

Core Topic 2

The immune system and how vaccines work



Learning outcome



To be able to describe in outline the immune system and how vaccines work in individuals and populations

Learning objectives



- Explain the difference between innate, passive and active immunity
- Describe the basic immune response to a vaccine
- Describe herd immunity and explain why it is important
- List conditions that affect the immune response to vaccines



Basic immunology

Immune response to vaccination



Aim of an ideal vaccine:

- To produce the same immune protection which usually follows natural infection but without causing disease
- To generate long-lasting immunity
- To interrupt spread of infection

Immune system: Innate (natural) immunity



Physical barriers - skin and mucous membranes

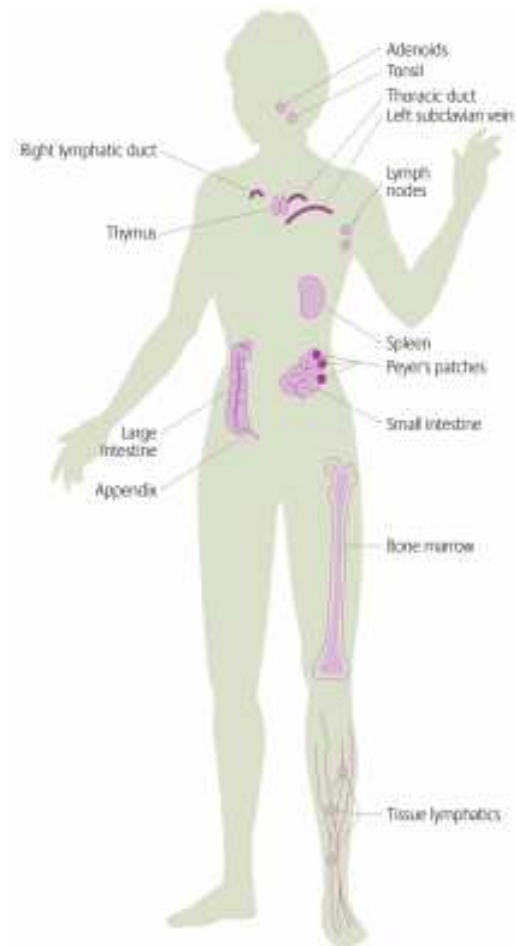
Physiological factors - pH, temperature and oxygen tension
limit microbial growth

Protein secretions – lysozyme, complement, interferons etc

Phagocytic cells – macrophages and polymorphonuclear leucocytes

Defining characteristic: No memory persists afterwards

Adaptive immunity



Adapted from illustration by Nick Holmes

The second level of defence

Increases in strength and effectiveness with each encounter

The foreign agent is recognised in a specific manner and the immune system acquires memory of it

Immunity: Active and Passive

Active immunity



Naturally acquired



Artificially acquired

Passive immunity



Naturally acquired



Artificially acquired

Artwork by Jeannine Kelly, ©2004

Active and Passive Immunity



Passive immunity

B and T cells are not activated and plasma cells have not produced antibodies.

The antigen doesn't have to be encountered for the body to make the antibodies.

Antibodies appear immediately in blood but protection is only temporary.

Active and Passive Immunity



Artificial passive immunity

Used when a very rapid immune response is needed e.g. after infection with tetanus.

Human antibodies are injected. In the case of tetanus these are antitoxin antibodies.

Antibodies come from blood donors who have recently had the tetanus vaccination.

Only provides short term protection as abs destroyed by phagocytes in spleen and liver.

Active and Passive Immunity



Natural passive immunity

A mother's antibodies pass across the placenta to the foetus and remain for several months.

Colostrum (the first breast milk) contains lots of IgA which remain on surface of the baby's gut wall and pass into blood

Active and Passive Immunity



Active immunity

Lymphocytes are activated by antigens on the surface of pathogens

Natural active immunity - acquired due to infection

Artificial active immunity – vaccination

Takes time for enough B and T cells to be produced to mount an effective response.



What is an antigen?

An **antigen** is defined as "anything that can be bound by an antibody"

Antibodies interact specifically with relatively small parts of molecules. These are known as antigenic determinants or epitopes

Small antigens are referred to as haptens. They are not immunogenic and need to be coupled to a carrier to elicit an immune response

Cellular components of immune response



Antigen presenting cells (eg. macrophages)

T cells

respond to many epitopes

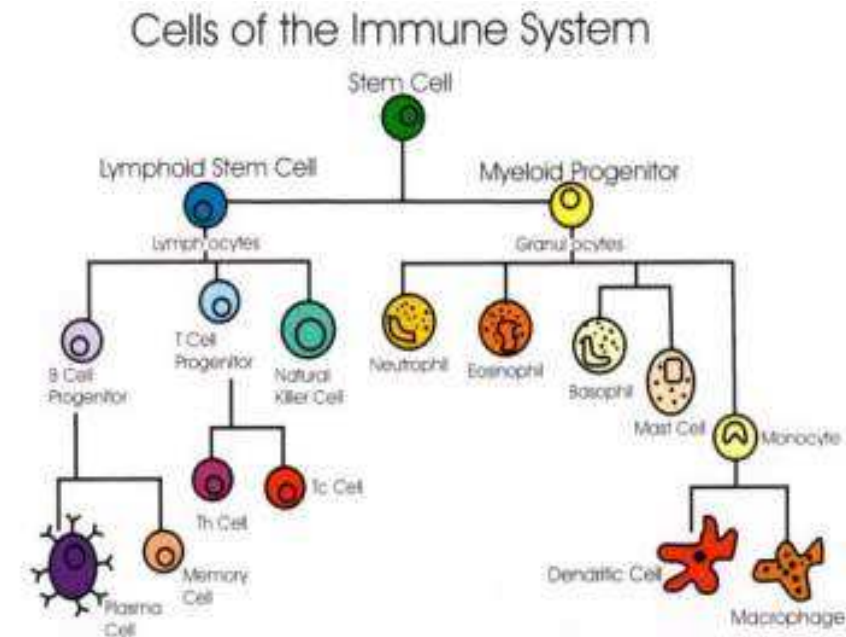
Tc cytotoxic - direct lysis of target cells

Th helper - help B, T cells and macrophages

B cells

Make antibody (IgG, IgM, IgA, IgD, IgE)

Memory cells

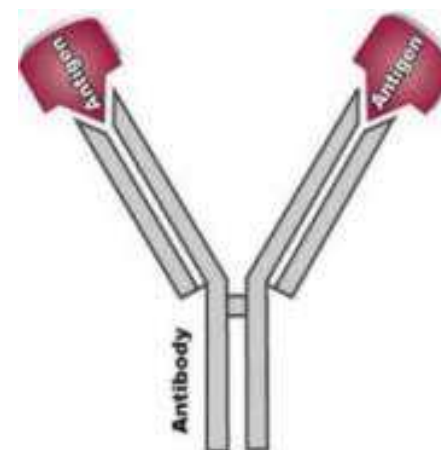


With kind permission from Nick Holmes

Antibody



- Is produced to one specific epitope
- Neutralises toxins
- Block adhesion/cell entry
- Kills via complement
- Neutralises viral infectivity and prevents replication
- Different types of antibody: IgM, IgG, IgA, IgE



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Actions of antibody



Neutralisation

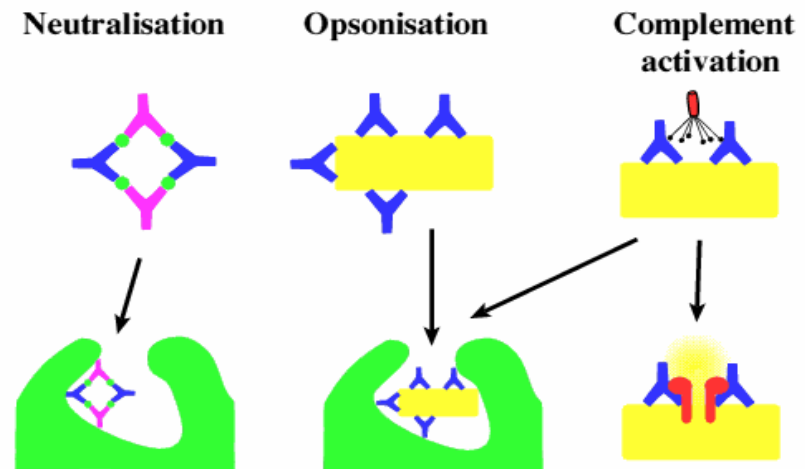
Block biological activity of target molecule e.g a toxin binding to its receptor

Opsonisation

Interact with special receptors on various cells, including macrophages, neutrophils, basophils and mast cells allowing them to "recognise" and respond to the antigen

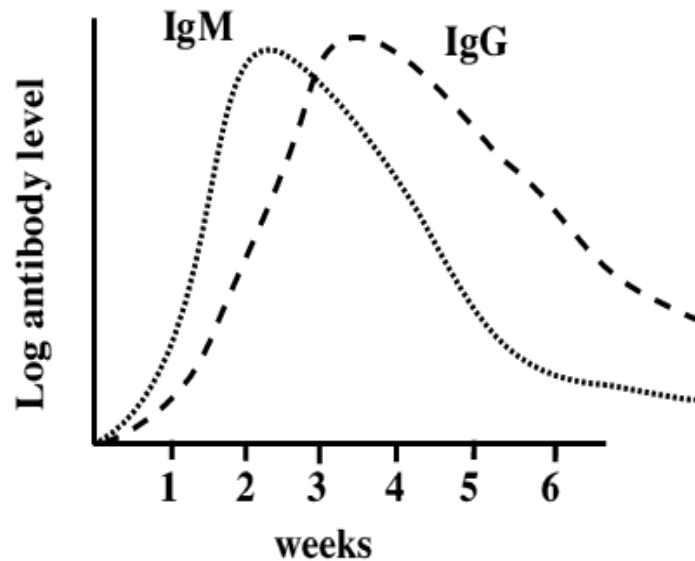
Complement Activation

Cause lysis by complement, also enhancing phagocytosis

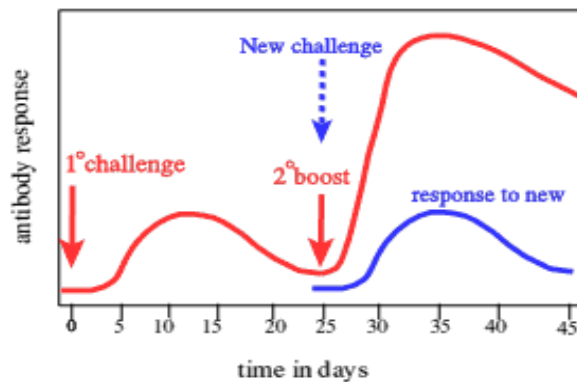


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Primary immune response



Specific memory is the hallmark of the adaptive immune response



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Primary immune response develops in the weeks following first exposure to an antigen

Mainly IgM antibody

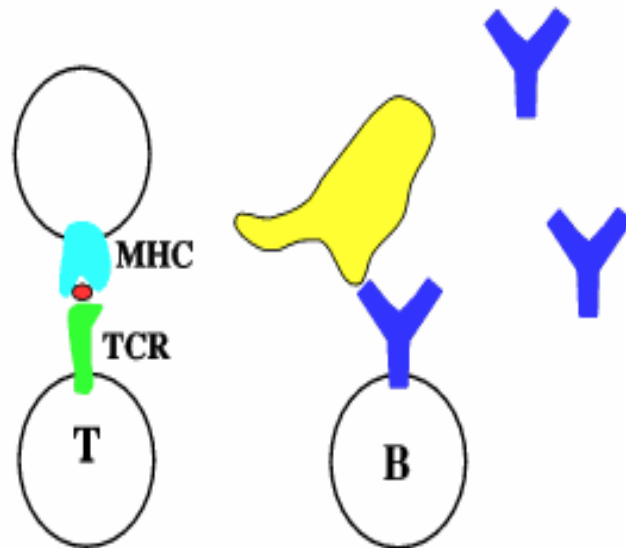
Secondary immune response is faster and more powerful
Predominantly IgG antibody

More complexity...



B cells recognise native antigen

T cells recognise processed antigen



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Immune system has to distinguish “self” from “non-self”

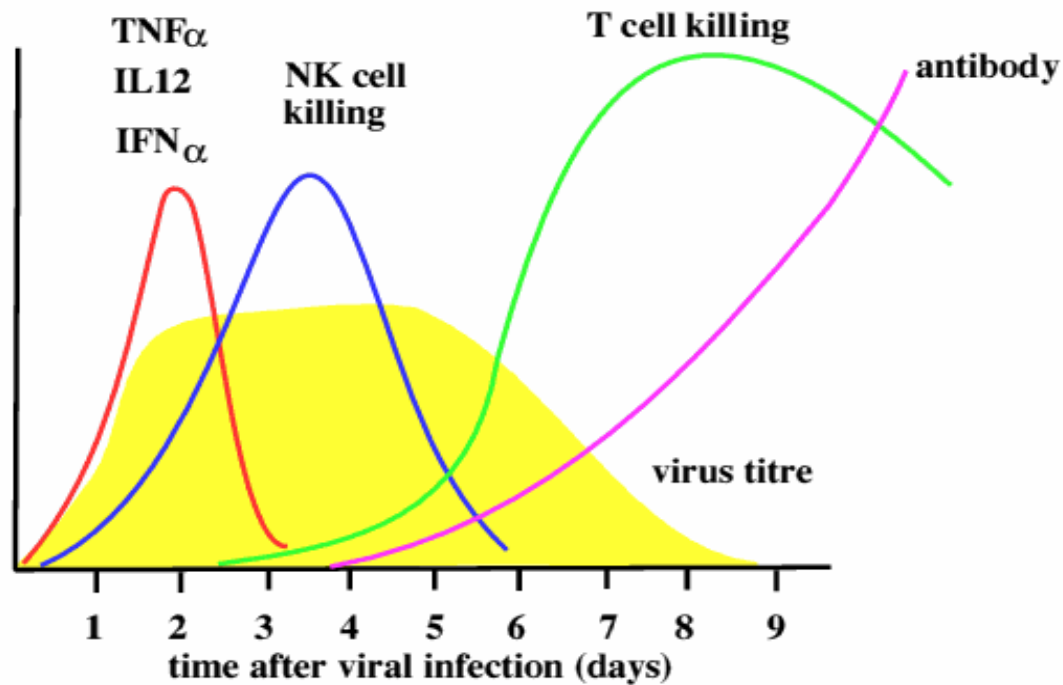
Major Histocompatibility Complex (MHC) Class II antigens (“self”) important for recognition of antigen by T helper cells

Communication between different immune cells is by a range of chemical messages, “cytokines”, which include interleukins and interferon

Innate and adaptive immunity work together

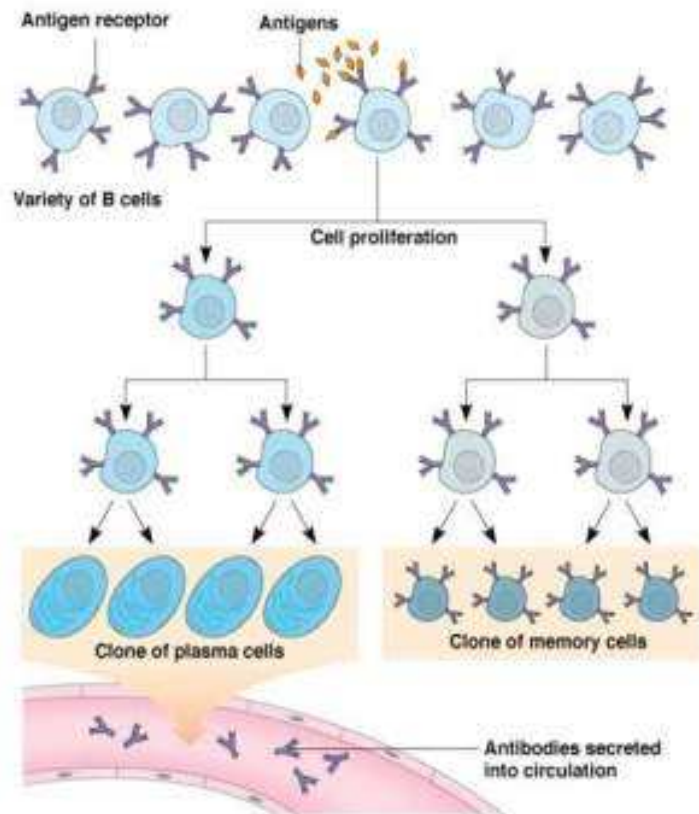


Cytokines and NK cells combine to provide early defense against virus infections



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Immune response to an ideal vaccine: summary



- Vaccine is taken up by antigen-presenting cells
- activates both T and B cells to give memory cells
 - generates Th and Tc cells to several epitopes
 - antigen persists to continue to recruit B memory cells and produce high affinity antibody

Vaccines



Dead (inactivated)

Intact

- Polio
- Rabies
- Influenza
- Hepatitis A
- Old pertussis
- Old typhoid

Fragments

- Influenza
- Hepatitis B
- Tetanus
- Diphtheria
- Pertussis

Polysaccharide

- Conjugated (Men C)
- Unconjugated (ACWY)

Live (attenuated)

Heterologous

- Vaccinia/smallpox/monkeypox
- BCG
- Attenuated
 - Measles
 - Mumps
 - Rubella
 - Oral polio
 - Varicella
 - Yellow fever



Dead (inactivated) vaccines



Partially simulate immune aspects of infection

Don't cause a real infection

Antibody levels and protection wane

Vaccine has sufficient antigen to produce a reaction

Repeated doses to compensate

Boost antibody levels

Provide more refined antibody response

Enhance memory

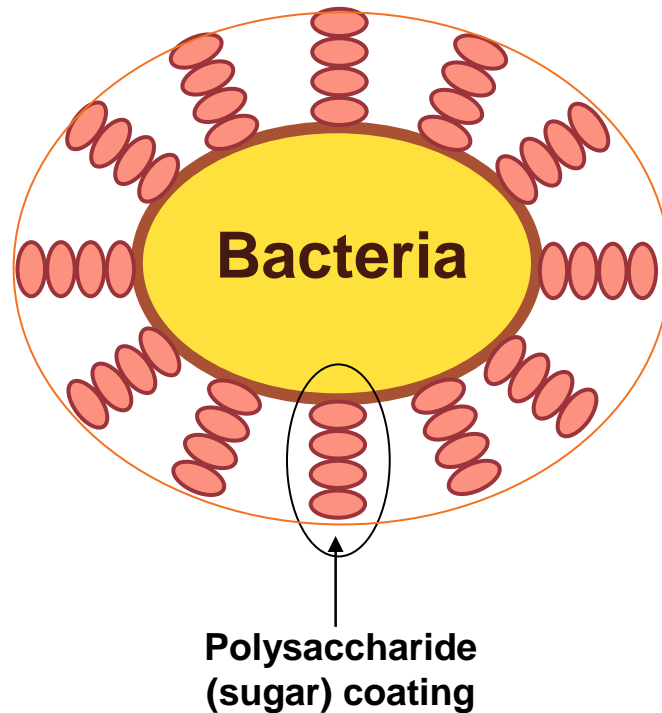
Technologies to increase response

Adjuvants

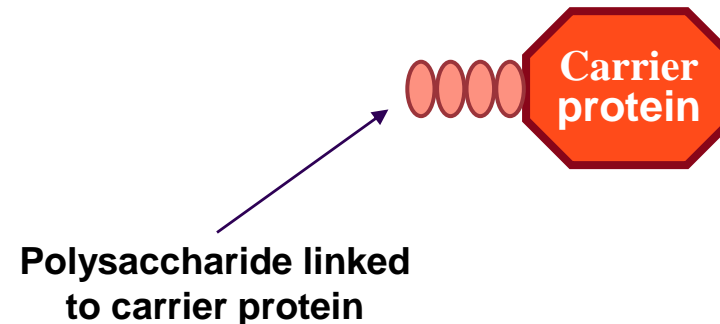
Conjugation



Conjugation



Conjugate vaccine



Conjugation is the process of attaching (linking) the polysaccharide antigen to a protein carrier (e.g. diphtheria or tetanus) that the infant's immune system already recognises in order to provoke an immune response

Vaccine composition



In addition to the antigen, vaccines may contain some or all of the following components:

Component	Purpose	Example
Adjuvants	enhance the immune response to a vaccine	aluminium salts
Preservatives	prevent bacterial or fungal contamination of vaccine	thiomersal
Additives	stabilise vaccines from adverse conditions such as freeze-drying or heat, thereby maintaining a vaccine's potency	gelatine
Residuals from manufacturing process	Inactivating agents Antibiotics - prevent bacterial contamination during manufacturing process Egg proteins- some vaccine viruses are grown in chick embryo cells Yeast proteins	formaldehyde neomycin, streptomycin, polymyxin B influenza, yellow fever HepB vaccine

Immunology and understanding policy and practice



A basic understanding of immunology helps explain

- How vaccine failure occurs
- Adverse events
- Intervals between vaccines
- Why vaccines cant overload the immune system
- Timing of adverse events



Gaps needed between each dose of vaccine

To allow each immune response to develop – eg primary immunisation (1 month)

This allows the next response to be a true secondary response – ie faster and bigger and with higher affinity IgG

To avoid immune interference

If another live vaccine is given while the immune system is making a primary immune response, the activation of the innate immune system may neutralise the second live vaccine so that it does not work. Hence we wait 4 weeks to allow the immune system to recover

Human normal immunoglobulin contains antibodies to many infections including measles. These antibodies will neutralise any live vaccine. Hence we wait 3 months for the antibody level to fall

Can vaccines overload the immune system?



The bacteria in our bodies outnumber our own cells
the human body is composed of 10 trillion cells and contains 100 trillion bacteria

On average there are:

1000 bacteria on each cm² of your skin

1,000,000 bacteria on each cm² of your scalp

100,000,000 bacteria per gram of saliva

10,000,000 bacteria per gram of nasal mucus*

The maximum number of antigens in a UK vaccine was ~3000 (DTwP, most from wP) – with the new vaccines this number is much lower still

*The Human Immune System: Schoolscience Website

<http://www.schoolscience.co.uk/content/4/biology/abpi/immune/immune3.html>

Do vaccines overload the immune system?



Within hours of birth, a baby's gastrointestinal & respiratory tract are heavily colonised with bacteria

Rather than overwhelming the immune system, vaccines help stimulate and strengthen it

Immune systems need stimulation to develop well: allergies may result from too little immune stimulation in our cleaner environments

There is no evidence that vaccines can overload the immune system. The immune system is designed to deal with a constant stream of foreign antigens on the surface and inside our bodies.

Vaccine failures



Primary failure

an individual fails to make an adequate immune response to the initial vaccination (e.g. in about 10% of measles and mumps vaccine recipients)

Secondary failure

an individual makes an adequate immune response initially but then immunity wanes over time (a feature of most inactivated vaccines, hence the need for boosters)

Timing of Vaccine Reactions



Inactivated vaccines: generally within 48hrs following vaccination

Live vaccines: occur according to time taken for virus to replicate

e.g. MMR vaccine:

reactions to measles component (malaise, fever, rash) tend to occur in 1st week following vaccination

reactions to rubella component (pain, stiffness or swelling of joints) tend to occur in 2nd week following vaccination

reactions to mumps component (parotid swelling) tend to occur in 3rd week following vaccination (although may occur up to 6 weeks following vaccination)

Adverse events



Live vaccines: frequency of adverse events falls with number of doses

E.g. MMR

If antibody is made in response to live vaccine, it neutralises the small amount of vaccine virus in any subsequent vaccine dose

Inactivated vaccines: frequency of adverse events increases with number of doses

E.g. tetanus, pertussis

If antibody levels are good following previous vaccination, the antibody binds to the vaccine antigen in a subsequent dose of vaccine, produces a good secondary immune response which, if big enough, is inflammatory (i.e. produces a sore arm).



Susceptible populations

- Any person who is not immune to a particular pathogen is said to be susceptible
- Not all individuals are able to produce an immune response
- Not all individuals can be given certain vaccinations
- Susceptibility can be caused by immune suppression or deficiency as a result of drugs or certain conditions



Conditions Which May Affect or Contradict Vaccination

- Primary immunodeficiency
- Standard and intensive chemotherapy
- Haemopoietic stem cell transplant
- Solid organ transplant
- Systemic corticosteroid use
- Immunosuppressive drug therapy
- HIV infection
- Other conditions

These headings are taken from “Immunisation and the Immunocompromised Child” Royal College of Paediatrics and Child Health Best Practice Statement (Feb 2002).

Severity of infection depends upon age



Death (measles, pertussis)

Clinical manifestations (polio)

Latent infection (hepatitis B)

Fetal infection (rubella)



Herd immunity

Herd immunity



Herd immunity only applies to diseases which are passed from person to person

For each disease there is a certain level of immunity in the population which protects the whole population because the disease stops spreading in the community

A disease can therefore be eradicated even if some people remain susceptible

Herd immunity provides indirect protection of unvaccinated as well as vaccinated individuals. This may be the most important aspect of how they work. For example, MMR given to infants protects pregnant women from rubella.

Definitions



Herd immunity is best thought of as a threshold

It is measured by the “reproduction number”

This is the average number of new people infected by each infectious case

Basic reproduction number, R_0

The number of secondary infections produced by a typical infective in a totally susceptible population

Effective reproduction number, R

The number of secondary infections produced by a typical infective

Takes account of the fact that some people are already immune because of previous infection or vaccination

Effective Reproduction Number, R



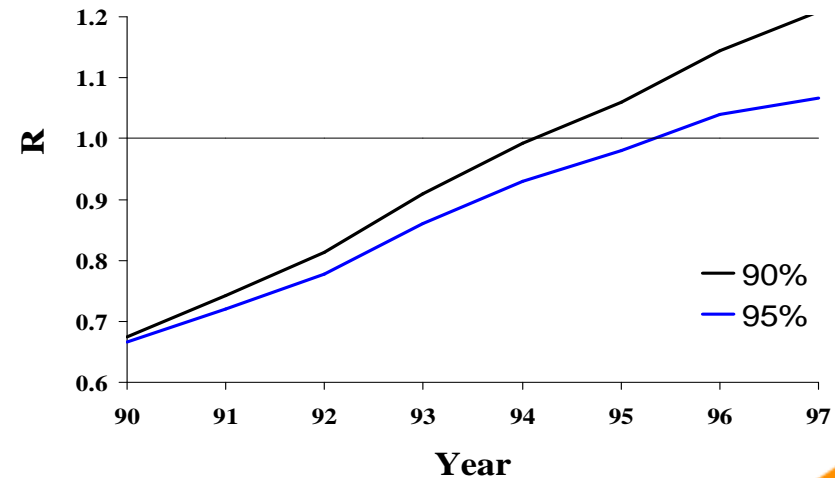
If $R > 1$ the number of cases increases

If $R < 1$ the number of cases decreases

To achieve elimination need to maintain $R < 1$

Measles reproduction number, R

Calculated from serological data in England



Conclusions



Control of infectious diseases through vaccination requires an understanding of the natural history and biology of the infection and the immune response

For most infections we cannot protect all children effectively without herd immunity

Many queries can be answered by reference to basic principles about the mode of action of inactivated and/or live vaccines