
Immunity & How Vaccines Work

Immunisation Study Day

8th November 2013

Dr Regina Kiernan

Learning outcome

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

Learning Objectives

- To understand the immune system
- To understand the differences between Passive and Active immunity
- To understand the role of Antigens and Antibodies
- To understand how vaccines work
- To understand the differences between inactivated vaccines, toxoids and live vaccines
- To understand what is meant by the term “vaccine failure”
- To understand why it is necessary to leave time intervals between vaccinations.
- To understand herd immunity

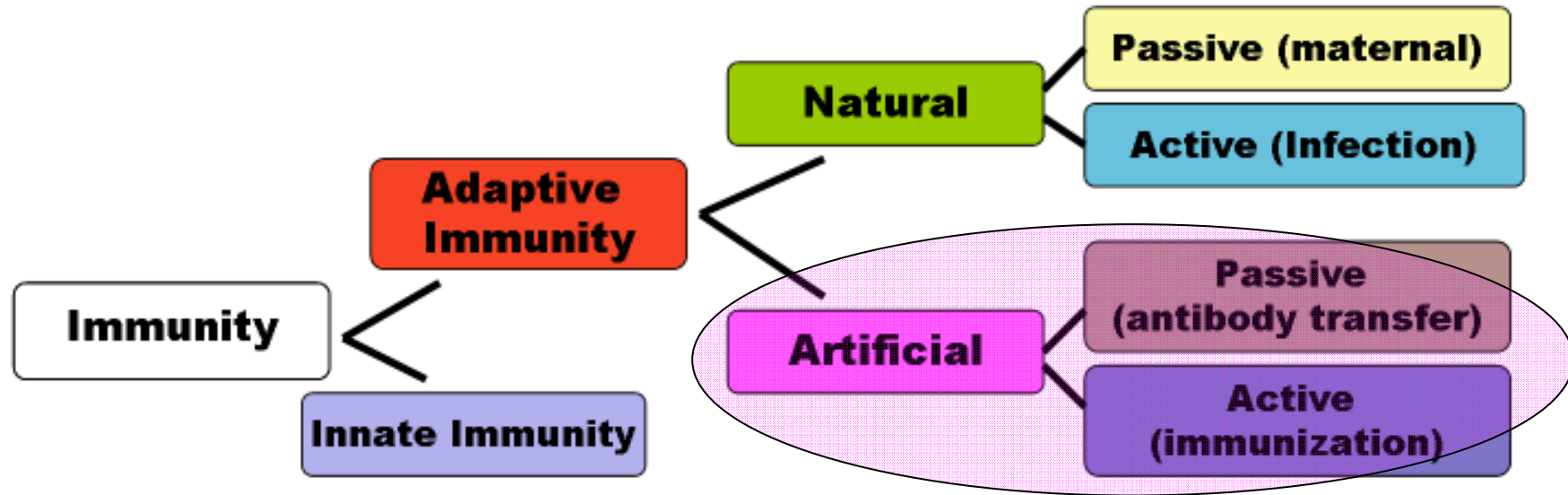
Immunisation vs. Vaccination

- *Vaccination* means having a vaccine – that is actually getting the injection.
- *Immunisation* means both receiving a vaccine and becoming immune to a disease, as a result of being vaccinated

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

Types of Immunity



Source: http://en.wikipedia.org/wiki/Immunological_memory

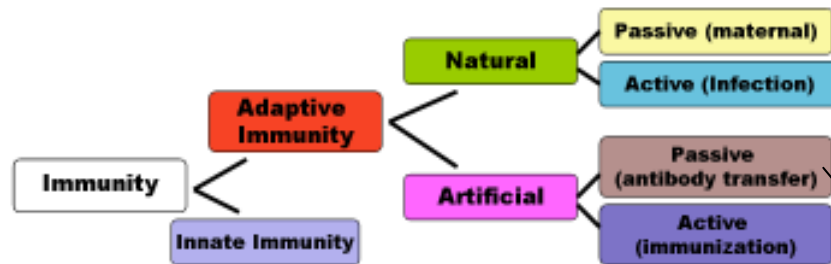
Immune system: Innate (natural) immunity

- Physical barriers - skin and mucous membranes
 - Chemical barriers – gastric and digestive enzymes
 - Cellular and Protein secretions – lysozyme, complement, interferons, macrophages and white blood cells
 - Defining characteristic: No memory persists afterwards
-

Adaptive (Acquired) immunity

- 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

Passive Immunity – adaptive mechanisms



■ Natural

- Maternal transfer of antibodies to infant via placenta

■ Artificial

- Administration of pre-formed substance to provide immediate but short-term protection (immunoglobulin, anti-toxin)

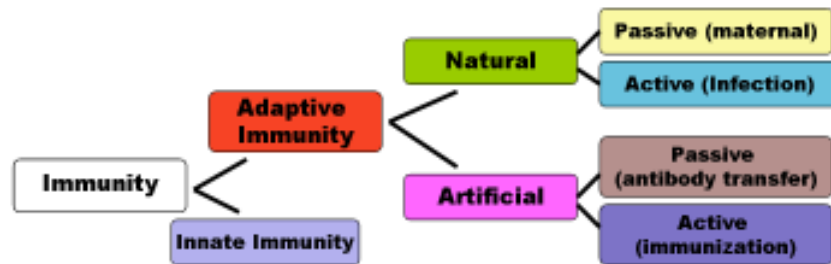
- Give rapid protection within 48 hours

- Protection is temporary and wanes with time (usually few months)

Passive Immunity

- Provided by administering Immunoglobulins for post-exposure prophylaxis e.g.
 - Human Normal Immunoglobulin (HNIG)
 - Collected from pooled human donations – contains antibodies to infectious agents common in the community,
 - Hepatitis B immunoglobulin (HBIG),
 - Varicella Zoster Immunoglobulin(VZIG),
 - Rabies Immunoglobulin etc.
- Involves using a blood derived product

Active Immunity – adaptive mechanisms



■ Natural

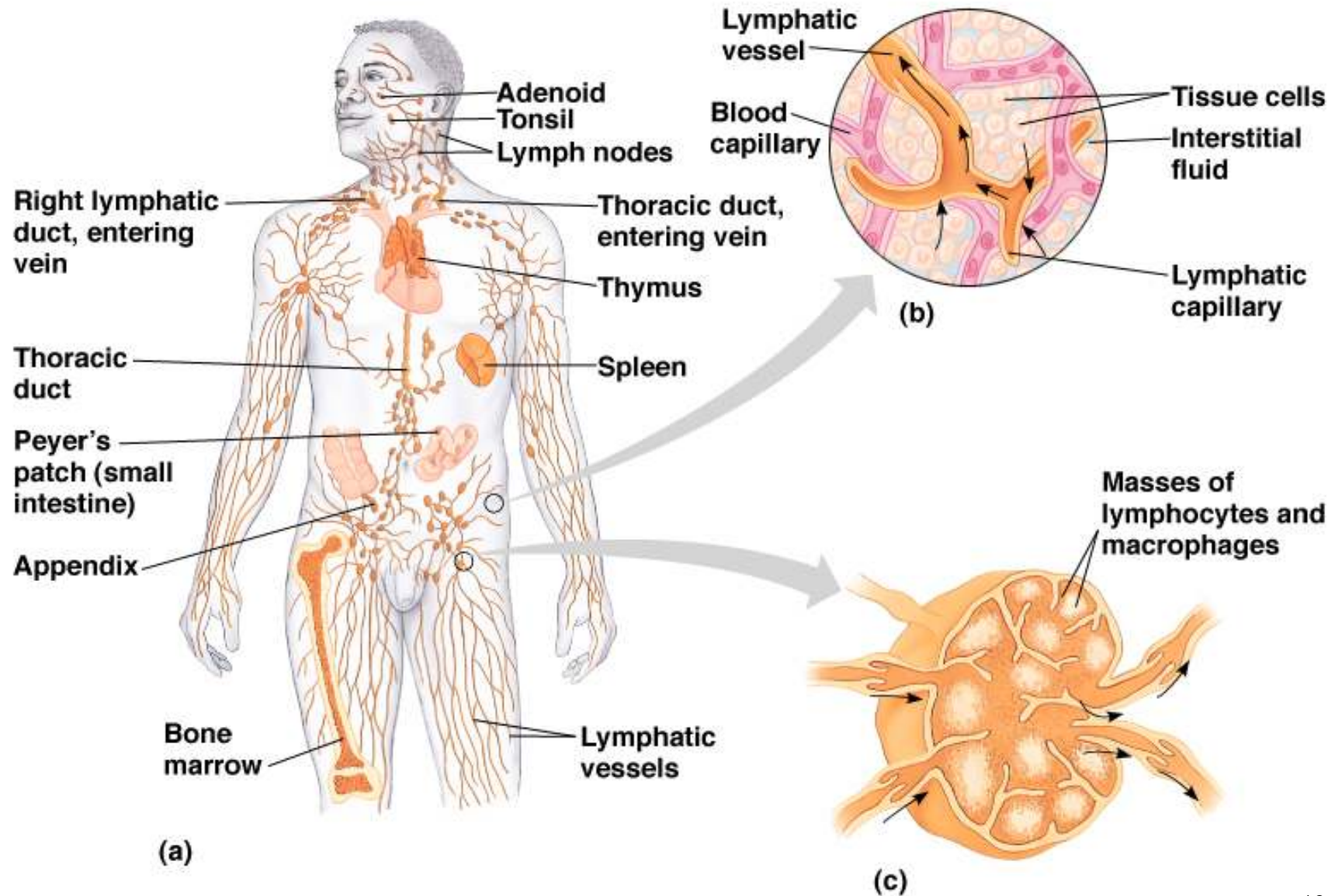
- Following contact with the organism

■ Artificial

- Administration of agent to stimulate immune response (immunisation)

- Acquired through contact with a micro-organism / antigen
- Protection produced by the individual's own immune system
- Protection often life-long but may need boosting

Components of Human Immune System



Body's natural response to infection

- Immune system is a complex network of cells and organs
- The initial defence are wbc's called macrophages ("big-eaters"). They eat as many of the infecting micro-organisms as they can. Also called innate / natural killer cells
- Organism is recognised as "foreign" because of unique molecules on it's surface – **antigens***

Antigen

- A live or inactivated substance (e.g. protein or polysaccharide) capable of producing an immune response
- “Anything that can be bound by an antibody”

Body's natural response to infection

- Macrophages digest most of the micro-organism except the antigens
- They “regurgitate” these antigens (In) displaying them on their surface (antigen presenting cells) so that other wbc's called lymphocytes can take over the attack
- Two types; T cells and B cells

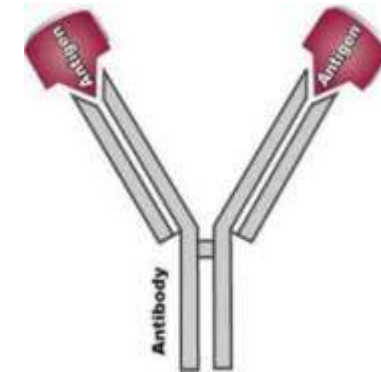
Active immunity

- Humoral / Antibody mediated
 - B cells

- Cell mediated
 - T cells
 - Killer / cytotoxic – destroy infected cells and micro-organisms
 - Helper – stimulate and direct activity of B cells

Antibodies

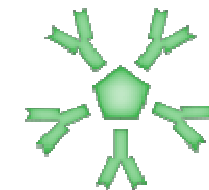
- Different types
 - IgM, IgG, IgA, IgD, IgE
- Each antibody is specific for its antigen – no cross protection
- We have millions of different antibodies
- When B cells come into contact with their matching antigen, they are stimulated to divide into larger cells called plasma cells, which secrete huge amounts of antibodies



Monomer
IgD, IgE, IgG



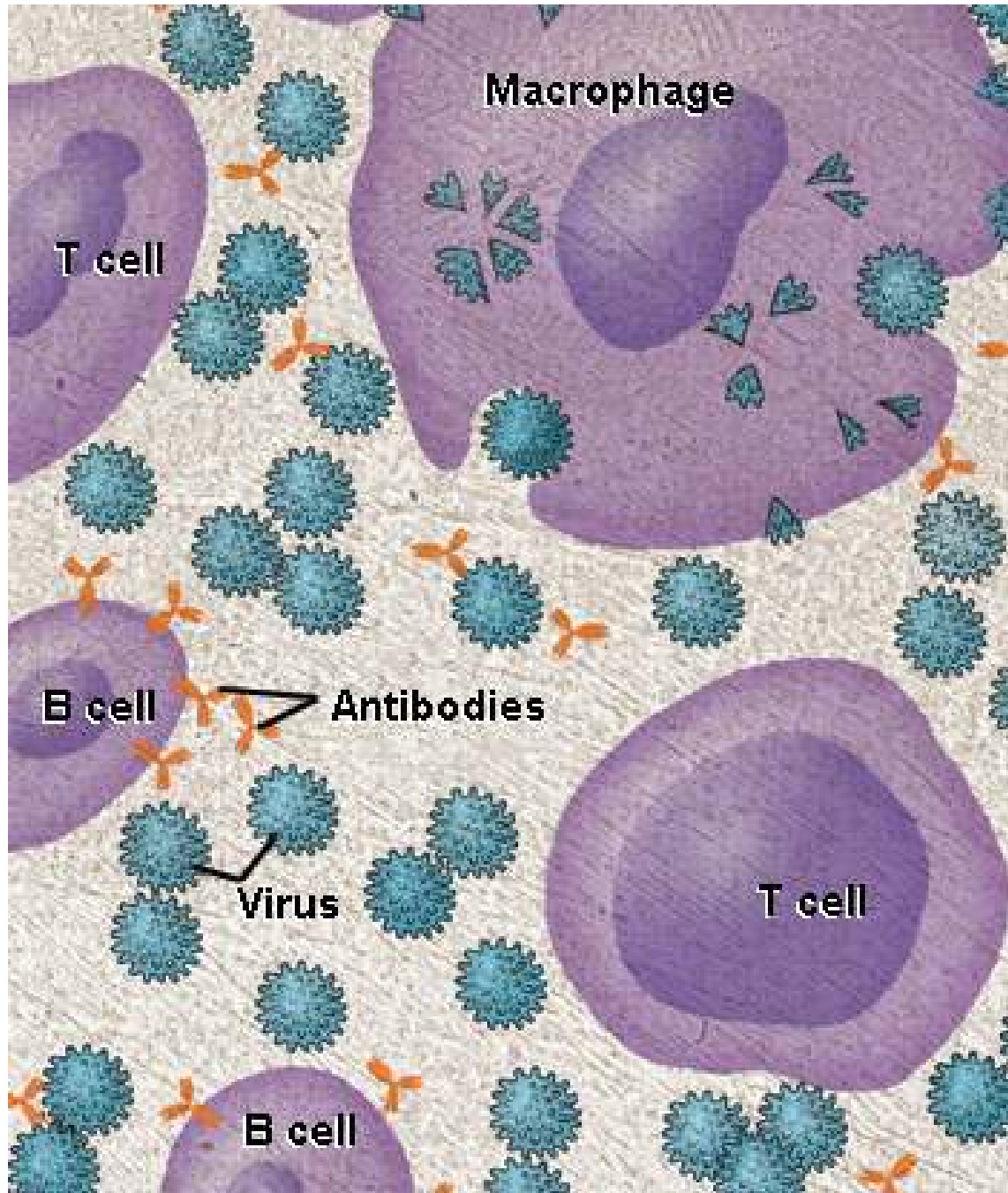
Dimer
IgA



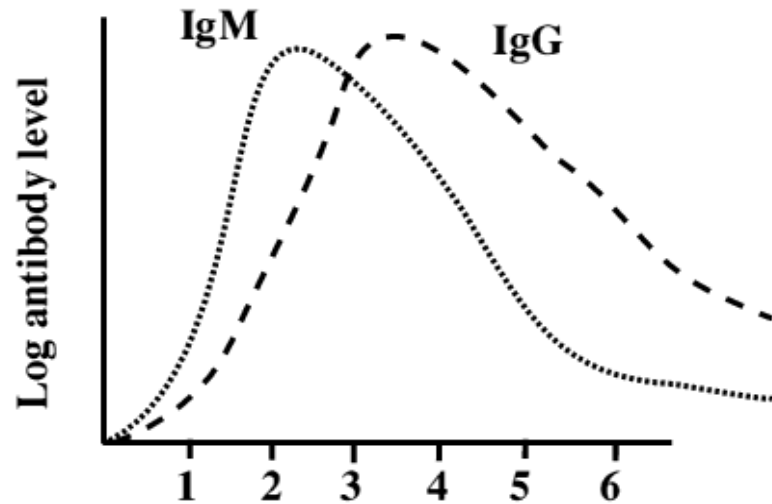
Pentamer
IgM

Antibodies - functions

- These antibodies circulate and attack the micro-organisms that have not yet infected cells
- Antibodies gather on the micro-organism's surface
- This blocks adhesion / cell entry of the antigen
- Neutralises and prevents organism's replication
- Signals (cytokines) macrophages and other wbc's to come
- Kills organism via complement proteins – lysis
- Neutralises toxin
- Goal of vaccines is to stimulate this response



Immune response



Specific memory is the hallmark of the adaptive immune response



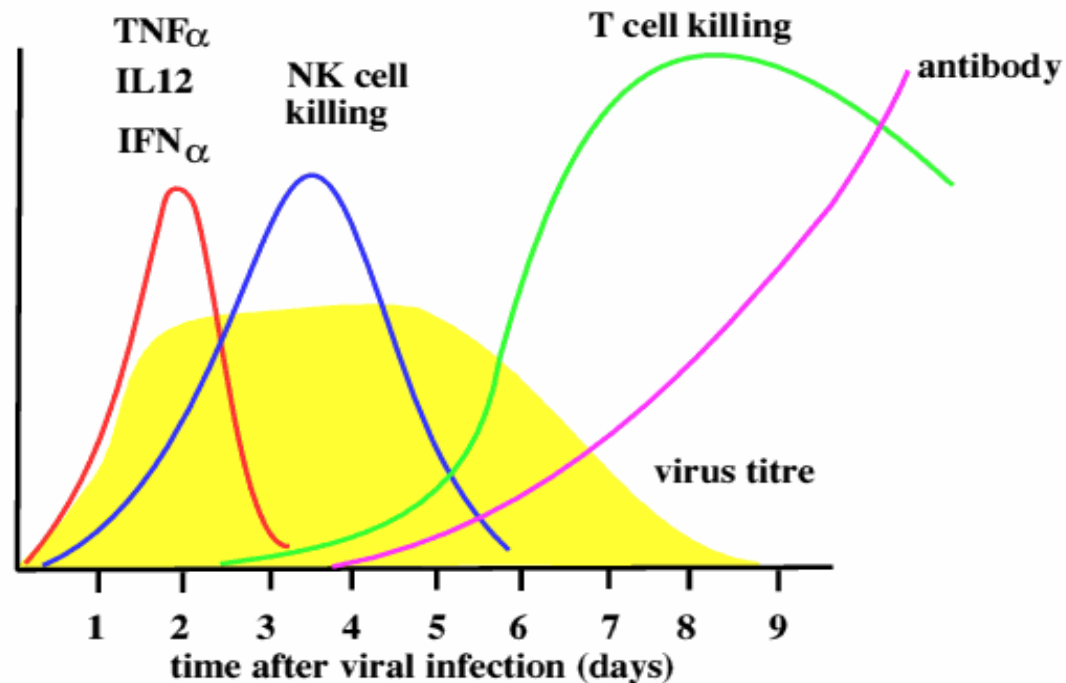
With kind permission from Nick Holmes

- 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

Source: HPA

Innate and adaptive immunity work together

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



With kind permission from Nick Holmes

Memory cells

- After the body has eliminated the infection some of the B and T cells are converted into memory cells
- These can quickly divide into the specialised B and T cells if re-exposure to the infection occurs
- The immune system's capacity to have a memory of previous encounters with an infection is the basis for vaccination.

How vaccines work

- Induce active immunity
 - Immunity and immunologic memory similar to natural infection but without risk of disease
- Immunological memory allows
 - Rapid recognition and response to infection
 - Prevents or modifies effects of disease

Immune response to an ideal vaccine:

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

Types of Vaccine

Live Attenuated	Live organism with low virulence
Inactivated	Organism with no virulence
Inactivated toxins	“Toxoids”
Subcellular fraction (incl conjugated vaccines)	No virulence
Genetically engineered	Contains no original antigen product

Live attenuated vaccines

- Weakened viruses / bacteria
 - Achieved by growing numerous generations in lab
 - Stimulates immune system to react as it does to natural infection
 - Produces long lasting immune response after one or two doses
 - Can cause mild form of the disease e.g. mini measles which is not transmissible
 - CANNOT be given to immuno-compromised persons
 - E.g. BCG / MMR / Varicella / Yellow Fever

Inactivated vaccine and toxoids

- When adequate attenuation of live virus is not possible the vaccine is inactivated by chemical process or heat
- Toxoids are toxins that have been inactivated and chemically modified
- Cannot cause the disease they are designed to protect against
- Doses
 - Two or more doses plus booster doses usually required

Inactivated vaccine and toxoids

- Whole cell
 - Viruses (IPV, hep A, influenza)
- Subcellular fraction
 - Protein-based
 - Toxoid (diphtheria, tetanus)
 - Subunit (Hep B– genetically engineered, acellular pertussis, influenza)
 - Polysaccharide – pure or conjugate
- Often require adjuvant or conjugation to stimulate immune response

What is the role of an adjuvant

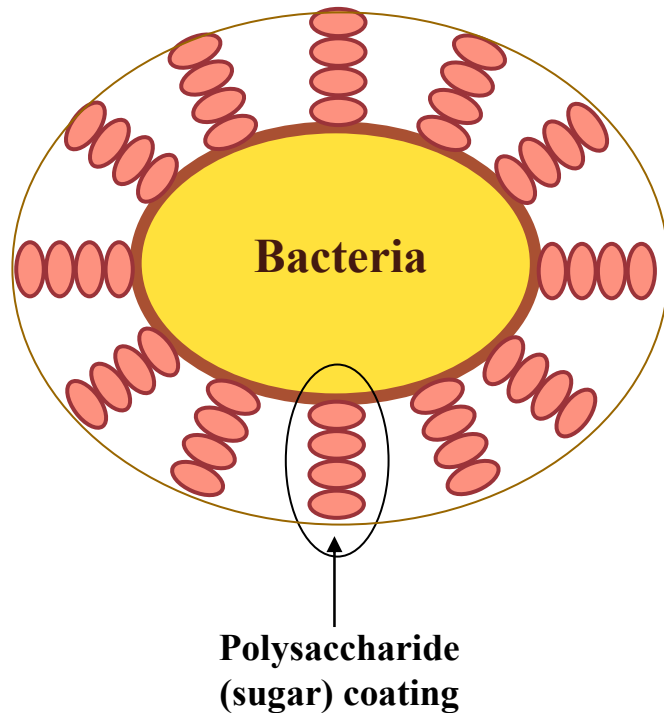
- To enhance the immune response to the vaccine's antigen
- Mode of actions are not precisely defined:
 - To carry the vaccine antigen and to slow its release
 - To provoke a local inflammatory response
 - Activates innate cells
 - E.g. Hep B, tetanus toxoid, diphtheria toxoid



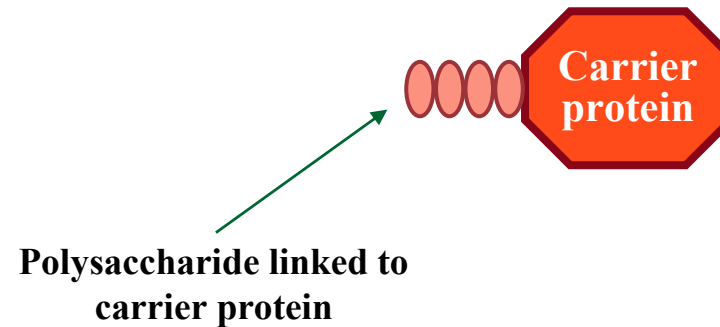
Conjugation

- **Some bacteria** (e.g. *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Streptococcus pneumoniae*) have an outer coating of sugar molecules (called polysaccharides)
- Polysaccharide coatings make it difficult for a baby or young child's immature immune system to see and respond to the bacterium inside
- Polysaccharide vaccines are poorly immunogenic in children under 2 years old and do not stimulate long term immunological memory
- Conjugate vaccines have enabled us to effectively protect children against Hib, Men C and pneumococcal diseases

Conjugation

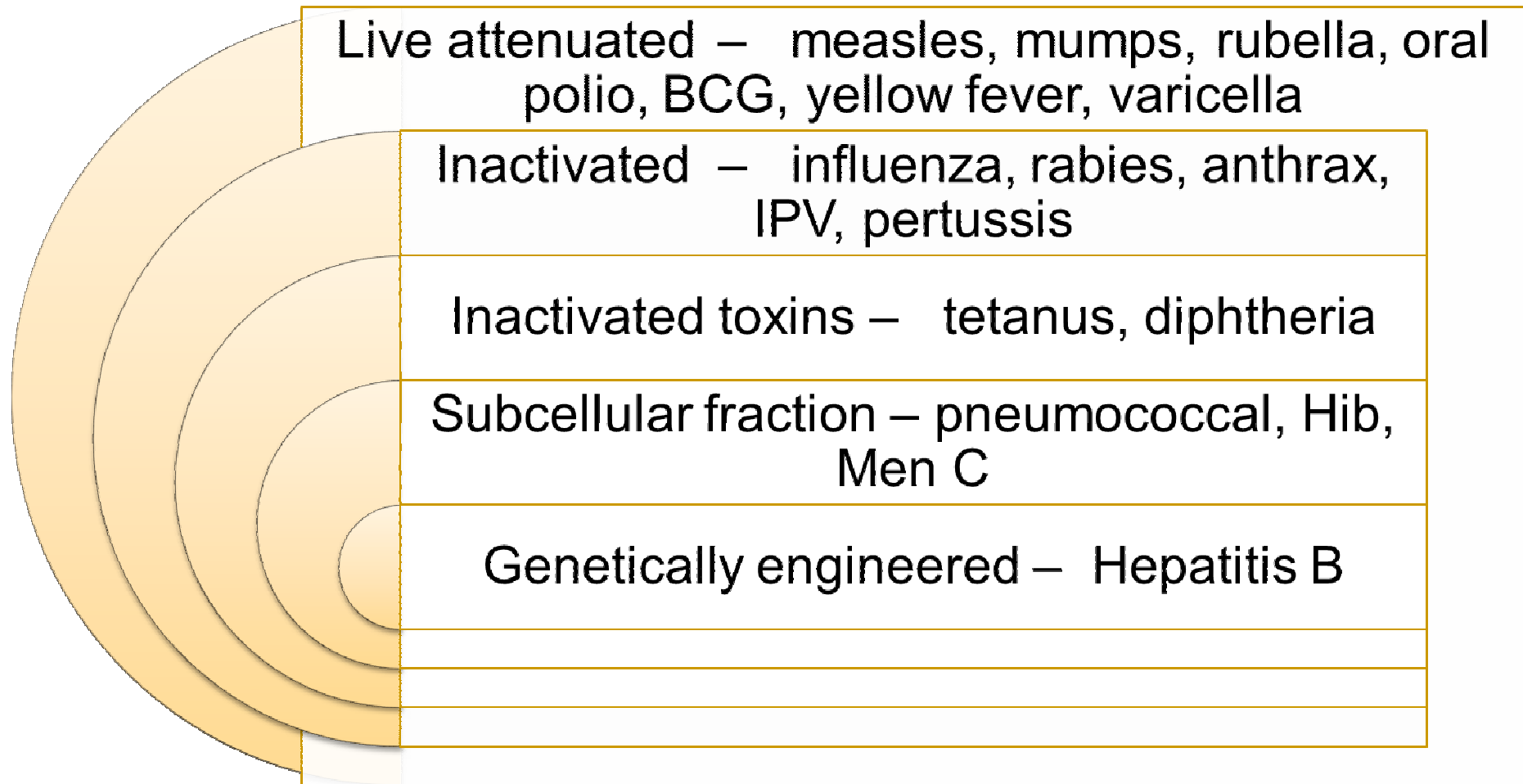


Conjugate vaccine



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

Examples of Vaccines



Live Attenuated Vaccines

- Advantage
- Potent, response close to the optimal naturally acquired immune response
- Disadvantage
- May reproduce features of the disease as sub-clinical or mild form of the infection
- May revert to virulent form (e.g. OPV)
- Cannot be given to immunosuppressed or pregnant patients

Inactive Vaccines

- Advantages
 - Cannot cause infection
 - Can be given to immunosuppressed and pregnant individuals
- Disadvantages
 - Less immunogenic and require addition of adjuvants and booster doses

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)
- Infection possible any time post vaccination

- 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

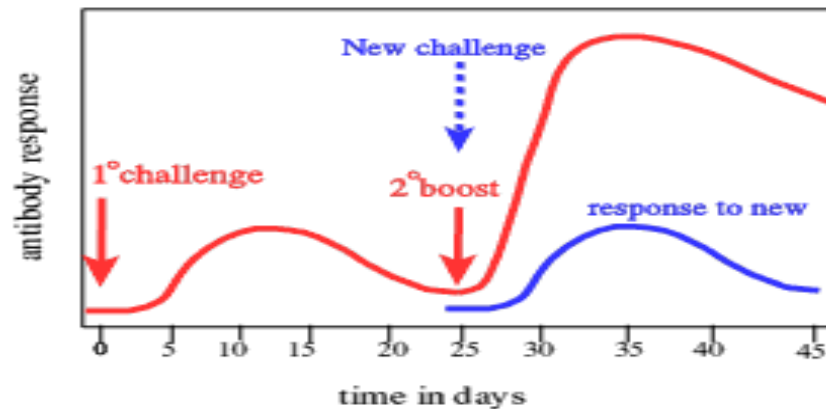
Timing of Primary Immunisation Course

- Maternal IgG is transferred across the placenta
- Passively acquired IgG from mother can suppress response to DTP, Polio, Men C and Hib vaccine for about 2 months
- Maternal antibody to measles may interfere for up to a year

Time intervals between vaccine doses

- Allows each immune response to develop – e.g. primary immunisation (1 month)
 - This allows the next response to be a true secondary response – i.e. faster and bigger and with higher affinity IgG

Specific memory is the hallmark of the adaptive immune response



Time intervals between vaccine doses

- Avoids 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

Time intervals between vaccine doses

Antigen combinations	Recommended minimal interval between doses
2 or more killed vaccines	No minimum interval Doses of <i>same</i> killed vaccine 4 weeks apart, 8 weeks for PCV
Killed and live vaccines	No minimum interval
2 or more live vaccines	4 week minimum interval if not administered simultaneously
Immunoglobulin and live vaccines	3 months

WHAT CONDITIONS CAN AFFECT RESPONSE TO VACCINES?

- Simultaneous administration of immunoglobulin
- Immunosuppression
- Sickle cell disease and other causes of hyposplenism
- Malnutrition and chronic disease
- Nephrotic syndrome
- Prematurity (some evidence premature babies may have sub-optimal response to Hib and Hep B vaccines but should be scheduled on basis of their actual date of birth)

What is herd immunity?

- The indirect protection from infection of susceptible members of the population, and the protection of the population as a whole, which is brought about by the presence of immune individuals

Herd immunity

- To achieve herd immunity the percentage of individuals who need to be vaccinated depends on the disease and the vaccines used.
- Only for transmissible infectious diseases

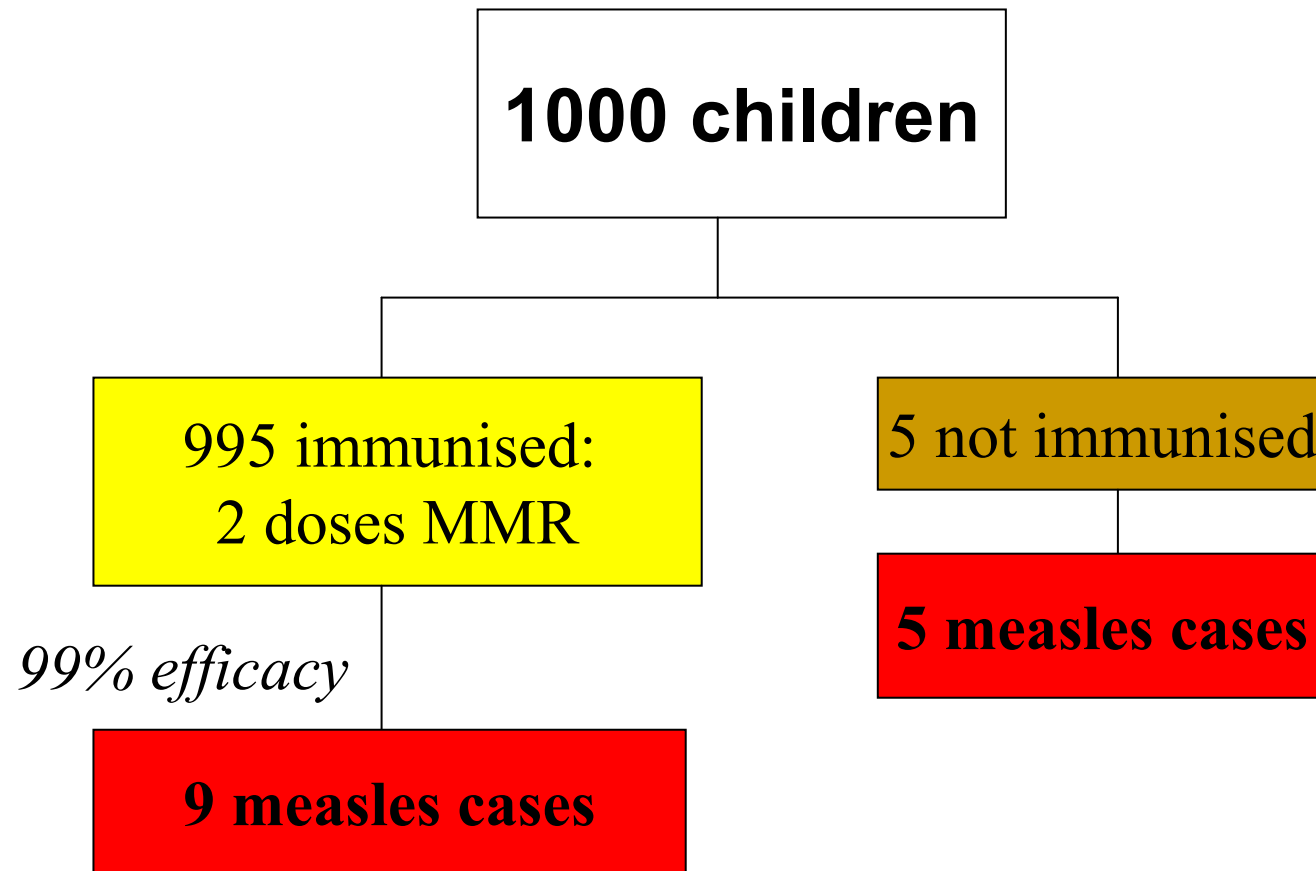
Dynamics of transmission

- If an infection is to persist, each infected individual must, on average, transmit that infection to at least one other individual. If this does not occur, the infection will disappear progressively from the population

Infection/ Infectious agent	Average age at infection, in yr	Inter- epidemic period (yr)	R_o	Critical vaccination coverage to block transmission, (%)
Measles	4-5	2	15-17	92-95
Pertussis	4-5	3-4	15-17	92-95
Mumps	6-7	3	10-12	90-92
Rubella	9-10	3-5	7-8	85-87
Diphtheria	11-14	4-6	5-6	80-85
Polio Virus	12-15	3-5	5-6	80-85

Source HPA

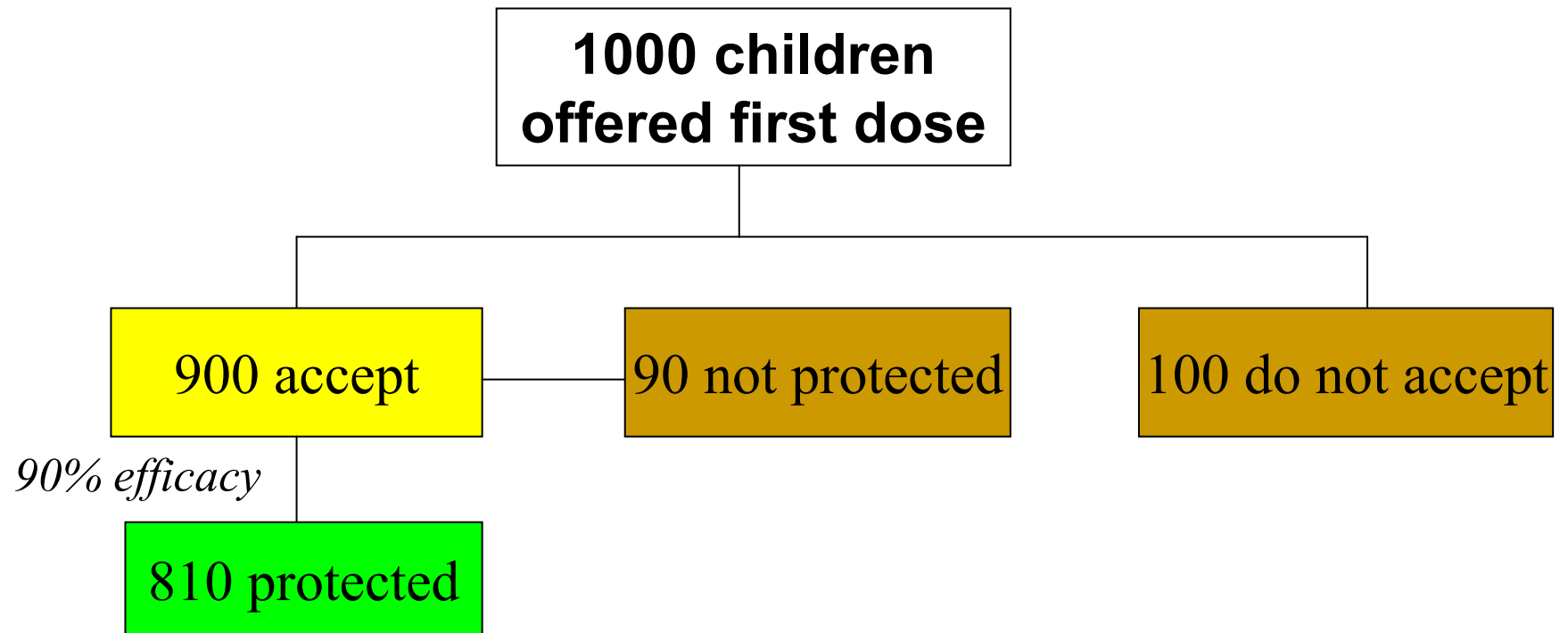
Outbreaks occur in populations with high coverage



First dose of MMR protects:

90% against measles, 80% mumps

95% against rubella



Why herd immunity is important

- No vaccine is 100% effective e.g. measles vaccine is 90- 95% effective so out of every 100 children given the vaccine 5-10 will not be protected
- Some people unable to receive live vaccines e.g. the immunocompromised
- Herd immunity is the most effective way of protecting people who do not respond to vaccines or can't be given them for medical reasons

Summary

1. It is possible to provide passive immunity by using immunoglobulins or active immunity by using vaccines. There are different types of vaccine manufactured by different methods
2. Vaccines contain antigens resembling those of natural infections and stimulate the immune system to make a primary response and a memory response . Booster doses of vaccine reinforce the memory response
3. Knowledge of how vaccines stimulate the immune system can be applied to answering questions such as scheduling intervals, age-dependent responses, the basis for non-response in some individuals, herd immunity and elimination of infection.

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