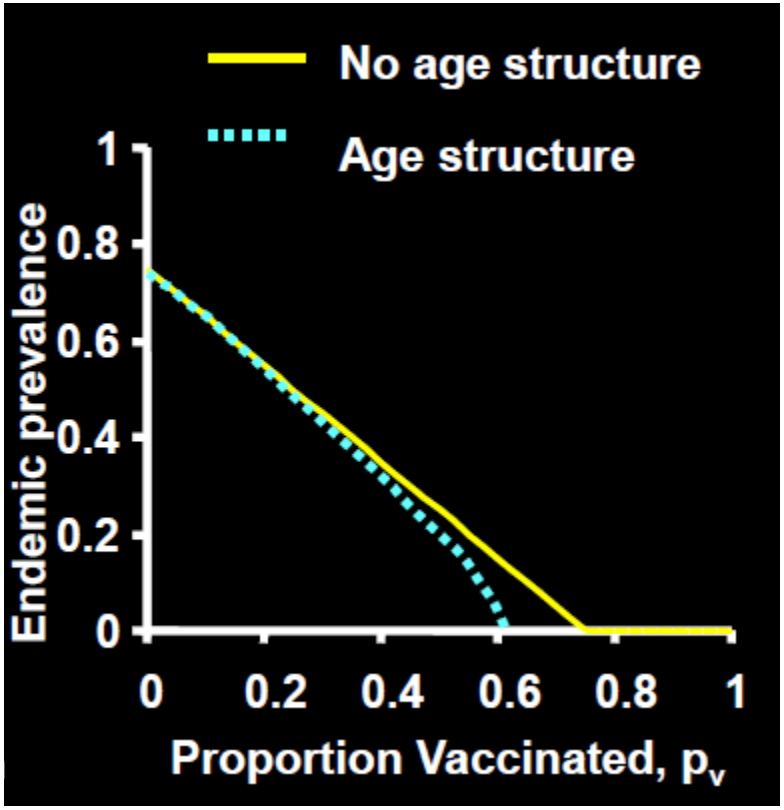
- Risk of spread can vary with behaviour e.g.
  - STI/ partner number, sex
  - RTI/ age
- Therefore some individuals may account for more infections.
- If these are vaccinated, you can get elimination for a lower overall vaccination rate, e.g HPV

This assumes the activity groups mix assortatively

Another way of thinking about it



Age Structured Models

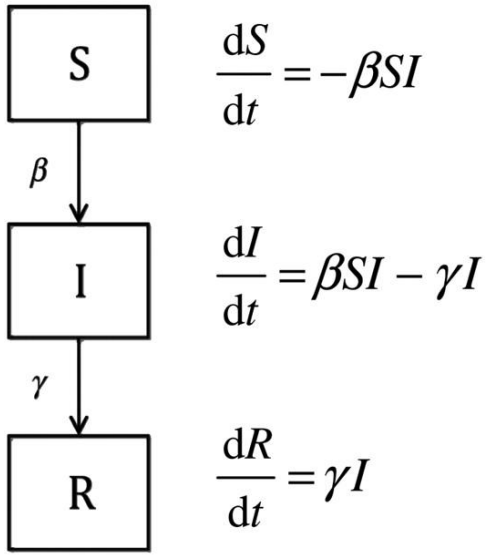


- Age is a key determinant in many of the factors described above
- The models can be structured to cohort for age
- Applying this can reduce the proportion vaccinated (Pv) e.g. HPV (again)

SIR, SIS and others!

The SIR (susceptible/ infectious/ recovered) model is a good and simple model for many infectious diseases including measles, mumps and rubella.

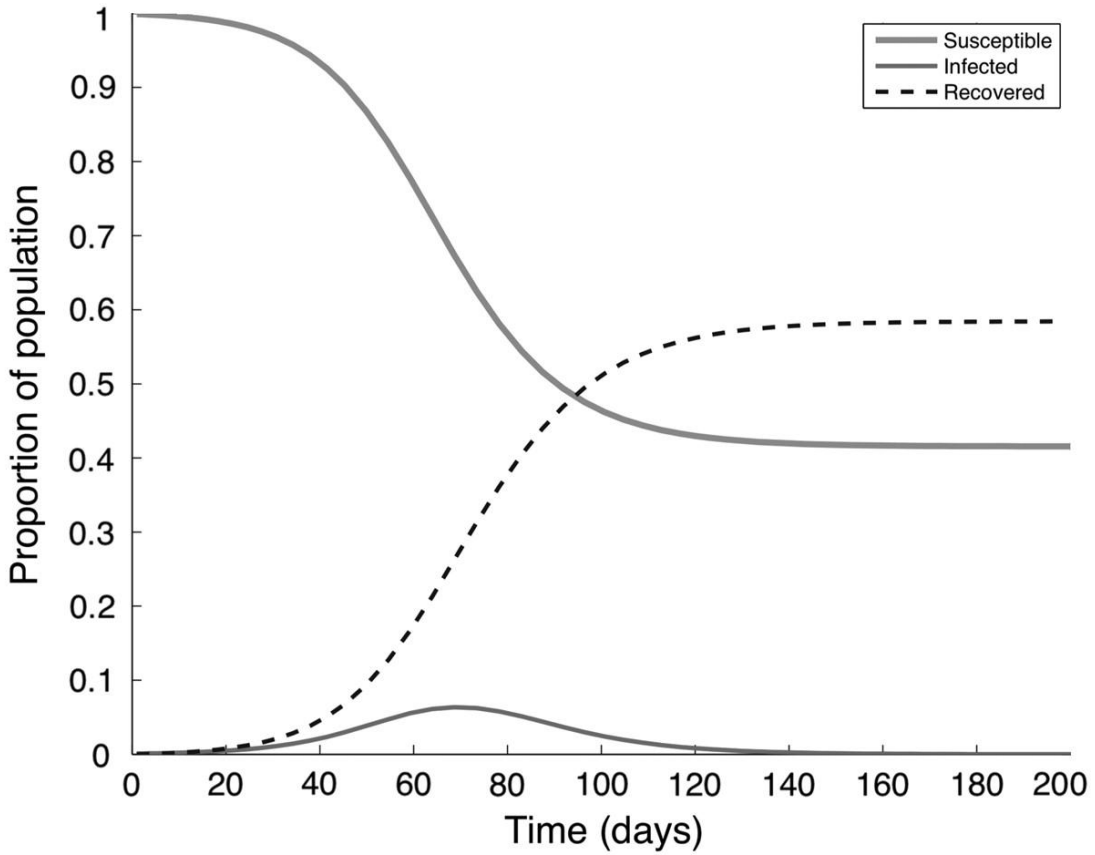
From left to right: a pictorial representation of the flow of individuals between classes in the SIR model.



$$\frac{dS}{dt} = -\beta SI$$

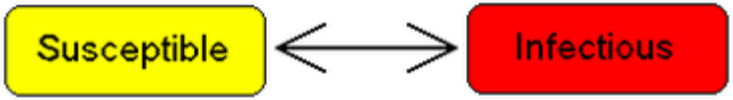
$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

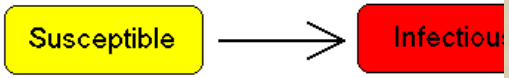


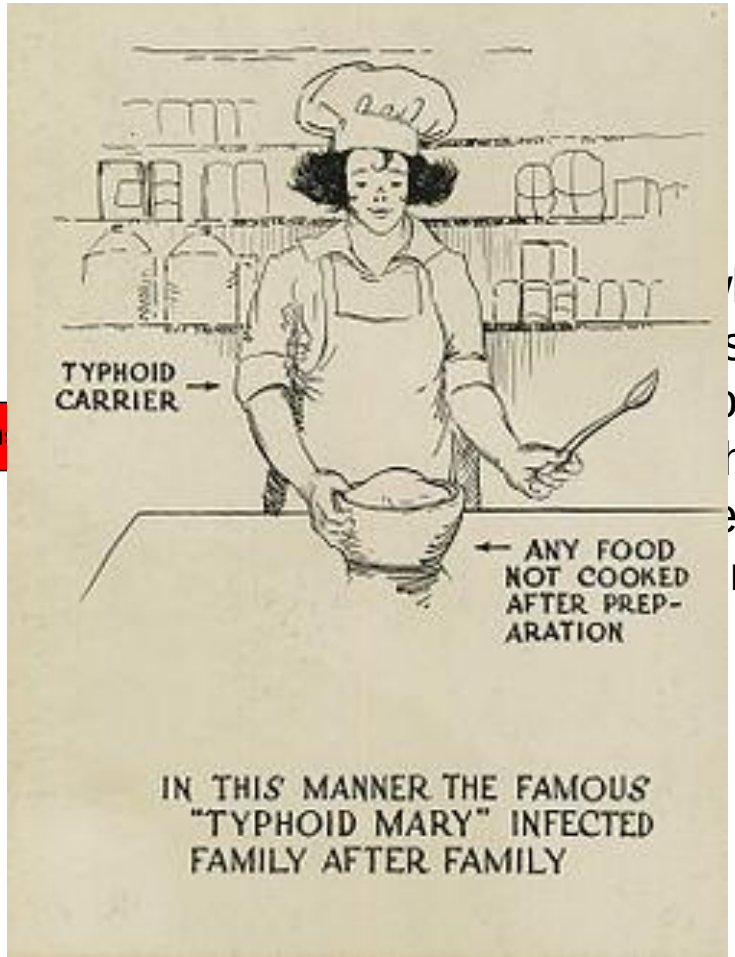
Keeling M J , Danon L Br Med Bull 2009;92:33-42

BRITISH MEDICAL BULLETIN

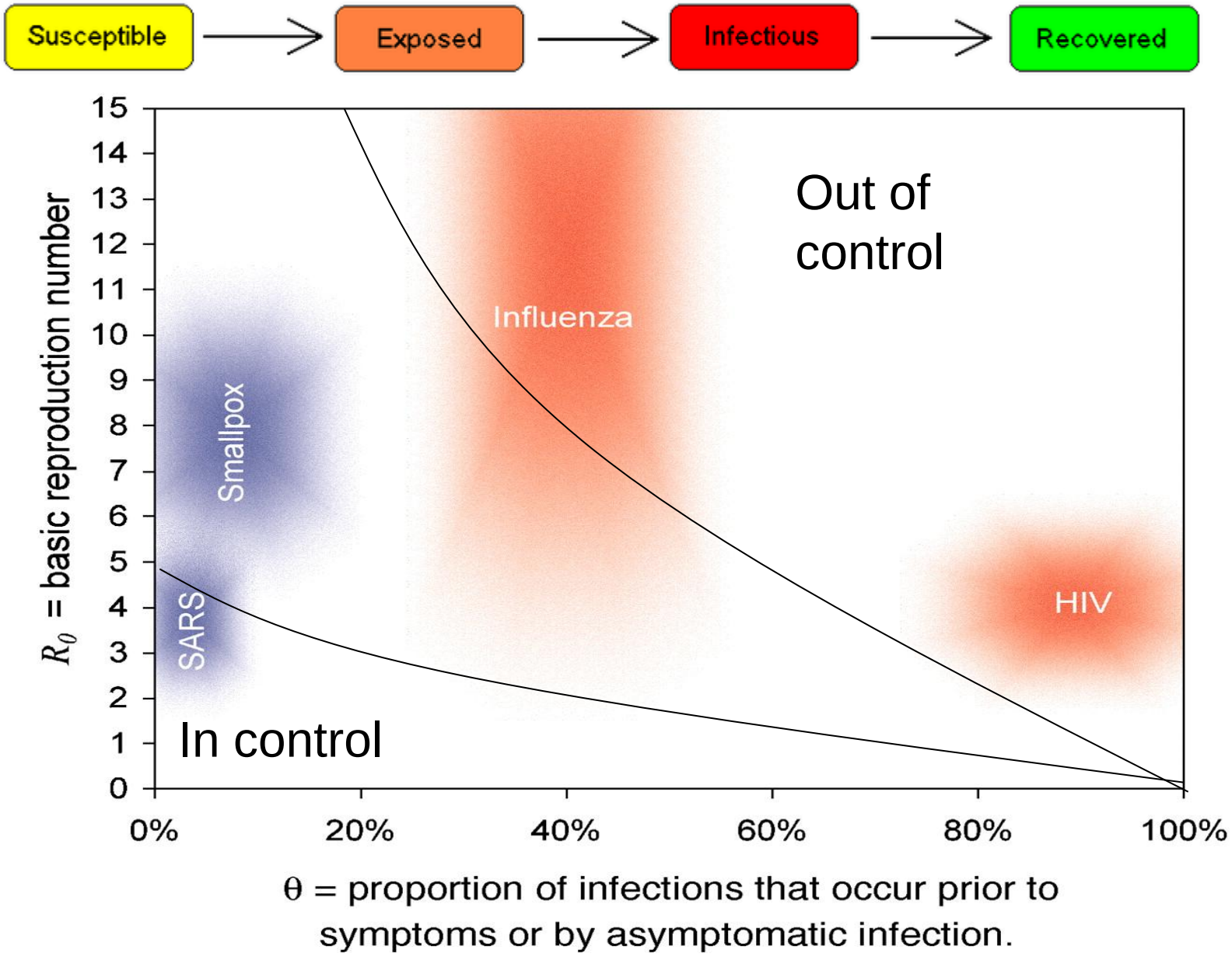


SIS model: Some infections, for example the group of those responsible for the common cold, do not confer any long lasting immunity. Such infections do not have a recovered state and individuals become susceptible again after infection.





ho have had an infectious
s tuberculosis never
ver and continue to carry
ilst not suffering the
lves.
n.



Fraser C, Riley S, Anderson RM, Ferguson NM PNAS U S A. 2004 Apr 20;101(16):6146-51.

So What!

- The application of epidemiological models allows a targeted approach for immunisation e.g. age structure – PCV or HPV
- Targeted approaches increase the coverage for reduced cost
- There are other considerations e.g. Risk severity (mumps/rubella in 80’s)

Conclusions

- By understanding the immune response to infection we can understand how to create vaccines that prevent future infections (lectures on Tuesday)
- By understanding disease transmission patterns we can focus vaccination programs (e.g. Nick Grassly Polio lecture/ Simmon Beddows HPV lecture)