Biomedical Engineering for Global Health

Lecture 9

Vaccine development: from idea to product

Review of lecture 8

- Pathogens: Bacteria and Virus

- Levels of Immunity:
  - Barriers → First line of defense

  - Innate → Inflammation
    - Phagocytes
    - Complement

  - Adaptive → Immunologic memory
    - Antibody mediated immunity → Extracellular pathogens
    - Cell mediated immunity → Pathogens within cells
    - Diversity to recognize 100 million antigens

Review of lecture 8

- Infectious diseases are still a serious global health problem
  - Example of bacterial pathogen of public health relevance
  - Example of viral pathogen of public health relevance

Review of lecture 8

- There are 3 levels of immunity
  - Which are they?
  - Which cells in the blood mediate <u>innate</u> immune response?

Review of lecture 8

- The adaptive immune response offers great advantage to vertebrates
  - What is adaptive immunity?
  - What is immunologic memory?

How can technology help?

Science

1. Understanding biology: pathogens & disease
   immune system

Engineering

2. Developing vaccines: from idea to product
   - vaccine design
   - production
   - testing safety & effectiveness

3. Addressing challenges for vaccine development:
   - Developed vs. developing countries
   - The AIDS vaccine challenge

How can technology help?

Science

1. Understanding biology: pathogens & disease
   immune system

Engineering

2. Developing vaccines: from idea to product
   - vaccine design
   - production
   - testing safety & effectiveness

3. Addressing challenges for vaccine development:
   - Developed vs. developing countries
   - The AIDS vaccine challenge

Lecture map

The case of the Flu
- Viral Life cycle
- Antigenic drift
- Antigenic shift & pandemics

Vaccines
- Types of vaccines
- Are they effective?
  - History of Vaccines
  - Childhood Immunizations in US and the World
  - The HERD effect
- Are they safe?
  - FDA approval process
  - The thimerosal debate
- Vaccine manufacture
  - How are vaccines made?
  - Challenges for vaccine development

Lecture map

The case of the Flu
- **Viral Life cycle**
- **Antigenic drift**
- **Antigenic shift & pandemics**

Vaccines

- Types of vaccines
- Are they effective?
  - History of Vaccines
  - Childhood Immunizations in US and the World
  - The HERD effect
- Are they safe?
  - FDA approval process
  - The thimerosal debate

Vaccine manufacture

- How are vaccines made?
- Challenges for vaccine development

The case of the flu

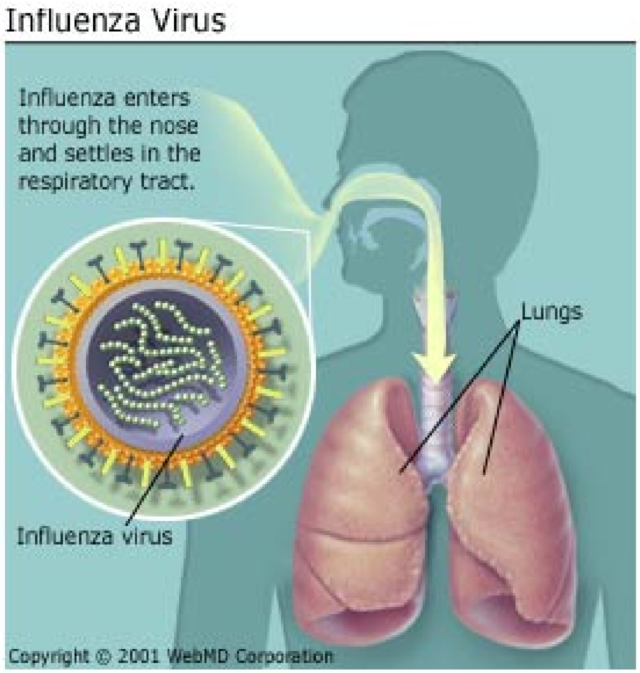
Influenza virus *A* (B, C)

Infects respiratory tract

-Cells killed by virus or immune response

Immune mediators: Interferon

-fever
-muscle aches
-headaches
-fatigue



Adaptive immunity: Humoral & cell-mediated responses clear infection, but:

- Yearly outbreaks, in spite of previous infections
- Yearly vaccination needed

Influenza A


Andrew Dandhazy, Rochester Institute of Technology

- **Viral Spread**
  - Infected person sneezes or coughs
  - Micro-droplets containing viral particles inhaled by another person
  - Penetrates epithelial cells lining respiratory tract

- **Influenza kills cells that it infects**
    - Can only cause acute infections
    - Cannot establish latent or chronic infections

- **How does it evade immune extintion?**
    - Antigenic drift
    - Antigenic shift: reassortment

Influenza A virus

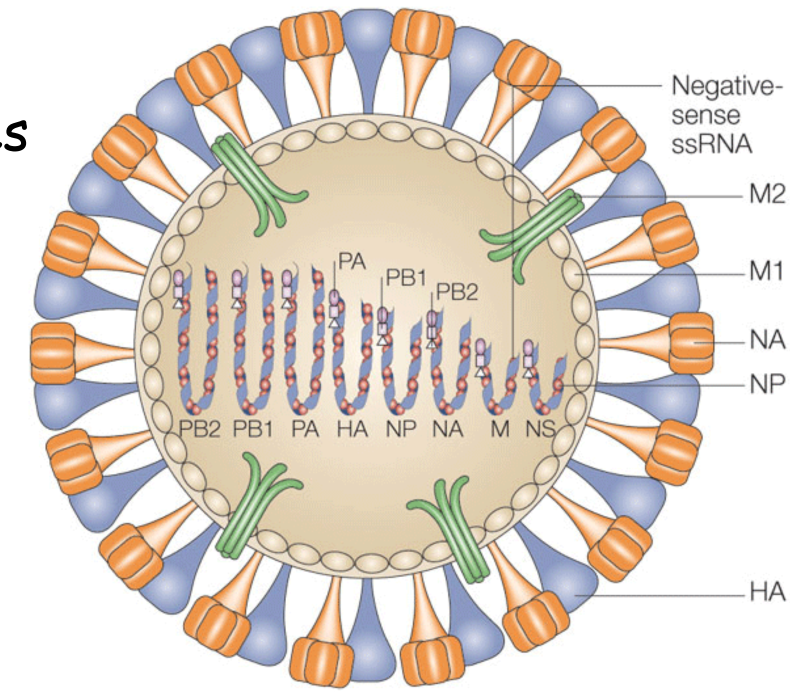
-RNA core: 8 segments

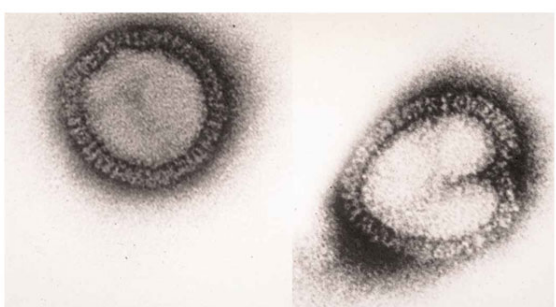
-Protein capsid: w/RNA polymerases

-Envelope

-2 major glycoproteins:

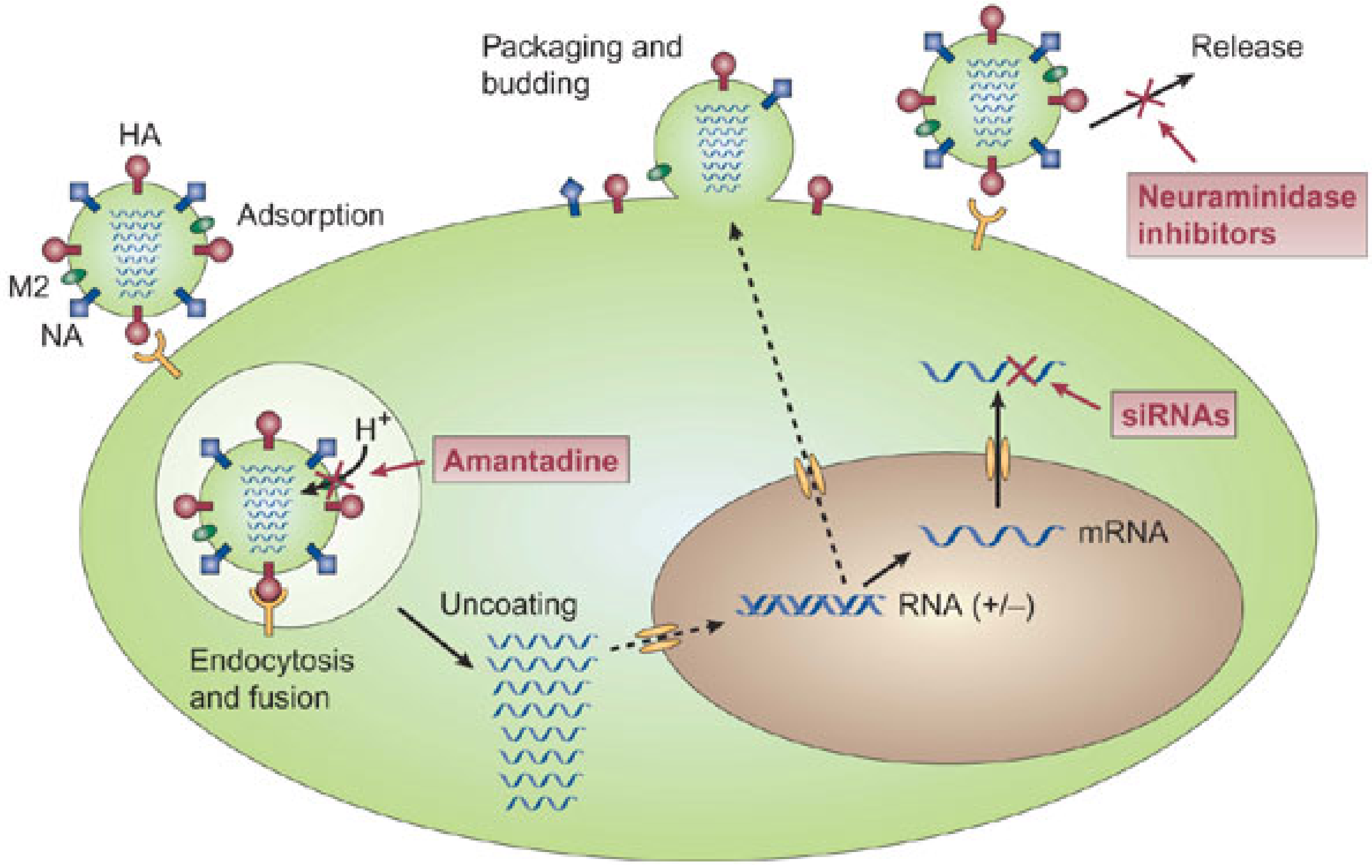
- -Hemagglutinin (HA)
- -Neuraminidase (NA)





Size = 80-120nm

The influenza virus life cycle:

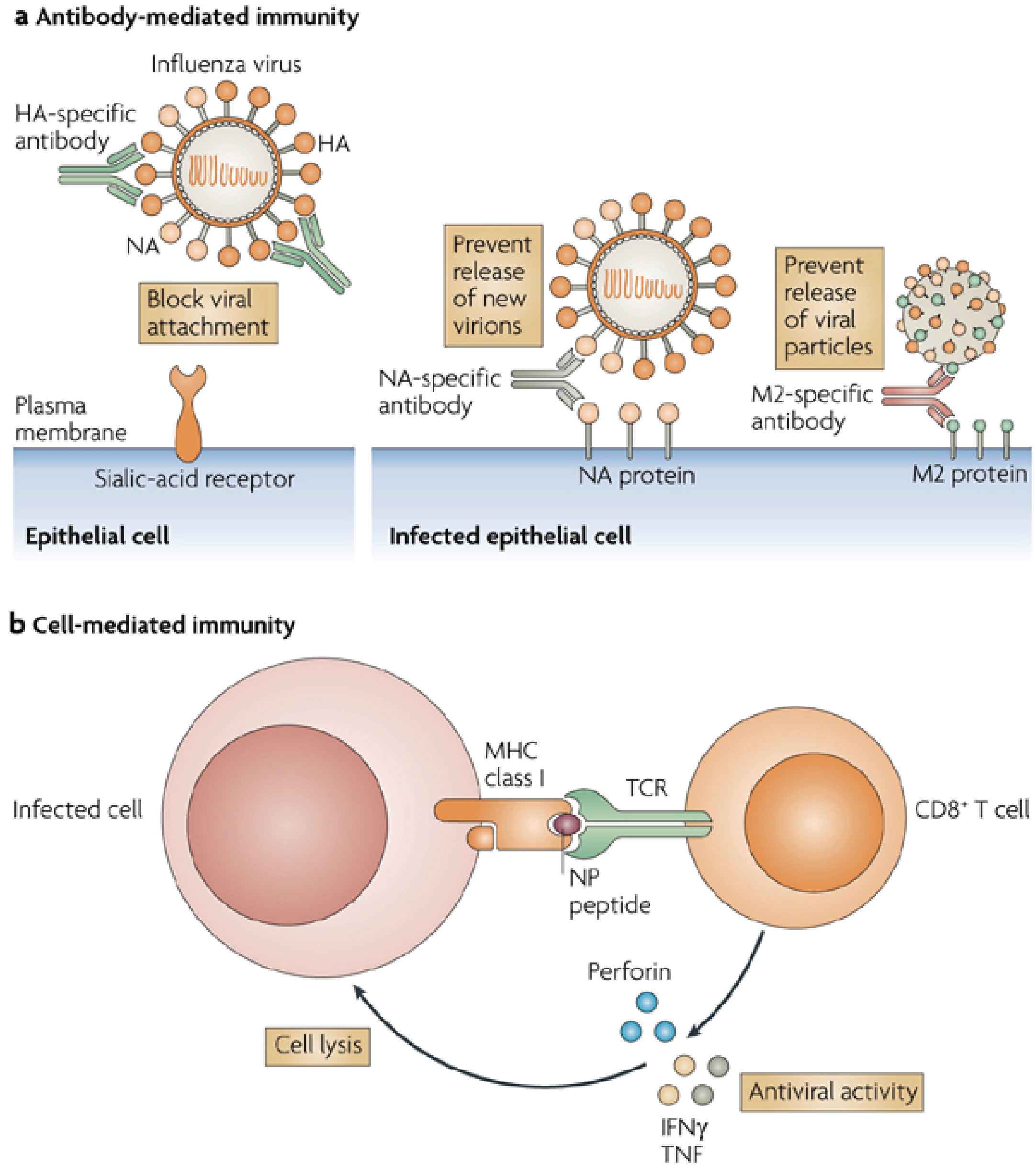


HA- mediates entry,

-main target of humoral immunity

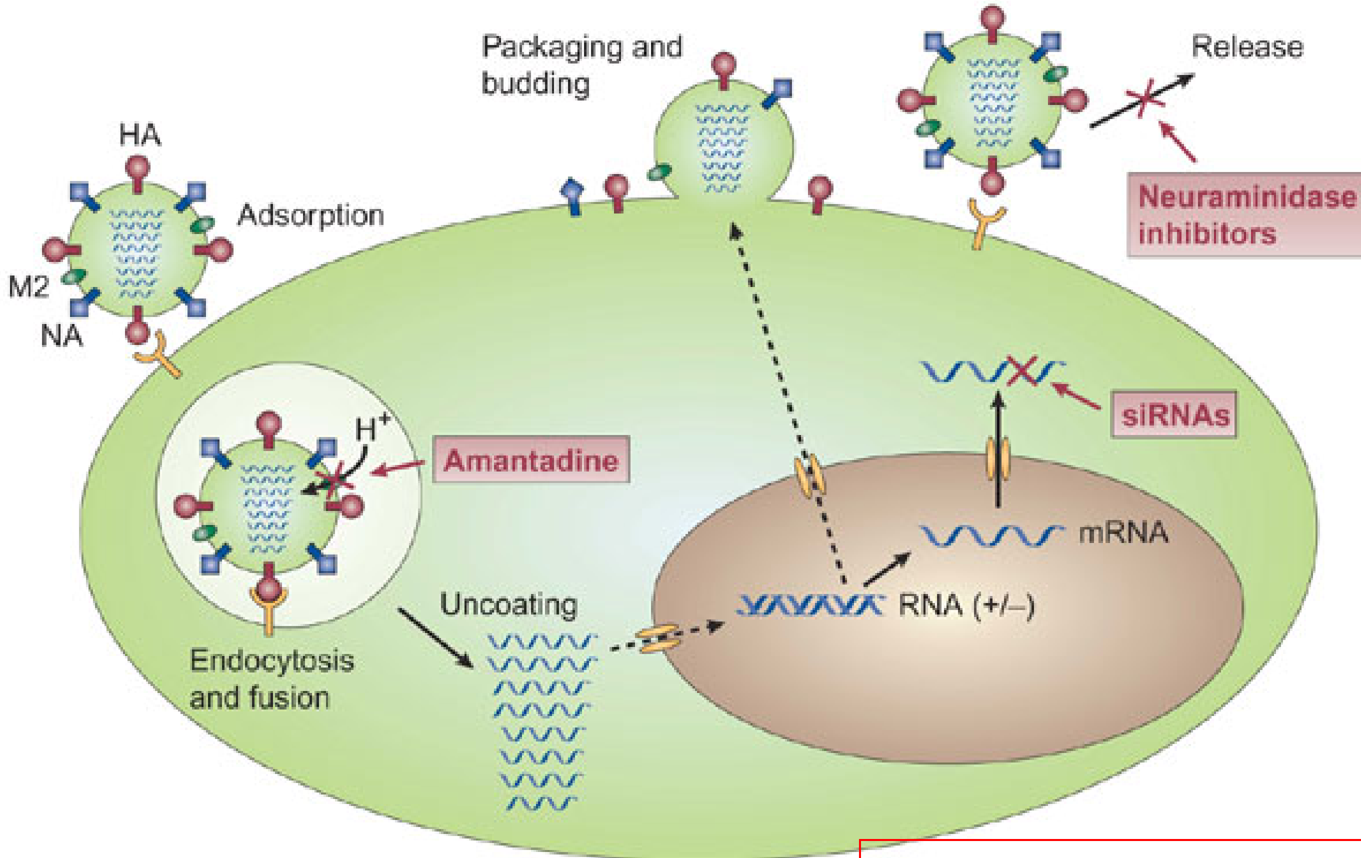
NA- mediates release

The Adaptive Immune response to influenza



Nature Reviews | Immunology

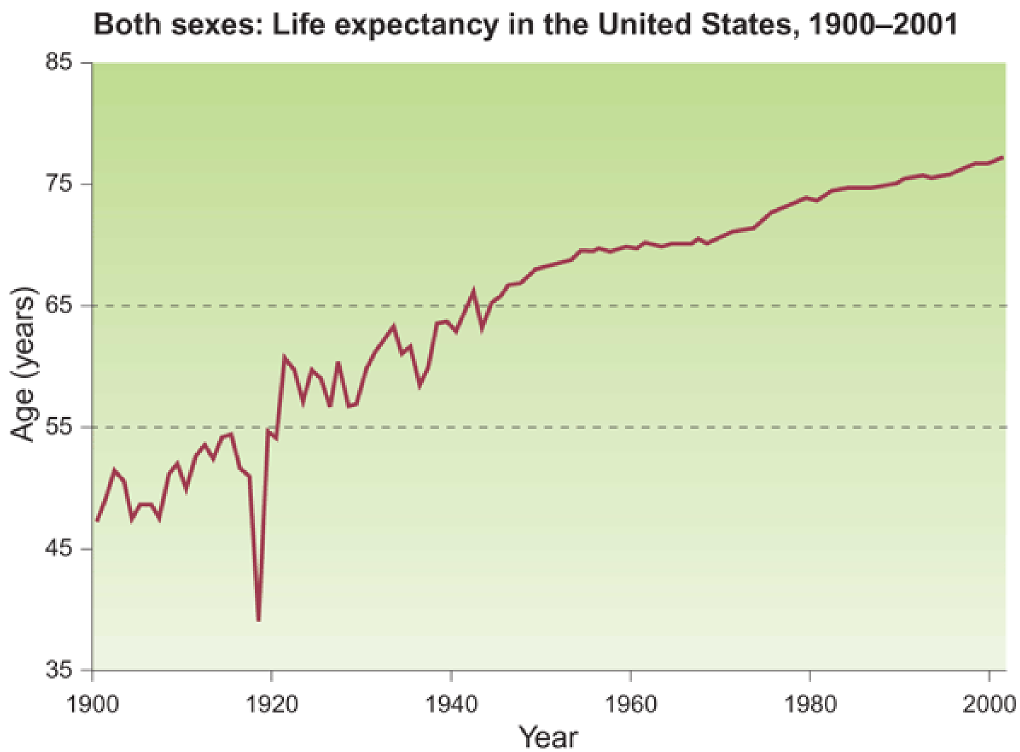
The influenza virus life cycle:



HA- mediates entry,
-main target of humoral immunity
NA- mediates release

Antigenic drift:
-Viral RNA polymerases don't proofread reproduction
-point mutation changes in HA/NA change antigenicity

The 1918 Spanish Influenza Flu Pandemic



-Population lacked immunity to new H1N1 strain: 40 million deaths in <1 yr!

-Today widely circulating human viruses: H1, H2, H3

-Birds are predominant host for all H1-H16/ N1-N9 strains

Antigenic shift and flu pandemics

Shift (Reassortment): viral gene segments randomly reassociate

-Achieved by co-infection of a single cell with these viruses

How does this happen?

1. Virus shed in bird feces gets into pigs drinking water

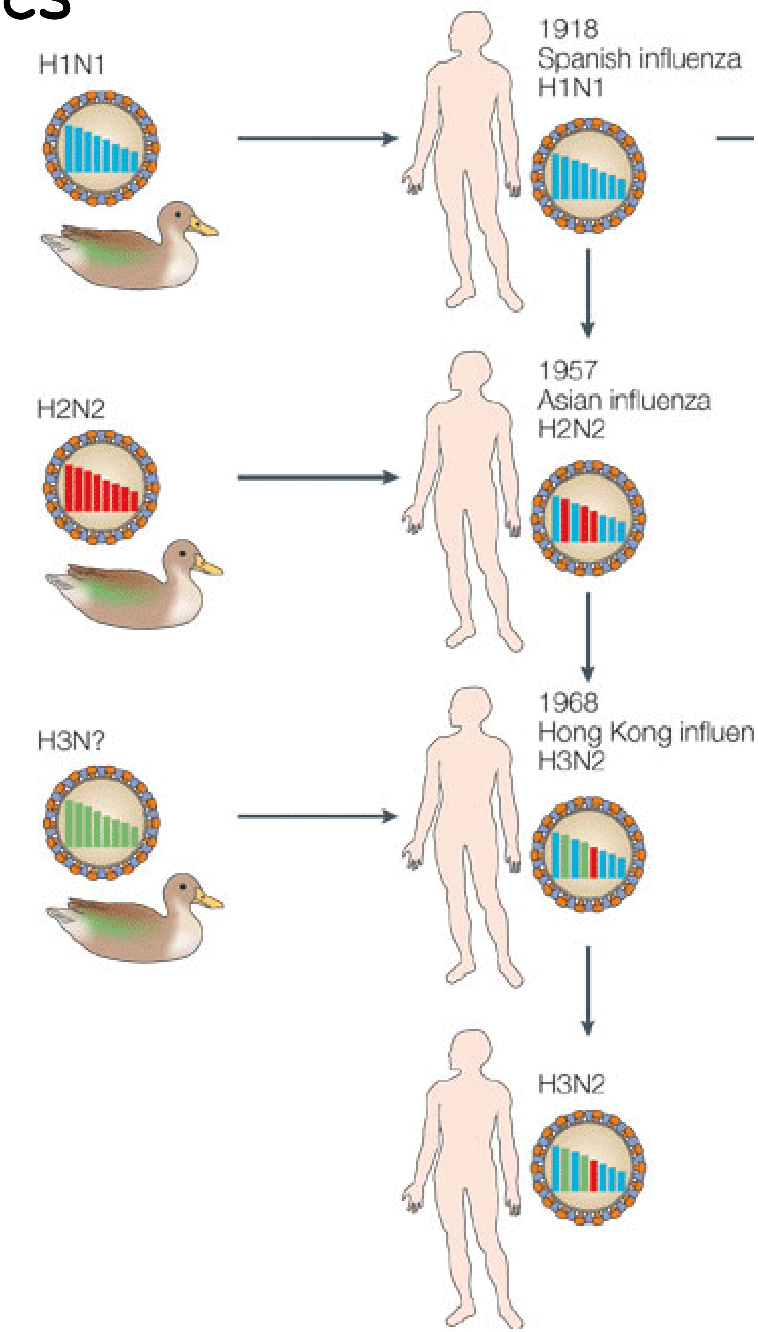
2. Humans handle and/or cough on the pig

= New virus: segments from human birds & pigs virus

China: Guangdong Province

-breeding ground: proximity of humans, pigs, birds:

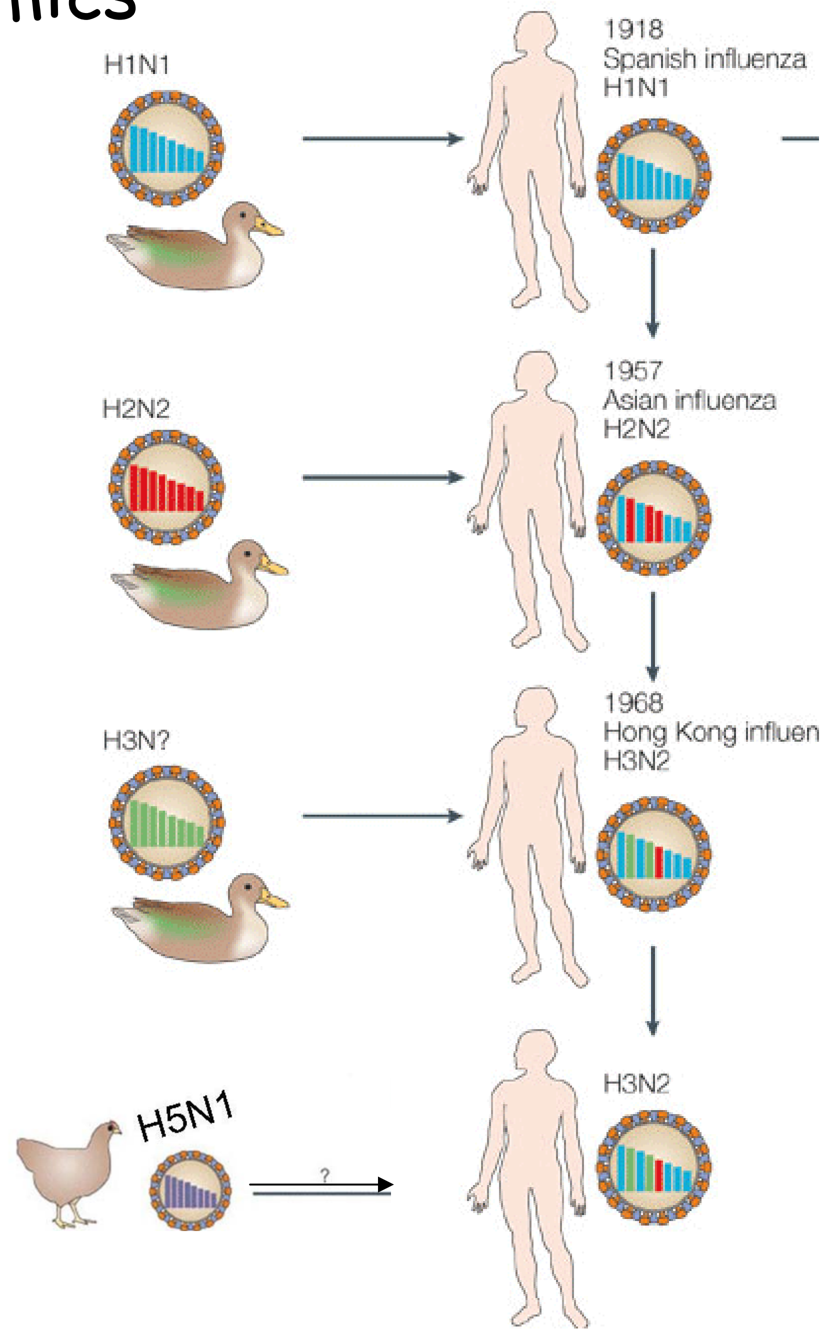
- H5N1: 50% lethal, no human-human transmission yet



Antigenic shift and flu pandemics

Shift - Reassortment: viral gene segments randomly reassociate

-Achieved by co-infection of a single cell with these viruses



How does this happen?

1. Virus shed in bird feces gets into pigs drinking water

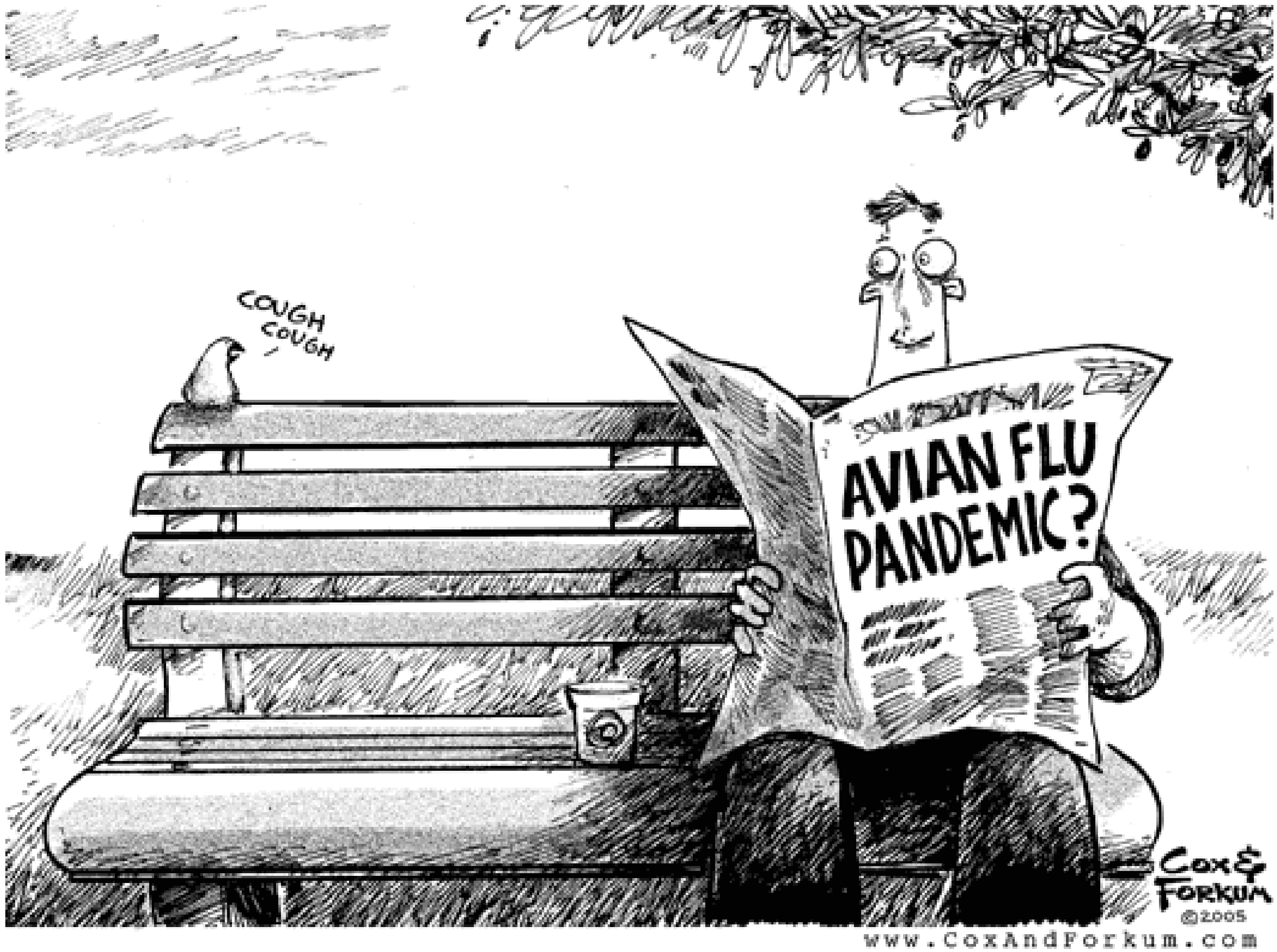
2. Humans handle and/or cough on the pig

= New virus: segments from human birds & pigs virus

China: Guangdong Province

-breeding ground: proximity of humans, pigs, birds:

- H5N1: 50% lethal, no human-human transmission yet


COUGH
COUGH
AVIAN FLU
PANDEMIC?
COX & FORKUM
©2005
www.CoxAndForkum.com

Lecture map

The case of the Flu
- Viral Life cycle
- Antigenic drift
- Antigenic shift & pandemics

Vaccines

Types of vaccines

Are they effective?

History of Vaccines
Childhood Immunizations in US and the World
The HERD effect

Are they safe?
FDA approval process
The thrimersoal debate

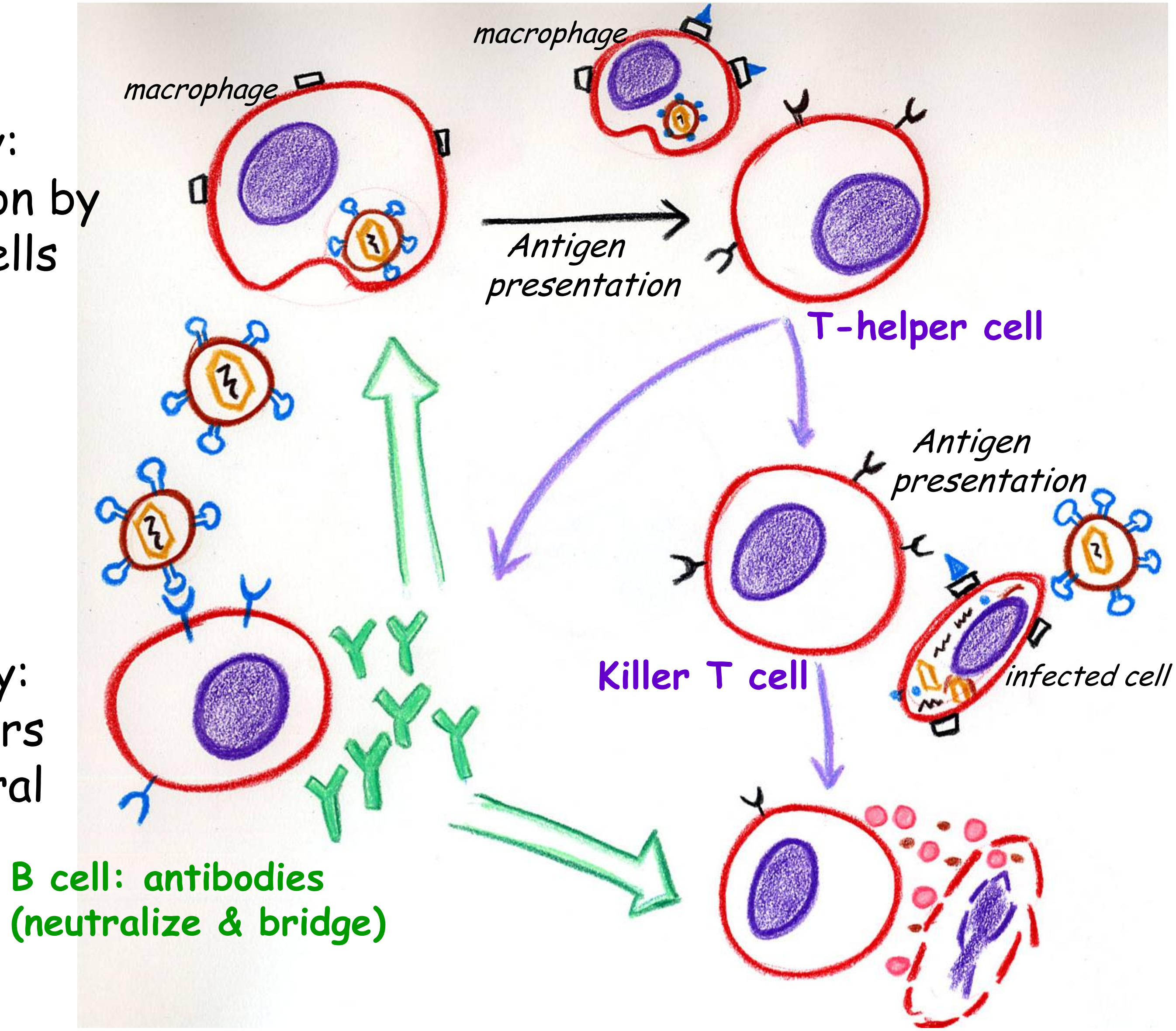
Vaccine manufacture
How are vaccines made?
Challenges for vaccine development

Adaptive immunity and vaccines

What do we need to achieve MEMORY?

1. Cellular Immunity: Antigen presentation by APCs or infected cells

2. Humoral Immunity: B and T cell receptors must see virus or viral debris



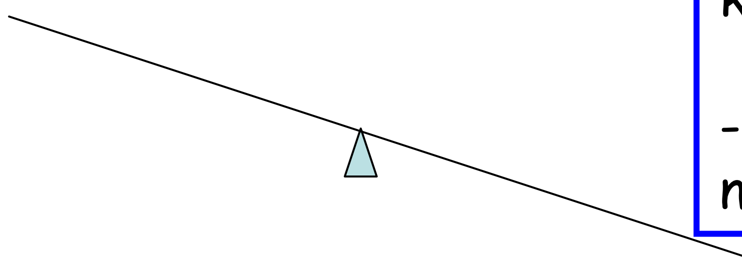
Types of vaccines

- Non-infectious vaccines
- Live attenuated vaccines
- Carrier vaccines
- DNA vaccines

Non-infectious vaccines

- **Inactivated or killed pathogen:** Salk Polio Vaccine, rabies vaccine
- **Subunit vaccines:** Hepatitis A & B, Haemophilus Influenza type B
- **Toxoid vaccines:** diphteria, tetanus and pertussis

-Will make B-memory cells and T-helper memory cells
= good antibody response



-Will not make memory killer T cells

-Booster vaccines usually needed

Live attenuated vaccines

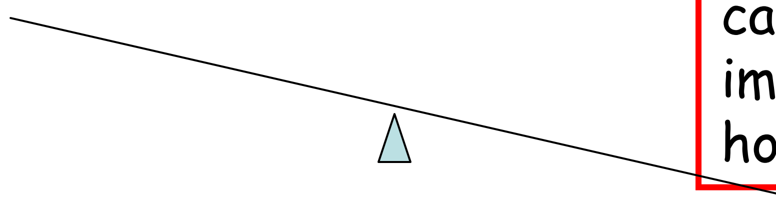
- Grow pathogen in host cells
- Produces mutations which:

  - weaken pathogen so it cannot produce disease in healthy people
  - yet still elicits strong immune reaction: and protection

- Sabin Polio Vaccine, Measles, Mumps Rubella, Varicella

-Makes memory cells: B-cells, T helper and Killer T cells

- Usually life-long immunity



Some viral shedding: can produce disease in immunocompromised host

Carrier vaccines

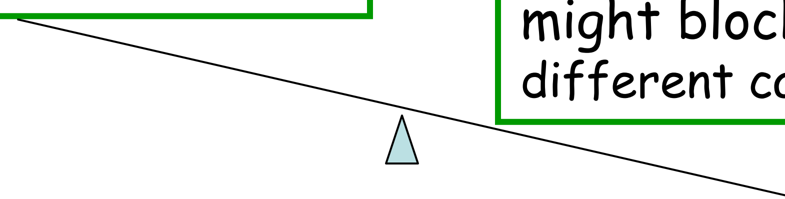
- Use virus or bacterium that does not cause disease to carry viral genes to APCs
  - e.g. vaccinia for Smallpox vaccine
  - http://www.bt.cdc.gov/agent/smallpox/vaccination/facts.asp

-Makes memory B cells, memory helper T cells, AND memory killer T cells

- Does not pose danger of real infection

-Immuno-compromised individuals can get infection from carrier

-Pre-existing immunity to carrier might block effect (must use different carrier for booster)

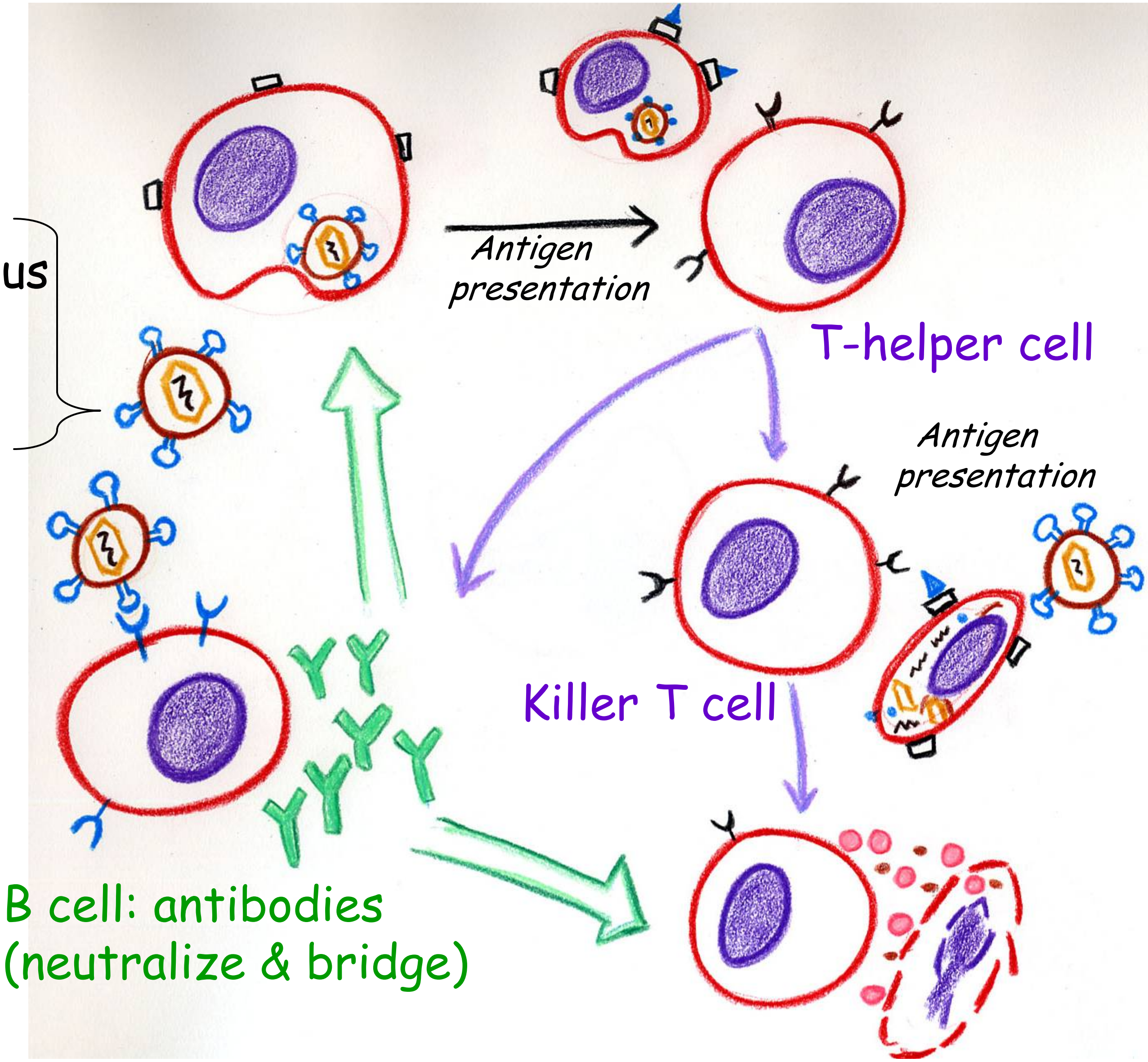


DNA vaccines

- DNA injections can transduce cells so antigens are expressed and presented.
- Reasons are not fully understood, but it can make memory B cells and memory T killer cells!
- Make a DNA vaccine from a few viral genes
- No danger that it would cause infection

How do vaccines work?

- Live attenuated virus
- Carrier vaccines
- DNA vaccines



- Non-infectious vaccines

…By inducing adaptive immunity & memory!

Types of vaccines

- Non-infectious vaccines
  - No danger of infection
  - Does not stimulate cell mediated immunity
  - Usually need booster vaccines
- Live, attenuated bacterial or viral vaccines
  - Makes memory B cells, memory helper T cells, AND memory killer T cells
  - Usually provides life-long immunity
  - Can produce disease in immuno-compromised host
- Carrier Vaccines
  - Makes memory B cells, memory helper T cells, AND memory killer T cells
  - Does not pose danger of real infection
  - Immuno-compromised individuals can get infection from carrier
- DNA Vaccines

Lecture map

The case of the Flu
- Viral Life cycle
- Antigenic drift
- Antigenic shift & pandemics

Vaccines

Types of vaccines

Are they effective?

History of Vaccines
Childhood Immunizations in US and the World
The HERD effect

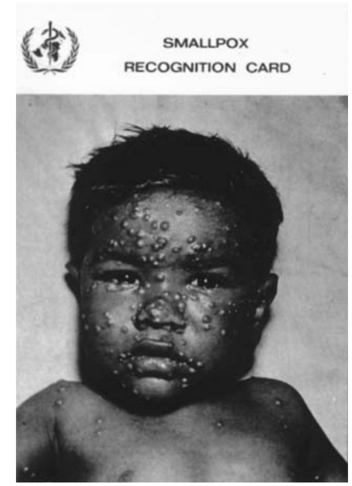
Are they safe?

FDA approval process
The thrimersoal debate

Vaccine manufacture

How are vaccines made?
Challenges for vaccine development

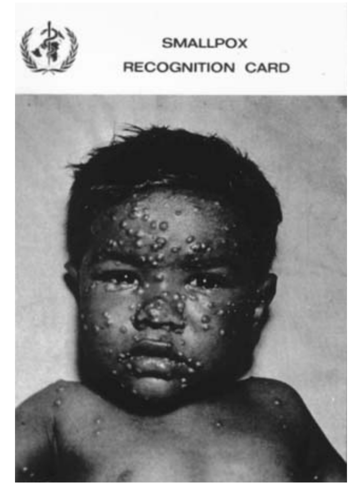
Are vaccines effective?



- History: 1798 - Edward Jenner noted:
  - Smallpox and Cowpox:
    - Milkmaids frequently contracted cowpox which caused lesions similar to that smallpox
    - Milkmaids who had cowpox almost never got smallpox
  - Jenner's (unethical) experiment:
    - Collected pus from cowpox sores
    - Injected cowpox pus into boy named James Phipps
    - Then injected Phipps with pus from smallpox sores
    - Phipps did not contract smallpox
  - First to introduce large scale, systematic immunization against smallpox

Are vaccines effective?

- History: 1798 - Edward Jenner



Are vaccines effective?

- 1885: Attenuated viral vaccine
  - Louis Pasteur - first vaccine against rabies
- Early 1900s: Toxoid vaccines
  - Diphtheria, tetanus
- 1936
  - Influenza
- 1950s: Tissue Culture-attenuated Poliovirus vaccine
  - Polio (Nobel Prize for Enders, Robbins, Weller)
- 1960s:
  - Live attenuated: Measles, Mumps, Rubella (MMR) vaccines

Are vaccines effective?

US vaccine schedule: Dec 2007-Sept 2008

Recommended Immunization Schedule for Persons Aged 0–6 Years—UNITED STATES • 2008

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼ Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB		*see footnote1*	HepB						
Rotavirus[2]			Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP	*see footnote3*	DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	*Hib*[4]	Hib					
Pneumococcal[5]			PCV	PCV	PCV	PCV				PPV	
Inactivated Poliovirus			IPV	IPV	IPV						IPV
Influenza[6]					Influenza (Yearly)						
Measles, Mumps, Rubella[7]						MMR					MMR
Varicella[8]						Varicella					Varicella
Hepatitis A[9]						HepA (2 doses)				HepA Series	
Meningococcal[10]										MCV4	

Range of recommended ages

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2007, for children aged 0 through 6 years. Additional information is available at www.cdc.gov/vaccines/recs/schedules. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. **Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations, including for high risk conditions:** http://www.cdc.gov/vaccines/pubs/ACIP-list.htm. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete VAERS form is available at www.vaers.hhs.gov or by telephone, 800-822-7967.

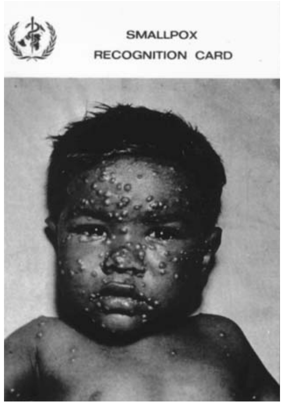
Are vaccines effective?

Effects of vaccination in the US

Disease	Max # of Cases	# Cases in 2000	% Decrease
Diphtheria	206,929 (1921)	2	-99.99
Measles	894,134 (1941)	63	-99.99
Mumps	152,209 (1968)	315	-99.80
Pertussis	265,269 (1952)	6,755	-97.73
Polio	21,269 (1952)	0	-100
Rubella	57,686 (1969)	152	-99.84
Tetanus	1,560 (1923)	26	-98.44
HiB	~20,000 (1984)	1,212	- 93.14
Hep B	26,611 (1985)	6,646	-75.03

Are vaccines effective?

Global effects of vaccination



- Smallpox
  - First human disease eradicated from the face of the earth by a global immunization campaign

- 1974
  - Only 5% of the world's children received 6 vaccines recommended by WHO

- 1994
  - >80% of the world's children receive basic vaccines
  - Each year: 3 million lives saved

Are vaccines effective?

1977: Goal to immunize at least 80% of world's children against six antigens by 1990

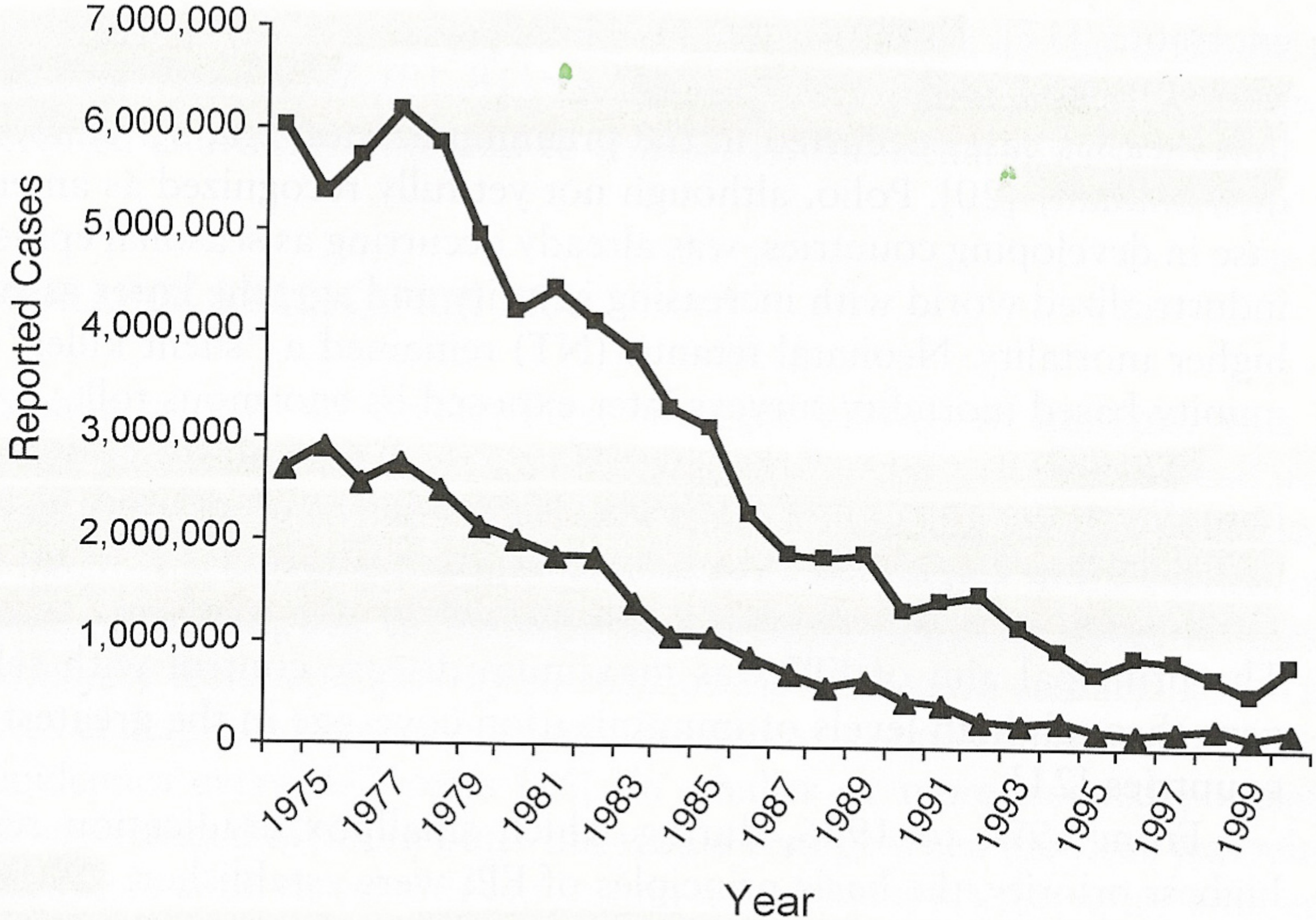


FIGURE 1 Measles (■) and pertussis (▲) cases reported to WHO, 1974–2000.

Effectiveness through THE HERD effect

• 1-2 out of every 20 immunized people will not develop and adequate immune response

• Still,

–Vaccinated people are much less likely to transmit a pathogen to others

-So even people that are not vaccinated are protected

85-95% of the community must be vaccinated to achieve herd immunity

http://www.npr.org/templates/story/story.php?storyId=11226682

Effectiveness through THE HERD effect

The case of diphtheria in the Soviet Union

FIGURE 3 Diphtheria cases reported to WHO globally (shaded bars) and from the European region (solid bars), 1974–2000.

Lecture map

The case of the Flu
- Viral Life cycle
- Antigenic drift
- Antigenic shift & pandemics

Vaccines

Types of vaccines

Are they effective?

History of Vaccines
Childhood Immunizations in US
The HERD effect

Are they safe?

FDA approval process
The thimerosal debate

Vaccine manufacture

How are vaccines made?
Challenges for vaccine development

Are vaccines safe?

Testing safety and effectiveness:

The case of Thimerosal (mercury preservative) in vaccines and autism

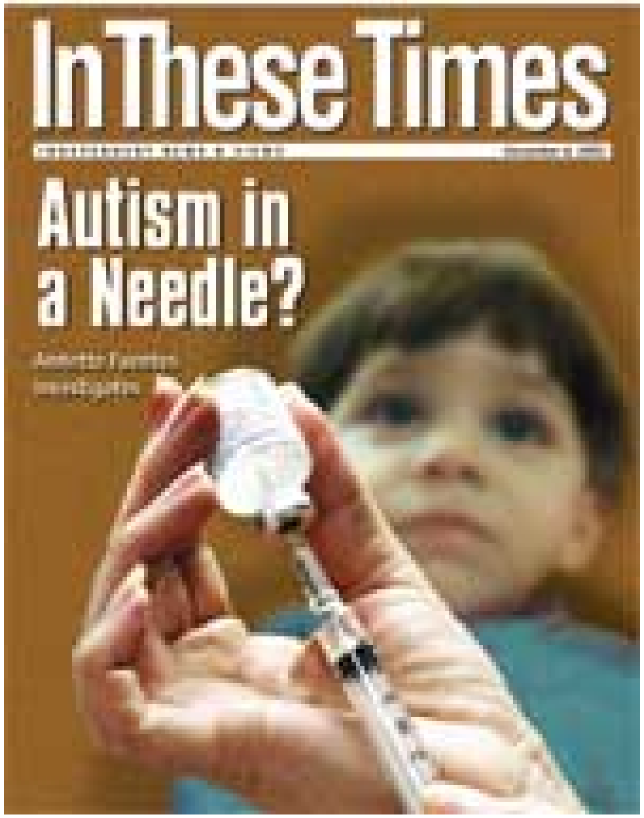
- Andrew Wakefield Lancet's paper (1998):

  Temporal relation between chronic gastro-intestinal disease and autism, and MMR vaccination.

-Advocates single vaccination over combined shot.

-MMR vaccination rates in UK drop from 80% to 62%

- Study tainted by conflict of interest!



Autism in the news: http://youtube.com/watch?v=u1TZUoG6mPk

http://www.cbsnews.com/stories/2007/06/11/health/main2911164.shtml

Are vaccines safe?

Testing safety and effectiveness

- Laboratory testing : Cell models
  Animal models

- Human trials: Phase I
  Phase II
  Phase III
  Post-licensure surveillance

Are vaccines safe?

Human trials:

- Phase I
  - 20-100 healthy volunteers
  - Last few months
  - → Determine vaccine dosages & side effects
- Phase II
  - Several hundred volunteers
  - Last few months to years
  - Controlled study: vaccine vs. placebo (or existing vaccine)
  - → Effectiveness & safety
- Phase III
  - Several hundred to several thousand volunteers
  - Last Years
  - Controlled **double blind study**: vaccines vs. placebo (Neither patient nor physicians know which)
- Post-licensure surveillance: Vaccine Adverse Effect Reporting System
  - VAERS: 12,000/yr, only ~2000 serious

Are vaccines safe?

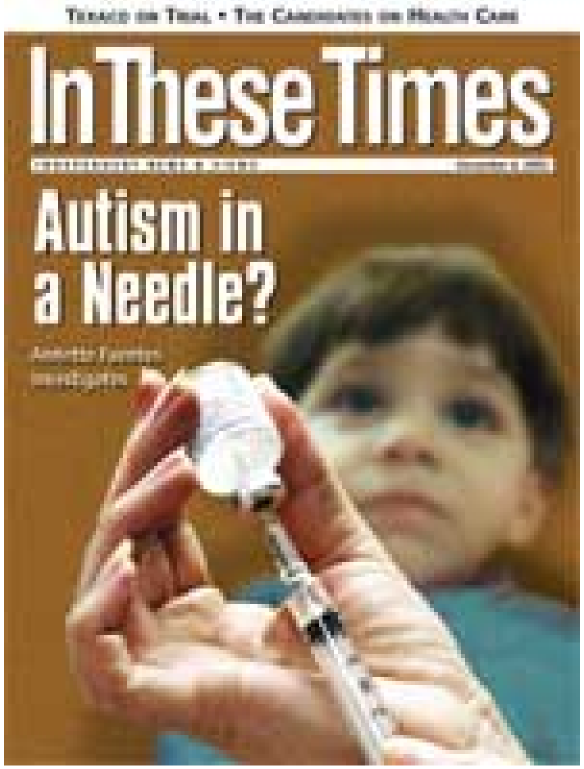
National Institutes of Medicine:
Immunization Safety Review Committee

1999: Evidence inadequate to accept or reject a causal relation.

-Relation biologically plausible

-Recommends "Full consideration be given to removing thimerosal from any biological product to which infants, children and pregnant women are exposed".

2004: More evidence from Denmark, Sweden, UK and more biological studies: reject causal relation.



FDA recommendations: http://www.fda.gov/Cber/vaccine/thimerosal.htm#thi

Lecture map

The case of the Flu
- Viral Life cycle
- Antigenic drift
- Antigenic shift & pandemics

Vaccines

Types of vaccines

Are they effective?

History of Vaccines
Childhood Immunizations in US
The HERD effect

Are they safe?
FDA approval process
The thrimersoal debate

Vaccine manufacture

How are vaccines made?

Challenges for vaccine development

How are vaccines made?

The trivalent influenza vaccine

1. CDC/WHO experts gather to decide which strains to target.

7 weeks

2. Virus reassortment in cell culture

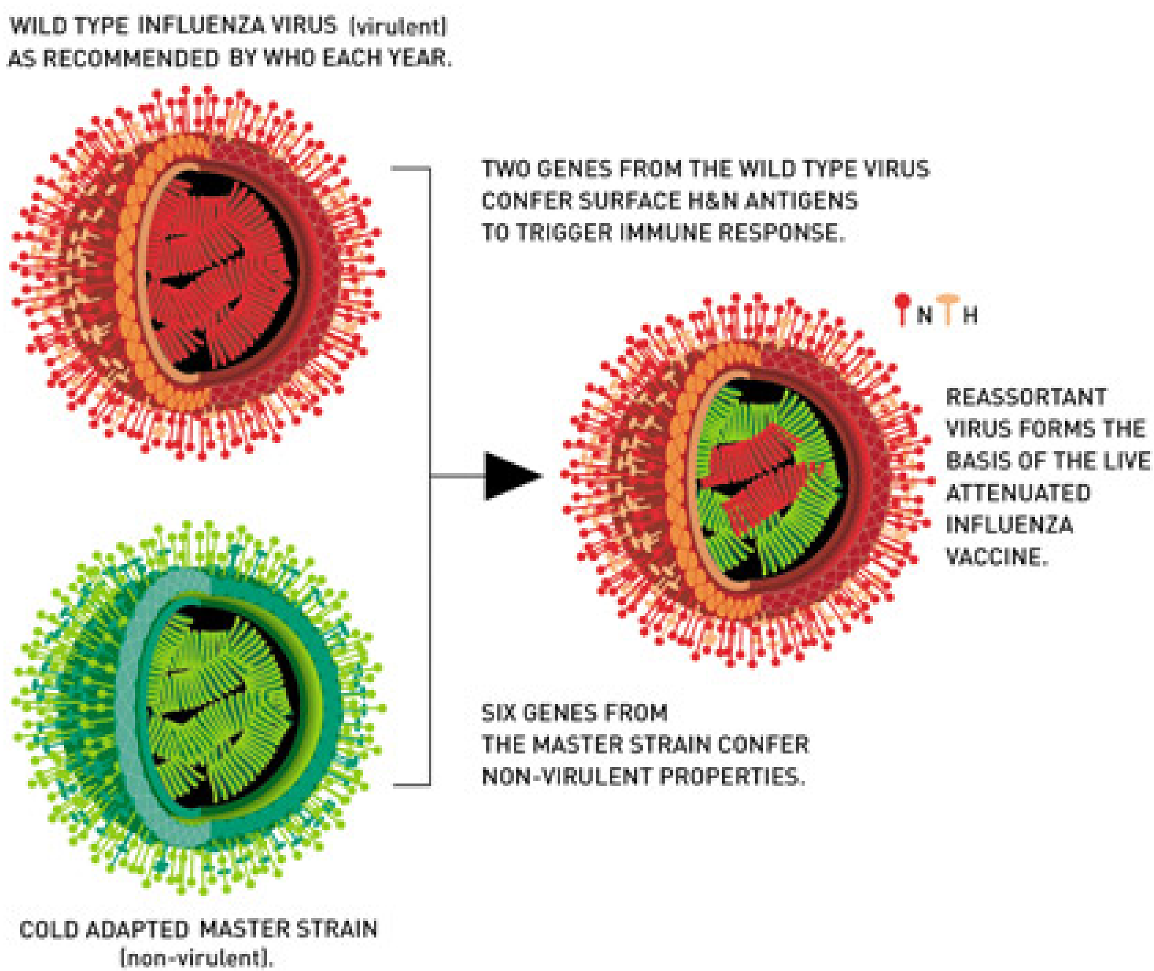
3. 300 million fertilized eggs are cleaned and inoculated with reassorted virus

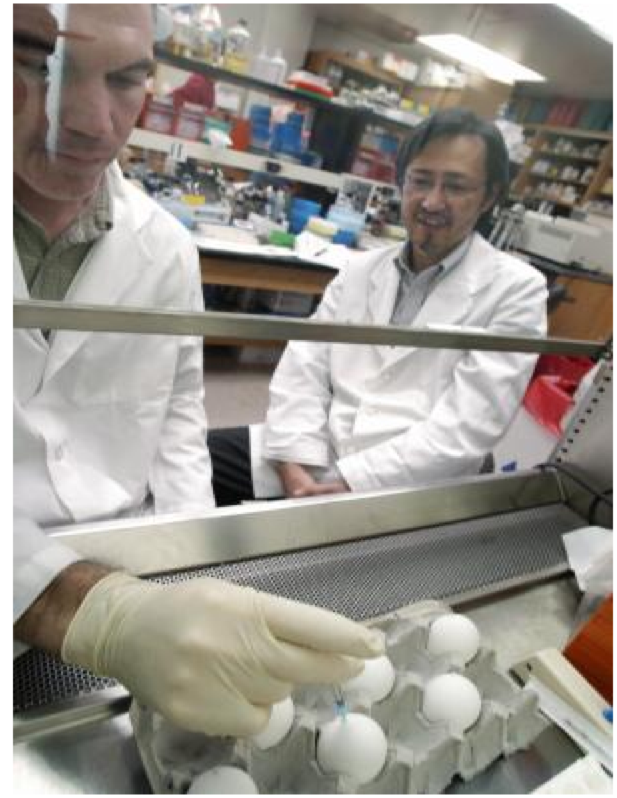
4. Viral fluid from eggs is harvested, centrifuged and filtered. Virus is inactivated with formalin

5. Purified inactivated virus from each strain is combined and packaged into doses

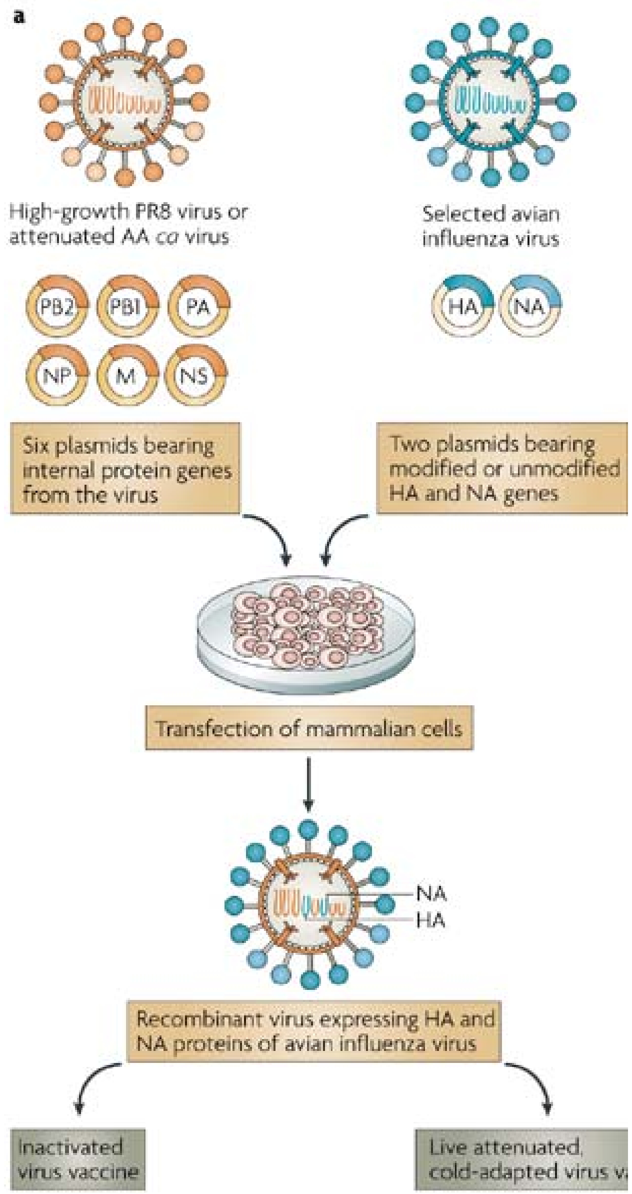
How are vaccines made?

The influenza vaccine

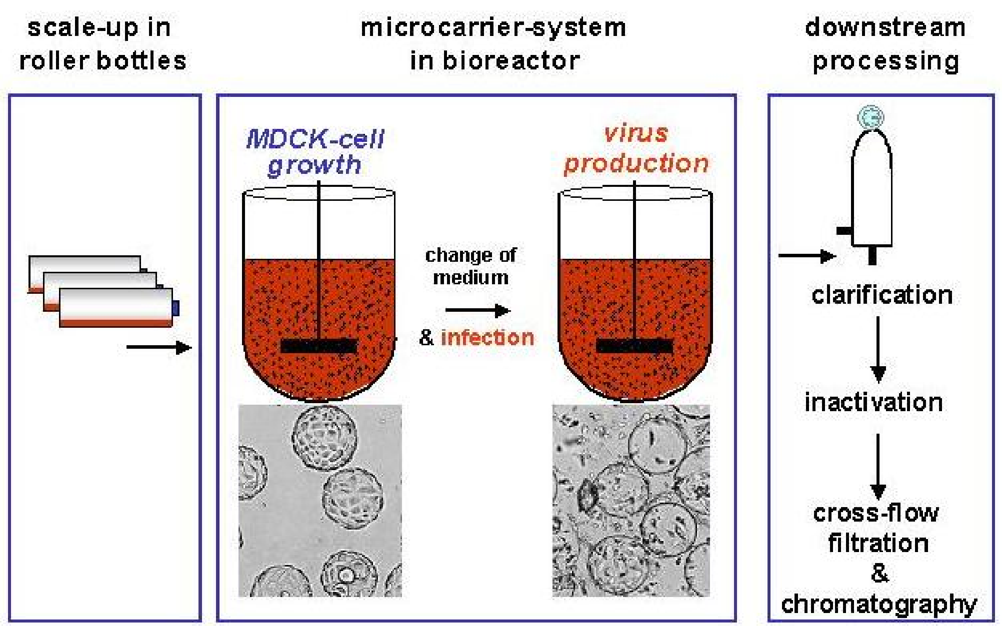




An alternative production approach:



1. Genetic engineering of virus
2. Growth in tissue culture cells



How are vaccines made?

The influenza vaccine

"I hate it when we're not sure we're inoculating against the right strain of flu virus."

Challenges for vaccine development

- In the developed world
  - **Cost of development:** facilities, regulations, litigation
  - **Market size** : only given once, 57% bought by public sector
  - **Litigation costs:** National Vaccine Injury Compensation Program

- In the developing world
  - Storage and transportation conditions
    - UV protection
    - The 'cold chain' / Freeze watch label
  - Syringe use
    - Auto-disposable syringes *eg. Solo-shot syringe*
    - Needle free methods
  - Cost
    - GAVI: Unicef, WHO, Gates, NGOs

How can technology help? The case of Smallpox

- One of world's deadliest diseases
  - Vaccine available in early 1800s
  - Difficult to keep vaccine viable enough to deliver in developing world

- Elimination of smallpox
  - 1950: stable, freeze dried vaccine
  - 1950: Goal → Eradicate smallpox from western hemisphere
  - 1967: Goal achieved except for Brazil
  - 1959: Goal → Eradicate smallpox from globe
    - Little progress made until 1967 when resources dedicated, 10-15 million cases per year at this time
      - Strategies:
        - » Vaccinate 80% of population
        - » Surveillance and containment of outbreaks
  - **May 8, 1980: world certified as smallpox free!**

Vaccines: what is still needed?

- The big three:
    - HIV
    - Malaria
    - Tuberculosis

Summary of lecture 9

- How do vaccines work?
  - Stimulate immunity without causing disease
- Different types of vaccines
  - Non-infectious vaccines
  - Live, attenuated bacterial or viral vaccines
  - Carrier Vaccines
  - DNA Vaccines
- Are vaccines effective?
- How are vaccines tested?
  - Lab/Animal testing
  - Phase I-III human testing
  - Post-licensure surveillance

For next time, 2/12/2008:

-Read: **The Vaccine** by Michael Specter.

It can be found on Michael Specter's website through the following link:

http://www.michaelspecter.com/ny/index.html