Vaccination

Course	Immunology
Date	@April 12, 2024
Status	Completed
Reading	☐

Previously in humoral immunity:

- Humoral immunity refers to immunity which exists n the cell-free part of blood, plasma or serum
- It is mediated predominantly by antibody and complement
- Antibodies are produced from B cells after they develop into plasmablasts or plasma cells
- Antibodies have specialised functions due to the isotype which controls location and FC-dependent effector functions
- Antibodies undergo SHM to improve antigen binding in germinal centres in a process called affinity maturation
- Antibodies can directly inactivate a pathogen (neutralise or lysis), or act indirectly by promoting phagocytosis and cellular recruitment (inflammation)
    - After being trained against a particular antigen
- Monoclonal antibodies are the most important example of the new class of biologics: drugs from biological macromolecules

What is a vaccine?

- Antigen, normally a protein from a pathogen
- Vaccines are designed to induce a specific immune response
    - Vaccinations utilise the body's own immune system to create immunological memory to fight future pathogen exposure
- This specific immune response can:
    - Prevent infection (e.g. Polio vaccine) or disease (whooping cough)

        - Symptoms developing and spreading
    - Control existing infection (e.g. Shingles vaccine带状疱疹)
        - Vaccinate older people and boost up their immune system and protects them from post-infection syndrome
    - Prevent disease developing post-exposure (e.g. Rabies狂犬病)
    - Prevent fetal infection after immunisation of mother (e.g. whooping cough百日咳)
    - Prevent or control cancer (e.g. HPV, Human papillomavirus causing cervical cancer /HBV hepatitis B virus causing liver cancer)
        - Note that this is only limited to virus-causing cancer

Discovery of vaccination

The modern era of vaccination was introduced by Edward Jenner

In 1776, discovered the principle that individuals could be protected from infection by smallpox virus by prior exposure to Vaccinia (hence the name vaccination), a closely related virus.

Smallpox - Vaccination success story

Vaccination is a tool for the population

- If enough people are vaccinated, there is not enough virus to circulate IF there is no animal reservoir
    - Smallpox has no animal reservoir

Vaccination is the most effective means of controlling infectious disease

- Second most impactful public health intervention in human history to decrease mortalities, after provision of clean water
- Relies on everybody continue to be vaccinated or else there would be enough circulating cases to cause spreading again e.g. measles

How do vaccine work?

Vaccines: measles, pertussis, smallpox, mumps, rebulla, polio, hepatitis

Vaccine protection is by mimicking natural immunity

- Vaccines aim to mimic the effect of the infectious agent in generating memory cells, but without the disease-causing properties of the infectious agent itself.
- Thus, the immune system is already primed to immediately make a secondary immune response upon the first encounter with the pathogen.

> 💡 Immunisation with a vaccine bestows a heightened state of immunity in case the organism is encountered in the future.

Immunity is not dependent on severity of illness caused

Vaccines are harmless versions of disease-causing organisms, or of their individual components.

- Vaccines contain non-infectious versions of a pathogen
  - **RNA**

    Provide 1 antigen

    Protein made by body itself
  - **Subunit vaccines**

    Provide 1 antigen

    Purified protein
  - **Vectored vaccines**

    Provide 1 antigen

    Take another virus or pathogen that does not cause human disease and insert genetic material of the target antigen, producing a non-infectious virus producing target protein
  - **Killed vaccines**

    Present whole pathogen and show all proteins of the virus

    Require dynamic interaction with immune system

    Used when requiring different antigens for protection
  - **Modified live vaccines**

    Same as above

    People with weaker immunity might get sick by the vaccine itself

- Vaccines can utilise **live attenuated** organisms, **killed** organisms, **subunits** of the organism produced chemically or using recombinant DNA technology, or inactivated bacterial toxins (**toxoids**).

These incomplete or weakened versions don't cause illness, but the body will still mount an immune response against them, creating memory B cells in the process so that protective antibodies are produced on re-exposure

The ideal vaccine

- Completely without side-effects in all individuals
- Completely effective in all individuals
- Cheap to produce and distribute
- Long shelf life without additives or refrigeration
- One administration to provide life-long and appropriate immunity
- Effective against all variants of the organism
- Administered using a non-invasive means.

No such vaccine exists.

However, there are many very successful vaccines

- Polio (Sabin oral live attenuated vaccine)
- Meningitis (Haemophilus influenzae type B (Hib)
- Meningococcus group C vaccines comprising capsular polysaccharides conjugated to a protein carrier)
- Hepatitis A and B, diphtheria/tetanus/acellular-pertussis (DTaP)
- Measles/mumps/rubella (MMR)

Types of vaccines in current use:

Live attenuated organism.

Advantages

- Induce a systemic and local response
    - It goes everywhere in the body like the actual virus
    - Induces a strong and usually appropriate immune response

- Immunity is long lasting
  - A single dose often induces long-term immunity
- Often cheap to produce
  - And fast since it is self-replicating

Disadvantages

- Potential danger of reversion to virulence
  - Since it is a live organism
- Spread from vaccine
  - E.g. polio
- Problems for immunocompromised
  - As it requires interaction with immune system
- Poses difficulties in quality control and storage.

Examples: BCG, OPV (oral polio vaccine), MMR (measles, mumps, rubella).

Production process

- The pathogenic virus is isolated from a patient and grown in human cultured cells
- The cultured virus is used to infect monkey cells
- The virus acquires many mutations that allow it to grow well in monkey cells
- The virus no longer grows well in human cells (it is attenuated) and can be used as a vaccine

> 💡 Attenuated vaccine: involve an avirulent form of the infectious agent, induce both B cell and T cell response

Inactivated killed organism.

- Induces weaker and often inappropriate immunity
- Can cause some immunopathology.
- However, no danger of reversion to virulence, and can be used in immunocompromised individuals.

- *Examples: Hepatitis A, Rabies, Inactivated Polio vaccine (IPV), Influenza (although most flu vaccines contain inactivated virus, a live attenuated vaccine is also produced as a nasal spray).*

Subunit vaccines.

- The antigen in these cases may be a toxin, a viral coat protein, or a bacterial cell wall component.
- Relevant proteins can be purified form the pathogen or more recently **recombinant** proteins are often used.
    - non-replicating and lack any of the infectious components
- This approach has been limited by the problem of **appropriateness,** because all subunit vaccines currently in use only induce an antibody response.
    - No T cell response because unable to infect cell to be presented via MHC I
- Subunit vaccines require multiple doses (**booster**) and require the addition of an **adjuvant** (*pertussis, hepatitis B*).
- A new form of a subunit vaccine is the **mRNA vaccine**, which enables the local production of the antigen subunit protein within the recipient rather than recombinant production which is more costly and time consuming.
    - mRNA vaccines also offer the potential to deliver multiple variants of a given subunit in one shot.
    - Some mRNA vaccine able to induce T cell response
- **Toxoid vaccines** use a inactivated bacterial toxins (toxoid) to induce strong antibody response which prevents disease caused by toxins
    - *Examples: tetanus, diphtheria*

Conjugate vaccines.

- Many bacteria have an outer capsule made of polysaccharides.
- In this case the **capsule carbohydrates** rather than proteins are crucial target for vaccine.
- This is a problem because the carbohydrates are T cell independent antigens and do not lead to a good long term antibody response, especially

in babies and young children.

    - Protein antigens can be presented on MHC molecules on APCs, but carbohydrates cannot
    - B cells are activated independent of T cells - memory less long-lasting
    - Polysaccharides are T-independent antigen - no memory generation
- The solution is to conjugate (chemically) bacterial polysaccharide to a protein carrier.
    - This leads to the activation of CD4 T cells which provide B cell help and result in generation of long term immunological memory against the specific polysaccharide (memory B cells, long-lived plasma cells)
    - A full immune response is generated
- *Examples: Meningococcus (Men C), Haemophilus (Hib), H. influenza, N. meningitidis, S. pneumoniae*

What kind of protection could an vaccine provide?

- **Prophylactic to limit infection**
    - *Flu, measles, SARS-CoV-2*
- Therapeutic to prevent or delay severe disease
    - *ditto*
- Post-exposure
    - *Rabies*
- Therapeutic to control existing infection
    - *Shingles带状疱疹, Herpes*
- Altruistic to prevent onward transmission
    - *Maternal immunisation (whooping cough)*
- Limit long-tern consequences e.g. cancer
    - *HPV and HBV*

Antibodies to prevent infection

- Block infections of new cells via neutralisation
    - Nothing to do about infected cells

T cells to control

- Get rid of infected cells with help of NK cells etc.
- CD8 activated via endogenous pathway (cells have to be infected)

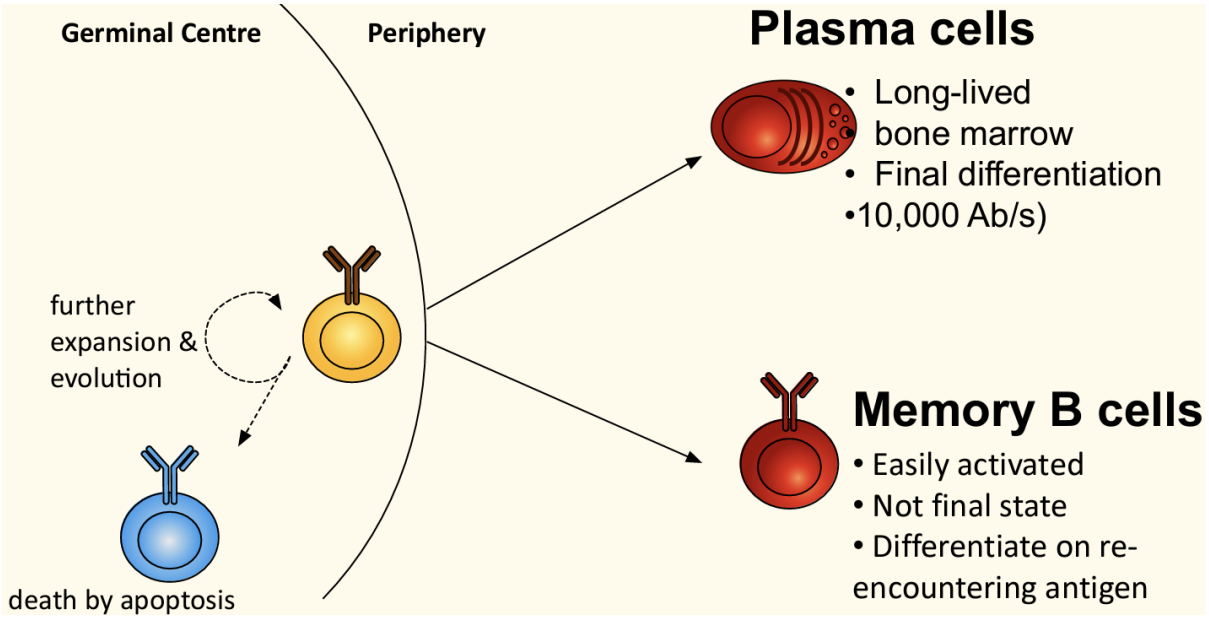
Prophylactic: Sterilising immunity

- Upon re-exposure after vaccination, there would be no infection at all - not of a single cell (gold standard)
- Very little evidence this occurs
    - Even having no symptoms develop and no transmission, there would still be local infection at the site of infection
    - This has implication in latency: a few cells are infected may have long term consequences (HIV?)
- E.g. SARS-CoV-2
    - Less infection (by PCR)
    - Less transmission
    - Less disease
- Does this equal sterilising

Antibodies needed to prevent disease soon after exposure

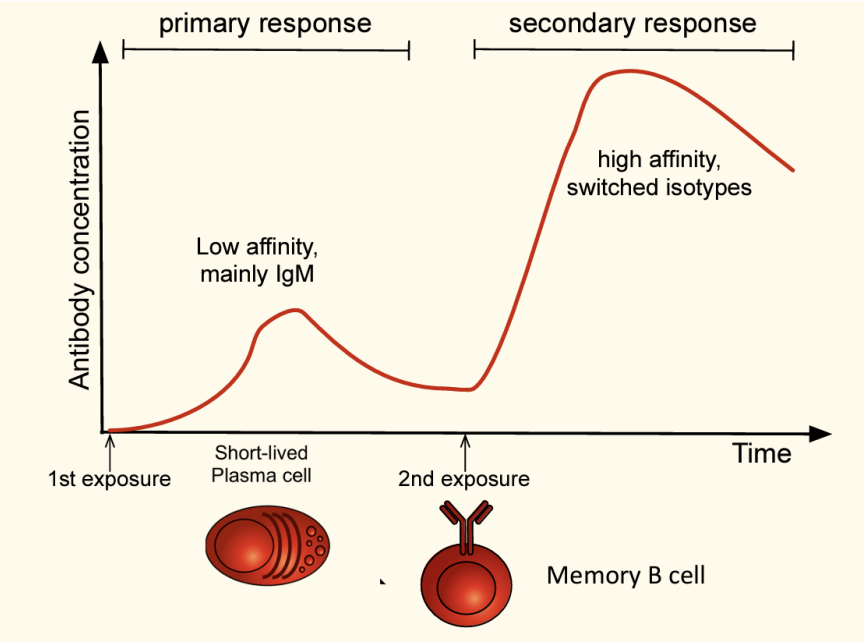
- First exposure: low affinity antibodies (IgM) are produced as time required to generate high affinity IgG are generated within the germinal centre
    - 1 week for appearance of antibody
- Second exposure: High affinity IgG have been generated and their production within 4-5 days not weeks as in primary response
    - There is a steady state after vaccination and antibody can be generated rapidly

After the germinal centre: memory or antibody production?



- After B cells exposed to the pathogen, it goes through the training in the germinal centre and differentiate into
  - Plasma cells
    - Long-lived in the bone marrow constantly producing antibody
      - Making the steady state after vaccination
    - Final differentiation
    - 10000 Ab/s
  - Memory B cells
    - Came out the germinal centre and found in the LN (resident B cells)
    - Not final state
    - Differentiate on re-encountering antigen
      - Short-lived plasmablasts to produce a large amount of antibodies
      - Travel back the the germinal centre and improve their affinity if the antigen has changed a bit
- Which cells are making the antibodies in a vaccine response?
  - Plasmablasts (periphery) or plasma cell (bone marrow), not memory B cell

    - They are antibody producing factories with lots of lots of ER and vesicles
    - Memory B cells keep their BCR on the surface
- For a rapid response: both memory B cells and plasmablasts need to already be in place



Germinal centre summary

Germinal centre is a safe space for B cells to evolve after meeting antigen

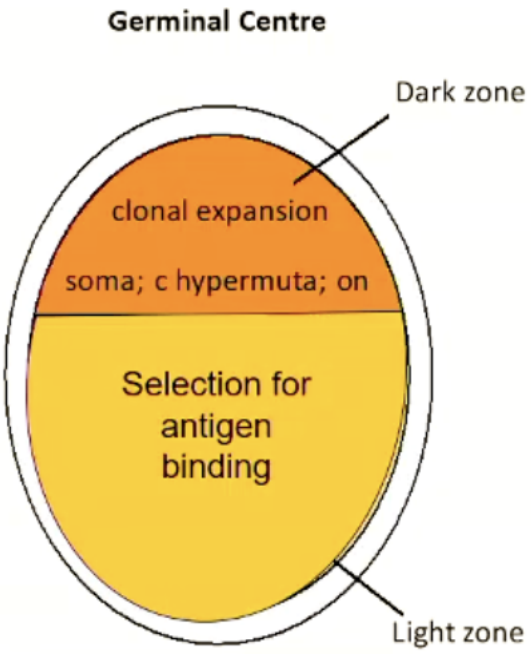
GC form in lymph nodes

2 activities:

- Proliferation (cell division) in the dark zone
- Selection (cell death) in the light zone

2 outputs:

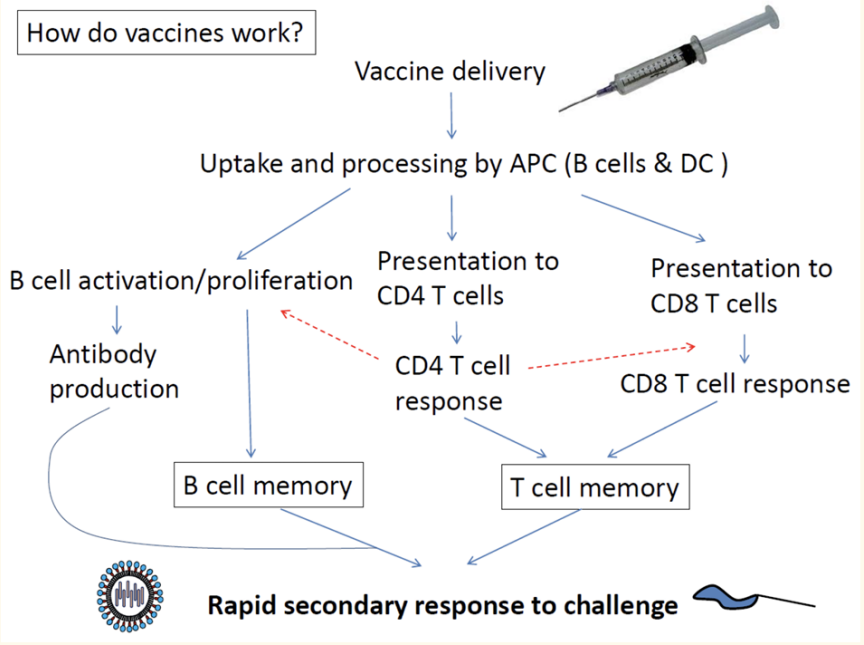
- Affinity maturation
- Class switching



- Mainly found in the LN, requires antigen, B and T cell to form and is organised into dark and light zones
- B cells clonally expand and undergo SHM in dark zone
- Clones with improved binding “win” the competition for antigen and T cell help in the light zone
- They return to dark zone for another round
- Clones with worse binding die out
- Cyclic process resulting in “survival of the fittest” B cell for binding to antigen
- Eventually improved B cells exit to become antibody producing cells
- Produces **high affinity IgG** associated with vaccine protection
- Class switch also occurs in GC

> 💡 If no GC training occur, the antibodies produced against the pathogen would be relatively weak

How does the immune system coordinate to enable vaccines to work?



Note that presentation to CD8 T cells only occur with live attenuated vaccine when there is some infected cells to present the peptide via endogenous pathway

HOWEVER

- To prevent sickness, pathogen are modified
- This means viral replication is decreased or eliminated
- Less inflammation with viral exposure

> 💡 A robust response is required for a strong immunity, thus adjuvants are used to “help” vaccines

Adjuvants

- Adjuvants accomplish the task by mimicking **pathogen-associated molecular patterns**
  - Include liposomes, lipopolysaccharide (LPS), molecular cages for antigens, components of bacterial cell walls, and endocytosed nucleic acid such as RNA, dsRNA, single-stranded DNA, and unmethylated CpG dinucleotide-containing DNA
- They **trigger innate immunity** which supports the development of adaptive immunity
  - Need innate stimulation to hype up the immune system overall
- Both great vaccine and adjuvants are required for a good immunity
  - Vaccine: appropriate adaptive immunity
  - Adjuvants: innate immunity to boost up the adaptive one triggered by vaccine

Neutralising antibodies bind viruses and block virus entry into cell

- Vaccine protection from neutralising antibodies
  - Evidence: serum transferral gives protection

Passive immunisation.

- Preformed antibody (usually made in animals or in culture) can be administered to provide immediate, but temporary immunoprotection.
- Not really vaccination, but occasionally used therapeutically post-exposure.

T cell vaccines

- Cytotoxic T cells help control infection
  - Does not work with latent viruses as latently infected cells survive cytotoxic T cell surveillance
  - Then become activated and produce new virus
- T cell vaccines will not prevent infection
  - Control virus levels
  - Reduce damage to immune system/tissue
  - Delay/limit disease progression
  - *E.g. BCG against tuberculosis*

Cytomegalovirus-vector vaccine

- Live-attenuated vaccine carrying genetic information from HIV
- Persistent viral vector
  - Weird result: Post vaccination infection, 50% of the animal protected, 50% stay infected
- Stimulates unusual virus killing response: MHC E restricted response
- There are basic rules of vaccine design but sometimes unexpected result come up when twitching around normal kind of immunity (put a virus into another virus)
  - Future development T cell vaccines mimicking the MHC E restricted response as they are more resistant to viral variation than antibodies

Why don’t some vaccines work?

- Antibodies are too specific, broad reactivity needed against variation
  - E.g. Influenza, strain mutates so vaccine strain predicted every year
- Antibodies binding but not neutralising

    - E.g. HIV - most of antibody response is ineffective
- Antibody levels are not well maintained
    - Boosts are required
    - *Mumps, Pertussis, Influenza?*

Vaccination and an aging population

- Vaccination results in lower antibody titre and reduced antibody efficacy
- Four vaccines are now recommended for people 60+
    - Flu, pneumococcal, tetanus, Shingles
- Often protective immunity is not achieved in a large proportion of the population, however disease severity may be reduced
- Problems associated with decreased vaccine response is associated with immune senescence
- Chemotherapy in cancer would also cripple the immune system

Flu vaccine development

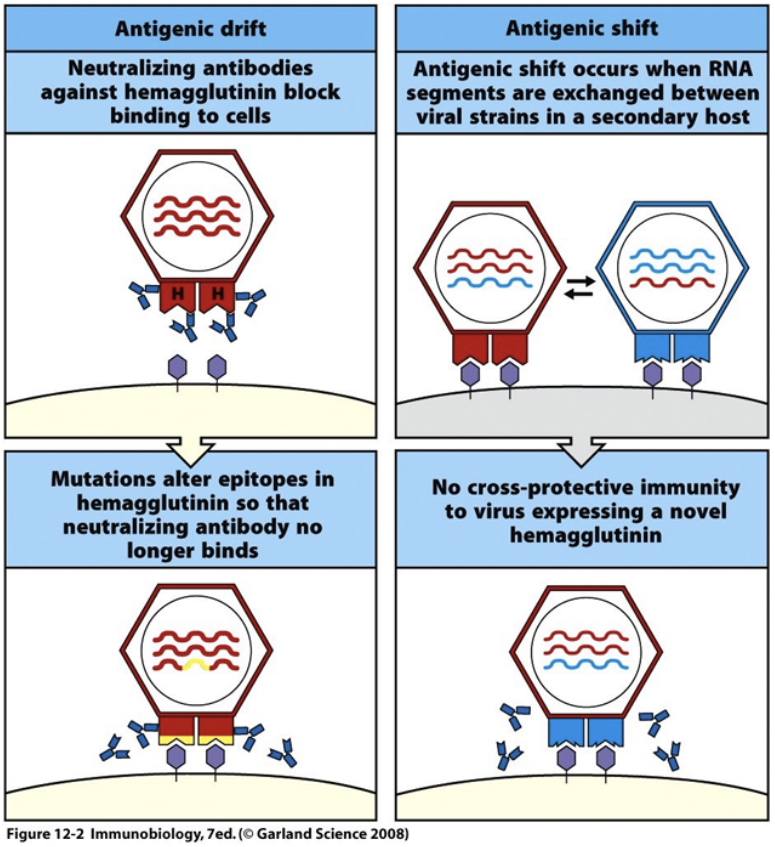


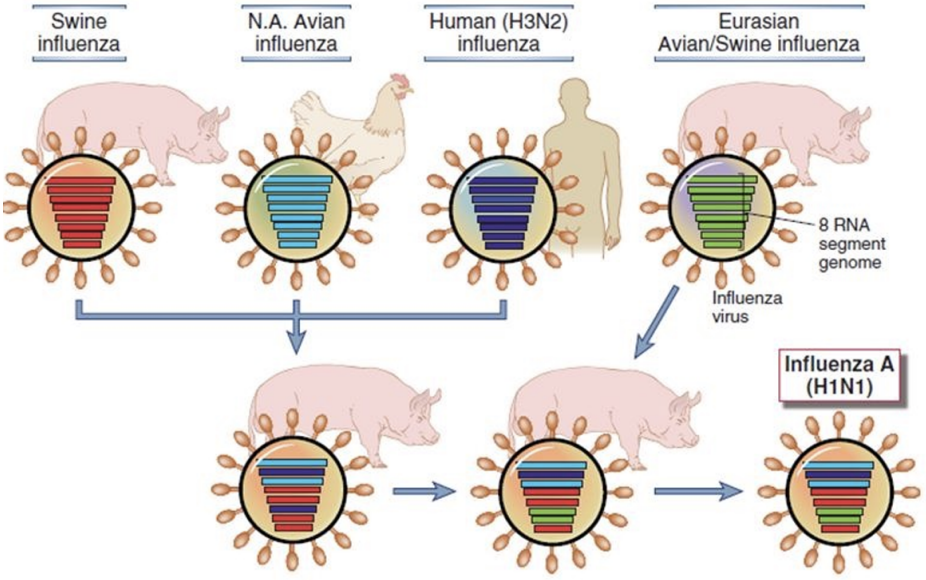
Figure 12-2 Immunobiology, 7ed. (© Garland Science 2008)

Antigenic drift

- Gradual accumulation of mutations in the gene that encode virus surface protein (hemaglutinin HA, nuraminidase NA)
  - Due to errors in viral RNA replication process
  - Can lead to production of new viral strain
  - Contribute to seasonal flu epidemics

Antigenic shift

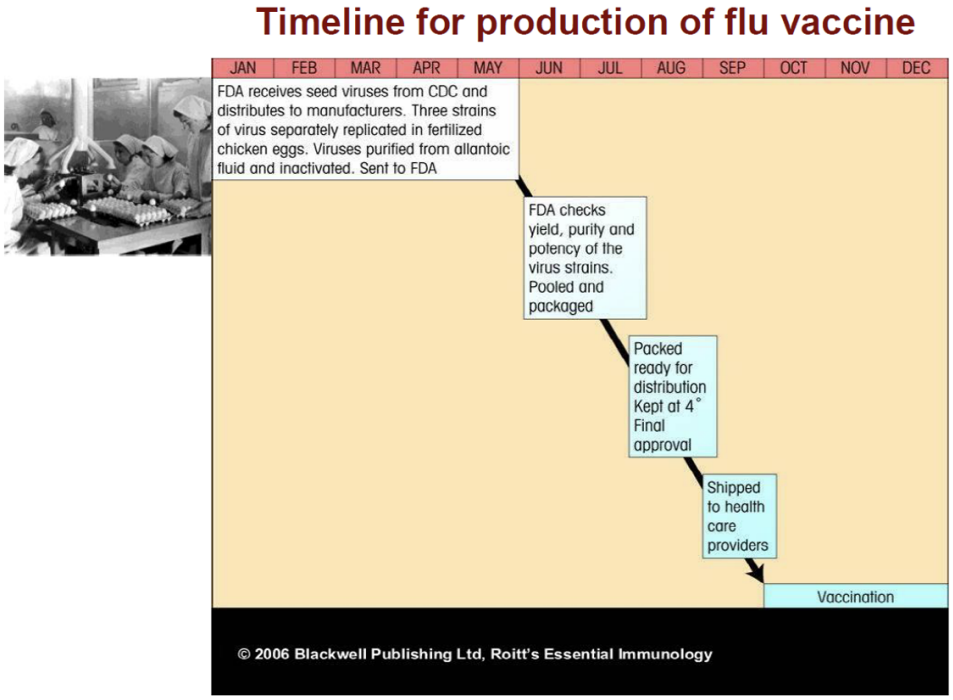
- Abrupt and substantial change in influenza virus's antigenic composition
  - Typically involving HA and NA
  - Usually results from reassortment of genetic material when 2 different viruses infect a single host cell and RNA segment exchange
  - Results in new subtype with significant different HA or NA antigen
  - Potential leading to pandemics
- Alluded to animal reservoir



Process

- Flu vaccines are made using an egg-based manufacturing process to make either the inactivated (killed) vaccine for adults of the live attenuated vaccine for children

- The candidate viruses are injected into fertilised hen’s eggs and incubated to allow the virus to replicate
- The influenza virus is isolated and killed and the virus antigen is purified
- Undergo rigorous testing before use
- Flu vaccine development takes about one year
    - Prediction made in January which might not be quite right
    - In comparison to RNA technology, which is much faster



Vaccination works at the population level

Vaccination is predominantly a prophylactic, rather than therapeutic intervention.

In addition, the effectiveness of vaccines is strongly influenced by the rate of **compliance** (so-called “herd immunity”).

These two factors have important implications when assessing the cost/benefit and the risk/benefit ratios of vaccination programmes.

The main issue with vaccination in the developed world today, is the issue of **vaccine hesitancy.**

Due to misinformation, there are individuals who do not get vaccinated or who do not vaccinate their babies, which leads to decreased herd immunity and an

increased incidences of diseases which have all but disappeared, such as measles.

Diseases that still need vaccines to be developed

Despite the successes of the above vaccines, many more vaccines are urgently required, including new or improved vaccines against **HIV**, **influenza**, **malaria** and **tuberculosis**.

The BCG vaccine against tuberculosis is only effective in certain parts of the world and for some of the disease types.

No effective vaccine is available for either HIV or malaria. Although influenza vaccines are very effective against the strain to which they are directed, due to constant changes to its **haemagglutinin** and **neuraminidase** antigens, a different vaccine formulation has to be produced each year.

New and improved vaccines are urgently required.

Relatively recently introduced vaccines include the Pneumococcal conjugate vaccine (PCV), the Meningococcal Group C conjugate vaccine (MenC), and the Cervarix cervical cancer vaccine against human papilloma virus strains 16 and 18.

Novel technologies which may contribute to the development of vaccines include the use of live recombinant vectors and DNA immunisation.

> 💡 Older people respond well to vaccine that contains strong adjuvants, often have a weaker antibody response to vaccine compared to the young

Summary

What are vaccines

- Antigens from pathogens that trigger and beneficial immune response in the host without causing disease

How do vaccine work

- They create an immune memory which lets the body respond rapidly or better when real pathogen is encountered. Most work through induction of antibodies

What can vaccines achieve immunologically?

- Limit infection, prevent disease, limit population spread

Give examples of successful vaccines