Immunity and How Vaccines Work

Immunisation Conference

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The Immune System

- Network of cells and tissues which:
    - defend body against invading pathogens
      remove worn out cells and other debris
      destroy abnormal cells in the body

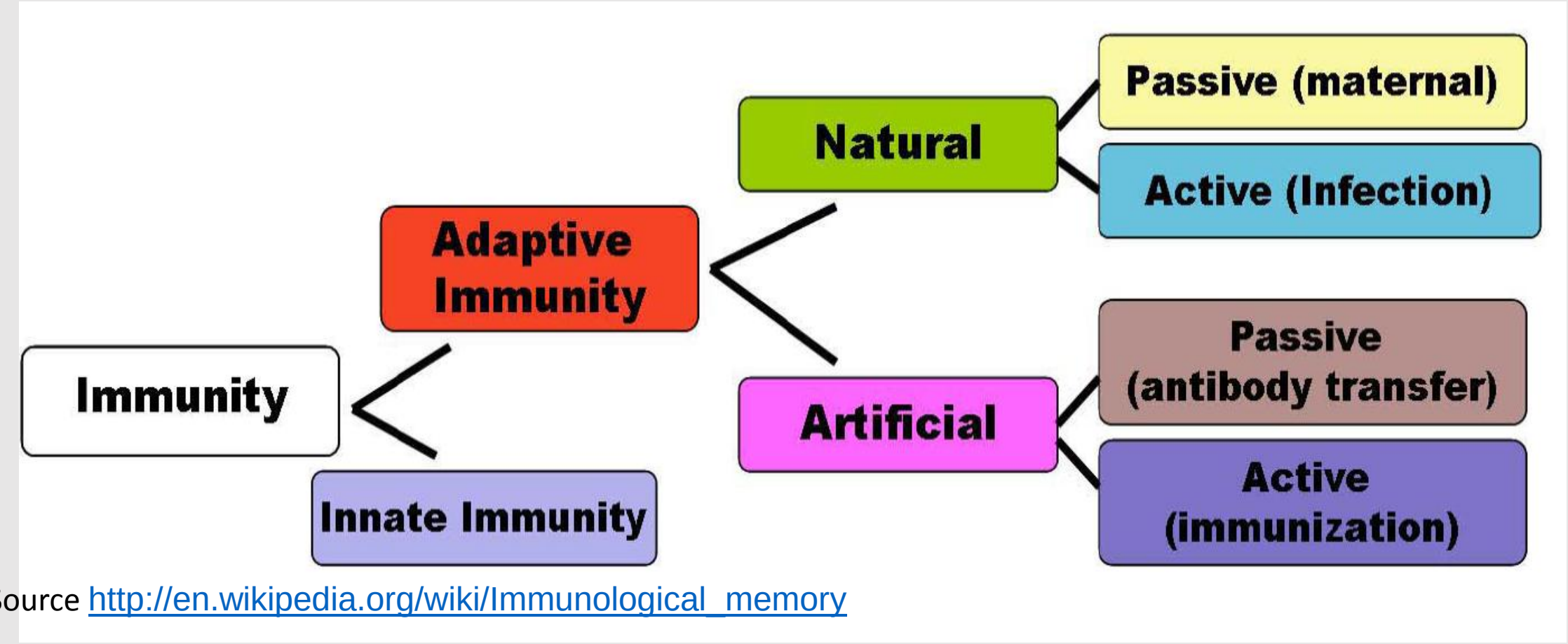
The key to a healthy immune system is its remarkable ability to distinguish between the body's own cells —self—and foreign cells—nonself because of antigens on the foreign surface.

Immune System Components

- White blood cells

- Lymphoid Tissues:
  - Bone marrow - site of B cell development
  - Thymus -site of T cell maturation
  - Spleen, lymph nodes, Gut Associated Lymphoid Tissue, adenoids, appendix, tonsils

Organisation of the Immune System



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

Innate Immunity (Natural)

- 1st line of defence.
  - Non specific host defences
  - Initial and immediate response to pathogen invasion

- Physical barriers - skin and mucous membranes
- Chemical barriers – gastric and digestive enzymes
- Cellular and Protein secretions –complement, phagocytes, macrophages, mast cells, white blood cells.

<u>Defining characteristic: No memory persists afterwards</u>

Adaptive Immunity (acquired)

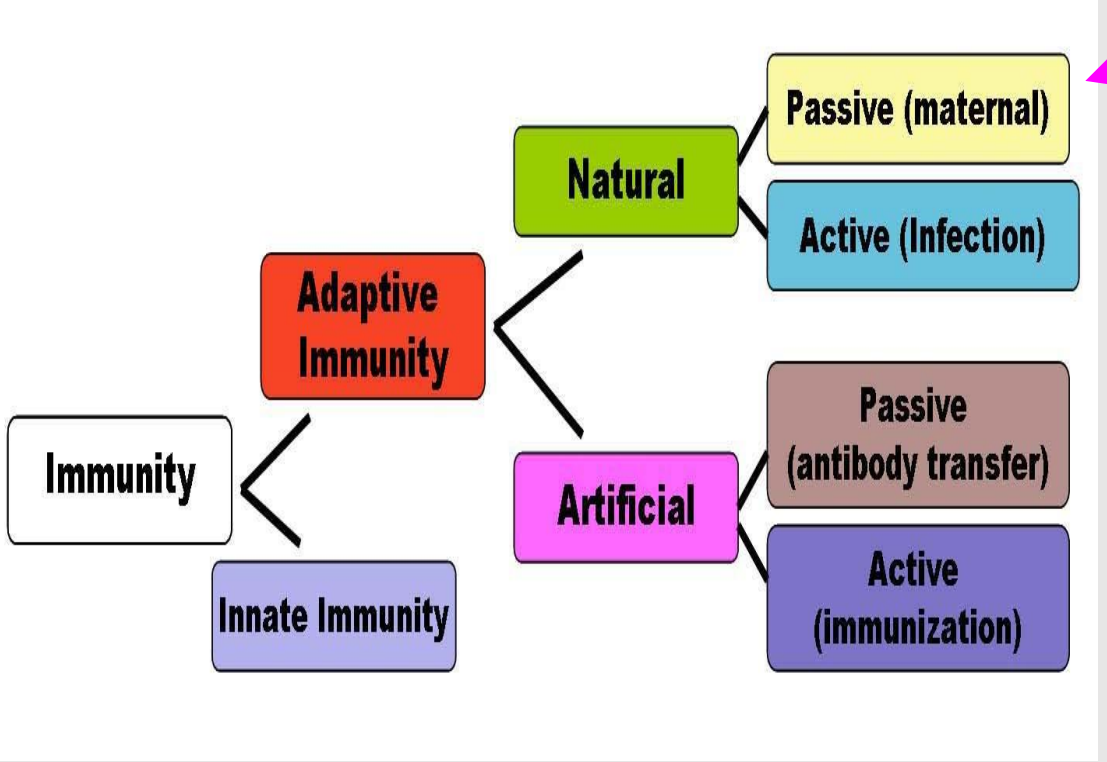
- 2nd line of defence. Develops as a response to infection.
- Adaptive means immune system adapts to previously unseen molecules.
- Slow, can take days or weeks.

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

- The response increases in strength and effectiveness with each encounter.

- Cell mediated (T cells) and Humoral mediated (B cells)

Passive immunity – adaptive mechanisms



Natural

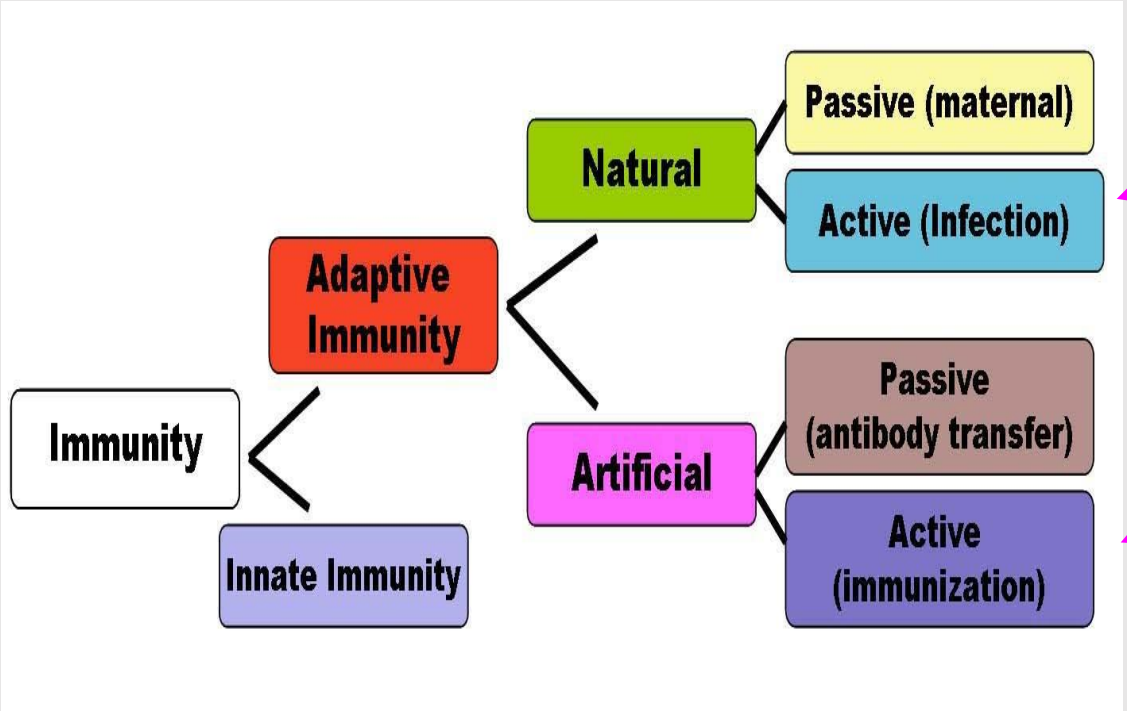
•maternal transfer of antibodies to infant via placenta

Artificial

•administration of pre- formed substance to provide immediate but short-term protection (antitoxin, immunoglobulin)

Protection within 48 hours but is temporary and wanes with time (usually few months)

Active immunity – adaptive mechanisms



Natural
- **following contact with organism**

Artificial
- **administration of agent to stimulate immune response (immunisation)**

Induction of immunity by infection or vaccination is active immunity
Protection produced by individual's own immune system
Protection often life-long but may

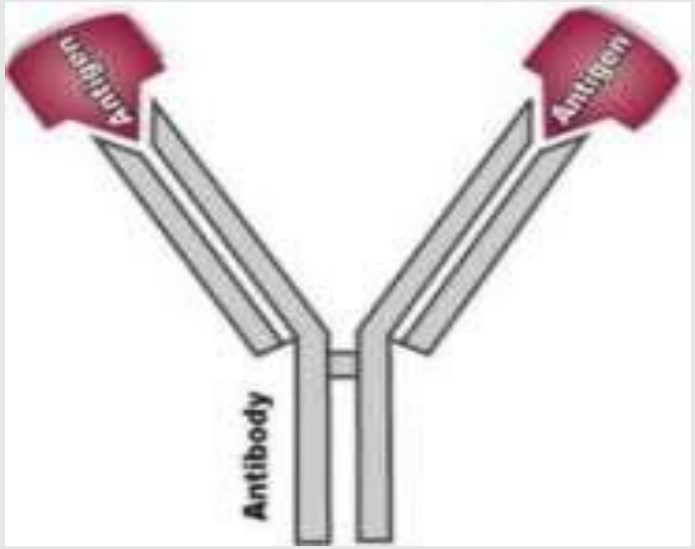
How does adaptive (acquired) immunity work

- The invading organism has antigens on the exterior of its cells.
- Antigen is a live or inactivated substance capable of producing an immune response.
- Antibodies are proteins on cells in the immune system which react with antigens forming an antigen-antibody complex.
- The immune system is activated making more specific antibodies marking the antigen for destruction.
- The concept of the immune response to a specific antigen is central to development of vaccines

Active Immunity

- Macrophages digest most of the micro- organism except the antigens.
- They 'regurgitate' the antigens displaying them on their surface so that white cells called lymphocytes can take over the attack (T cells and B cells)
- <u>Humoral Immunity</u>
- B cells (antibodies)
- <u>Cell mediated Immunity</u>
  - T cells activate immune response
  - Killer cells destroy infected cells and micro-organisms
  - Helper cells stimulate and direct activity of other immune cells e.g. T and B cells..

Antibodies

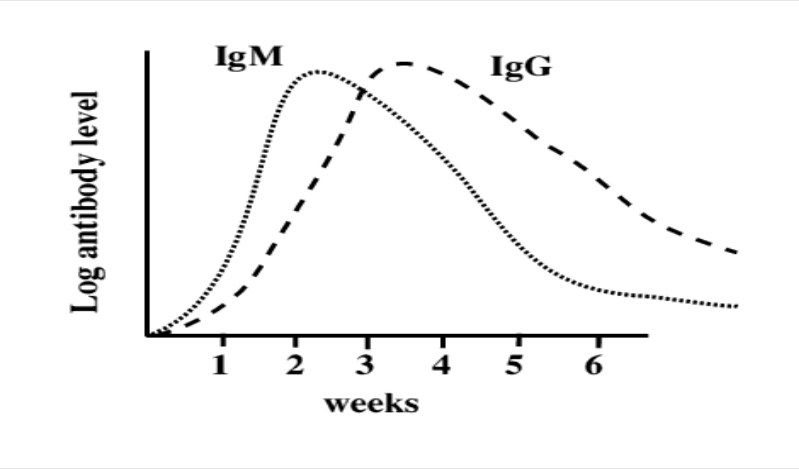


- Different types
  - IgM, IgG, IgA, IgD, IgE made by B cells
- Functions
  - Neutralise toxins
  - Block adhesion/cell entry of the antigen
  - Neutralise and prevent organisms replication
    Signals macrophages etc to come
    Kills organism via complement -lysis
- Antigen specific
  - Cannot cross-protect different type of micro-organism

Memory cells

- After the body has eliminated the infection, some B cells and T cells become memory cells.
- These retain memory of the pathogen
- On re-exposure to the antigen, the different B and T cell clones will increase to form a polyclonal response and mount a powerful immune response.
- This ability of the immune system to have a memory for previous antigens is the basis for vaccination.

How soon after immunisation are we protected?

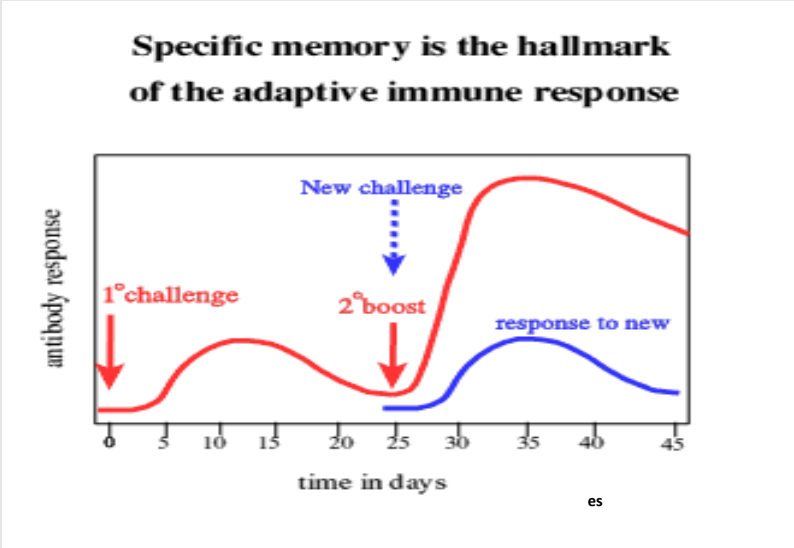


Takes 4-7 days to generate immune response.

>7 days get Primary immune response

••Mainly IgM

Primary response turned off after about 3 weeks. Memory B cells made.



Secondary/subsequent immune response

- More powerful and faster
- Mainly IgG.
- Occurs as memory cells secrete Ab when agent reencountered.

Takes 2 weeks to get optimum immune response after vaccination

Source: HPA

- Vaccine is a suspension of live attenuated or inactivated micro-organisms or fractions thereof given to induce immunity and prevent infectious disease.

- Vaccination is the administration of any vaccine or toxin.

- Immunisation means receiving a vaccine and also becoming immune because of being vaccinated.

How vaccines work

- Induce active immunity artificially
- Immunity and immunological memory similar to natural infection but without the risk of disease

- Immunological memory allows
  - Rapid recognition and response to the antigens of the micro-organism
  - Prevents or modifies effect of the 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
- Causes immune response closest to that which the natural infection would – has cellular (T-cell) and humoral(B-cell) components.

- Produces long lasting immunity after 1 or 2 doses
- Can cause mild version of the disease e.g. mini measles which is <u>not transmissible</u>
- Can cause active disease in immunocompromised persons

- E.g. BCG / MMR / Varicella / Yellow Fever/Rotavirus

Non live vaccines

- Cannot cause disease they are designed to protect against
- Cannot replicate
- Immune response mostly antibody based.
- Antibody titre falls with time.
  Often need adjuvant or conjugation to stimulate the immune response.
- Doses
  - 3-5 doses usually required

- Classified as
  - Inactivated
  - Conjugate
  - Recombinant
  - Sub unit

Inactivated vaccine and toxoids

•contains killed bacteria or viruses, or a portion thereof e.g. inactivated polio vaccine

•toxoids

e.g. tetanus, diphtheria

Conjugate vaccine

•where a protein or polysaccharide antigen is linked to a carrier protein

e.g. meningococcal C conjugate vaccine

Recombinant vaccine

•produced through recombinant DNA technology

e.g. hepatitis B and HPV vaccine

Sub unit vaccine

•contains only specific antigenic proteins of an infectious agent

e.g. acellular pertussis and some influenza vaccines

Vaccine Components

- Conjugating agents

  Some bacteria have an outer polysaccharide coat to disguise the antigens -encapsulated organisms- making it difficult for the immune system to respond to the bacterium inside. So

  - Carrier proteins are used which combine with antigens to improve immunogenicity.
  - Men C, PCV, Hib

- Suspension fluid
  - Fluid (water, saline, tissue-culture mixture)

- Preservatives, stabilisers, antimicrobial agents
  - Trace amounts used to stabilise vaccine
  - May cause allergic reaction

Vaccine Components

- <u>Adjuvants</u>
  - Aluminum salts used to increase immunogenicity of vaccines containing inactivated micro-organisms or their products.

e.g.

- Hepatitis B vaccine
- Tetanus toxoid
- Diphtheria toxoid

Thiomersal*

- Mercury containing compound used as a preservative in some multidose 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 reactions.
- 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*

Time intervals between vaccine doses

Antigen combination	Recommended minimal interval between doses
≥2 killed antigens	No minimum interval
Killed and live antigens	No minimum interval
≥2 live antigens	Four-week minimum interval if not administered simultaneously

Time intervals between vaccine doses

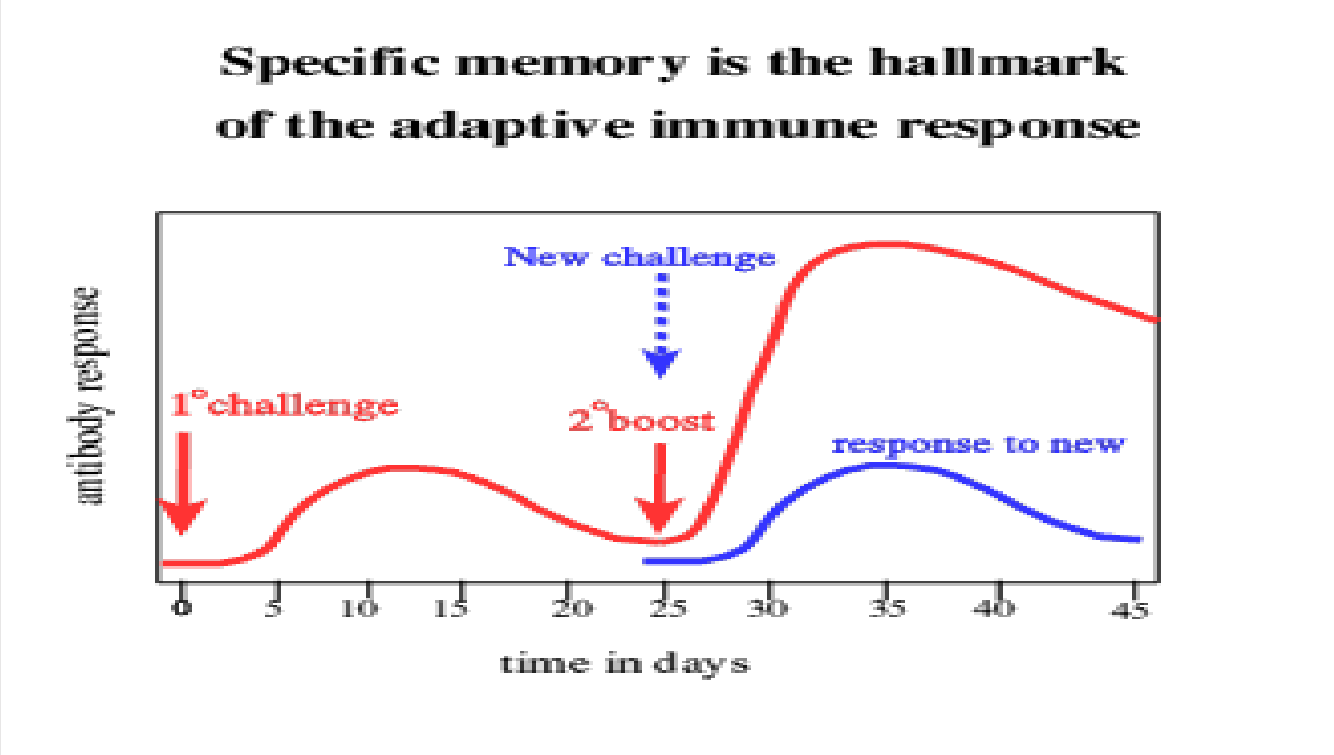
Diminishes immune interference

- 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

- 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



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 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

Vaccine overload

- The human body is composed of 10 trillion cells and contains 100 trillion bacteria

On average there are

- 1000 bacteria on each cm^2 of skin
- 1,000,000 bacteria on each cm^2 of the scalp
- 100,000,000 bacteria per gram of saliva

- The maximum number of antigens in a vaccine is about 3000
- With the new vaccines this number is much lower still

- No evidence that vaccines can overload the immune system

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

Adverse events

- Live vaccines:
  - frequency of adverse events falls with number of doses
  - If antibody is made -> neutralises small amount of vaccine virus in any subsequent vaccine dose
  - E.g. MMR

- Inactivated vaccines
  - frequency of adverse events increases with number of doses
  - Good antibody levels ->greater secondary immune response

  So may be inflammatory effects (i.e. produce a sore arm)
  - E.g. tetanus, pertussis

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

Herd immunity

- Only applies to diseases which are passed from person to person

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

- Provides indirect protection of unvaccinated as well as vaccinated individuals.
  Some cannot receive live vaccines eg immunocomprised.
  No vaccine is 100% effective.

- May be the most important aspect of how vaccines work
  - MMR given to infants protects pregnant women from rubella.
  - Can eradicate disease even if some people remain susceptible

Resources

A Practical Guide to Immunisation HSE
http://www.hse.ie/eng/health/immunisation/hcpinfo/trainingmanual/

- Immunity and how vaccines work. National Immunisation Office

http://www.immunisation.ie/en/Downloads/TrainingManual/PDFFile_16731_en.pdf

- Immunity and how vaccines work. Chapter 1 Green Book (UK)

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/144249/Gree

n-Book-Chapter-1.pdf

- How Vaccines Work, NIH – National Institute of Allergy and Infectious Disease US

www.niaid.nih.gov/topics/vaccines/understanding/pages/howwork.aspx

The immune system and vaccination
immunisation advisory centre,university of auckland
http://www.immune.org.nz/immune-system-and-vaccination

The immune system and vaccination
NIH Publication No. 03-5423 September 2003 www.niaid.nih.gov