IMMUNITY & HOW VACCINES WORK

Immunisation Study Day
2nd October 2015

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Learning outcome

- To understand and be able to describe how the immune system works
- To understand and be able to describe how vaccines work
- To understand the differences between various vaccines
- To be able to explain to our patients concepts such as herd immunity, adverse effects, vaccine overload and vaccine failure

Immunisation vs. Vaccination

- *Immunity* – the ability of the human body to protect itself from infectious disease
- *Immune system* consists of layered defences of increasing specificity
- *Vaccination* means having a vaccine – 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 that occurs following natural infection but without causing the disease
- To generate long-lasting immunity
- To interrupt spread of infection

To understand how vaccines work it is helpful to first look at how the body fights infection …

Tonsil /Adenoids- trap germs coming in through the mouth and nose

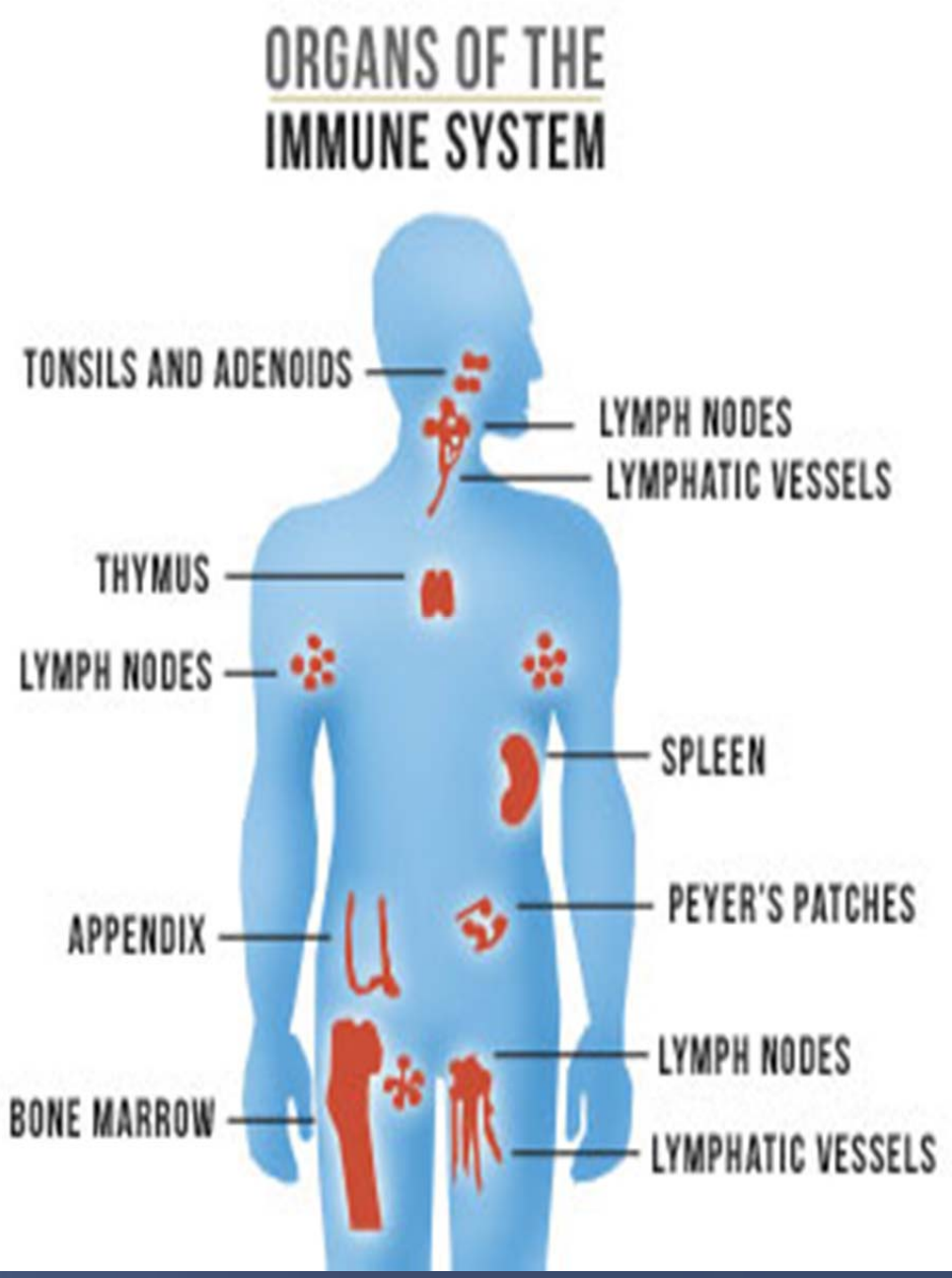
Bone Marrow – produces and turns immature RBCs, WBCs and platelets (stem cells) into mature cells

Thymus – site where T lymphocytes produced in the bone marrow go to mature

Spleen - Old RBCs are recycled; Platelets and WBCs are stored. Also helps fight encapsulated organisms

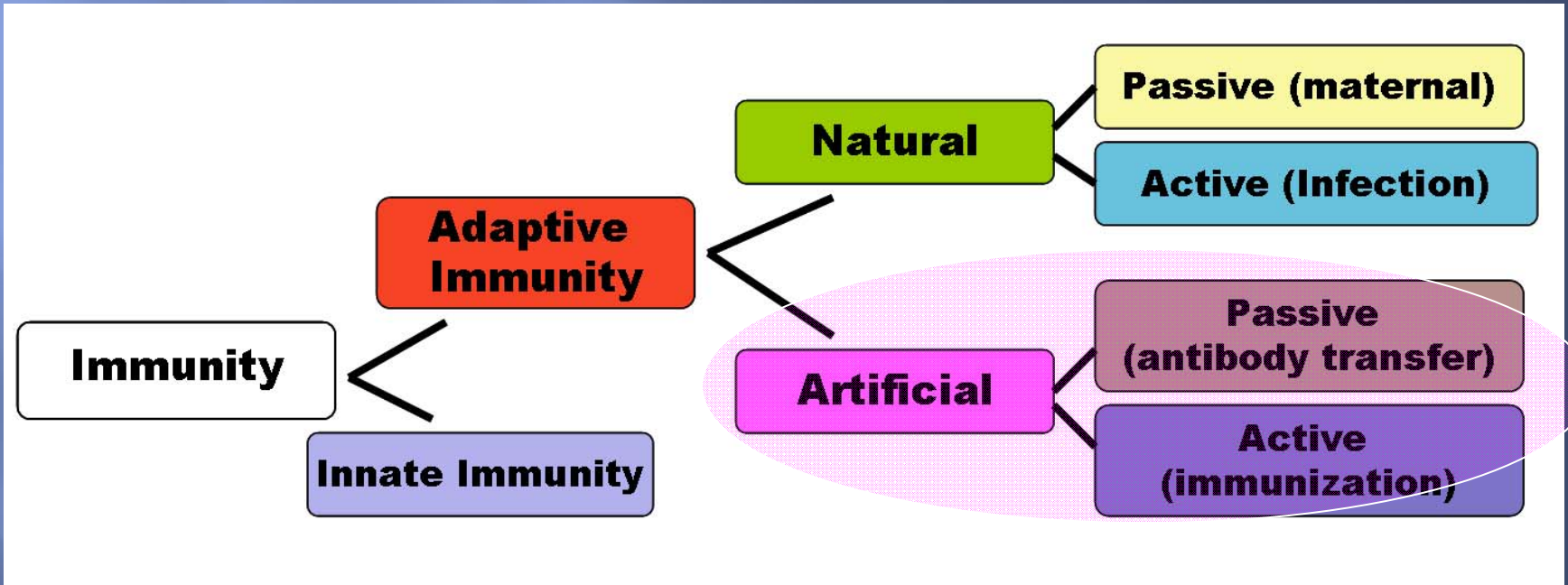
Peyer's Patches – small areas of lymphatic tissue found in the ileum. Immune sensors of intestine.

Lymph nodes – Gathering site for B & T lymphocytes and other immune cells. Filters foreign particles and cancer cells



Source: www.aids.gov

Types of Immunity



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

Innate (natural) immunity

The 1st level of defence

- Physical barriers - skin and mucous membranes
- Chemical barriers – gastric and digestive enzymes
- Cellular and Protein secretions –complement, phagocytes, macrophages

Defining characteristic: No memory persists afterwards

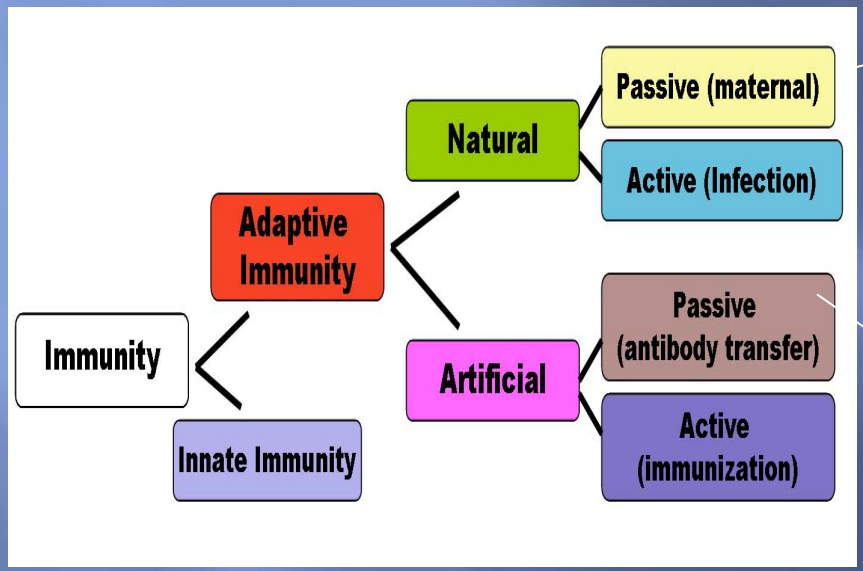
Adaptive (Acquired) immunity

The 2nd 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/breastfeeding

Artificial

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

- Rapid protection within 48 hours
- Short term protection and wanes over time (weeks to months)

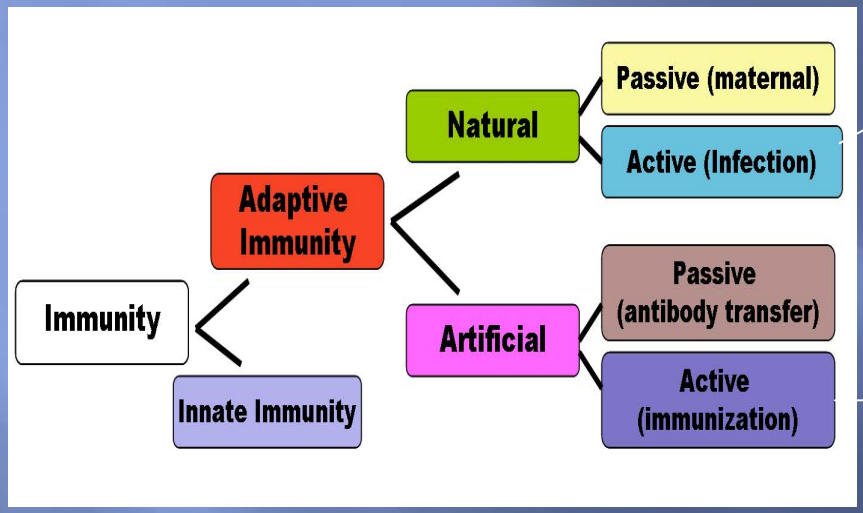
Passive Immunity

Administration of 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.

Derived from blood products

Active Immunity – adaptive mechanisms



Natural

- Following contact with the organism

Artificial

- Administration of agent to stimulate immune response (immunisation)

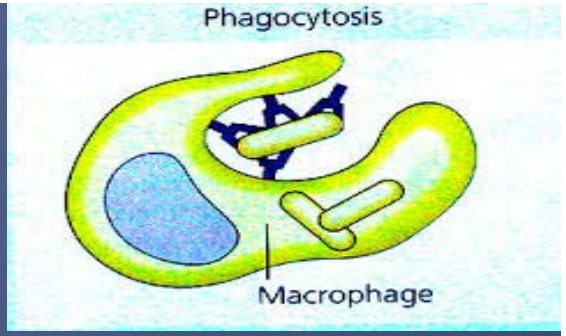
- Protection produced by the individual's own immune system
- Protection often life-long but may need boosting

Antigens

- Microbe is recognised as "foreign" because of unique molecules on it's surface – antigens*
- Antigens = A live or inactivate substance capable of producing an immune response
- Antigen is short for "Antibody Generator"

The concept of the immune response to a specific antigen is central to development of vaccines

Immune response



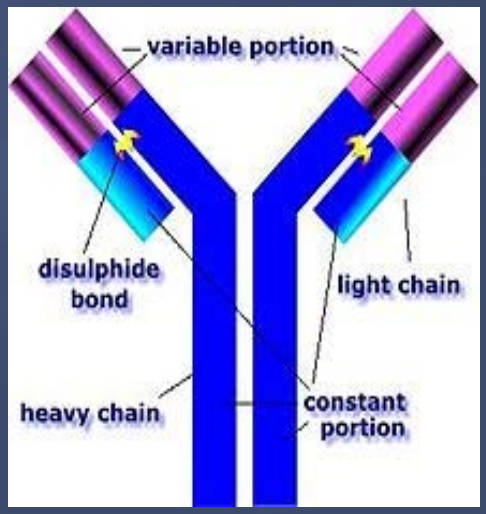
- The initial defence are WBCs called macrophages (literally: “big-eaters”). They engulf as many of the infecting micro-organisms as they can.
- Macrophages are also called natural killer cells and are part of the innate immune system.
- Macrophages digest most of the microbe except the antigen, which they display on their surface.
- They carry the antigen to the lymph nodes where they stimulate the Adaptive/Active immune system (B cells & T cells lymphocytes) to join the fight

Active immunity

- Humoral / Antibody mediated
  - B cells
- Cell mediated
  - T cells
    - Killer/cytotoxic – destroy infected cells and microbes
    - Helper – messenger cells which stimulate and direct activity of other immune cells e.g. T-killer & B cells

Antibodies

- Antibody Isotypes:
  - 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

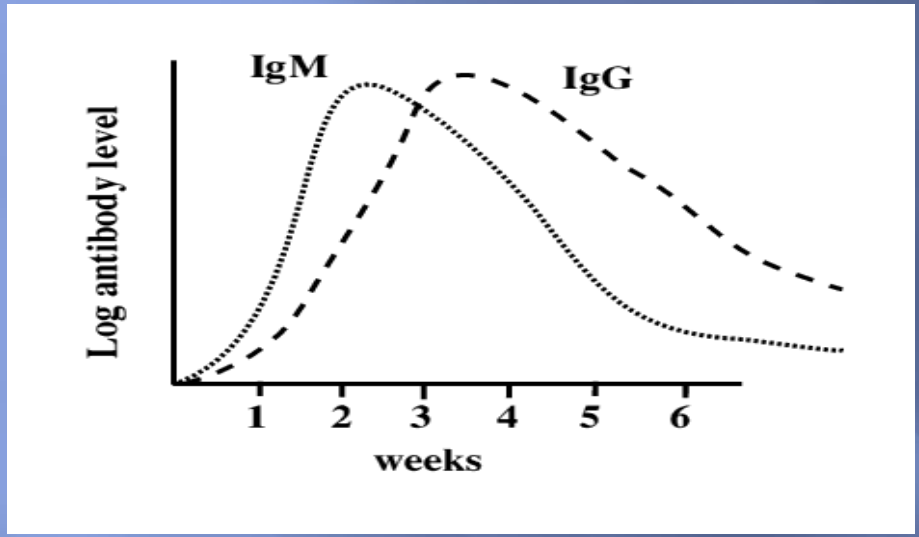


Antibodies - functions

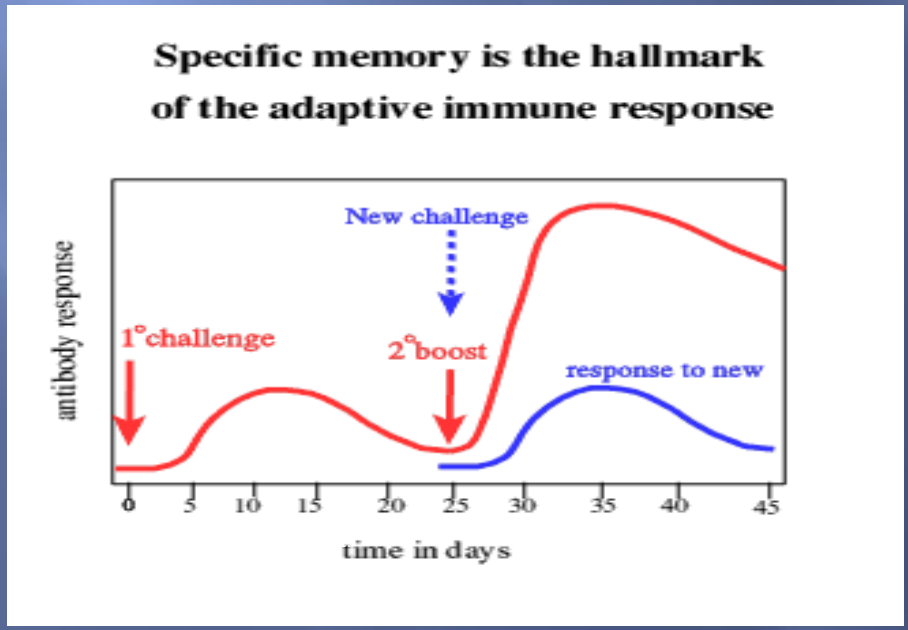
- Antibodies gather on the micro-organism's surface
- This blocks adhesion / cell entry of the antigen
- Neutralises and prevents organism's replication
- Signals macrophages and other WBCs to come via cytokines
- Kills organism via complement proteins – lysis
- Neutralises toxin

Goal of vaccination is to stimulate this response

How soon after immunisation are we protected?



Primary immune response
- Rapid
- Mainly IgM



Secondary immune response
- More powerful and faster
- Mainly IgG

Takes 2 weeks to get optimum immune response after vaccination

Source: HPA

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
- This immunological memory allows the body to mount faster and stronger responses with each exposure

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

Classification of Vaccines

1. Live attenuated
2. Inactivated
   - Whole cell
   - Fractionated
     - Protein based
       - Subunit
       - Toxoid
     - Polysaccharide
       - Pure
       - Conjugate

Live attenuated vaccines

Weakened viruses / bacteria

- Achieved by growing numerous generations in lab
- Good teachers for the immune system as causes immune response closest to that which the 'wild' microbe would – cellular (T-cell) and humoral(B-cell)

- Produces long lasting immunity after 1 or 2 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/Rotavirus

Inactivated vaccine and toxoids

- When adequate attenuation of live virus is not possible the vaccine is inactivated by chemical process or heat
- Toxoid vaccines = toxins that have been inactivated/weakened through chemical modification
- Cannot cause the disease they are designed to protect against so can be used in immunocompromised
- Produce immune response in a different way to live vaccines and response is often weaker - 2 or more doses + periodic boosters usually required
- Mostly humoral, little or no cellular immunity

Inactivated vaccine and toxoids

Whole cell

- Viruses (IPV, hep A, influenza)
- Bacteria (whole cell pertussis - wP)

Subcellular fraction (Fractionated)

- Protein-based
  - Toxoid (diphtheria, tetanus)
  - Subunit (Hep B, acellular pertussis -aP)

- Polysaccharide – pure or conjugate (pneumococcal, Hib)
  - Less immunogenic - require adjuvant or conjugation to enhance response

Conjugation

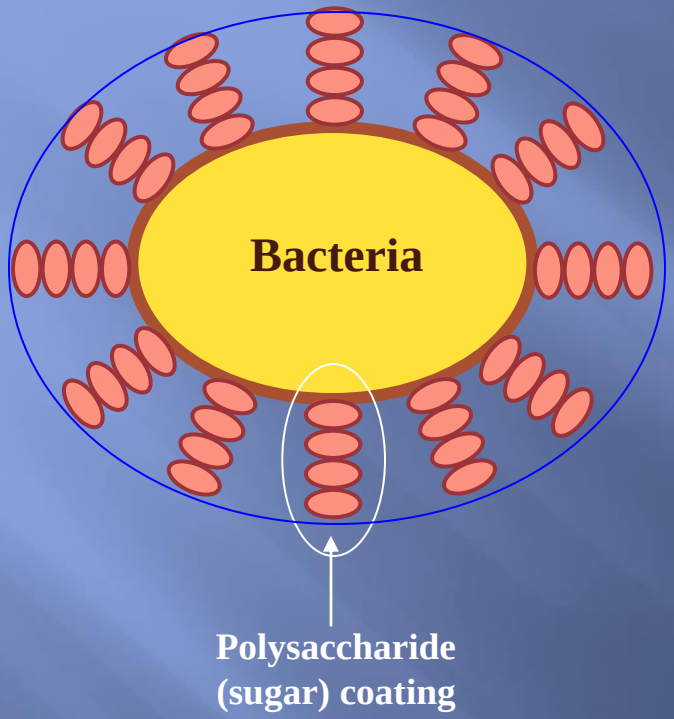
- Some bacteria (e.g. Hib, *N. meningitidis, Strep. pneumoniae*) have an outer coating of sugar molecules (polysaccharides) that disguise the antigens - Encapsulated organisms

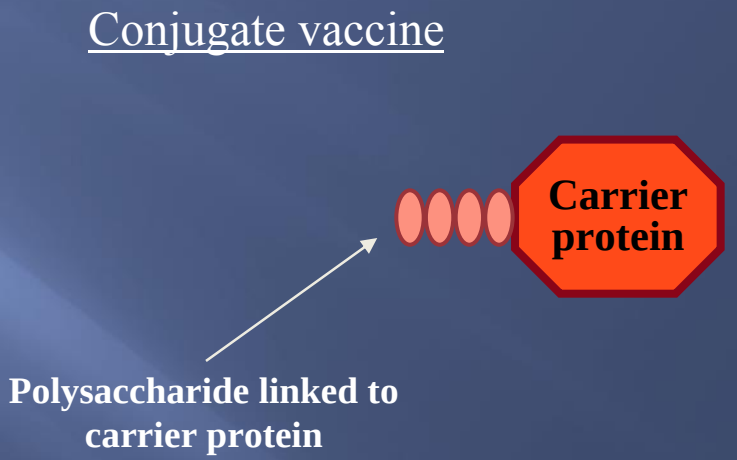
- Polysaccharide coatings make it difficult for a baby or young child's immature immune system to see and respond to the bacterium inside

- Conjugating agents are carrier proteins which combine with antigens to improve immunogenicity
- Conjugate vaccines have enabled us to effectively protect children against Hib, Men C and pneumococcal diseases

Source HPA

Conjugation





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

Source HPA

Adjuvant

- Adjuvants - aluminium salts that increase immunogenicity of vaccines containing inactivated micro-organisms or their products
- Enhances the immune response to the vaccine's antigen by:
  - Slowing down the release of antigen at injection site
  - Improved delivery of antigen to lymph node
  - Assist macrophage in presentation of antigens to lymphocytes
- E.g. Hep B, tetanus toxoid, diphtheria toxoid

Thiomersal*

Mercury containing compound used as a preservative in some vaccines to prevent bacterial and fungal growth

- Also used as inactivating agent in early stage production of some killed vaccines

- In 1999 E.U. and U.S. manufacturer's decided to decrease thiomersal levels in vaccines as a precaution and to retain trust in vaccine supply

- WHO state that there is no evidence of toxicity in infants, children or adults exposed to thiomersal other than hypersensitivity rxns.

- All vaccines used in the routine infant immunisation programme are thiomersal free. Some vaccines used in older children and adults contain trace amounts including some formulations of the influenza vaccine

**Also known as thimerosal*

Adverse Effects

Most of the common side effects of vaccination are mild, whereas the diseases that they are designed to prevent can be serious or deadly

Serious side effects are reported infrequently – 1 per 100,000 doses on average

Inactivated Vaccines

- Adverse events increase with number of doses
- Good antibody levels results in greater secondary immune response

E.g. May be inflammatory e.g. tetanus, pertussis

Live Vaccines

- Frequency of adverse events falls with number of doses because antibody that is made neutralises small amounts of vaccine in subsequent doses.

Do vaccines overload the Immune system?

The human body contains 100 trillion bacteria.

On average there are:

- 1000 Bacteria on each cm^2 of skin
- 1 million Bacteria on each cm^2 of scalp
- 100 million Bacteria per gram of saliva

- Max. number of antigens in a vaccine is ~ 3000

- Vaccines help stimulate and strengthen immune system
- Allergies may result from too little immune stimulation in our cleaner environments

- No evidence that vaccines overload the immune system.
- One study estimates that children could easily handle 10,000 Vaccines at once.

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

Vaccine failure

Primary failure

- 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

- 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

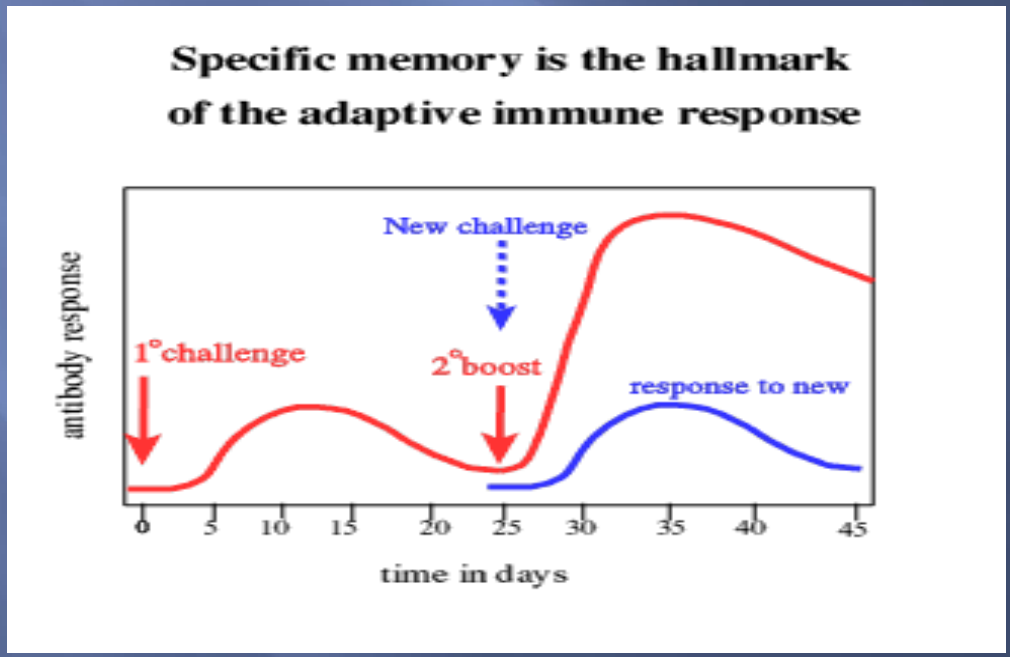
- Maternal IgG is transferred across the placenta
- Passively acquired IgG from mother can suppress response to DTP, Polio, Men C and Hib vaccine for about 2 months
- Maternal antibody to measles may interfere for up to a year

Source HPA

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



Time intervals between vaccine doses

Diminishes 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 *same* 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

Time Interval Exceptions

- Influenza & PCV
  - In those aged 12-23 months these should be separated by at least 1 week due to slight increased risk of fever if given together
- Rotavirus
  - No interval needed between it and other live vaccines
- Yellow Fever and MMR
  - Ideally separate by 1 month as may be suboptimal response if given together

Herd immunity

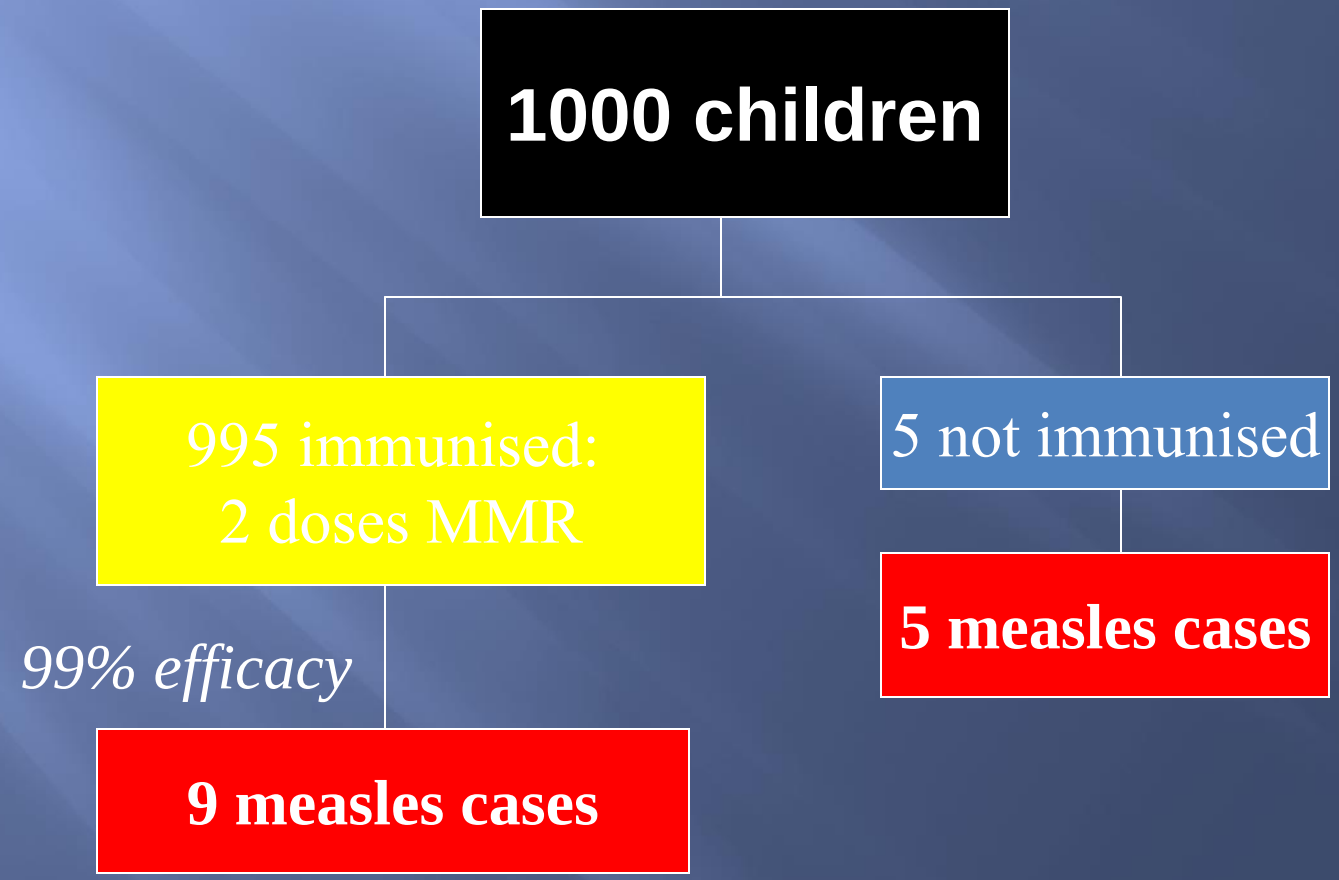
- A certain level of immunity in the population which protects the whole population because the disease stops spreading
- It provides indirect protection of unvaccinated as well as vaccinated individuals
- To achieve herd immunity the % of individuals who need to be vaccinated depends on the disease 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

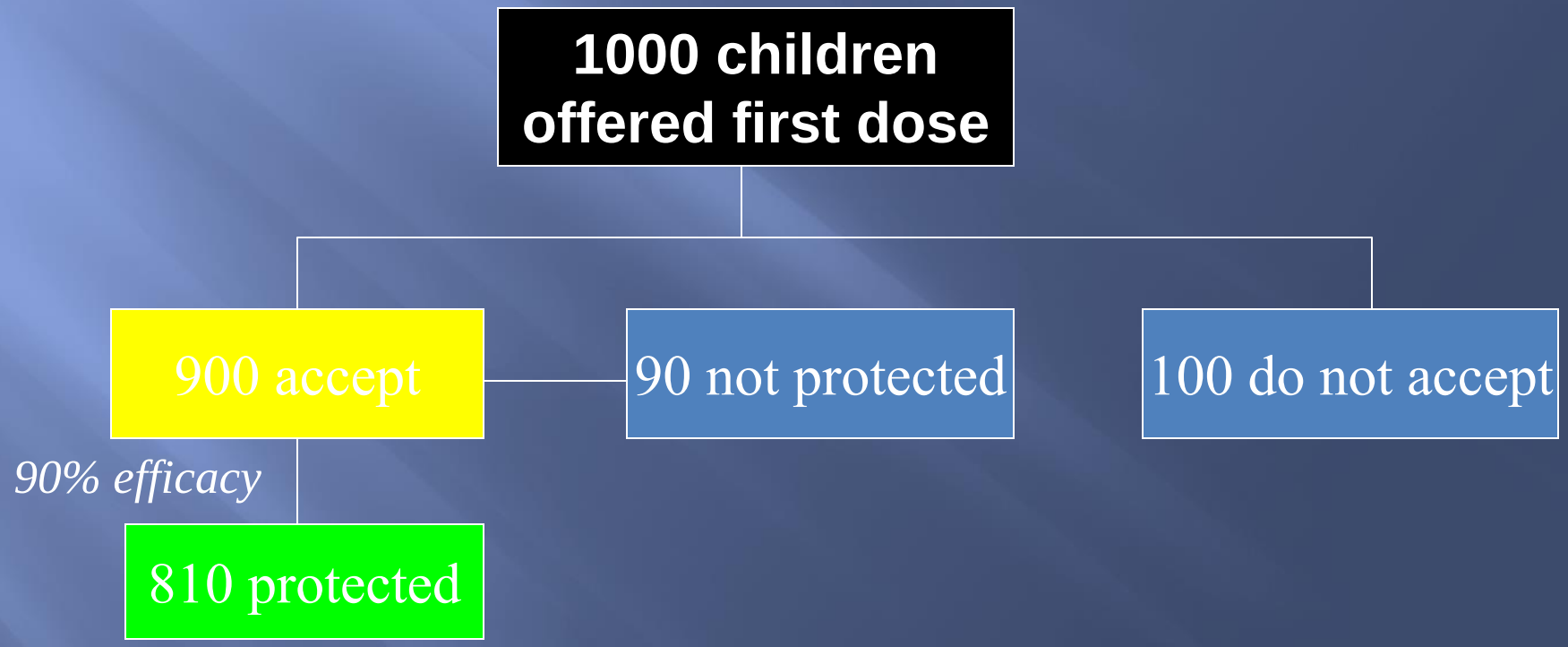
Source HPA

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

Source HPA

Summary

- Scientists take many approaches when designing vaccines and these are based on knowledge about the germs the vaccines will prevent
- Vaccines contain antigens resembling those of natural infections and stimulate the immune system to make a primary response and a memory response
- Booster doses reinforce the memory response
- Knowledge of how vaccines stimulate the immune system can be applied to answering questions such as :
  - Scheduling intervals
  - Age-dependent responses
  - The use of conjugates and adjuvants
  - Vaccine overload
  - Herd immunity

- Immunity and How Vaccines Work, NIO

  https://www.google.ie/url?sa=t&rct=j&q=&esrc=s&source=web&cd=4&cad=rja&ved=0CDoQFjAD&url=http%3A%2F%2Fwww.immunisation.ie%2Fen%2FDownloads%2FTrainingManual%2FPDFFile_16731_en.pdf&ei=5qJzUu2zD6Pe7AaIxoHgAQ&usg=AFQjCNGEqNBHdB_oggY7a_Hg7WoLVxf52A
  www.immunisation.ie

- How Vaccines Work, HPA, UK

  https://www.google.ie/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&ved=0CCoQFjAA&url=http%3A%2F%2Fwww.hpa.org.uk%2Fwebc%2Fhpawebfile%2Fhpaweb_c%2F1279888300493&ei=5qJzUu2zD6Pe7AaIxoHgAQ&usg=AFQjCNElYuqDCZPh52DFrHNfyHNdepEvnA

- Core Topic 2 Training Slides, HPA, UK 2012

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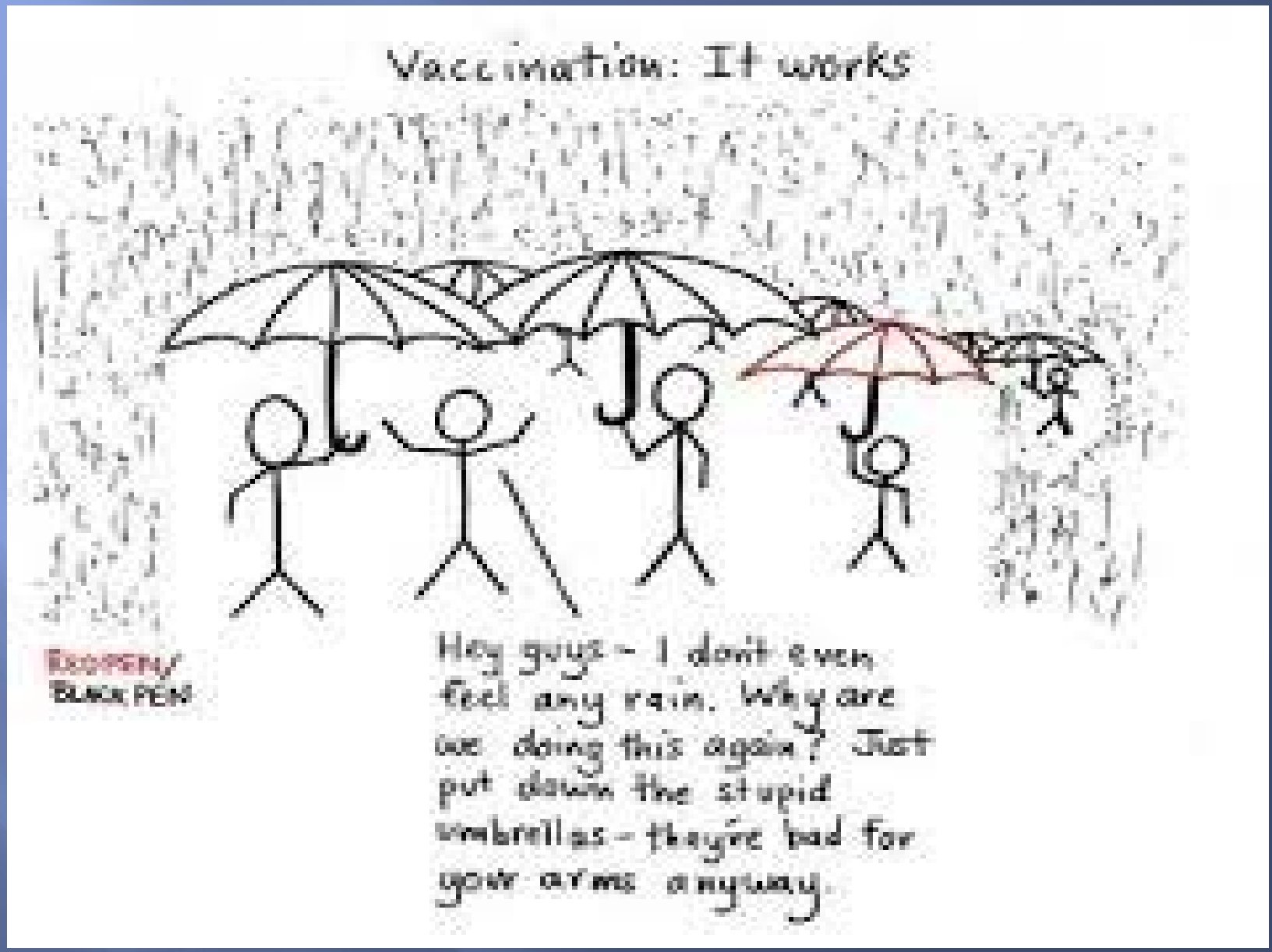
  https://www.google.ie/url?sa=t&rct=j&q=&esrc=s&source=web&cd=5&cad=rja&ved=0CEcQFjAE&url=http%3A%2F%2Fwww.unc.edu%2Fcourses%2F2006spring%2Fenvr%2F133%2F001%2FENVR133_Lecture9.ppt&ei=wphzUp3CJeqw7Abf5ICIBA&usg=AFQjCNG5vLdm66i_7FmexsigYiui7OG2pA


Vaccination: It works
Hey guys - I don't even feel any rain. Why are we doing this again? Just put down the stupid umbrellas - they're bad for your arms anyway.