Immunity to Microbes
Principles of Vaccination

Rami Sommerstein, MD
Universitätsklinik für Infektiologie
Inselspital
Aims – immunity to microbes

> Understand the responses of the innate, adaptive, humoral and cellular immune system to the major classes of microbes
  — Extracellular bacteria
  — Intracellular bacteria
  — Fungi
  — Viruses
  — Parasites

> Mechanisms of immune evasion by microbes

> Understand key concepts of immunological pathogenicity mediated by microbes
Cellular and Molecular IMMUNOLOGY

Eighth Edition

Abul K. Abbas
Andrew H. Lichtman
Shiv Pillai

Figures from 6th/8th Ed.
Innate and adaptive immunity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>For structures shared by groups of related microbes</td>
<td>For antigens of microbes and for nonmicrobial antigens</td>
</tr>
<tr>
<td>Diversity</td>
<td>Limited; germline-encoded</td>
<td>Very large; receptors are produced by somatic recombination of gene segments</td>
</tr>
<tr>
<td>Memory</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Nonreactivity to self</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular and chemical barriers</td>
<td>Skin, mucosal epithelia; antimicrobial chemicals</td>
<td>Lymphocytes in epithelia; antibodies secreted at epithelial surfaces</td>
</tr>
<tr>
<td>Blood proteins</td>
<td>Complement, others</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Cells</td>
<td>Phagocytes (macrophages, neutrophils), natural killer cells</td>
<td>Lymphocytes</td>
</tr>
</tbody>
</table>
Innate immune response to extracellular bacteria

> **Complement activation** (alternative pathway) through
> - Peptidoglycan in the cell wall of Gram-positive bacteria
> - Lipopolysaccharide in Gram-negative bacteria by
>   - by mannose on bacterial surface

Leads to

> **Opsonization and enhanced phagocytosis**
> **Lysis of susceptible bacteria** by membran attack complex
> **Activation of phagocytes and inflammation**
Alternative pathway

C3 hydrolysis

C3b and C3a fragments

C3b cleaves C5 into C5a and C5b

Cell swells and bursts

C5b, C6, C7, C8 and C9 together form the cylindrical membrane attack complex
Adaptive immune response to extracellular bacteria

Antibody production

CD4 response
Bacterial superantigen may lead to injurious effects of the immune response

**A**
Conventional TCR recognition of peptide-MHC

- APC
- HLA-DR
- Peptide X
- TCR

Peptide-specific T cell (rare)

**Activation of peptide X specific T cell clones only; protective immunity**

**B**
Superantigen binding to Class II MHC and TCR Vβ3

- SEB
- TCR
- Vβ3
- Any peptide

Polyclonal activation of Vβ3+ T cells: cytokine storm and deletion of T cells

Vβ3-expressing T cells (2% of all T cells)
Immune response to intraacellular bacteria

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Examples of Human Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular Bacteria</td>
<td></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Tuberculosis, leprosy</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Listeriosis</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>Legionnaires’ disease</td>
</tr>
</tbody>
</table>
Dynamic of the immune response to intracellular bacteria
Adaptive immune response to intracellular bacteria: CD4+/CD8+ cooperation

**FIGURE 16-5** Cooperation of CD4+ and CD8+ T cells in defense
Cell-mediated immunity to *Listeria monocytogenes*
Granulomatous reaction – pathologic response to persistent intracellular bacteria

> Example *Mycobacterium* spp
> With T-cell help (IFN-gamma) macrophages are activated and have enhanced ability to kill intracellular bacteria
> **Cell wall components inhibit fusion of phagocytic vacuoles with lysosomes**
> Some mycobacteria persist
> Granulomatous reaction: central necrosis, multinucleated giant cells, walled off by lymphocytes contains «latent» infection in 90% of patients
> Genetic polymorphism or any kind of immunosuppression can lead to loss of control either shortly or years after infection
Importance of $T_H^1$ and $T_H^2$ response

- **$T_H^1$ cell**
  - Naive CD4$^+$ T cell
  - IFN-$\gamma$, TNF
  - Inhibits microbicidal function of macrophages
  - Macrophage activation: cell-mediated immunity

- **$T_H^2$ cell**
  - IL-10, IL-4

<table>
<thead>
<tr>
<th>Mycobacterium leprae</th>
<th>Some patients: $T_H^1$</th>
<th>$\Rightarrow$ Tuberculoid leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some patients: Defective $T_H^1$ or dominant $T_H^2$</td>
<td>$\Rightarrow$ Lepromatous leprosy (high bacterial count)</td>
</tr>
</tbody>
</table>


Leprosy
*Mycobacterium leprae*

$T_H1$ Tuberculoid leprosy  $T_H2$ Lepromatous leprosy
# Immune evasion by bacteria (examples)

<table>
<thead>
<tr>
<th>Mechanism of Immune Evasion</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular Bacteria</td>
<td></td>
</tr>
<tr>
<td>Antigenic variation</td>
<td><em>Neisseria gonorrhoeae</em>, <em>Escherichia coli</em>, <em>Salmonella typhimurium</em></td>
</tr>
<tr>
<td>Inhibition of complement activation</td>
<td>Many bacteria</td>
</tr>
<tr>
<td>Resistance to phagocytosis</td>
<td><em>Pneumococcus</em>, <em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td>Scavenging of reactive oxygen species</td>
<td>Catalase-positive staphylococci</td>
</tr>
<tr>
<td>Intracellular Bacteria</td>
<td></td>
</tr>
<tr>
<td>Inhibition of phagolysosome formation</td>
<td><em>Mycobacterium tuberculosis</em>, <em>Legionella pneumophila</em></td>
</tr>
<tr>
<td>Inactivation of reactive oxygen and nitrogen species</td>
<td><em>Mycobacterium leprae</em> (phenolic glycolipid)</td>
</tr>
<tr>
<td>Disruption of phagosome membrane, escape into cytoplasm</td>
<td><em>Listeria monocytogenes</em> (hemolysin protein)</td>
</tr>
</tbody>
</table>
Immune evasion by bacteria (schematic, example *N. gonorrhoeae*)
Immunity to fungi: innate response

- Innate response mainly by phagocytes (neutrophils and macrophages)
- Liberation of radical oxygen species, lysozyme, intracellular digestion

Romani 2011
Adaptive Immunity to fungi

> Adaptive response to fungi
  — Intracellular: mainly CD4/CD8 cooperation (similar as for bacteria); Th1 responses; tendency to chronic granulomatous inflammation
  — Antibodies may exert some protection

> Immune evasion (inhibition of cytokine production in phagocytes)
a) Dendritic cell

MR → DC-SIGN → Langerin → TLR4 → TLR9 → IL-10 → DC

Dectin 2 → Mincle → FcγR

SYK → CARD9 → Dectin 1

Cysteine leukotrienes → RAF → MYD88

- Aspergillus
- Aspergillus fumigatus
- Aspergillus hyphae
- Blastomyces
- Candida yeasts
- Candida hyphae
- Cryptococcus
- Dermatophytes
- Fungal allergens
- Histoplasma
- Malassezia
- Paracoccidioides
- Pneumocystis
- Saccharomyces
- Sporothrix

b) Macrophage

TLR4 → CX3R → CR3

IFN-α/β, IL-12, IL-1β, IL-6

Type I IFN → NF-κB

IL-10, IL-12, IL-23, IL-22

Cytokines

- IL-1β, IL-6
- IL-10
- TGFβ

T-cell subtypes
- T helper 1 (Th1)
- T helper 2 (Th2)
- T regulatory (Treg)

Promotion of fungal clearance and inflammation
Recruitment of neutrophils and inflammasome
Inhibition of fungal clearance and allergy
Limited pathology and immunosuppression

Promotion of fungal clearance and inflammation
Recruitment of neutrophils and inflammasome
Inhibition of fungal clearance and allergy
Limited pathology and immunosuppression

IL-25, CCL11, IL-10, IL-6

c) Epithelial cell

Canonical and non-canonical NF-κB

IL-25, CCL11, IL-10, IL-6

Romani 2011
Innate and adaptive immune responses against viruses
Innate immune responses against viruses

**FIGURE 4-16** Mechanisms of induction of type I interferons by viruses. Viral nucleic acids and proteins are recognized by several cellular receptor families (TLRs, the family of cytosolic RIG-like receptors, or RLRs, which include MDA-5, RIG-I, DAI and others, and cytosolic DNA sensors), which activate transcription factors (the IRF proteins) that stimulate the production of type I interferons IFN-α and IFN-β.
### Viral immune evasion: overview

<table>
<thead>
<tr>
<th>Mechanism of immune evasion</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Antigenic variation</td>
<td>Influenza, rhinovirus, HIV</td>
</tr>
<tr>
<td>Inhibition of antigen processing</td>
<td></td>
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<tr>
<td>Blockade of TAP transporter</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Removal of class I molecules from the ER</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Production of cytokine receptor homologs</td>
<td>Vaccinia, poxviruses (IL-1, IFN-γ)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (chemokine)</td>
</tr>
<tr>
<td>Production of immunosuppressive cytokine</td>
<td>Epstein-Barr virus (IL-10)</td>
</tr>
<tr>
<td>Infection of immunocompetent cells</td>
<td>HIV</td>
</tr>
</tbody>
</table>

**Abbreviations:** ER, endoplasmic reticulum; HIV, human immunodeficiency virus; TAP, transporter associated with antigen processing.
Evasion from immune response: Inhibition of antigen processing by viruses

- Inhibition of proteasomal activity: EBV, human CMV
- Block in MHC synthesis and/or ER retention: adenovirus, human CMV
- Block in TAP transport: HSV
- Removal of class I from ER: CMV
- Interference with CTL recognition by "decoy" viral class I-like molecules: murine CMV
Evasion from immune response: Glycan Shield

Sommerstein et al PLoS Pathogen 2015
Interferon-driven deletion of antiviral B cells at the onset of chronic infection


IFN-I–induced short-lived plasmablast differentiation in viral infection (d3 after adaptive B-cell transfer and iv LCMV)
## Immune response to protozan parasites

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Diseases</th>
<th>Principal mechanisms of protective immunity</th>
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</thead>
<tbody>
<tr>
<td><strong>Protozoa</strong></td>
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<tr>
<td><em>Plasmodium species</em></td>
<td>Malaria</td>
<td>Antibodies and CD8$^+$ CTLs</td>
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<tr>
<td><em>Leishmania donovani</em></td>
<td>Leishmaniasis (mucocutaneous, disseminated)</td>
<td>CD4$^+$ TH1 cells activate macrophages to kill phagocytosed parasites</td>
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<tr>
<td><em>Trypanosoma brucei</em></td>
<td>African trypanosomiasis</td>
<td>Antibodies</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>Amebiasis</td>
<td>Antibodies, phagocytosis</td>
</tr>
<tr>
<td><strong>Metazoa</strong></td>
<td></td>
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<tr>
<td><em>Schistosoma species</em></td>
<td>Schistosomiasis</td>
<td>ADCC mediated by eosinophils, macrophages</td>
</tr>
<tr>
<td><em>Filaria, e.g., Wuchereria bancrofti</em></td>
<td>Filariasis</td>
<td>Cell-mediated immunity; role of antibodies?</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADCC, antibody-dependent cell-mediated cytotoxicity; CTLs, cytotoxic T lymphocytes.

![TH1](TH1.png)  
![TH2](TH2.png)
Helminth infection induces T$_H$2 response

Helminths to big for «normal» immune response (phagocytosis, CTL)

But basic protein of eosinophils can destroy helminths and mast cell mediators lead to expulsion of helminths
**T_{H2} effector functions**

**FIGURE 13-13 Effector functions of T_{H2} cells.** CD4^{+} T cells that differentiate into T_{H2} cells secrete IL-4 and IL-5. IL-4 acts on B cells to stimulate production of antibodies that bind to mast cells, such as IgE. IL-4 is also an autocrine growth and differentiation cytokine for T_{H2} cells. IL-5 activates eosinophils, a response that is important for defense against helminthic infections. Cytokines from T_{H2} cells also inhibit macrophage activation and T_{H1}-mediated reactions. APC, antigen-presenting cell.
# Immune evasion by parasites

<table>
<thead>
<tr>
<th>Mechanism of Immune Evasion</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenic variation</td>
<td>Trypanosomes, <em>Plasmodium</em></td>
</tr>
<tr>
<td>Acquired resistance to complement, CTLs</td>
<td>Schistosomes</td>
</tr>
<tr>
<td>Inhibition of host immune responses</td>
<td>Filaria (secondary to lymphatic obstruction), trypanosomes</td>
</tr>
<tr>
<td>Antigen shedding</td>
<td>Entamoeba</td>
</tr>
</tbody>
</table>

*CTL,* cytotoxic T lymphocyte.
Immunological pathogenicity mediated by microbes

> Direct killing of host cells infected
> Killing or functional impairment of host cells by toxins
  — Endotoxins: liberated by lysis of the microbe, component of cell envelope or cytoplasm
  — Exotoxins: secreted
> By stimulating immune responses damaging infected and uninfected (innocent bystander) host cells
> Immunological sequelae: molecular mimicry, immune complexes…
<table>
<thead>
<tr>
<th>Microbe</th>
<th>Examples of Human Diseases</th>
<th>Mechanisms of Pathogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular Bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Skin and soft-tissue infections, lung abscess</td>
<td>Skin infections: acute inflammation induced by toxins; cell death caused by pore-forming</td>
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<tr>
<td></td>
<td>Systemic: toxic shock syndrome, food poisoning</td>
<td>toxins</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Pharyngitis</td>
<td>Acute inflammation induced by various toxins (e.g., streptolysin O damages cell membranes)</td>
</tr>
<tr>
<td>(group A)</td>
<td>Skin infections: impetigo, erysipelas; cellulitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic: scarlet fever</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Pneumonia, meningitis</td>
<td>Acute inflammation induced by cell wall constituents; pneumolysin is similar to streptolysin O</td>
</tr>
<tr>
<td>(pneumococcus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Urinary tract infections, gastroenteritis, septic shock</td>
<td>Toxins act on intestinal epithelium chloride and water secretion; endotoxin (LPS) stimulates cytokine secretion by macrophages</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Diarrhea (cholera)</td>
<td>Cholera toxin ADP ribosylates G protein subunit, which leads to increased cyclic AMP in intestinal epithelial cells and results in chloride secretion and water loss</td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td>Tetanus</td>
<td>Tetanus toxin binds to the motor end plate at neuromuscular junctions and causes irreversible muscle contraction</td>
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<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Meningitis</td>
<td>Acute inflammation and systemic disease caused by potent endotoxin</td>
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<tr>
<td>(meningococcus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Diphtheria</td>
<td>Diphtheria toxin ADP-ribosylates elongation factor 2 and inhibits protein synthesis</td>
</tr>
<tr>
<td>Intracellular Bacteria</td>
<td></td>
<td>Macrophage activation resulting in granulomatous inflammation and tissue destruction</td>
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<tr>
<td>-----------------------------------------------</td>
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<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><em>Mycobacteria</em></td>
<td>Tuberculosis, leprosy</td>
<td>Listeriolysin damages cell membranes</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Listeriosis</td>
<td></td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Legionnaires’ disease</td>
<td>Cytotoxin lyzes cells and causes lung injury and inflammation</td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Candidiasis</td>
<td>Acute inflammation; binds complement proteins</td>
</tr>
<tr>
<td><em>Aspergillus fumigatus</em></td>
<td>Aspergillosis</td>
<td>Invasion and thrombosis of blood vessels causing ischemic necrosis and cell injury</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>Histoplasmosis</td>
<td>Lung infection caused by granulomatous inflammation</td>
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<tr>
<td>Viruses</td>
<td>Poliomyelitis</td>
<td>Inhibits host cell protein synthesis (tropism for motor neurons in the anterior horn of the spinal cord)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Polio</td>
<td>Poliomyelitis</td>
<td>Inhibits host cell protein synthesis (tropism for motor neurons in the anterior horn of the spinal cord)</td>
</tr>
<tr>
<td>Influenza</td>
<td>Influenza pneumonia</td>
<td>Inhibits host cell protein synthesis (tropism for ciliated epithelium)</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies encephalitis</td>
<td>Inhibits host cell protein synthesis (tropism for peripheral nerves)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Various herpes infections (skin, systemic)</td>
<td>Inhibits host cell protein synthesis; functional impairment of immune cells</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Viral hepatitis</td>
<td>Host CTL response to infected hepatocytes</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Infectious mononucleosis; B cell proliferation, lymphomas</td>
<td>Acute infection: cell lysis (tropism for B lymphocytes)</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>Acquired immunodeficiency syndrome (AIDS)</td>
<td>Multiple: killing of CD4$^+$ T cells, functional impairment of immune cells (see Chapter 20)</td>
</tr>
</tbody>
</table>
Aims – Principles of Vaccination

Introduction

The federal vaccine program

Types of vaccines currently in use, including their advantages and disadvantages

The impact of the route of administration of a vaccine

Important effectors of vaccine response

Importance of adjuvant / examples

Introduction to the term „herd immunity“

„New“ vaccines
Introduction to vaccines

- Continuous race between host and pathogen
- For exclusive human pathogens: important co-evolution
- Different pathogens – different strategies
- Co-existence may be desired or not
- Vaccine efforts exert evolutionary pressure
Introduction to vaccines

> 1796: First vaccination by Jenner
Basic principle of vaccination

- **Active**: expose individual with attenuated, killed or split organisms that leads to the development of an immune response without the risk of (severe) disease  
  vs.
- **Passive**: adoptive transfer of specific effector mechanisms from other, previously actively immunized individuals
## Federal vaccine program

### Tabelle 1

**Empfohlene Basisimpfungen 2016**  
Stand 2016  
Empfehlungen der Eidgenössischen Kommission für Impffragen und des Bundesamtes für Gesundheit

<table>
<thead>
<tr>
<th>Alter 1)</th>
<th>Diphtherie (D / d) 3)</th>
<th>Tetanus (T) 4)</th>
<th>Pertussis (Pₐ / Pₐ) 3)</th>
<th>Haemophilus influenzae Typ b (Hib)</th>
<th>Poliomyelitis (IPV)</th>
<th>Masern (M) Mumps (M) Röteln (R)</th>
<th>Hepatitis B (HBV) 17)</th>
<th>Varizellen (VZV)</th>
<th>Humane Papillomaviren (HPV)</th>
<th>Influenza</th>
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<td>IPV</td>
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<td>4–7 Jahre</td>
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<td>≥ 65 Jahre</td>
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1) 2) 3) 4) 5) 6) 7) 8) 9) 10) 11) 12) 13) 14) 15) 16) 17) 18) 19) 20) 21) 22) 23) 24)
### Additional vaccines for special indications:
- **Travel**: Yellow fever, Japanese encephalitis, etc..
- **Special exposures**: FSME, Rabies, etc..
- **Patients at risk**: Influenza
„THE GOOD OLD DAYS…“ some examples

<table>
<thead>
<tr>
<th>Disease</th>
<th>Morbidity/Mortality per year in CH</th>
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<tr>
<td></td>
<td>without vaccine</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>4'000 cases</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>800 cases</td>
</tr>
<tr>
<td>Invasive <em>H. influenzae</em> type b</td>
<td>180 cases</td>
</tr>
<tr>
<td>Tetanus</td>
<td>50 cases</td>
</tr>
<tr>
<td>Congenital Rubella</td>
<td>30-50 cases</td>
</tr>
<tr>
<td>Pertussis</td>
<td>140 deaths</td>
</tr>
</tbody>
</table>

GOALS OF A VACCINE

Protect individual: infection
(disease)
(clear disease)

By mimicking infection in terms of long lasting immune response without doing harm

“Optional”: Give indirect protection (herd immunity)
Support global eradication of pathogen
Types of vaccines

Passive: antibodies

Active: live, attenuated

Active: inactivated

Active: component

Newer technologies

- Recombinant (e.g. VSV-ZEBOV)

- Vector based (e.g. lactobacilli)

DNA vaccines
# Types of vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive (antibodies)</td>
<td>Rapid protection</td>
<td>Short duration</td>
</tr>
<tr>
<td></td>
<td>Minimal side effects</td>
<td>No memory</td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole cell/virus</td>
<td>Variety of antigens</td>
<td>Side effects</td>
</tr>
<tr>
<td>Live, attenuated</td>
<td>Replicates: antigen↑</td>
<td>May cause disease</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Does not replicate</td>
<td>pot. less immunogenic</td>
</tr>
<tr>
<td>Component</td>
<td>Target antigen known</td>
<td>Restricted immune response to target antigen</td>
</tr>
</tbody>
</table>
# Passive immunisation

<table>
<thead>
<tr>
<th>Infection or disease</th>
<th>Evidence of effects of passive antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial toxins</strong></td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>Passive antibodies and maternal immunization are highly effective; can also provide post-exposure prophylaxis in nonimmune individuals</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Passive antibodies prevent intoxication; effects on infection are unknown</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Maternal antibodies are effective if present in high titer; passive antibodies have been used as therapy, resulting in decreased pathology</td>
</tr>
<tr>
<td><strong>Encapsulated bacteria</strong></td>
<td></td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>In high-risk infants, BPIG given at 2, 6 and 10 months of age provides significant protection from invasive infection during infancy</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>Passive immunoglobulin can prevent disease and transmission to susceptible contacts</td>
</tr>
<tr>
<td>Rabies</td>
<td>Human rabies immunoglobulin is used in conjunction with vaccine to neutralize virus at site of entry and prevent its spread to CNS</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Passive immunoglobulin prevents spread of smallpox to contacts; treatment of vaccine complications</td>
</tr>
<tr>
<td><strong>Hepatitis A</strong></td>
<td>Vaccine shows 85–90% efficacy in high-risk individuals; also used as post-exposure prophylaxis</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>HBIG shows 80–90% efficacy in high-risk liver transplant to prevent recurrence of infection</td>
</tr>
<tr>
<td>RSV</td>
<td>Humanized monoclonal antibody (palivizumab) shows 55% efficacy in preventing hospitalization in high-risk infants</td>
</tr>
</tbody>
</table>

**BPIG**, bacterial polysaccharide immunoglobulin; **CNS**, central nervous system; **HBIG**, hepatitis B immunoglobulin; **RSV**, respiratory syncytial virus; **VZIG**, varicella zoster immunoglobulin.
Route of administration

Parenteral:
- Intradermal
- Subcutaneous
- Intramuscular

Mucosal:
- Ingestion
- Aerosol
# Poliomyelitis vaccines: oral-live vs. parenteral inactivated

<table>
<thead>
<tr>
<th>Whole virus</th>
<th>Inactivated</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum antibody titres</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Duration of protection</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal viral excretion</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Prevent intestinal infection</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Spread of vaccine virus</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Vaccine disease</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Interference with other enteroviral infection in the intestine</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Immunologic interactions in successful Vaccines

Adaptive B cell

Innate

Adaptive T Help

Pollard et al 2009
Vaccines against bacterial polysaccharides

*Streptococcus, pneumoniae, Haemophilus influenzae, Neisseria meningitidis*

**UN-conjugated**

**Vs**

**conjugated**

Pollard et al 2009
Primary immune response to vaccines

What have we learned (in retrospect)

- Early protection: antibody-dependent
- Quality (e.g. avidity) → efficacy
- Mucosal vaccines: IgA response
- Duration: B-cell memory persis. Ab prod. (early response)
- T-cell response: important less well described
- Complicating: antigenic variation strain diversity influence of age

Boosting, affinity maturation

→ favors short term response
Rapid vaccine schedules
(several, closely spaced doses)

→ support immune memory
Lower antigen dose
Antigen persistence? (animal models)
“Nature of antigen”
Booster dose

Adjuvant

Goal: enhance Ab affinity maturation process

mostly by enhancing innate response

specially important for inactivated and component vaccines

Adjuvant: Aluminium salt

Experimental
- CpG oligos
- (mod.) *E. coli* heat labile toxin

Importance of early response: depends on infectious agent etc.

Example:
**Tetanus-Toxin (TeNT)**

Neutralization before up-take into neuron !!

Example:
**Hepatitis B virus**

Memory → long lived protection
= anti-HBs Ag titer ever >100 U/L

Incubation period 4-12 wks
Time to recruit memory cells

Role of T-cell response??

---

Passive/active immunisation after exposure?

Need to know natural history of infection
Often narrow time window (48-72-96h after first exposure)

Example: Varizella-Zoster virus:
Can vaccine protection be measured in the individuum?

**Importance:** Surrogate for clinical efficacy studies
Document individual protection for high risk situations

**Measurement of antibody titres in serum:**
- Threshold defined for relatively few vaccines, examples:
  - Hepatitis B
  - Tetanus toxin
  - FSME
  - Rabies
  - etc.

  - Cannot extrapolate to wild-type infection (e.g. measles)
  - Quantity ≠ quality (e.g. avidity of antibodies, route of administration)

**Surrogate:** Vaccine record!! (= empiric), e.g. 2 doses MMR vaccine
Antigen variation / strain diversity

Example: influenza virus / vaccine

- Hämagglutinin (H, n=15)
- Neuraminidase (N, n=9)

RNA, segmented → AG drift / shift

Seasonal vaccines
- Four strains
- Yearly up-date (WHO)

“Pandemic vaccine”

H5N1 vaccine: conserved epitope crossreactive?

Reverse genetics for new strains??

Get away from egg embryos?
Antigenic sin

Vaccine efficacy might be modulated by prior vaccination

“Original antigenic sin”

Cross-reactive epitopes preferentially reactivate high-affinity memory B-cells rather than lower affinity naive B-cells.

Individuals exposed 50 yrs earlier to H1N1 Influenza virus strain respond differently to a new H1N1 vaccine strain than adults that had never been exposed to H1N1

Herd immunity
= indirect protection of susceptibles by reduced circulation of pathogen

Conjugated pneumococcal polysaccharide vaccines
→ Reduce colonisation
→ Reduce transmission

Vaccine was given to <2 yrs old!!

Kyaw MH et al. NEJM 2006;354:1455.
Vaccination at the extremes of age

Newborns to 1 year of life

Immature immune system

*Poor response to T-cell indep. ag*
- IgM to IgG2 switch ↓
- Complement-mediated reaction ↓
- Splenic marginal zone organ ↓

*Response to T-cell dep. ag* ↓
- IFN-γ by CD4+T<sub>H</sub>1 cells ↓

Inhibiting maternal antibodies

*Affects B-cell response - mechanisms?*
- Inhibition of live virus vaccines
- FcR mediated inhibition of B-cell activation

- Specific epitope neutralization/competition with antigen specific B-cell receptors → ratio maternal ab : vaccine antigen (impact of adolescent immunization?)

Siegrist CA. Vaccine 2003;21:3406
Vaccination at the extremes of age

Elderly: impaired immune response – very late in life
Not well investigated

Not all vaccines are equally affected by immune senescence:
- Pneumococcal polysaccharid vaccine: +++
- Tetanus-Toxoid booster: (+)

Immunology:
- Rapid waning of antibody response
- Relativ restriction of T-cell repertoire
Evidence for the importance of T-cell response for vaccine immunity

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Negligible antibody response; protection is lost if CD4 T-cell deficiency; <em>in vitro</em> <em>M. tuberculosis</em> 'clearing' from infected cells</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Persistence of protective efficacy after antibody decline</td>
</tr>
<tr>
<td>Measles</td>
<td>Reduced disease severity in absence of detectable antibody response</td>
</tr>
<tr>
<td>Influenza</td>
<td>Some protection against cross-reactive A strains in absence of protective levels of antibody</td>
</tr>
</tbody>
</table>
DNA vaccines

Vaccine =
- naked DNA on plasmid with strong promoter
- Enters cell nucleus → antigen production

Current problems
- Limited immunogenicity
- Various strategies for enhancement proposed


http://www.brookscole.com/
The future: Viral vector vaccines?
-> Example rLCMV

Principle:
- commensal / «attenuated» pathogen*
- biological property of interest:
  e.g. compartmentalization to intestinal mucosa)
- genetic engeneering: vaccine antigen(s)

Pinschewer et al, SMW 2017
The future: Viral vector vaccines?
-> Example rLCMV