B cells
develop in the bone marrow
range from 2,000 to 5,000/ml in blood, but only ~5% of B cells are in the blood - rest in secondary lymphoid tissues

each B cell deploys a receptor (Ab) with a unique specificity

antibody repertoire is highly diverse
Chromosomal Organization of the Immunoglobulin Heavy & Light Chain Gene segments

**Heavy Chain**

- V region genes: 38-46
- D region genes: 23
- J region genes: 6
- Constant region genes: μ, δ, γ³, γ¹, α¹, γ², γ⁴, ε, α²

**Light Chain**

- V region genes: 34-38
- J region genes: 5
- Ck
heavy chain genes rearranged first followed by the light chain genes
<table>
<thead>
<tr>
<th></th>
<th>Ig</th>
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<tbody>
<tr>
<td></td>
<td>H</td>
</tr>
<tr>
<td>V segments</td>
<td>~40</td>
</tr>
<tr>
<td>D segments</td>
<td>23</td>
</tr>
<tr>
<td>J segments</td>
<td>6</td>
</tr>
<tr>
<td>base-line combinatorial</td>
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</tr>
<tr>
<td>diversity</td>
<td>1.9 x 10^6</td>
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<tr>
<td>estimated junctional</td>
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</tr>
<tr>
<td>diversity</td>
<td>~3 x 10^7</td>
</tr>
<tr>
<td>total diversity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>~5 x 10^{13}</td>
</tr>
<tr>
<td></td>
<td>50 trillion</td>
</tr>
</tbody>
</table>
• The majority of naive B cells are positioned inside B cell-rich follicles.
• After exposure to their antigen, antigen-specific B cells form microenvironments within follicles called germinal centers.
B cells undergo clonal selection by antigen

antigen selects for the antigen-specific B cells with the highest affinity antibody receptor

- follicle
- T cell rich zone
- germinal
- short-lived antibody-secreting cells
- memory cells
- long-lived plasma cells
Questions?
The titer of antigen-specific IgG increases after the first vaccination, reaching a peak after a lag period. The IgG half-life is 21 days.
The graph shows the titer of antigen-specific Ig over time.

- **1° vaccination**:
  - Lag period

- **IgG**: Increase in IgG after 1° vaccination

- **2° (booster) vaccination**:
  - Activate memory B cells
The graph illustrates the antibody response over time, with the primary antibody response (primary antibody response) and the secondary (anamnestic) antibody response.

- **Primary Antibody Response**: Following the first (1st) vaccination, there is a lag period before the IgG levels start to increase. The IgG levels rise significantly, reaching a peak at around 8-10 weeks post-vaccination.

- **Secondary Antibody Response**: After a few weeks, the secondary (anamnestic) antibody response begins. This response is characterized by a more rapid increase in IgG levels compared to the primary response, with a noticeable rise beginning around 2 weeks post-vaccination.
Increase in Ig concentration
Shortened lag period
Increase in mean affinity
antibody levels maintained by long-lived plasma cells
antibody levels maintained by long-lived plasma cells
Germinal Center
microanatomical niche where:
• antigen-specific B cells proliferate
• class switching
• somatic hypermutation
• selection leading to affinity maturation
• generation of Ig-producing plasma cells
• generation of memory cells

activated B cells
\[ T_{FH} \]
Ag-bearing FDC
macrophages
B cells are capable of recognizing and responding to soluble antigen.

However, cell-bound antigen represents a much more efficient, sensitive and effective trigger of B cell activation.

Evidence suggests that the predominant form of antigen that mediates B cell activation in follicles is bound to the surface of follicular dendritic cells (FDC).

Antigen attaches to FDC via opsonization with complement and Ig.
Cellular interactions in the GC

- FDC
- CR1
- CR2
- Ag
- BCR
- CD21(CR2)
- CD19
- CD88
- pMHCII
- CD40
- FcyRIIB

B cell
Real-time imaging of antigen capture by cognate B cells from FDCs

Two time-lapse movies of 20-µm z projection from inguinal LN explants showing acquisition of HEL-PE (red) by CFSE-labeled MD4 B cells from FDC processes.
Cellular interactions in the GC

- **TCR/CD3**
- **CD40L**
- **pMHCII**
- **T<sub>FH</sub>**
- **B cell**

**B cell**
- **FcγRIIB**
- **CR1**
- **CR2**
- **CD21**
- **CD19**
- **CD88**
- **BCR**

**T<sub>FH</sub>**
- **CD40**
- **CD40L**
- **TCR/CD3**

Cytokines that drive differentiation and proliferation
Germinal Centers & Antibody Production

GC - site of:
• antigen-specific B cell proliferation
• somatic hypermutation
• class switching
• selection mutants with enhanced affinity
high affinity antigen-specific memory B cell with surface IgG, IgA or IgE

long-lived plasma cells secrete large amounts of high affinity antigen-specific IgM, IgG, IgA or IgE

maintained long-term in the bone marrow or niches in the secondary lymphoid tissues

Ag-based selection for high affinity BCRs

proliferation

class switching

mutation of BCR

apoptosis
Short-lived Plasma Cell

heterochromatin forms a characteristic ‘cartwheel’ structure

~2,000 lgs/second

anti-Ig

anti-Ig
Long-lived plasma cells reside mainly in specialized niches in the bone marrow, secondary lymphoid organs and mucosa-associated tissues where they can live for decades.

doi: 10.1038/nri3795.
Why is Ab memory long-lasting for some antigens ($T^{1/2} > 200$ yrs for smallpox, polio, measles, rubella) and short-term for others ($T^{1/2} \sim 11$ yrs for tetanus, days to weeks for malaria vaccine antigens)?

The Enigmatic Nature of B cell Memory
Questions?
Immunization
Preventive vaccines
- prevent serious disease in individuals & epidemics in populations

Therapeutic vaccines
Immunomodulatory vaccines
<table>
<thead>
<tr>
<th>Established Vaccines</th>
<th>Experimental Vaccines</th>
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<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td><strong>Viral</strong></td>
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<tr>
<td>Cholera</td>
<td>Adenovirus-based</td>
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<tr>
<td>Diphtheria</td>
<td>Diseases</td>
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<tr>
<td><em>Haemophilus influenza</em></td>
<td>Hepatitis A</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>Hepatitis B</td>
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<tr>
<td>Plague</td>
<td>Human papillomavirus</td>
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<tr>
<td>Pneumococcal pneumonia</td>
<td>Influenza</td>
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<td>Tetanus</td>
<td>Japanese encephalitis</td>
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<tr>
<td>Tuberculosis</td>
<td>Measles</td>
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<td>Typhoid fever</td>
<td>Mumps</td>
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<td>Polio</td>
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<td>Rabies</td>
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<td>Rotavirus diarrhea</td>
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<td>Rubella</td>
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<td>Smallpox</td>
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<td></td>
<td>Tick-borne encephalitis</td>
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<td></td>
<td>Varicella zoster</td>
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<td>Yellow fever</td>
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- live attenuated vaccines

<table>
<thead>
<tr>
<th>Disease</th>
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<tbody>
<tr>
<td>Campylobacter</td>
<td>Enterovirus</td>
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<tr>
<td>Chlamydia</td>
<td>SARS cronovirus</td>
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<tr>
<td>Cytomegalovirus</td>
<td>Nipha virus</td>
</tr>
<tr>
<td>Dengue</td>
<td>Hendra virus</td>
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<tr>
<td>Epstein-Barr (mononucleosis)</td>
<td>Lasa fever</td>
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<tr>
<td><em>Helicobacter pylori</em>: Gastrointestinal ulcers</td>
<td>Hantavirus</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>Marburg virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Rift Valley Fever virus</td>
</tr>
<tr>
<td>Influenza (universal flu vaccine to replace need for annual flu vaccine)</td>
<td>Ebola</td>
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<tr>
<td>Leishmaniasis</td>
<td>Chikungunya virus</td>
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<tr>
<td>Malaria</td>
<td>Ebola</td>
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<tr>
<td>Respiratory syncytial virus</td>
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<td>Rhinovirus</td>
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<td>Schistosomiasis</td>
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<td>Shigella</td>
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<tr>
<td>Streptococcus groups A and B</td>
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<tr>
<td>Tuberculosis</td>
<td></td>
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<tr>
<td>Urinary tract infections</td>
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<tr>
<td>Other: Allergies, Autoimmune diseases, Cancers*</td>
<td></td>
</tr>
</tbody>
</table>
**Vaccine Approaches - Modes of Action**

- **Live-attenuated**
  - PAMPs
  - B cell
  - CD8
  - CD4
  - Vaccine-Induced
    - effector and memory CD4
    - effector and memory CD8
    - high affinity IgG/IgA
    - B cell memory

- **killed**
  - PAMPs
  - B cell
  - CD4
  - Vaccine-Induced
    - effector and memory CD4
    - high affinity IgG/IgA
    - B cell memory

- **subunit**
  - protein
  - VLP
  - B cell
  - CD4
  - Vaccine-Induced
    - effector and memory CD4
    - high affinity IgG/IgA
    - B cell memory

- **polysaccharide**
  - B cell
  - Vaccine-Induced
    - low affinity IgM
    - no B cell memory
Adjuvant

Adjuvants are compounds that increase and modulate the intrinsic immunogenicity of an antigen through activation of the innate immune response (TLR, NOD, NLR).

Why use an Adjuvant?

Increase the magnitude of an adaptive immune response

- Increase % seroconversion
  - boosts responses that can be blunted due to age, disease, therapeutic intervention, etc.
- Increase the titer in general population
- Permit smaller doses of vaccine
- Permit fewer doses of vaccine

Influence qualitative nature of adaptive immune response

- Provide functionally appropriate T cell responses
- Enhance memory
- Increase speed of initial response
- Alter scope, specificity and affinity
Aluminum Salts

- the major adjuvant for all human vaccines
- aluminum hydroxide and magnesium hydroxide have replaced alum
- recently discovered that aluminum salts have their action by activating the NLRP3 inflammasome

<table>
<thead>
<tr>
<th>common name</th>
<th>chemical formula</th>
<th>chemical name</th>
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</thead>
<tbody>
<tr>
<td>Alum</td>
<td>AlK(SO$_4$)$_2$</td>
<td>aluminum potassium sulphate</td>
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<tr>
<td>Alhydorgel</td>
<td>Al(OH)$_3$</td>
<td>aluminum hydroxide</td>
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<tr>
<td>Adju-Phos</td>
<td>Al(PO$_4$)$_3$</td>
<td>aluminum phosphate</td>
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<tr>
<td>Imject Alu</td>
<td>Al(OH)$_3$ and Mg(OH)$_2$</td>
<td>aluminum hydroxide and magnesium hydroxide</td>
</tr>
</tbody>
</table>
VPL of HPV types 16 and 18

- AS04 (monophosphoryl lipid A + alum)
- TLR-4
- NLRP3
- 3 doses
- induce protection against cervical intraepithelial neoplasia in young women who are seronegative at baseline

one month after last dose, Cervarix has ~4-fold more neutralizing antibodies than Gardasil and a better memory B cell response

VPL of HPV types 16 and 18

- NLRP3
- alum only
- 3 doses
- induce protection against cervical intraepithelial neoplasia in young women who are seronegative at baseline
Questions?
Immunization, Herd Immunity & Public Health
### Recommended Immunization Schedule for US

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
<th>7-10 yrs</th>
<th>11-12 yrs</th>
<th>13-15 yrs</th>
<th>16 yrs</th>
<th>17-18 yrs</th>
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</thead>
<tbody>
<tr>
<td>Hepatitis B (HepB)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>3rd dose</td>
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<tr>
<td>Rotavirus (RV) (2-dose series)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>3rd dose</td>
<td>4th dose</td>
<td>5th dose</td>
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<tr>
<td>Diphtheria, tetanus, &amp; acellular pertussis (DTaP)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>3rd dose</td>
<td>4th dose</td>
<td>5th dose</td>
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<tr>
<td>Haemophilus influenza type b (Hib)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>3rd dose</td>
<td>4th dose</td>
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<tr>
<td>Pneumococcal conjugate (PCV13)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>3rd dose</td>
<td>4th dose</td>
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<tr>
<td>Inactivated poliovirus (IPV)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>3rd dose</td>
<td>4th dose</td>
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<tr>
<td>Influenza (IV)</td>
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<td></td>
<td>Annual vaccination (IV) 1 or 2 doses</td>
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<tr>
<td>Measles, mumps, rubella (MMR)</td>
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<td>2nd dose</td>
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<tr>
<td>Varicella (VAR)</td>
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<tr>
<td>Hepatitis A (HepA)</td>
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<tr>
<td>Meningococcal B (Hib-MenCY)</td>
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<td></td>
<td>2nd dose</td>
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<tr>
<td>Tetanus, diphtheria, &amp; acellular pertussis (Tdap)</td>
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<td></td>
<td>2nd dose</td>
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<tr>
<td>Human papillomavirus (HPV)</td>
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<tr>
<td>Meningococcal B (Hib-MenACYW13)</td>
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<td>2nd dose</td>
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<tr>
<td>Pneumococcal polysaccharide (PPSV23)</td>
<td></td>
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<td>2nd dose</td>
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</tbody>
</table>

**Notes:**
- Range of recommended ages for all children
- Range of recommended ages for catch-up immunization
- Range of recommended ages for certain high-risk groups
- Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision making
- No recommendation

[http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm](http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm)
based on medical and other indications

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>INDICATION</th>
<th>Pregnancy</th>
<th>Immuno-compromising conditions (excluding human immunodeficiency virus [HIV])</th>
<th>HIV infection CD4+ T lymphocyte count</th>
<th>Men who have sex with men (MSM)</th>
<th>Kidney failure, end-stage renal disease, receipt of hemodialysis</th>
<th>Heart disease, chronic lung disease, chronic alcoholism</th>
<th>Asplenia (including elective splenectomy and persistent complement component deficiencies)</th>
<th>Chronic liver disease</th>
<th>Diabetes</th>
<th>Healthcare personnel</th>
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<td>2*</td>
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<td>1 dose IIV or LAIV annually</td>
<td>1 dose IIV annually</td>
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<td>1 dose IIV or LAIV annually</td>
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<td>3 doses through age 26 yrs</td>
<td>3 doses through age 26 yrs</td>
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<tr>
<td>Varicella</td>
<td>4*</td>
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<td>Human papillomavirus (HPV) Female</td>
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<td>3 doses through age 26 yrs</td>
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<td>Human papillomavirus (HPV) Male</td>
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<td>3 doses through age 21 yrs</td>
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<td>Zoster</td>
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<td>1 dose</td>
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<td>Measles, mumps, rubella (MMR)</td>
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<tr>
<td>Pneumococcal 13-valent conjugate (PCV13)</td>
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<td>1 dose</td>
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<td>Pneumococcal polysaccharide (PPSV23)</td>
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<tr>
<td>Meningococcal</td>
<td>11*</td>
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<tr>
<td>Hepatitis B</td>
<td>13,7*</td>
<td></td>
<td>3 doses</td>
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<tr>
<td>Haemophilus influenzae type b (Hib)</td>
<td>14,*</td>
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<td>1 or 3 doses</td>
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*Covered by the Vaccine Injury Compensation Program

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection, zoster vaccine recommended regardless of prior episode of zoster

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation
Herd immunity results in a decrease in the probability that a group or community will develop an epidemic when a pathogen is introduced even though a certain number of individuals are still susceptible.

An important practical aspect of herd immunity is that not all individuals of a population needs to be immunized to prevent an epidemic:

- very important from the standpoint of cost containment
- the last few individuals to receive a vaccine are the most expensive to find and administer the dose

Spread of Infection
all susceptible
$R_0 = 3$

$R_0 = $ basic reproductive rate
Average number of people infected by a case during entire infectious period
Spread of Infection
1 in 3 immune
$Ro = 3$
Figure 1 from Anderson and May. 1985. Nature. 318:323-9.

Model predictions for mumps

Vaccination coverage required for eradication

- Smallpox: 80-85%
- Polio: 80-86%
- Measles: 83-94%
- Mumps: 75-86%
- Borditella: 92-94%
- Rubella: 83-85%
- Diphtheria: 82-85%
- Malaria: 90-99%
- HIV: 95-99%

Graph denotes weeks. b, Model predictions of the equilibrium (the state to which the system settles in the long term) ratio of the number of cases of mumps in the age range 14–50 yr (the age range in which males are at risk to serious disease resulting from infection) under the impact of a vaccination programme in which p of each yearly cohort are vaccinated at age 2 yr, divided by the number of cases in the same age range before vaccination. If the ratio is above unity, the control programme has a detrimental effect and vice versa. The average age at infection before control was assumed to be 6.5 yr (appropriate for the United Kingdom) and the calculations were based on a model defined in ref. 24. The straight line denotes the ratio of unity. c, Age-specific incidence of reported
Global Vaccine Confidence survey

In the first 5 months of 2018 France recorded 2,500 measles cases.
Challenges demographics

U.S. age pyramid

Infants and children
- Diphtheria
- Group A streptococcus
- H. influenzae type b
- Helicobacter pylori
- Hepatitis A virus
- Hepatitis B virus
- Inactivated poliovirus vaccine
- Influenza virus
- Measles
- Meningococcus serogroups A, B, C, Y and W135
- Mumps
- Pertussis
- Pneumococcus
- Respiratory syncytial virus
- Rotavirus
- Rubella
- Tetanus
- Varicella zoster virus

Source: http://www.ctmt.com/pdfs%5CemergingDirections%5Cdiagnosticsasdestiny.pdf

Elderly

Recurrent infections:
- Group B streptococcus
- Influenza virus
- Meningococcus serogroups A, B, C, Y and W135
- Pneumococcus
- Respiratory syncytial virus
- Varicella zoster virus

Antibiotic resistance:
- Acinetobacter baumannii
- C. difficile
- Candida spp.
- Enterotoxigenic E. coli
- Klebsiella pneumoniae
- P. aeruginosa
- S. aureus

Cancer:
- Breast cancer
- Colorectal cancer
- Prostate cancer

Questions?