# Immune System and how Vaccines Work

Kevin Connolly

Waterford, August 30th, 2012

# Causes of death, 1811, Boston

*The* DEATHS *preceding were caused by Diseases and Casualties as follows, viz.*

| | | | |
|---|---|---|---|
| Abscesses | 1 | Hernia, or Rupture | 3 |
| Aneurism | 1 | Jaundice | 10 |
| Apoplexy | 13 | Inflammation of the bowels | 1 |
| Burns or Scalds | 6 | ——— of the stomach | 1 |
| Cancer | 5 | Killed by lightning | 1 |
| Casualties | 15 | Insanity | 1 |
| Childbed | 14 | Intemperance | 2 |
| Cholera Morbus | 6 | Locked jaw | 2 |
| Colic | 2 | Mortification | 11 |
| Consumption | 221 | Old Age | 26 |
| Convulsions | 36 | Palsy | 12 |
| Cramp in the stomach | 2 | Pleurisy | 8 |
| Croup | 1 | Quinsy | 15 |
| Debility | 28 | Rheumatism | 1 |
| Decay | 20 | Rupture of blood vessels | 1 |
| Diarrhœa | 15 | Small-Pox, (at Rainsford's Island) | 2 |
| Drinking cold water | 2 | Sore throat | 1 |
| Dropsy | 21 | Spasms | 2 |
| ——— in the head | 23 | Stillborn | 49 |
| Drowned | 13 | Suicide | 1 |
| Dysentery | 14 | Sudden death | 25 |
| Dispepsia or Indigestion | 15 | Syphilis | 12 |
| Fever, bilious | 7 | Teething | 15 |
| ——— pulmonic | 46 | Worms | 11 |
| ——— inflammatory | 24 | Whooping Cough | 14 |
| ——— putrid | 6 | White swelling | 2 |
| ——— typhus | 33 | Diseases not mentioned | 48 |
| Flux infantile | 57 | | |
| Gout | 3 | Total, | 942 |
| Hœmorrhage | 4 | | |

# The Battle Between Us and the Bugs: What we can do

- We recognize them as something different not belonging inside the body
- Once recognized we try and kill them
- We have two systems of doing this:
  - The Innate system
  - The Adaptive system

# Host Defenses
# Innate and adaptive

| Nonspecific Resistance | | Specific Resistance (Responses of the Immune System, Chapter 17) |
|---|---|---|
| **First line of defense** | **Second line of defense** | **Third line of defense** |
| • Intact skin<br>• Mucous membranes and their secretions<br>• Normal microbiota | • Phagocytic white blood cells<br>• Inflammation<br>• Fever<br>• Antimicrobial substances | • Specialized lymphocytes: B cells and T cells<br>• Antibodies<br>• Cell-mediated immune response |

Tortora, et al. Figure 16.1

# Natural Defences

| Mechanism | Explained |
| --- | --- |
| Skin | Impenetrable **collagen** and **keratin**<br>Skin surface **commensal bacteriae** compete with pathogenic bacteria. |
| Tears | Contain **lysozyme** which breaks down cell wall of pathogens |
| Saliva | Contains lysozyme<br>Pathogens swallowed are destroyed in the stomach. |
| Mucous | Traps microorganisms that may be breathed in. |
| Cilia | move the mucous. |

# Innate immune system

**Definition**: cells and mechanisms that defend the host from infection by other organisms in a non-specific manner.

**Functions**

-Acting as physical and chemical barrier to infectious agents.

-Recruiting immune cells to sites of infection, through production of cytokines

-Activation of the complement cascade to identify bacteria, activate cells and promote clearance of dead cells or antibody complexes.

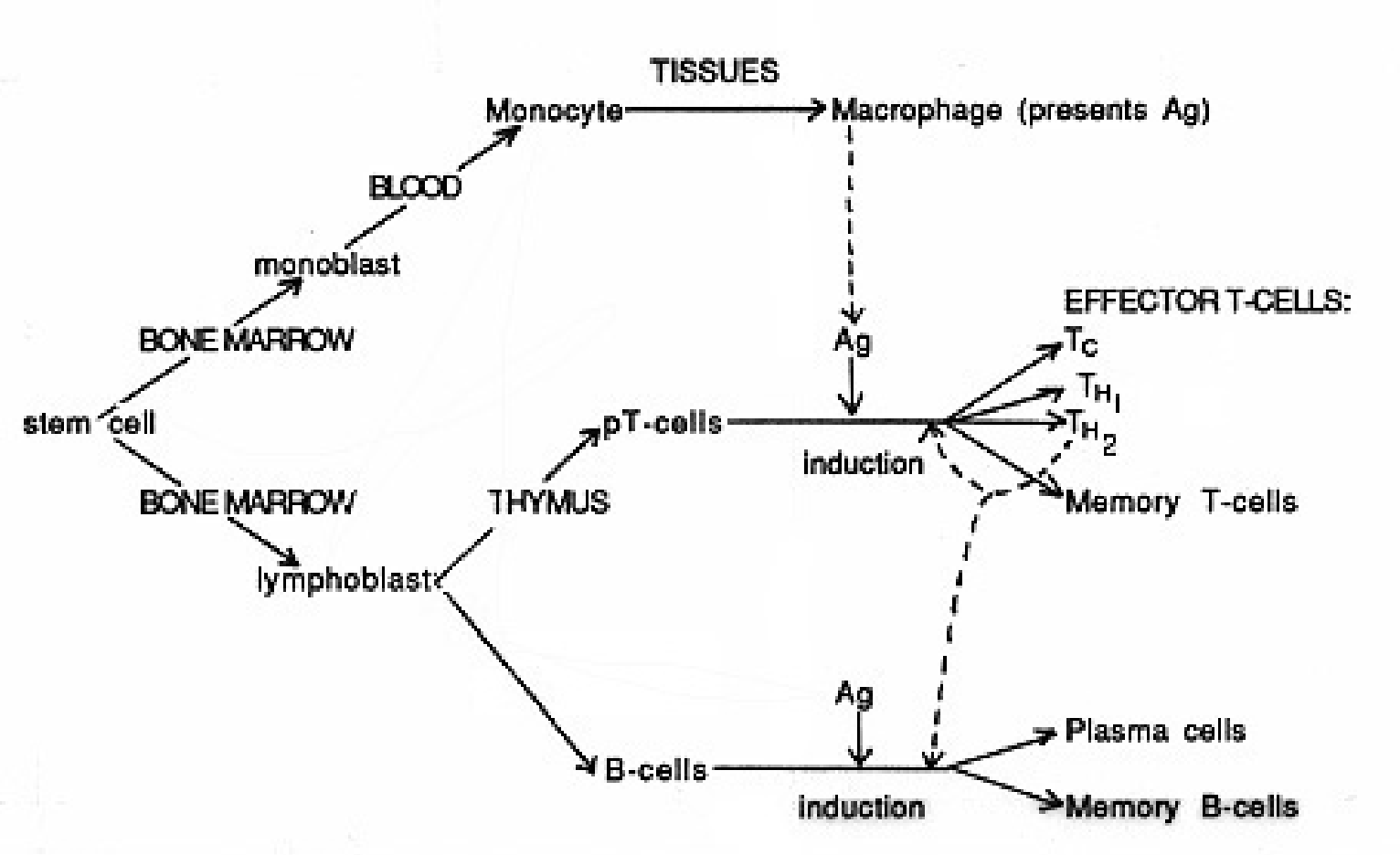
T -Identification and removal of foreign substances (present in organs, tissues, blood and lymph) by WBCS.

-Activation of the adaptive immune system through antigen presentation.

# Cellular participants in the Immune responses

- Phagocytic cells (dendritic cells, macrophages, and granulocytes)
- Antigen presenting cells (dendritic cells, macrophages, B lymphocytes, helper T cells)
- Antibody producing cells (plasma cells)
- Cytotoxic cells (CTL, NK)
- Regulatory cells (APCs, helper T cells, regulatory T cells)
- Cells-in-waiting (memory B cells, monocytes)
- Chemical releasing cells (basophils, eosinophils, neutrophils; mast cells - histamine, cytokines; hepatocytes - complement proteins)

# Cells of the Immune system



# Adaptive immunity

**Lymphocytes** are present, but **few in number** and **not** ready to respond immediately (must "wait" until it binds to the antigen for which it is specific)

Each lymphocyte can bind to only one antigen.

Responses **improve** with use (the lymphocyte population expands as an "**adaption**" to the first exposure to the antigen -> "memory" cells)

Generally effective against **bacterial** pathogens, **extracellular viruses, virus-infected cells** and **exotoxins**

**Antibodies** are the **molecular** component of the adaptive immune system

Adaptive response can also assist the innate immune system

- Can help macrophages ($TH_1$-helper lymphocytes)
- Can activate complement (antibody when it binds to antigen)

# LYMPHOCYTES

- Responsible for the specific immune response.

  Represent 20-40% of circulating WBC in blood
- 

- T lymphocytes, B lymphocytes and natural killer (NK) cells.
- T and B lymphocytes cannot be distinguished from each other morphologically.
- Once stimulated with antigen differentiate into effector cells or memory cells. [Plasma cells, T-helper cells, T-cytotoxic cells].
- Memory cells are long-lived cells activated by a second encounter with antigen.
- Different lineages or stages of lymphocytes distinguished by their membrane CD molecules (Cluster of Differentiation (CD)

# NK (natural killer) Cells

- Cytotoxic - granules in cytoplasm contain proteins such as perforin and proteases.
- On release near a “baddie” cell, perforin forms pores in the cell membrane of the target cell,
- through which the proteases enter, inducing either apoptosis or cell lysis.
- Lysing a virus-infected cell would release the virions
- Apoptosis destroys the virus

# B lymphocytes

- Originate in the bone marrow,
- Mature in secondary lymphoid tissues
- Become activated in the spleen or nodes when their surface immunoglobulins bind to an antigen
- Differentiate either into plasma cells or memory B cells.

# T-lymphocytes

- Formed in **bone marrow**, **mature** in the **thymus**.
- Make up 65 to 85% of the peripheral blood lymphocytes.
- Have markers on their surfaces (antigens)
- Start to express these markers during their maturation in the thymus.
- Also populate the peripheral lymphoid tissues

**Three types of T-cell:**

- **Cytotoxic T-cells** (killer cells) destroy their targets by releasing perforin, which makes a hole in target cell wall, allowing $H_2O$, ions to enter, and thereby killing it.
- **Helper T cells**, which regulate immune responses by releasing cytokines.
- **Suppressor T-cells**, which downregulate both humoral and cell-mediated immune responses. (These last two types are known as **Regulatory T-cells**)

# Adaptive Immune System

**Def**.: antibody and cell-mediated responses carried out by B and T cells.

**Functions**:

-Antibody production.

-Activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes.

-Release of cytokines

-Recognition of “non-self” antigens

- Generation of responses tailored to maximally eliminate specific pathogens or pathogen infected cells.

-Development of immune memory

# Humoral Immunity

**Definition**: production of antibodies in response to an antigen.

Most effective against bacteria, bacterial toxins, and viruses prior to these entering cells.

**Antibodies** (immunoglobulins): proteins produced by B-lymphocytes and plasma cells in response to an antigen and capable of reacting with that antigen.

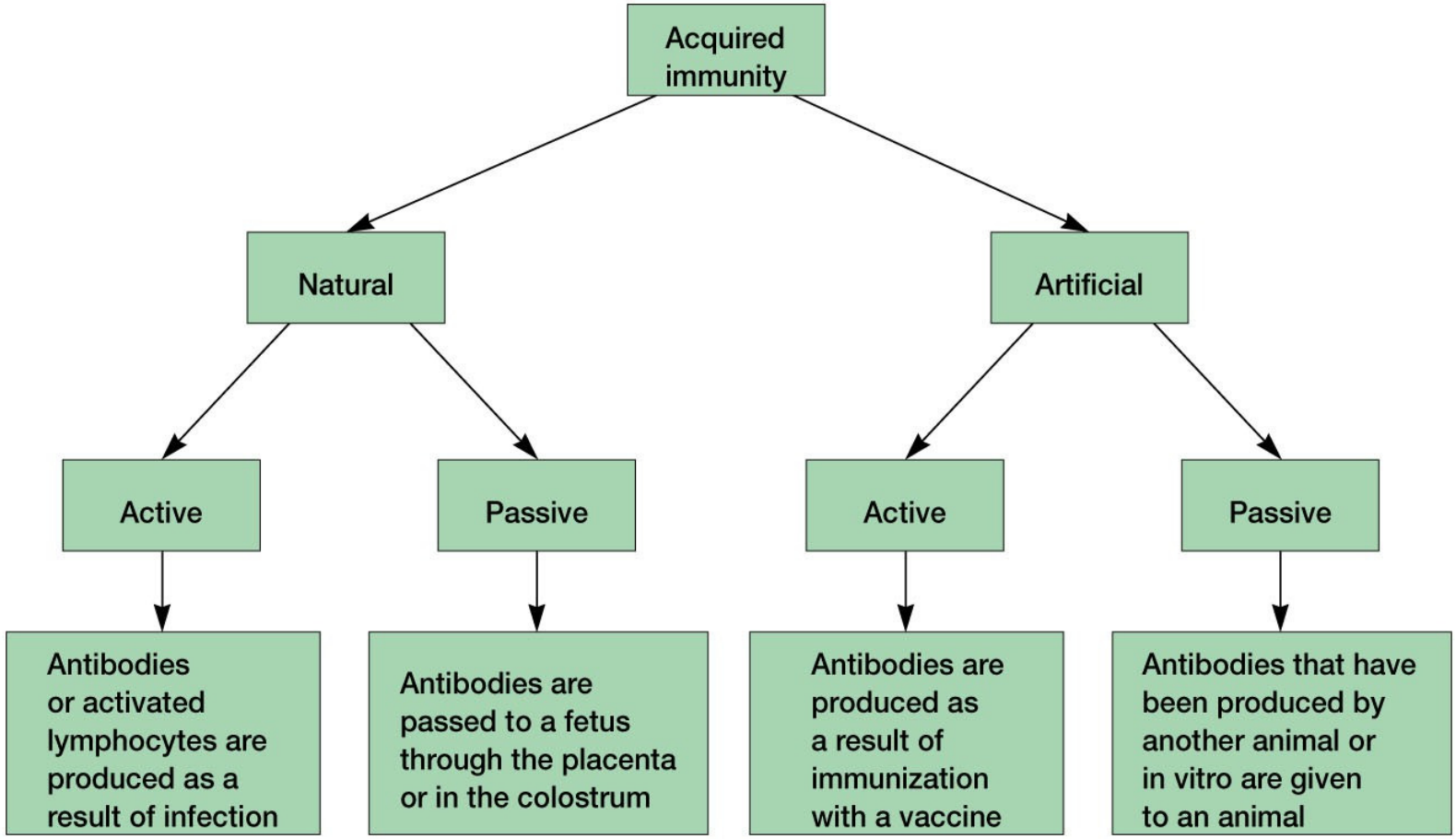
Antibodies work by::

1. Opsonization ( rendering bacteria and other cells subject to phagocytosis)
2. MAC (membrane attack complex) Cytolysis
3. Cellular Cytotoxicity by NK Cells
4. Neutralization of Exotoxins
5. Neutralization of Viruses
6. Preventing Bacterial Adherence to Host Cells
7. Agglutination of Microorganisms
8. Immobilization of Bacteria and Protozoans.

# Summary of Responses to Organisms

- Circulating antibodies inactivate or target organism
- Macrophage $\rightarrow$ inflammation, interferon, cell activation
- Th, Tc, NK & B cells $\rightarrow$ plasma cells$\rightarrow$ antibodies

# Types of Acquired Immunity



# Passive and Active Immunization

**Passive Immunization –**

Natural maternal serum/milk
Artificial immune serum
No immunological memory without $T_h$ cells.

**Active Immunization –**

Natural infection
Vaccination
- Live attenuated organisms
- inactivated organisms (dead)
- Cloned genes of microbiological antigens
- Subunit (purified microbial proteins)
- Synthetic peptides
- DNA

→ Induction of adaptive immune response, with protection and memory.

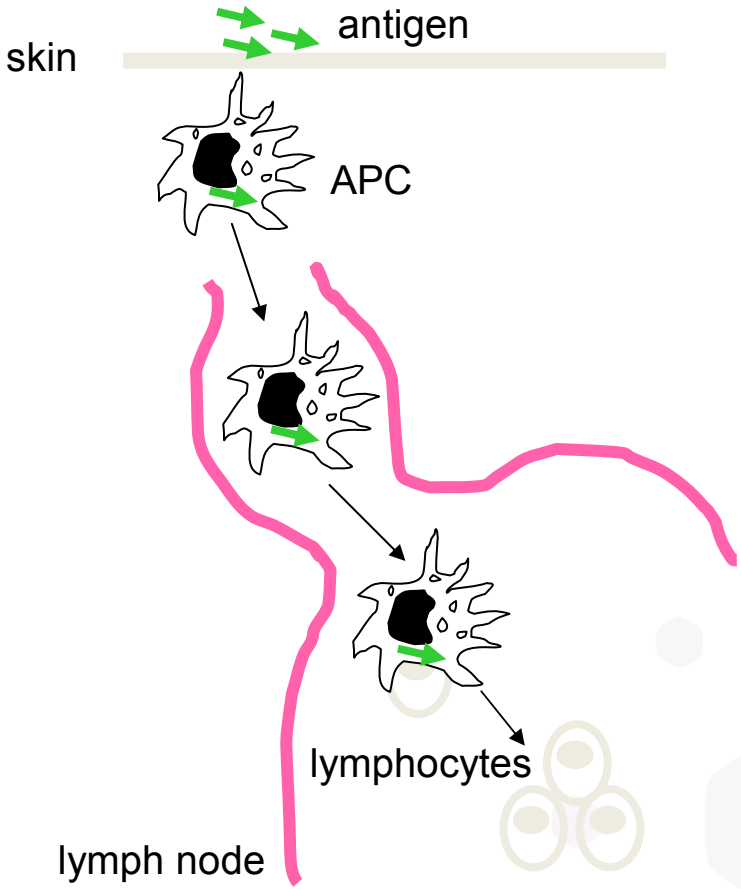
# Types of Vaccine

| **Vaccine** | **Examples** |
|---|---|
| Immunoglobulin (IG) | Varicella Zoster IG<br>Human Normal IG<br>Hep B IG, Tetanus IG |
| Anti-toxins | Diphtheria anti-toxin<br>Botulinum anti-toxin |
| Inactivated/subunit vaccine | Diphtheria/tetanus/acellular pertussis /inactivated polio/*Haemophilus influenzae* b (DTaP/IPV/Hib)<br>Meningococcal C (MenC),<br>Pneumcoccal (PPV & PCV)<br>Human papillomavirus vaccine (HPV)<br>Hepatitis A vaccine (HAV)<br>Hepatitis B vaccine (HBV), |
| Live attenuated | Measles, mumps and rubella (MMR),<br>Yellow fever |

# How vaccines work

- They fool the body into thinking it is infected with a bug so that next time when it sees the real thing it will be ready faster with a more powerful response
- They induce the adaptive system to remember, recognize, and kill baddies-- viruses, bacteria, parasites or cancer cells
- Sometimes they get the body to do something different and better then if it were naturally infected

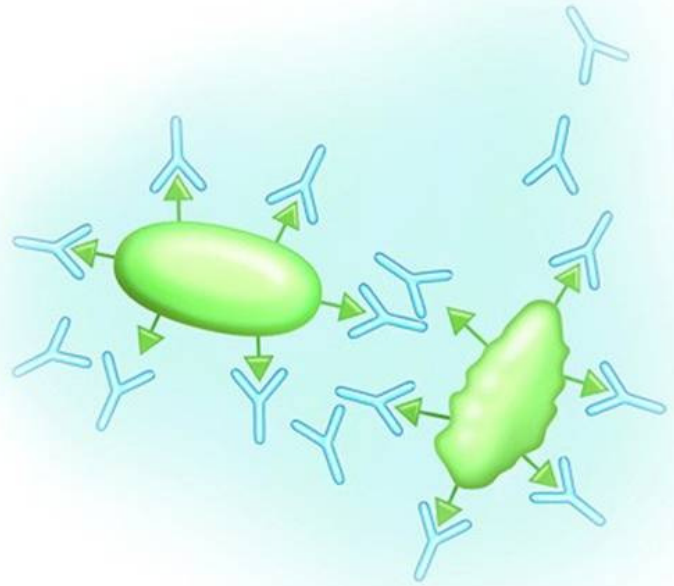
# How Do Vaccines Work?




- Vaccines deliver antigens to the skin or muscle.
  – antigens are fragments of infectious agents
- The antigen is ingested by an *antigen presenting cell* (APC)
- The APC travels to a lymph node where it interacts with lymphocytes.
- Antigen=anti(body) gen(erating)

Image: Sarah Keenihan

# How Do Vaccines Work?



- In the lymph node, specific lymphocytes targeted at the antigen in the vaccine are produced
  - these cells persist as memory cells
- Then if an infection occurs, the memory cells are primed and ready to produce antibodies specific to the antigen.

# Determinants of vaccine response

| Determinants | Mechanisms (presumed) |
|---|---|
| **Vaccine type** | |
| Live vs inactivated | Live vaccines generally induce more sustained Ab responses, presumably through Ag persistence within the host. |
| Polysaccharide antigens | Failure to generate GCs limits the induction of memory responses and of high-affinity long-live plasma cells. |
| **Vaccine schedule** | |
| Interval between primary doses | A minimal interval of 3 weeks between primary doses allows development of successive waves of Ag-specific primary responses without interference. |
| Interval before boosting | A minimal interval of 4 months between priming and boosting allows affinity maturation of memory B cells, and thus higher secondary responses. |
| Age at immunization | Early life immune immaturity and age-associated immunosenescence limit the induction/persistence of long-live plasma cells |
| Environmental factors | ? |

# Determinants of secondary B cell response

| Determinants | Mechanisms (presumed) |
|---|---|
| Post-primary antibody titers | As plasma cells and memory responses are generated in parallel in GCs, higher post-primary Ab titers reflect stronger GC reactions and generally predict higher secondary responses. |
| Residual antibodies at boosting | Neutralization of live viral vaccines; negative feedback mechanisms on non-live vaccines. |
| Lower antigen dose at priming | A limited quantity of antigen may induce B cell differentiation away from PCs, towards memory B cells (?). |
| Longer intervals before boosting | A minimal interval of 4–6 months is required for optimal affinity maturation of memory B cells. |
| Higher antigen dose at boosting | A higher availability of antigen may drive higher numbers of memory B cells into differentiation. |
| **Antigen availability** | |
| Exogenous exposure | Exposure to exogenous antigens may reactivate or favor the persistence of memory B cells. |
| In vivo persistence | Antigen persistence may reactivate or favor the persistence of memory B cells. |

- 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.

- 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

# 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.
- 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__animation

**Antigen presenting cells:**

- Cells that capture antigens by phagocytosis, process them into small peptides, display them at their surface and provide co-stimulation signals that help activate antigen-specifi c T cells. Antigen presenting cells include B cells, macrophages and dendritic cells,

**B lymphocytes:**

- Cells that originate in the bone marrow, mature in secondary lymphoid tissues, become activated in the spleen/nodes when their surface immunoglobulins bind to an antigen and differentiate either in a (plasma cells) or in memory B cells.

**Carrier protein:**

- A protein that is used as a template to which polysaccharide moieties are chemically conjugated to generate glycoconjugate vaccines.

**CD4+ T helper 1 lymphocytes:**

- CD4+ T cells that upon activation differentiate into cells that mainly secrete IL-2, IFN-γ and TNF-β, exerting direct antimicrobial functions (viruses) and providing support to cytotoxic T cells and macrophages.

**CD4+ T helper 2 lymphocytes:**

- CD4+ T cells that upon activation differentiate into cells that mainly secrete IL-4, IL-6, IL-6, IL-10, IL-13, exerting direct antimicrobial functions (parasites) and providing support to B lymphocytes.

**Central memory T cells:**

- Memory T cells trafficking through the lymph nodes, ready to proliferate and generate a high number of effector cells in response to specific microbial peptides.

**Dendritic cells:**

- Cells that constantly sample the surroundings for pathogens, detect dangers and initiate immune responses.
- Contact with a pathogen induces maturation and the expression of certain cell-surface
- molecules, greatly enhancing their ability to activate T cells.

**Effector memory T cells:**

- Memory T cells patrolling through the body to detect specifi c microbial peptides and capable of an immediate cytotoxic function in case of recognition

**Germinal centers:**

- Dynamic structure that develop in spleen/nodes in response to an antigenic stimulation.
- Contain antigen-specifi c B cells that proliferate and differentiate through the support provided by follicular dendritic cells and helper T cells.
- Immunoglobulin class switch recombination, affinity maturation, B cell selection and
- differentiation into plasma cells or memory B cells essentially occur in GCs.

**Regulatory T cells:**

- T cells that upon activation differentiate into cells that express specifi c cytokines (IL-10, TGF-β/surface markers) and act to suppress the activation of the immune system, maintaining tolerance to self antigens.

**T lymphocytes:**

- Cells that originate in the thymus, mature in the periphery, become activated in the spleen/nodes if
  - 1) their T cell receptor bind to an antigen presented by an MHC molecule and
  - 2) they receive additional costimulation signals driving them to acquire killing or supporting functions.

**T-independent B cell responses:**

- Differentiation pathway of B cells, mainly elicited by polysaccharides, that takes place in the spleen/nodes.
- Its hallmarks are to be rapid (days) but to elicit the transient (months) production of antibodies of low affi nity, without inducing immune memory.

**T-dependent B cell responses:**

- Differentiation pathway of B cells elicited by protein antigens that recruits T and B cells into spleen/nodes.
- Its hallmarks are to be slow (weeks) but to elicit long-lasting (years) production of antibodies of high affinity, and immune memory.

**Toll-like receptors:**

- Family of 10 receptors present at the surface of many immune cells.
- Recognize pathogens through conserved microbial patterns and activate innate immunity when detecting danger.