Immunity and How Vaccines Work

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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

Source: http://en.wikipedia.org/wiki/Immunological_memory
Innate Immunity (Natural)

• 1\textsuperscript{st} 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.

**Defining characteristic:** No memory persists afterwards
Adaptive Immunity (acquired)

• 2\textsuperscript{nd} 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 need boosting
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).

Humoral Immunity
- B cells (antibodies)

Cell mediated Immunity
- 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.
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 not transmissible
- 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

• **Adjuvants**
  • 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

<table>
<thead>
<tr>
<th>Antigen combination</th>
<th>Recommended minimal interval between doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 killed antigens</td>
<td>No minimum interval</td>
</tr>
<tr>
<td>Killed and live antigens</td>
<td>No minimum interval</td>
</tr>
<tr>
<td>≥2 live antigens</td>
<td>Four-week minimum interval if not administered simultaneously</td>
</tr>
</tbody>
</table>
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

http://www.immunisation.nhs.uk/About_Immunisation/Science/How_immunisation_works
Resources

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

- Immunity and how vaccines work. National Immunisation Office

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

The immune system and vaccination