Immunity and How Vaccines Work

Kevin Connolly
Waterford, Aug. 25, 2016
Definitions

**Antibody**: immunoglobulin (Ig) produced mainly by plasma cells, which identifies and neutralises pathogens

**Antigen**: Anti(body) gen(erator): substance that can provoke an immune response

**Epitope**: the specific piece of the antigen to which an antibody binds.

**Humoral**: relating to fluids

**Immunity**: resistance to infection (immunis = exempt, protected)

**Innate** – present from birth
Immune System Overview

- Hematopoietic
- Vasculature
- Lymphatic

(a) Innate defenses
- Surface barriers
  - Skin
  - Mucous membranes
- Internal defenses
  - Phagocytes
  - Fever
  - NK cells
  - Antimicrobial proteins
  - Inflammation

(b) Adaptive defenses
- Humoral immunity
  - B cells
- Cellular immunity
  - T cells
**Innate - Surface Defenses**

**Skin:** physical barrier to microbes
- keratin resistant to bacterial enzymes & toxins
- secretions are acidic

**Mucosa:** physical barrier
- produces a variety of protective chemicals

**Gastric mucosa:** physical barrier
- very acidic & produces proteolytic enzymes

**Saliva, tears**
- contain lysozyme

**Mucous**
- traps, moves bacteria away from epithelial surface
Primary lymphoid organs:

Where lymphocytes destined to become B and T cells mature

**Bone marrow** - B cells mature

**Thymus** - T cells mature, migrate to secondary lymphoid organs
Secondary lymphoid organs: Sites where lymphocytes gather to encounter antigens

Lymph nodes, spleen, tonsils, adenoids, appendix

Situated to allow for initiation of immune response from nearly any place in body
Immune Cells

- Leukocytes (white blood cells)
- Plasma Cells (make and secrete antibodies)
- Macrophages (engulf invading particles)
- Mast Cells (trigger inflammatory response)
Immune Cells

- Leukocytes (white blood cells)
  - Neutrophils (engulfing and inflammation)
  - Basophils (inflammation)
  - Eosinophils (destroy worms; hypersensitivity reactions)
- Plasma Cells (make and secrete antibodies)
- Macrophages (engulf invading particles)
- Mast Cells (trigger inflammatory response)
- Monocytes (engulfing)
- Lymphocytes (specific immune responses)
Immune Cells

- Leukocytes (white blood cells)
- Plasma Cells (make and secrete antibodies)
- Macrophages (engulf invading particles)
- Mast Cells (trigger inflammatory response)

Subtypes:
- Neutrophils (engulfing and inflammation)
- Basophils (inflammation)
- Eosinophils (destroy worms; hypersensitivity reactions)
- Monocytes (engulfing)
- Lymphocytes (specific immune responses)

Subtypes of lymphocytes:
- B cells (recognize foreign antigens; secrete antibodies to guide attack)
- Cytotoxic T Cells (recognize and attack cancerous and infected cells)
- Helper T Cells (help activate B cells and cytotoxic T cells)
- NK Cells (kill cells with guidance from antibodies)
**NK cells**

- Large granular lymphocytes, components of innate immunity
- 10-15% of peripheral blood lymphocytes
- Kill virus-infected and tumor cells
- Secrete cytokines and chemokines CCL3, CCL4 & CCL5

*Fig 2.41 © 2001 Garland Science*
Inflammation

(a) Tissue damage

1. Chemicals such as histamine, kinins, prostaglandins, and leukotrienes (represented as blue dots) are released by damaged cells.

2. Blood clot forms.

3. Abscess starts to form (yellow area).

(b) Vasodilation and increased permeability of blood vessels.

Figure 16.9a, b
Inflammation

(c) Phagocyte migration and phagocytosis

Scab
Blood clot
Regenerated epidermis (parenchyma)
Regenerated dermis (stroma)

(d) Tissue repair

4 Margination—phagocytes stick to endothelium
5 Emigration—phagocytes squeeze between endothelial cells
6 Phagocytosis of invading bacteria

Figure 16.9c, d
Phagocytosis

(a) Phases of phagocytosis

1. Chemotaxis and adherence of microbe to phagocyte.
2. Ingestion of microbe by phagocyte.
3. Formation of a phagosome.
4. Fusion of the phagosome with a lysosome to form a phagolysosome.
5. Digestion of ingested microbe by enzymes.
6. Formation of residual body containing indigestible material.

Figure 16.8a
Innate Immunity: A (Very) Broad Overview
Innate Immunity

Physical barriers
- Skin
- Mucosae
- Physical features
  - Gastric acid, Gut motility, Mucus, Sebum

Cellular responses
- Epithelial cells
  - Cytokine production
  - Reactive oxygen/nitrogen
  - Fluid secretion
- Antigen-presenting cells
  - Kupffer cells
  - Langerhans Cells
  - Dendritic Cells
  - Macrophages
Kupffer cells
Langerhans Cells
Dendritic Cells
Macrophages

Granulocytes

PMNs
Mast Cells
Eosinophils

Lymphocytes

NK cells
NKT cells
Innate Immunity

Cellular responses
- Epithelial cells
  - Cytokine production
  - Reactive oxygen/nitrogen
  - Fluid secretion
- Antigen-presenting cells
  - Kupffer cells

Humoral responses (proteins, etc.)
- Complement
  - Cytokines
  - Fever
  - Malaise
Innate Immunity

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- Humoral responses (proteins, etc.)
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  - Fever
  - Malaise

Adaptive Immunity

- NK cells
- NK T cells
- Lymphocytes

- Mast Cells
- Eosinophils
- PMNs
- Dendritic Cells
- Macrophages
- Kupffer cells
Adaptive Immune System

- Adaptive: responds to specific foreign substances
- **Innate and adaptive mechanisms work together**
Types of Adaptive Immunity

- Naturally acquired
  - Active: Infection; contact with pathogen
  - Passive: Antibodies pass from mother to fetus via placenta; or to infant in her milk

- Artificially acquired
  - Active: Vaccine; dead or attenuated pathogens
  - Passive: Injection of immune serum (gamma globulin)
Adaptive Immunity

Immune system adapts to previously unseen molecules

- Induction by infection, vaccination
- Immune system mounts response

Immune response must:
- Recognise micro-organism as foreign
- Respond by producing specific antibodies, lymphocytes
- Mediate elimination of organisms
<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen recognized by receptors encoded in the germline</td>
<td>Pathogen recognized by receptors generated randomly</td>
</tr>
<tr>
<td>Receptors have broad specificity, i.e., recognize many related molecular structures called PAMPs (pathogen-associated molecular patterns)</td>
<td>Receptors have very narrow specificity; i.e., recognize a particular epitope of antigen</td>
</tr>
<tr>
<td>PAMPs are <strong>polysaccharides</strong> and <strong>polynucleotides</strong> that differ little from one pathogen to another but are not found in the host.</td>
<td>Most epitopes are derived from <strong>polypeptides</strong> (proteins) and are specific to each pathogen</td>
</tr>
<tr>
<td>Receptors are PRRs (<strong>pattern recognition receptors</strong>)</td>
<td>The receptors are B-cell (<strong>BCR</strong>) and T-cell (<strong>TCR</strong>) receptors for antigen</td>
</tr>
<tr>
<td>Immediate response</td>
<td>Slow (3–5 days) response (need clones of responding cells to develop)</td>
</tr>
<tr>
<td>Little or no memory of prior exposure</td>
<td>Memory of prior exposure</td>
</tr>
<tr>
<td>Occurs in all multicellular animals</td>
<td>Occurs in vertebrates only</td>
</tr>
</tbody>
</table>
Active Humoral Immunity

**Naturally acquired**: natural exposure to antigen (i.e. infection)

**Artificially acquired**: vaccines
  - live attenuated, non-live (killed or fragmented pathogen injected to elicit an immune response

Primary response (immunity without disease)
Secondary response (boosters) - intensify response
Specific Memory and Adaptive Response
Adaptive Defenses: Components

**Humoral Immunity:** provided by antibodies in body fluids

**Cell mediated immunity:** lymphocytes directly attack specific invaders by lysis or indirectly by initiating inflammation and activating other lymphocytes and macrophages
Adaptive System: Cells

**Lymphocytes**: initially uncommitted
- **T-cells**: sorted in the Thymus
  - manage the immune response
- **B-cells**: sorted in the marrow

**Antigen Presenting Cells (APCs)**
Functions of $T_H$ Cells

Orchestrate immune response
- Recognize antigen presented by APC
- If $T_H$ cell recognizes antigen, cytokines are delivered
- Cytokines activate APC to destroy antigen

Activate B cell
- If $T_H$ cell encounters B cell bearing antigen
- $T_H$ cell produces cytokines
- Cytokines activate B cell
- B cell proliferates
- Drives formation of B memory cells
Adaptive Humoral Response

**B-cells**: Antigen challenge to naïve B-cell

- Antigen binds to B-cell receptors
- Antigen ingested by B-cell
- B cell presents antigen to T-cell
- B cell produces antibody
Adaptive Immune System: Cells

Antigen Presenting Cells (APCs)

- Macrophages & B lymphocytes
- Ingest foreign material
- Present antigenic fragments on their cell
- Fragments recognised by T-cells.
Innate Immunity can Trigger Adaptive Immunity

• Macrophages and dendritic cells "present" antigens to T cells

• This triggers cell- and humoral-mediated adaptive immune responses

• Interaction of PAMPs and TLRs on dendritic cells → secrete cytokines → production of T cells

• B cells are also antigen-presenting cells

• Pathogens coated with C3 bind more strongly to B cells → antibody production occurs at doses of antigen far lower than would otherwise be needed

Note: Several vaccine adjuvants contain PAMPs → stimulate innate immune system → enhances response of the adaptive immune system to the vaccine
Antigen Presenting Cell

1. A pathogen or extracellular antigen is phagocytized by an antigen-presenting cell (dendritic cell here) and placed into a vesicle. Ingested pathogens are digested by lysosomes to extract their antigens.

2. The antigens bind with MHC proteins that enter the vesicle.

3. The MHC proteins, now carrying antigens, are released from the vesicle and travel to the outer surface of the cell membrane.

4. The dendritic cell is now presenting antigens, which will activate T cells that bind with the MHC proteins.
Innate and Adaptive Immunity Work Together
Immune Responses

Leukocyte stem

Myeloid Stem

Mast Cell
Degranulation
Histamine
Leukotrienes
Inflammation

C4b2a3b
C5b6789
C5b

Angry Mφ

IFN-γ
MIF
LD-CF

Opsonization

Margination & Diapedesis
Phagocytosis
PMN dies after killing many bacteria & exhausting granules

C5a
C3a
C4b2a3b

C3b
C5
C2b
C4a
C1qrs
C1q
C3
C5
C6
C7
C8
C9
C1q

Continued phagocytosis & killing

Continued phagocytosis & killing

Lymphocyte stem

T cell
B cell

Activation
Activation

Opsonization
What is a Vaccine?

• Biological preparation that improves immunity to a particular disease

• Contains antigen(s) that resembles a pathogen

• Stimulates immune system to recognise antigen as foreign, destroy it, and "remember" it

• Pathogens later encountered cause memory response
Live Attenuated Vaccines

- Attenuated "wild" virus or bacterium
- Can replicate – immune response is similar to natural infection
- Usually effective with one dose
- Severe reactions possible
- Can revert to a wild-type pathogen
- Fragile – must be stored carefully
Non-live Vaccines

• No chance of recreating live pathogen
• Less interference from circulating antibody than live vaccines
• Cannot replicate, thus generally not as effective as live vaccines
• Usually require 3-5 doses
• Immune response mostly antibody based
How Vaccines Work
Primary and Memory Response

The diagram illustrates the concentration of antibody over time after antigen injection. It shows two responses:

1. **Primary response**
   - Initial reaction with peak antibody concentration.
   - IgM and IgG antibodies are present.
   - Duration: Days to Months.

2. **Secondary response**
   - Faster and more robust reaction.
   - Higher peak of IgG antibodies.
   - Duration: Days to Months.

The x-axis represents time after antigen injection, and the y-axis represents the concentration of antibody. The graph highlights the differences in antibody response between primary and secondary immune reactions.
### Reported Cases of VPDs, Europe

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<tbody>
<tr>
<td>Diphtheria</td>
<td>608</td>
<td>1,585</td>
<td>33</td>
<td>32</td>
<td>32</td>
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<tr>
<td>Measles</td>
<td>851,849</td>
<td>37,421</td>
<td>37,073</td>
<td>26,982</td>
<td>25,375</td>
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<td>Mumps</td>
<td>No data</td>
<td>243,344</td>
<td>27,448</td>
<td>38,141</td>
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<td>Pertussis</td>
<td>90,546</td>
<td>53,675</td>
<td>34,432</td>
<td>56,941</td>
<td>27,824</td>
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<td>Polio</td>
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<td>Rubella</td>
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<td>621,039</td>
<td>9,672</td>
<td>30,509</td>
<td>39,614</td>
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<tr>
<td>Rubella (CRS)</td>
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<td>48</td>
<td>7</td>
<td>60</td>
<td>50</td>
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<tr>
<td>Tetanus</td>
<td>1,715</td>
<td>412</td>
<td>197</td>
<td>194</td>
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### Vaccines Work-European Data

<table>
<thead>
<tr>
<th>Disease</th>
<th>20th Century Annual Morbidity</th>
<th>Cases reported in 2007</th>
<th>Percent decrease</th>
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<tbody>
<tr>
<td>Small pox</td>
<td>29,005</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Measles</td>
<td>530,217</td>
<td>43</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>800</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>10,454</td>
<td>95%</td>
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<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>0</td>
<td>100%</td>
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<tr>
<td>Rubella</td>
<td>47,745</td>
<td>12</td>
<td>&gt;99%</td>
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<tr>
<td>Cong. Rubella Synd.</td>
<td>152</td>
<td>0</td>
<td>100%</td>
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<tr>
<td>Tetanus</td>
<td>580</td>
<td>28</td>
<td>95%</td>
</tr>
<tr>
<td>Hib</td>
<td>20,000</td>
<td>22</td>
<td>&gt;99%</td>
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</table>
Innate Internal Defenses
Inflammatory Response

**Macrophages** “clean up” pathogens
Activation of the complement cascade occurs and elements of adaptive immunity join the process
Innate Internal Defenses

Antiviral proteins:

**Interferon**: some cells produce & release interferons (IFNs) when invaded by virus
IFNs stimulate nearby cells to produce proteins that interfere with viral replication

**Complement**: plasma proteins activated in the presence of foreign substances
Complement activation:
- enhances and amplifies inflammation
- enhances innate and adaptive defenses
- causes lysis of bacteria
Innate Internal Defenses

Complement activation pathways

*Classical pathway*: requires antibodies
- Antibodies bind to target (antigen)
- Complement protein C1 binds to the antibody-antigen complex (complement fixation)

*Alternative pathway*: complement factors interact with microorganism surface carbohydrates
- Both lead to a cascade of protein activation, leading to activation of C3
Innate Internal Defenses
Inflammatory Response

Phagocyte mobilisation: infiltration of damaged area by neutrophils and macrophages

Leucocytosis: leukocytosis-inducing factors released by injured cells promote rapid release of WBCs from marrow

Margination: increased vascular permeability causes decreased fluid in vessels; blood flow slows, neutrophils clinging to vessel margins
Innate Defenses
Inflammatory Response

**Diapedesis:** neutrophils migrate through capillary walls

**Chemotaxis:** inflammatory chemicals attract neutrophils to move up the chemical concentration gradient

As the process continues, monocytes move into the area and become macrophages.
Innate Defenses

- **Innate defenses**
  - **Surface barriers**
    - Skin
    - Mucous membranes
  - **Internal defenses**
    - Phagocytes
    - Fever
    - NK cells
    - Antimicrobial proteins
    - Inflammation

**Innate**: structural defenses; respond to nonspecific foreign substances

- **First line**: external surface epithelium and membranes
- **Second line**: inflammatory processes – antimicrobial proteins, phagocytes, etc.