THE SCIENCE, MANUFACTURE AND FUTURE OF VACCINES

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Harrisburg University of Science & Technology

Agenda

- Introduction
- Basic Immunology
- Historical Perspective
- Vaccine Manufacturing Case Studies
- Futures

Vaccine Development

WHY??

The spread of SARS: A worldwide problem

Severe acute respiratory syndrome was first reported in the Guangdong province of China and quickly spread across the globe. Scientists say a lack of knowledge about the syndrome and the Chinese government's initially slow and incomplete reporting of the disease have made it more difficult to contain the problem. A look at the spread of the disease, its cause and how it is being fought worldwide:

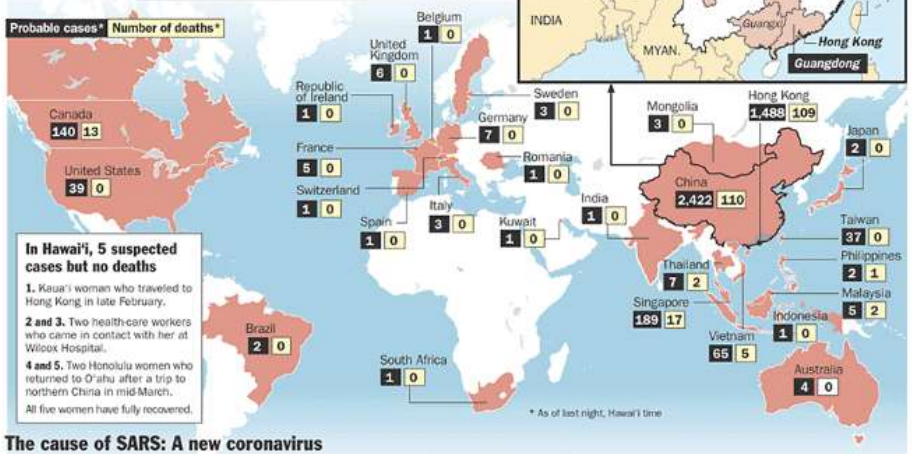
27 countries, 259 deaths: Total number of probable SARS cases*

4,443 people are suspected of having severe acute respiratory syndrome; of those 259 have died from the disease. The numbers change daily as more SARS cases are confirmed or cases mistakenly diagnosed as SARS are reclassified.

A masked pedestrian in Guangzhou, Guangdong Province, where the mysterious illness was first reported.

Was China the source?

The virus may have originated in the **Guangdong Province** in mid-November. The province, which is densely populated and has humans and animals living in close contact, provided an ideal breeding ground for the new virus. It migrated to **Hong Kong,** the launching pad to the rest of the world.



In Hawai'i, 5 suspected cases but no deaths

1. Kaua'i woman who traveled to Hong Kong in late February.

2 and 3. Two health-care workers who came in contact with her at Wilcox Hospital.

4 and 5. Two Honolulu women who returned to O'ahu after a trip to northern China in mid-March.

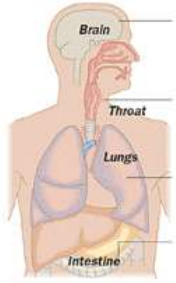
All five women have fully recovered.

The cause of SARS: A new coronavirus

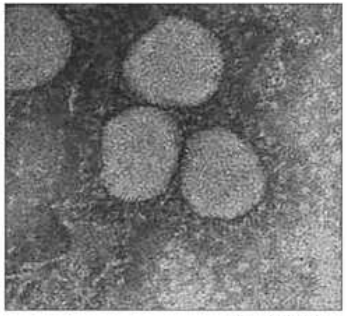
Working separately, scientists in Vancouver and the Centers for Disease Control and Prevention fully mapped the genome of a brand-new coronavirus, using viruses isolated from SARS cases in Asia and Canada. Tests on monkeys confirmed that the coronavirus causes SARS, according to the World Health Organization. The genetic information about the coronavirus could lead to more accurate diagnostic tests, more specific treatment and eventually, a vaccine.

Symptoms and treatment

Patients receive treatment similar to what would be used for community-acquired atypical pneumonia of unknown cause. Treatment regimens include antibiotics, antiviral agents and steroids. Presently, the most effective treatment regimen is unknown.



- The illness usually begins with a fever and a temperature greater than 100.4 degrees accompanied by headache, chills, discomfort and body aches.
- After two to seven days, patients may develop a dry, nonproductive cough that could lead to insufficient oxygen in the blood.
- In 10 percent to 20 percent of cases, the respiratory illness is severe enough to require mechanical ventilation.
- Some patients experience diarrhea with the onset of a fever.

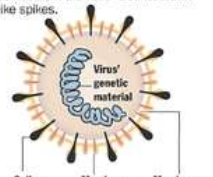


World Health Organization

Particles of the SARS coronavirus.

What is a coronavirus?

First isolated from chickens in 1937, there are now about 15 species in this family. Coronaviruses are what cause the common cold. They infect not only humans but cattle, pigs, rodents, cats, dogs and birds. The name "corona" comes from the virus' distinct crown-like spikes.

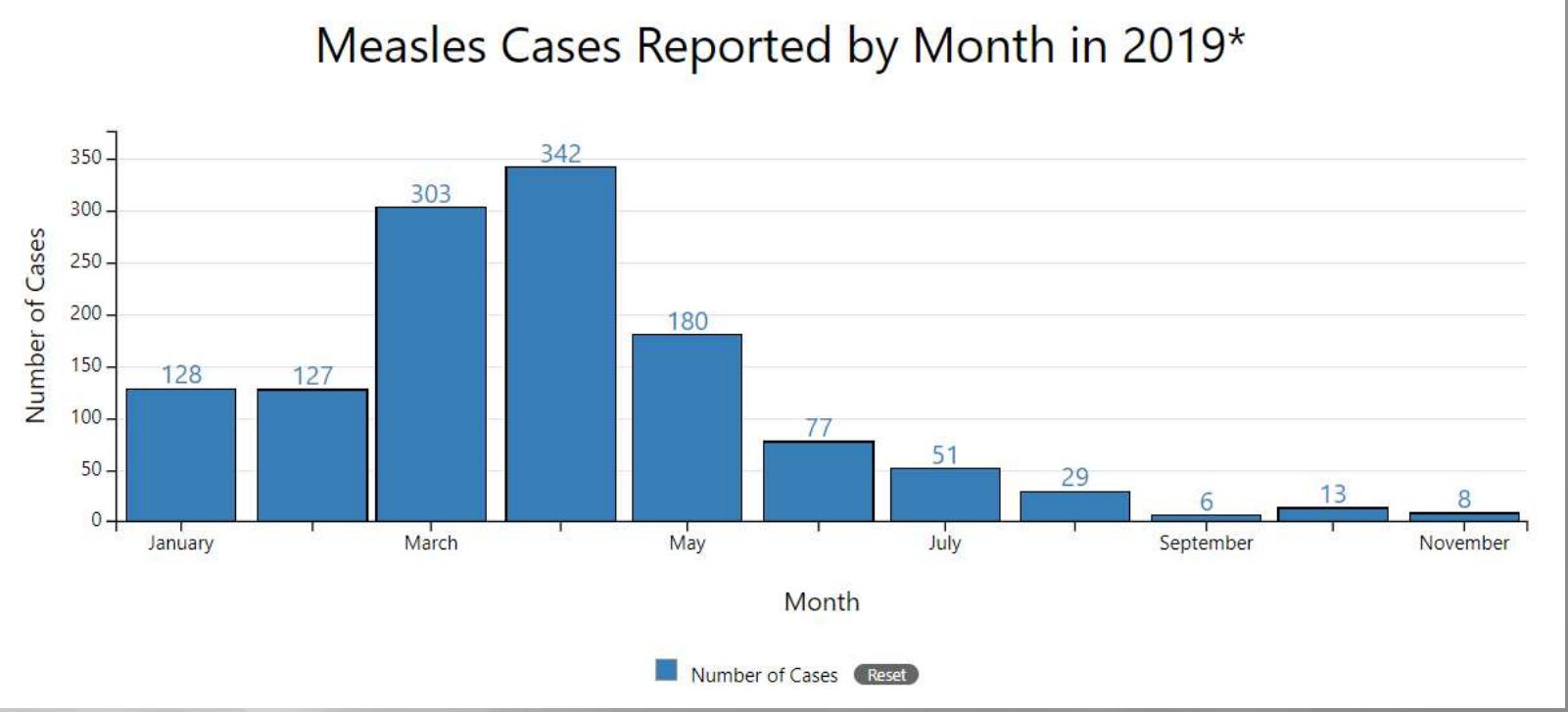


Spikes glycoproteins Binds to host cells and allow virus to enter new cell.

Membrane glycoproteins Works with spikes

Membrane enveloping virus

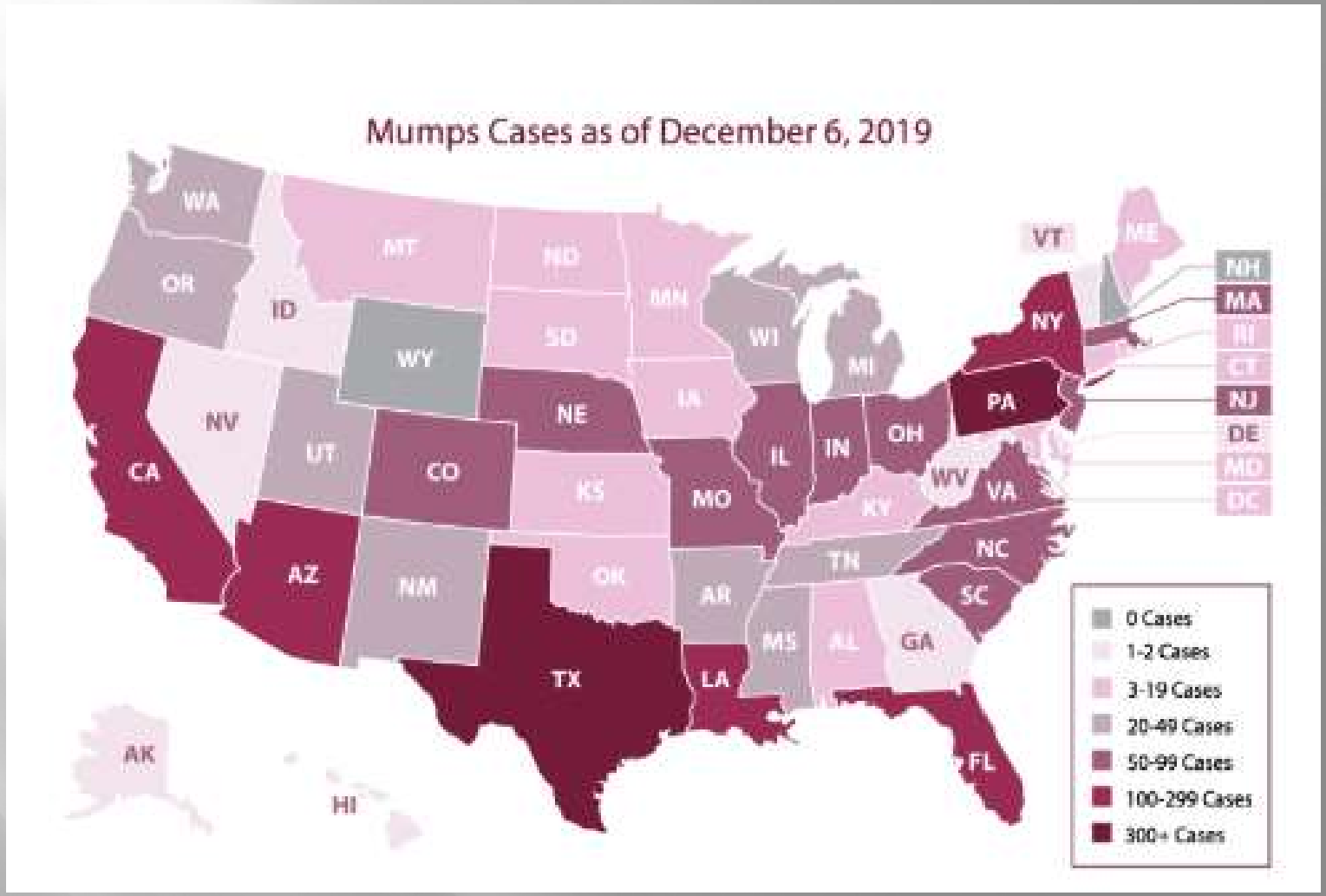
Vaccine Development



- From 1-Jan thru 5 December 2019: 1,276 cases in the US
- Most cases since 1992
- >75% of cases linked to outbreak in NY

Source: CDC

Vaccine Development



Source: CDC


冨嶽三十六景
神奈川沖
浪裏

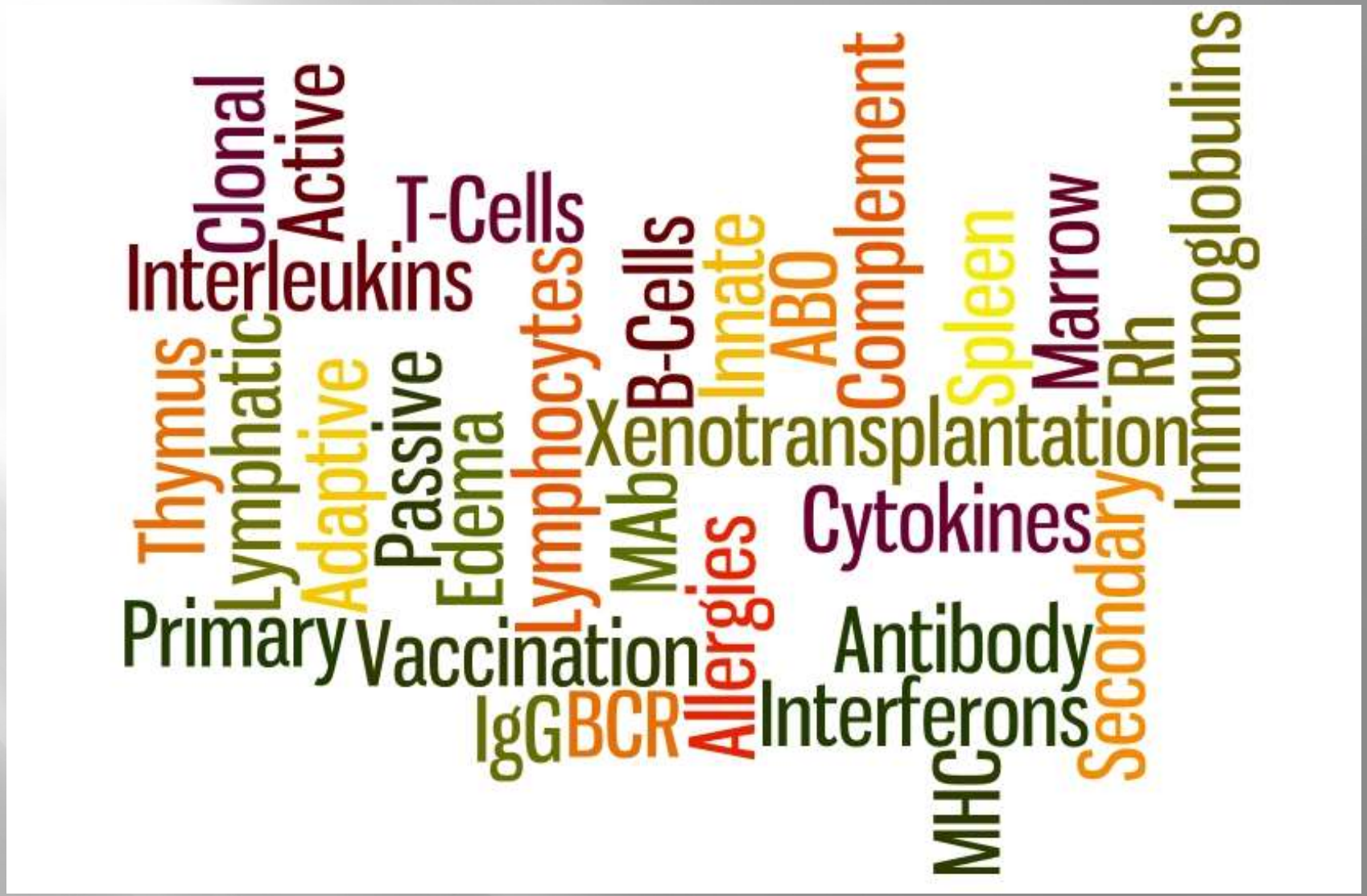
Emerging Diseases

Emerging Diseases

Emerging Diseases

Emerging Diseases


Dennis'
CRASH
COURSE
Immunology


Clonal
Active
T-Cells
Interleukins
Thymus
Lymphatic
Adaptive
Passive
Edema
Lymphocytes
B-Cells
Innate
ABO
Complement
Spleen
Marrow
Rh
Immunoglobulins
Xenotransplantation
MAb
Cytokines
Primary
Vaccination
Allergies
Antibody
IgG
BCR
Interferons
MHC
Secondary

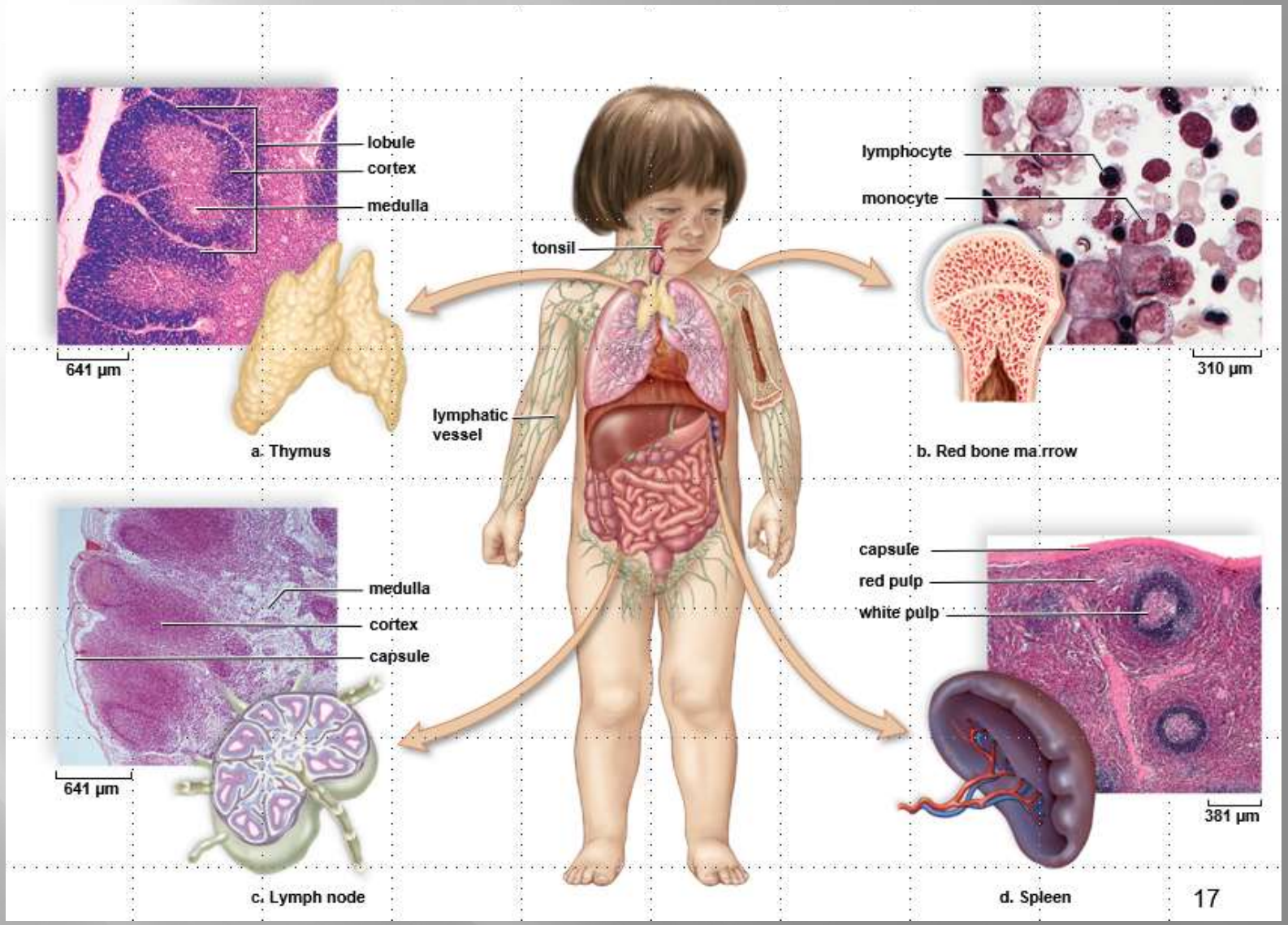
Definitions

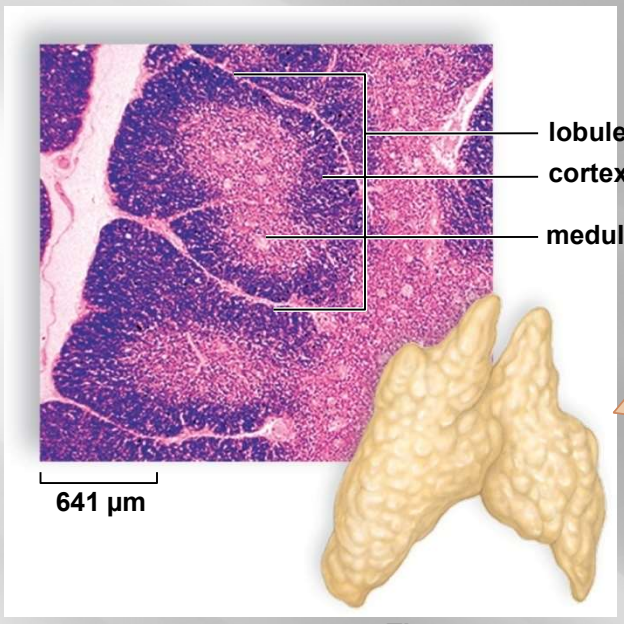
- Immune System: Cells, tissues, and molecules that mediate resistance to infections
- Immunology: Study of the structure and function of the immune system
- Immunity: Resistance of a host to pathogens and their toxic effects
- Immune Response: Collective and coordinated response to the introduction of foreign substances in an individual mediated by the components of the immune system.

Lymphatic System

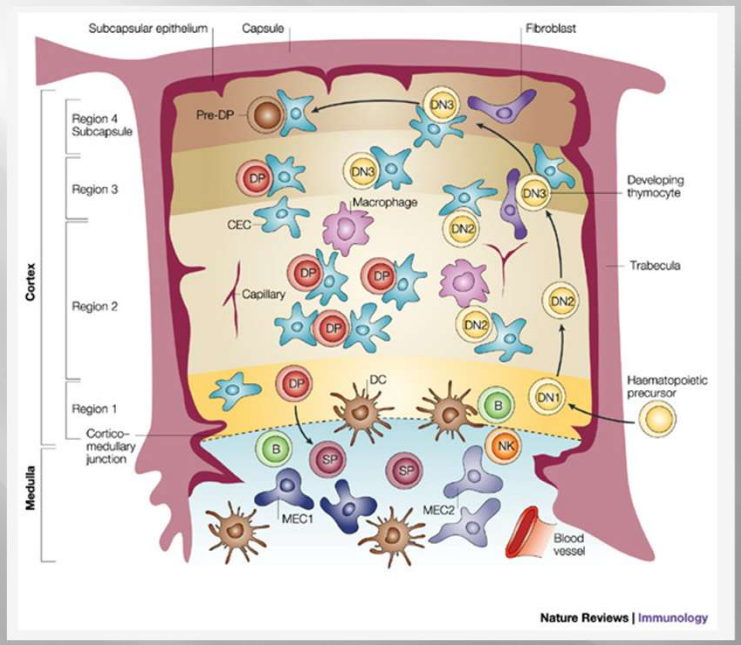
- Primary lymphoid organs
  - Red bone marrow
  - Thymus
- Secondary lymphoid organs
  - Spleen
  - Lymph nodes

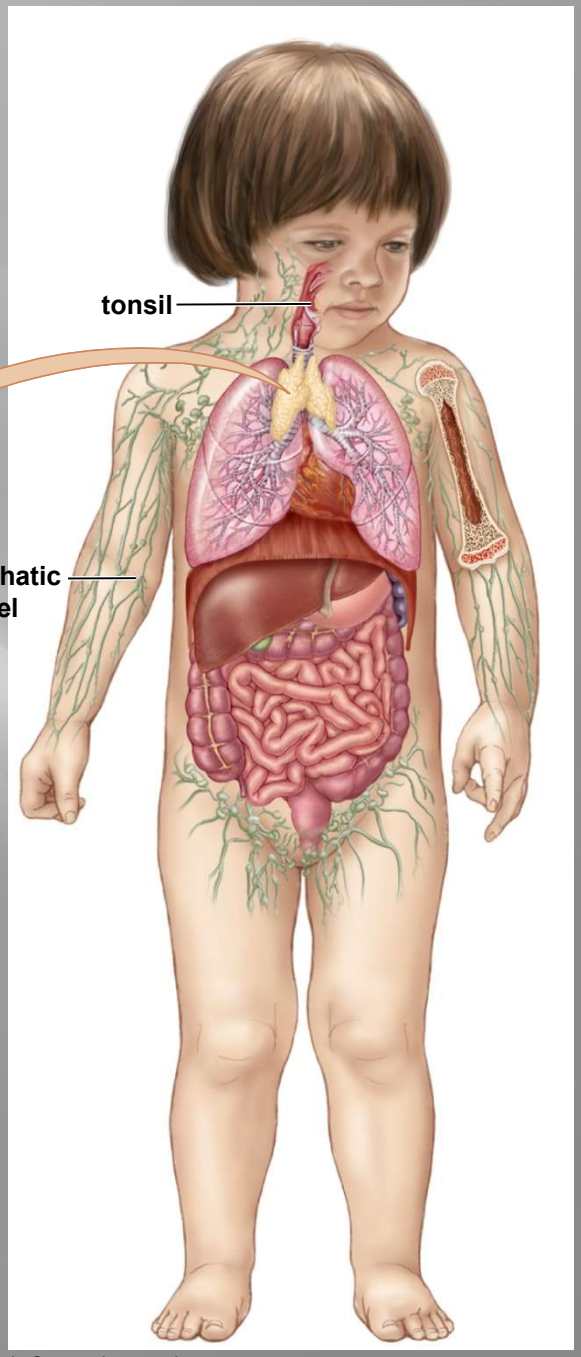
Lymphatic System



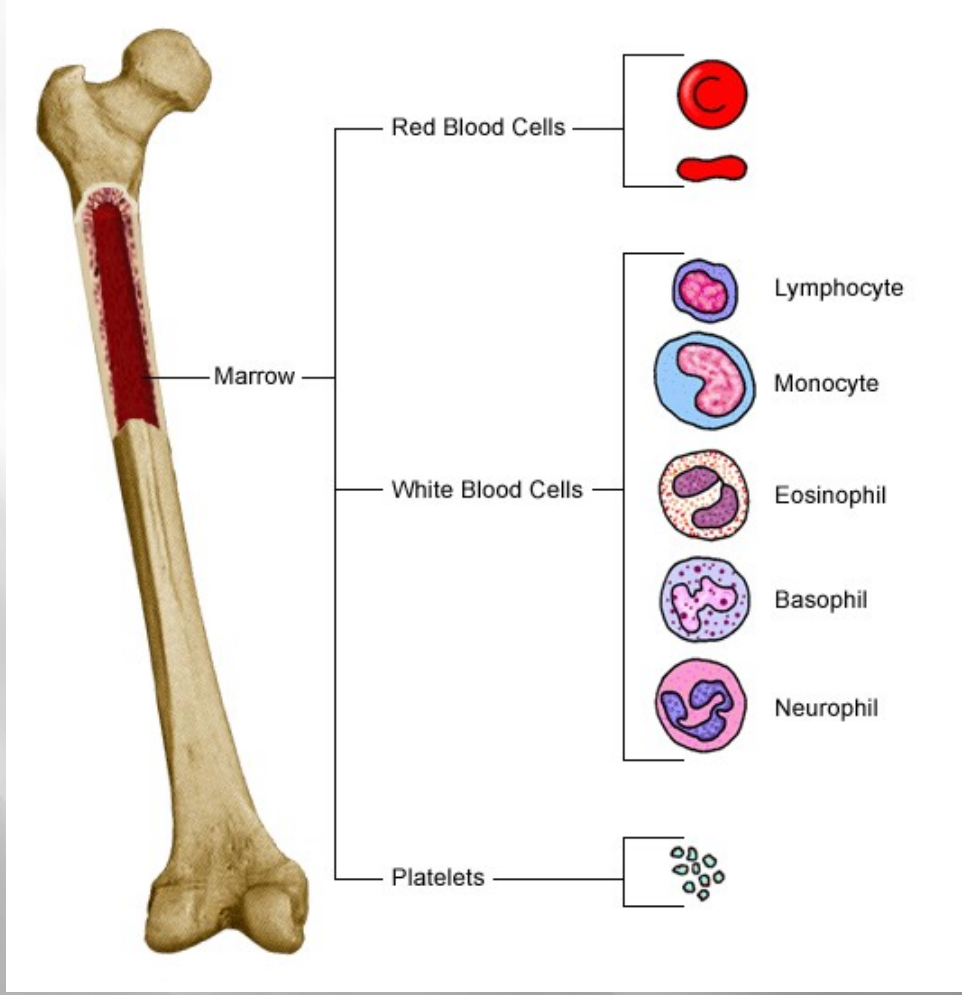


a. Thymus

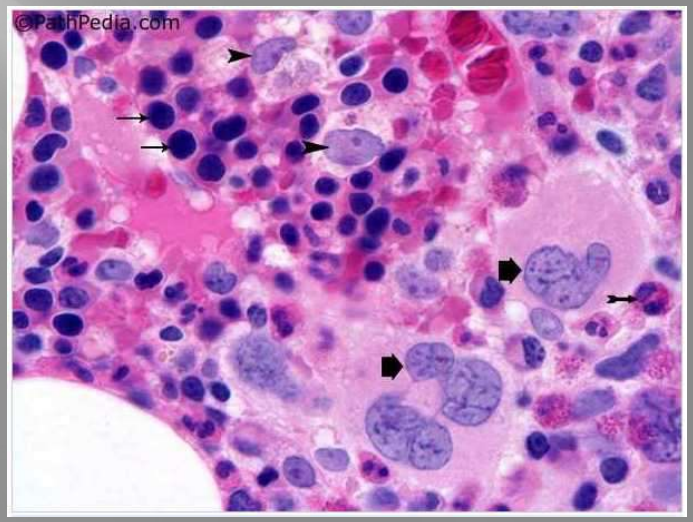




Bone Marrow


Marrow
Red Blood Cells
White Blood Cells
Platelets
Lymphocyte
Monocyte
Eosinophil
Basophil
Neurophil


©PathPedia.com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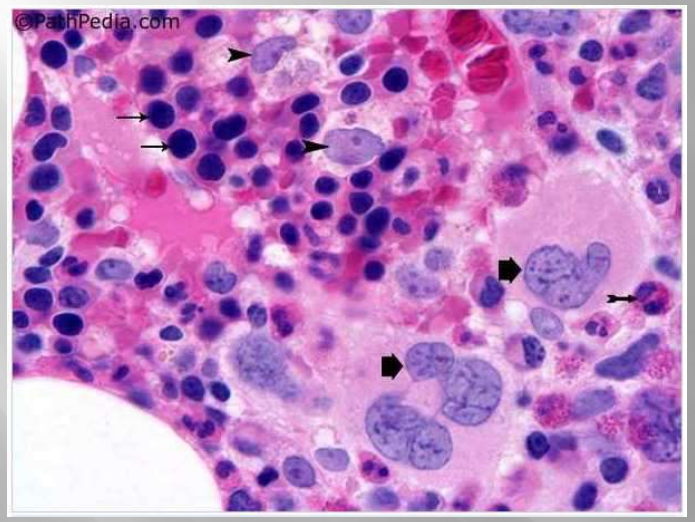
Bone Marrow

CHILDREN

- Most bones contain red bone marrow



ADULT

- Present only in the bones of:
  - Skull
  - Sternum
  - Ribs
  - Clavicle
  - Pelvic bones
  - Vertebral column

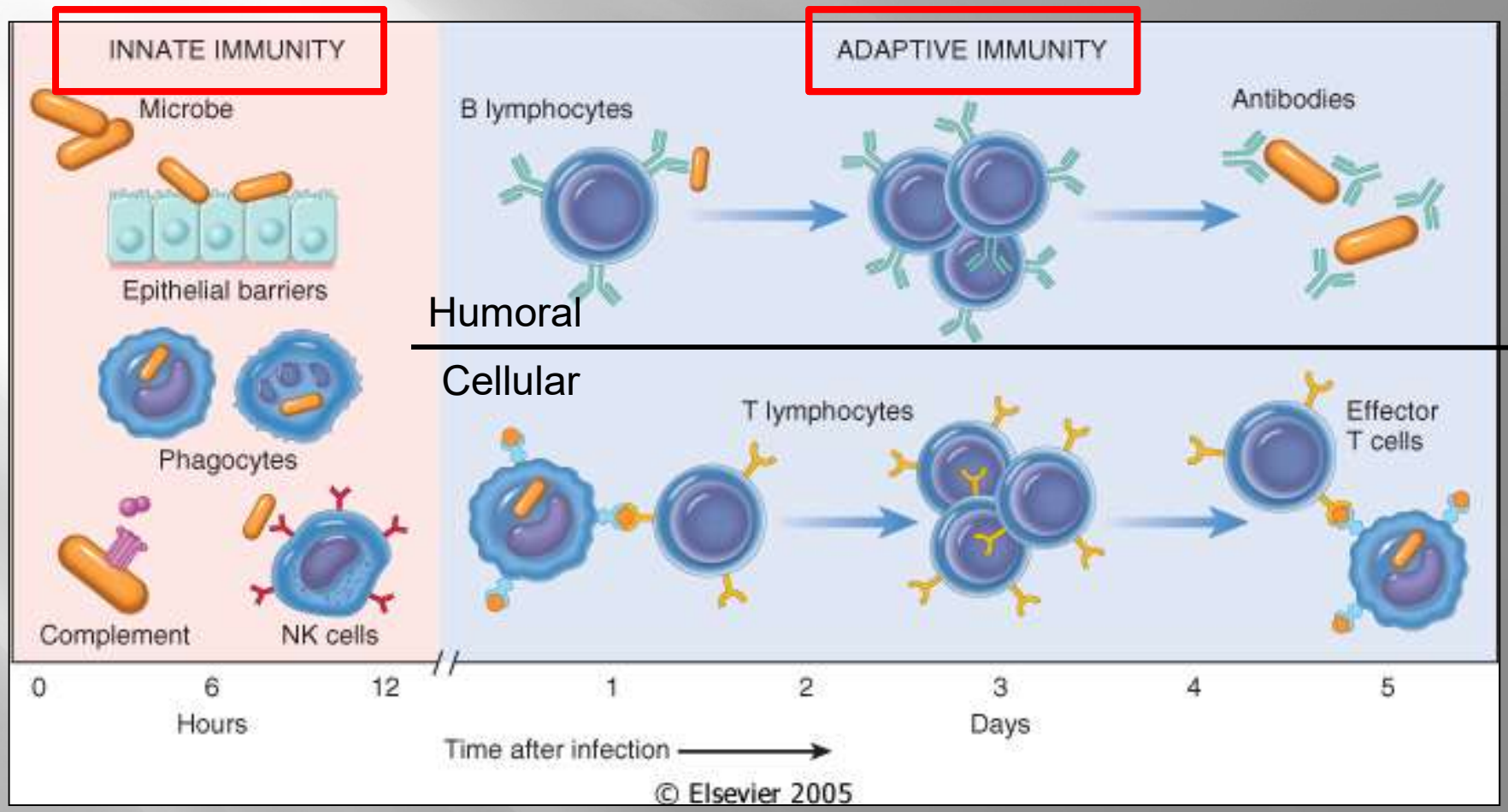
Characteristics of Innate and Adaptive Immunity

Characteristic	Innate	Adaptive
Species	All metazoans	Vertebrates only
Specificity	Molecular patterns	Pathogen specific
Chronology	Immediate	Days-weeks
Antigen contact	Irrelevant	Required
Memory	*No*	*Yes*

Arms of the Immune System

Broad range

Highly specific



Innate and Adaptive Immunity

- Immunity is the body's capability of removing or killing foreign substances, pathogens, and cancer cells
- Innate immunity mechanisms are fully functional without previous exposure to an unwanted substance
- Adaptive immunity is dependent upon exposure to specific antigens
  - Antigen: *Any molecule that stimulates an immune response*

Innate immunity

- Inborn
- First line of defense
- Components:
  - Physical barriers
  - Macrophages, natural killer cells, antigen-presenting cells
  - Soluble mediators

Innate Immunity

- **Physical and Chemical Barriers**
  - Skin and mucous membranes are mechanical barriers
  - Upper respiratory tract has cilia to remove mucus and trapped particles
  - Oil glands in the skin secrete chemicals to weaken or kill some bacteria
  - Stomach is acidic
  - Normal bacteria in the intestines and other areas out compete potential pathogens

Innate Immunity

- **Inflammation**
  - Inflammatory reaction caused by physical or chemical damage to tissue
  - Tends to wall off infections and increase exposure to immune system
  - Four signs
    - Redness, heat, swelling, and pain
  - Inflammatory reaction that persists may become harmful

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Adaptive [Acquired] Immunity

- **Antigen**
  - A substance (molecule) that the body identifies as foreign and it mounts an immune response.
  - It is also known as an immunogen
  - Most antigens are proteins and their structure is complex. Large proteins may have several epitopes or antigenic determinants
  - Some are glycoproteins, nucleoproteins, or polysaccharides.

Adaptive [Acquired] Immunity

- **Antibody**
  - Antibodies are molecules that are produced as a response to foreign invaders
  - It is specific for an antigen
  - It has the capacity to bind to the antigen.

Adaptive [Acquired] Immunity

- **Adaptive Immunity**
  - These defenses do not ordinarily react to our own normal cells
    - Immune system is able to distinguish "self" from "non-self"
  - Usually take 5 to 7 days to become fully activated
    - *The immunity may last for years*

Adaptive [Acquired] Immunity

- **B cells**
  - Give rise to plasma cells which produce antibodies
  - Antibodies combine with and neutralize particular antigens hence the term neutralizing antibodies.
  - After the binding of the antigen to the antibody, the B cells process the antigen by breaking it into tiny fragments.
- **T cells**
  - Do not produce antibodies
  - Differentiate into
    - Helper T cells – release chemicals [cytokines] to regulate immune system
    - Cytotoxic T cells – attack and kill virus-infected or tumor cells

What is a Vaccine?

- **Vaccine:** A preparation of microorganisms (*e.g.*, bacterium, virus), or their antigenic components administered for the prevention, amelioration or treatment of an infectious disease
  - Biologic preparation that elicits immune response with memory
  - Generates humoral (antibody) and/or cellular (cytotoxic or killer T-cell) response to eliminate pathogen or pathogen infected cell
  - The immune system is then primed to mount a secondary immune response with strong and immediate protection upon future exposure to the pathogen

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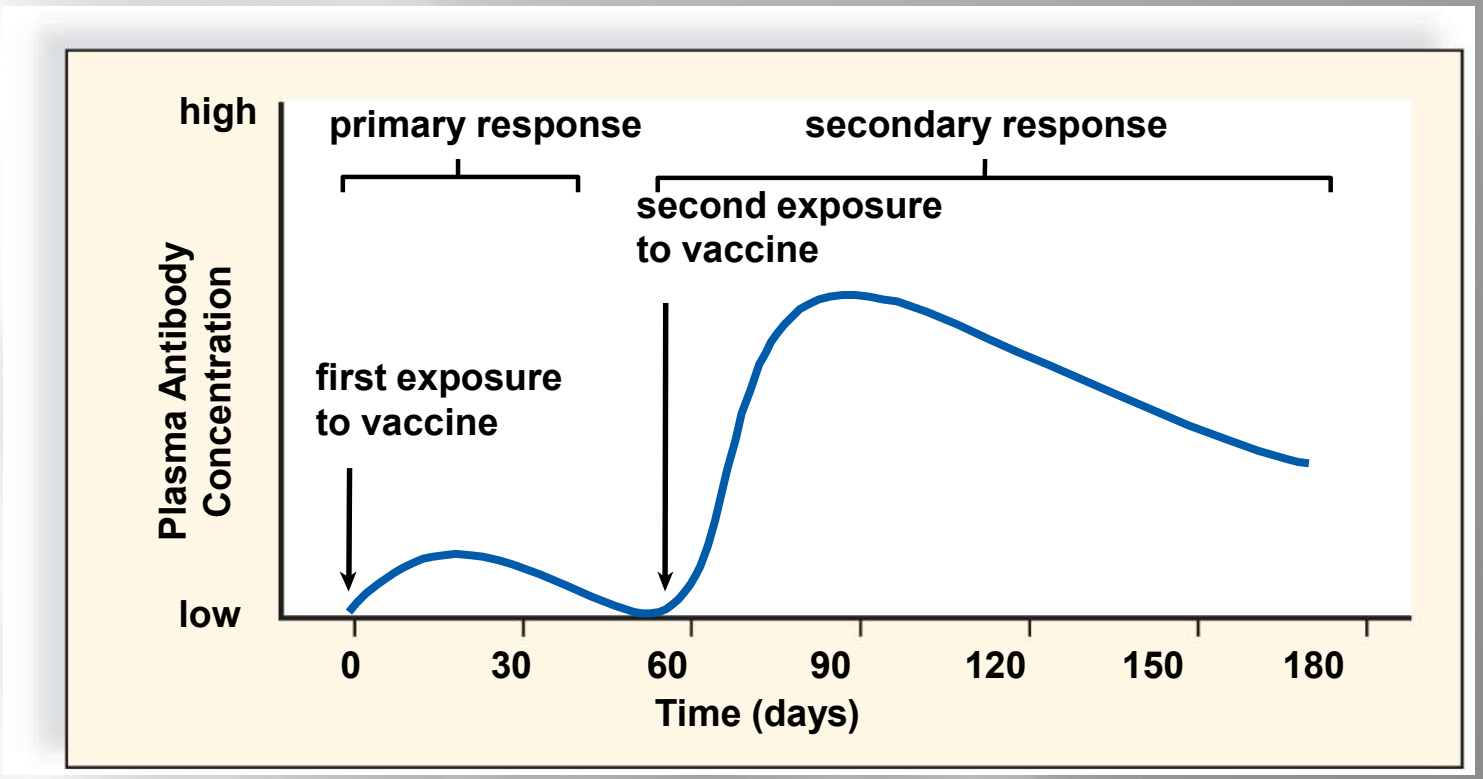
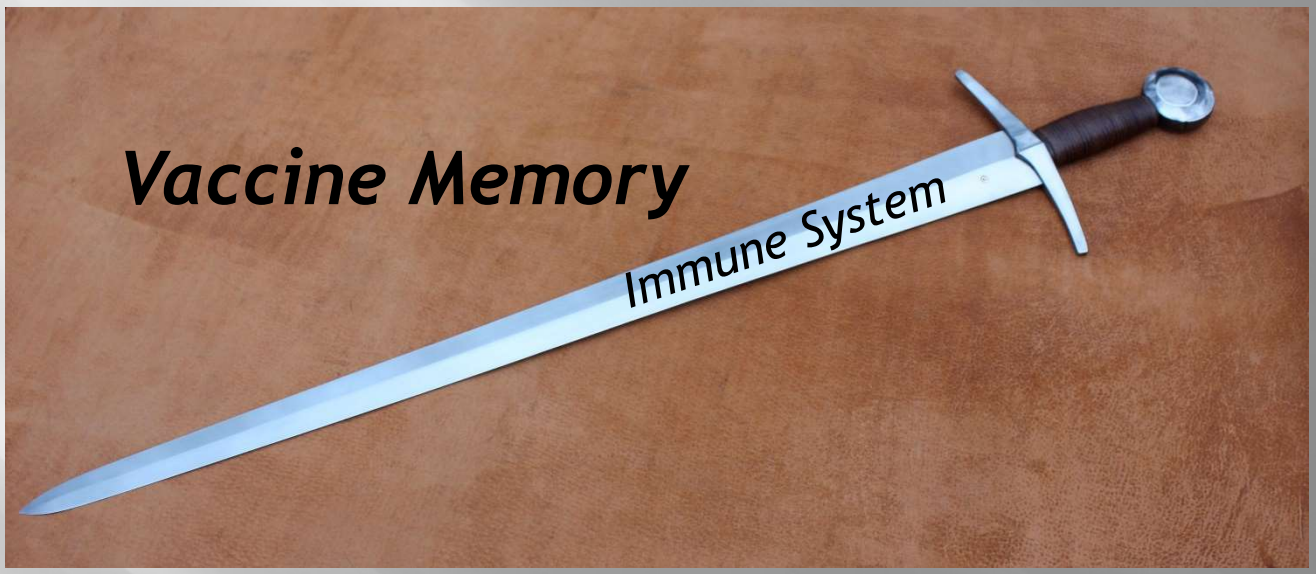


- Follow immune response using antibody titer
  - 1st exposure – titer rises slowly
  - 2nd exposure – titer rises rapidly and to a higher level

Memory: The Two-Edged Sword

Memory: The Two-Edged Sword



Memory: The Two-Edged Sword

Vaccines: Forms

- **Vaccines**
  - Attenuated: M-M-R, Rotavirus, Varicella, Zostavax
  - Killed or Inactivated: IPV, HepA, Flu
  - Toxoids: Diphtheria, Tetanus
  - Sub-unit: HepB, acellular Pertussis, HPV
  - Vector-based vaccine: Canary pox, Adenovirus,
  - DNA: In research phase
  - Peptide vaccine: Epitope vaccine, peptide immunogens (HER-2/neu);

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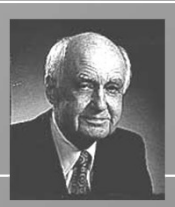
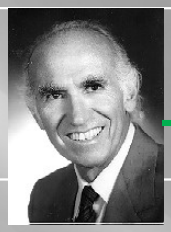
Vaccine History

Ref. Hilleman, Nature Medicine, 4, 504, 1998



Maurice Hilleman
1919 - 2005

Albert Sabin
1906 - 1993



Jonas Salk
1914 - 1995

Edward Jenner
1749 - 1823

Louis Pasteur
1822 - 1895

1796 Smallpox

1885 Rabies

1923 Diphtheria

1926 Pertussis

1927 Tetanus

1935 Yellow Fever

1955 Polio

1956 Adenovirus

1962 Oral Polio

1963, 1968 Measles

1965 Japanese encephalitis

1967 Mumps

1969 Rubella

1971, 1978 MMR

1974 Meningococcal

1977 Pneumococcal 14-valent

1981 Hepatitis B

1983 Pneumococcal 23-valent

1986 Hepatitis B (Recombinant)

1989 Hib Conjugate

1995 Varicella

1996 Hepatitis A

1996 Hib-Hep B

1996 DTacP

1998 Lyme

1999 Pneumococcal conjugate

1780 1800 1820 1840 1860 1880 1900 1920 1940 1960 1980 2000

Historical Perspective

- Smallpox
- Pertussis
- Polio
- Hepatitis B
- Influenza

Protection from Cholera

Picture courtesy of Wellcome Library, London

Smallpox - 1796
Live Virus

- 1796 - Edward Jenner
  - Vaccine made from pus of cowpox patients and milk maids
  - Coined the term “vaccination”
  - First recognized use of a vaccine

- *No purification!*

Smallpox - 1796

Live Virus

- 17th century Chinese practice
  - Vaccinating with scabs from smallpox patients

- 1796 - Edward Jenner
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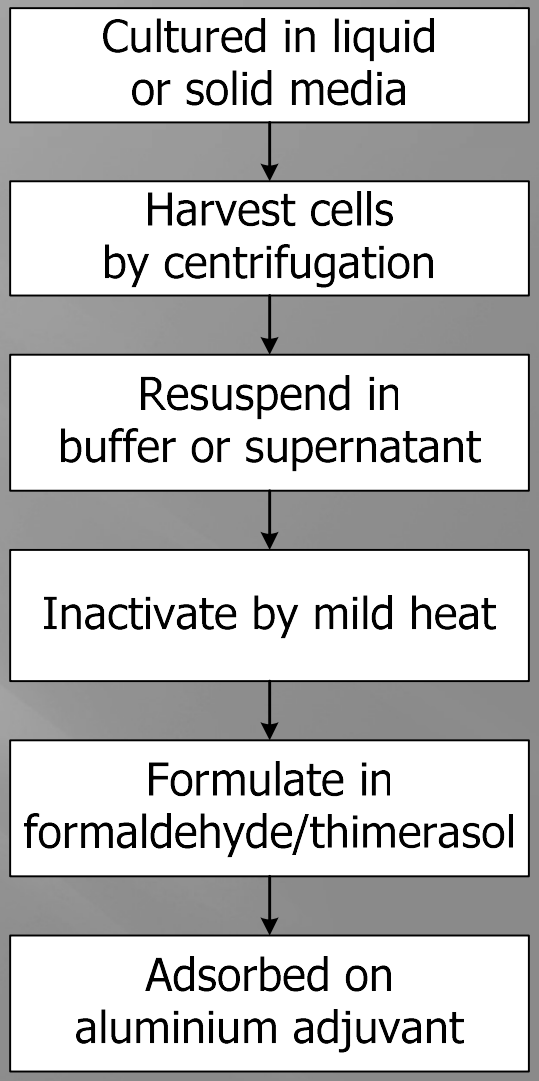
11 Substances in development: Antivirals and Vaccines

Pertussis (1914)

Inactivated Bacteria

- Whooping cough caused by *B. pertussis*, a small gram-negative bacteria
- Vaccine - suspension of killed whole cells of bacteria
- Whole cell pertussis vaccine first licensed in the US in 1914
  - Later combined with diphtheria and tetanus toxoids (DTP) in 1942
- Lack of purity caused some side effects
  - Led to the development of acellular pertussis (subunit vaccine)



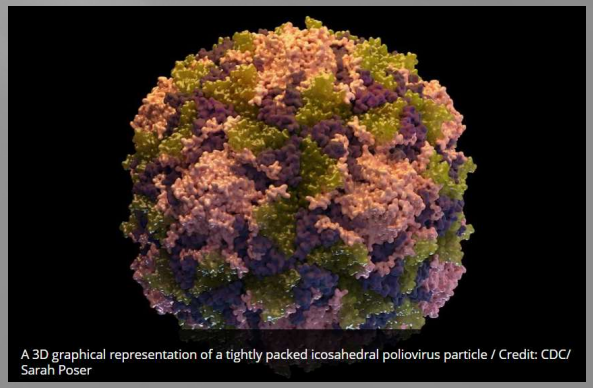
Ref. Aunins, Lee and Volkin, in The Biomedical Engineering Handbook, CRC Press, Boca Raton, 1995

Polio Vaccines

Inactivated and Live Attenuated Viruses

An Egyptian stele thought to represent a polio victim, 18th Dynasty (1403-1365 BC)

A girl with a deformity of her right leg due to polio



A 3D graphical representation of a tightly packed icosahedral poliovirus particle / Credit: CDC/ Sarah Poser

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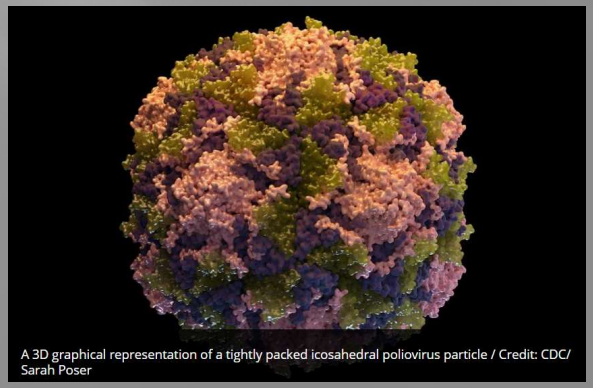

A 3D graphical representation of a tightly packed icosahedral poliovirus particle / Credit: CDC/ Sarah Poser

Polio Vaccines

Inactivated and Live Attenuated Viruses

- *Enders* successfully cultivated virus in tissue culture (1949)
- Inactivated virus developed by *Salk* (1955)
- Oral polio (Live virus) developed by *Sabin* (1963)
  - Less expensive and simple to use

IPV

Cell Culture → Centrifugation → Formalin Inactivation

Monkey Kidney Cells

Harvest extracellular medium

OPV

Cell Culture → Centrifugation → 0.22 um filtration

Monkey Kidney Cells

Harvest extracellular medium

Ref. Salk, JAMA, 151, 1081, 1953

Ref. Aunins, in Encyclopedia of Cell Tech., Ed. Spier, Wiley & Sons, NY, 2000

Polio Vaccines

Inactivated and Live Attenuated Viruses

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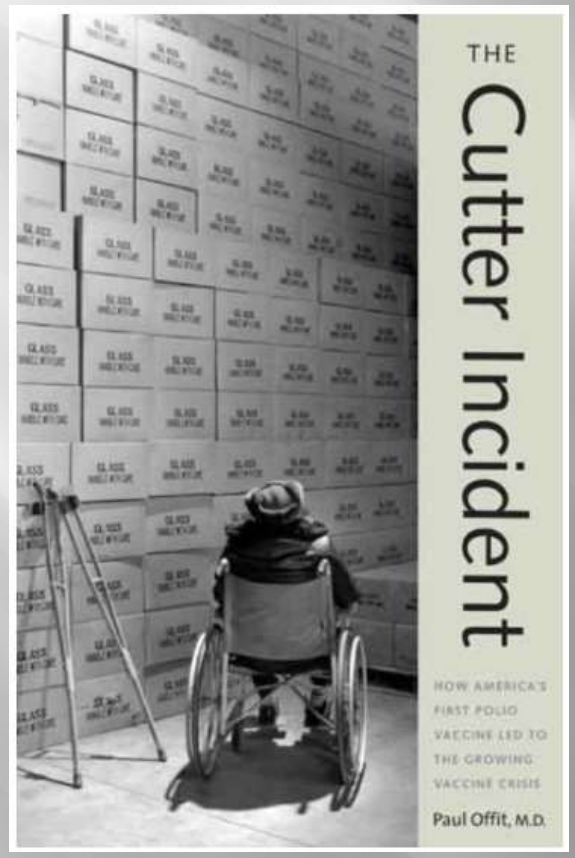
IPV



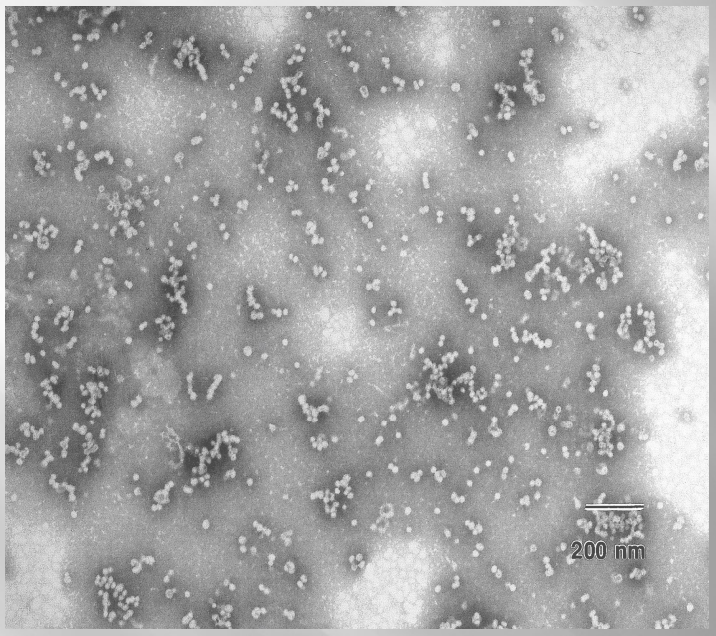
- Cutter departed from Salk's safe production protocols
- Lots of vaccine shipped containing live virus
- 40,000 children became ill
- 200 permanently paralyzed
- 10 died
- Tests for live virus were not sensitive enough

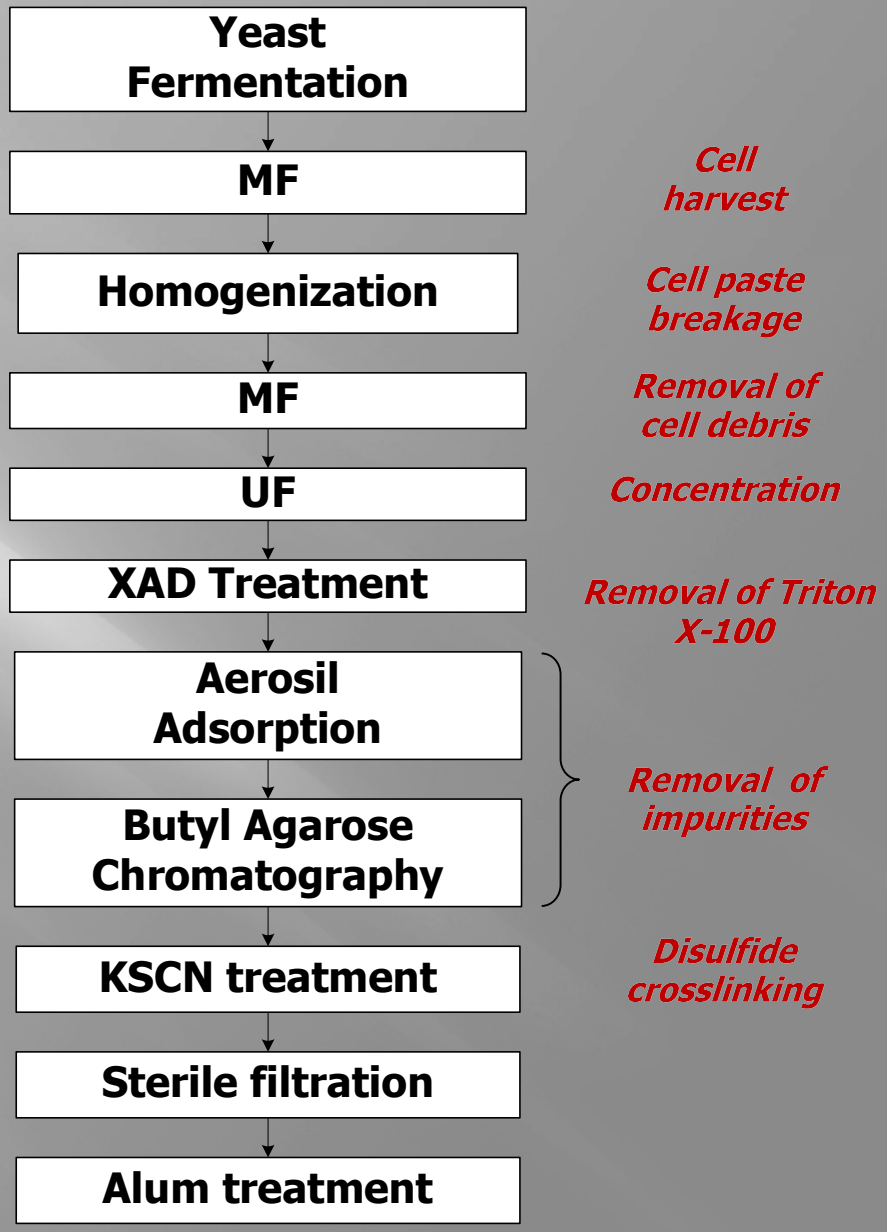
HEPATITIS B DISEASE

- Abdominal pain
- Dark urine
- Fever
- Joint pain
- Loss of appetite
- Nausea and vomiting
- Weakness and fatigue
- Yellowing of your skin and the whites of your eyes (jaundice)

Hepatitis B (1986)

RECOMBIVAX-HB®





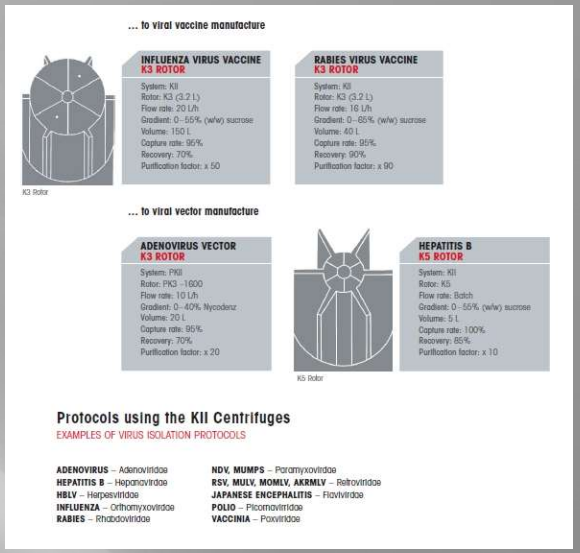
Ref. Sitrin et al., in Hepatitis B Vaccines in Clinical Practice, Ed. Ellis, R. W., Marcel Dekker, NY, 1993

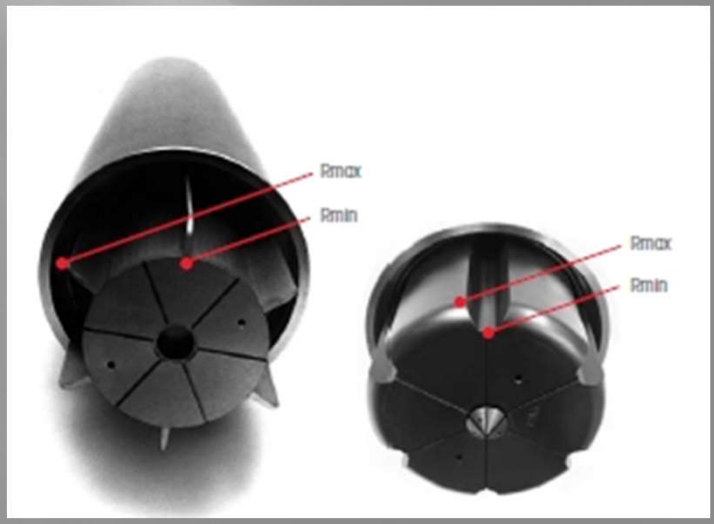
Chromotography

Centrifugation

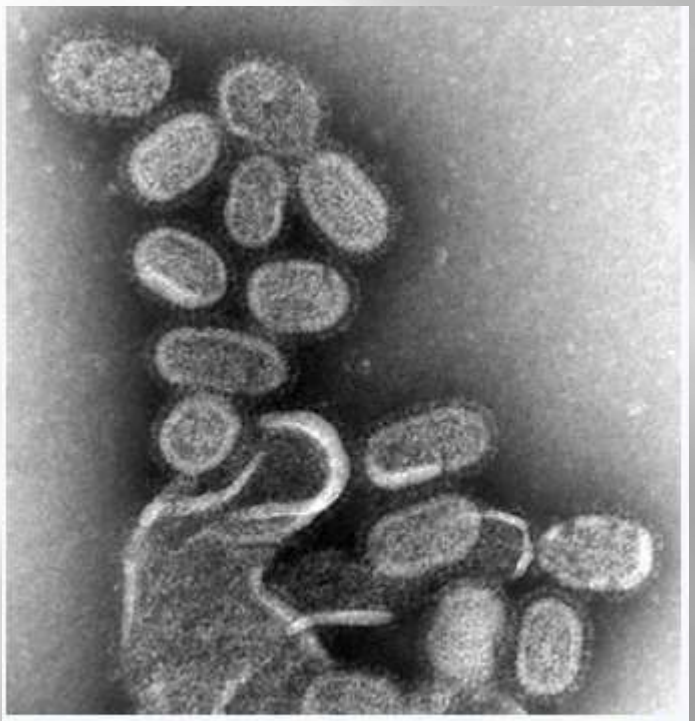
Centrifugation

Centrifugation

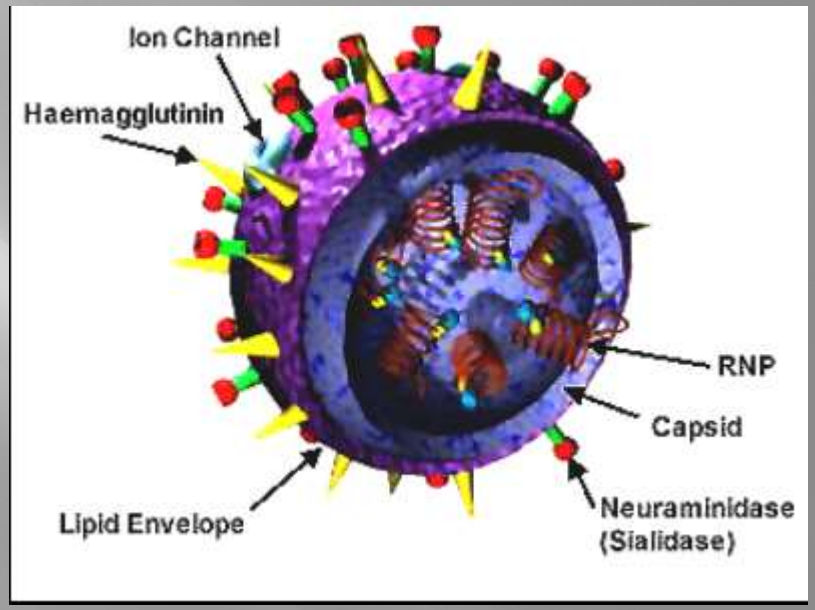




Influenza

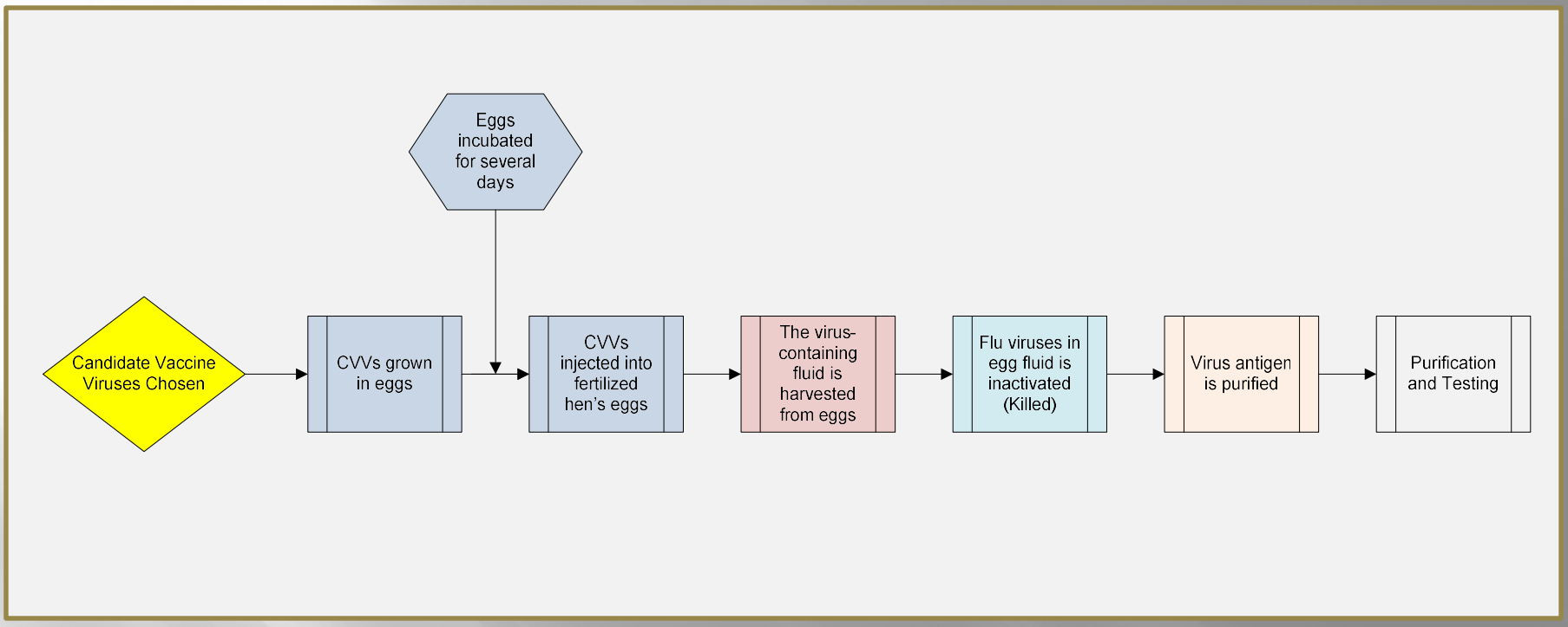


Influenza virus, magnified approximately 100,000 times



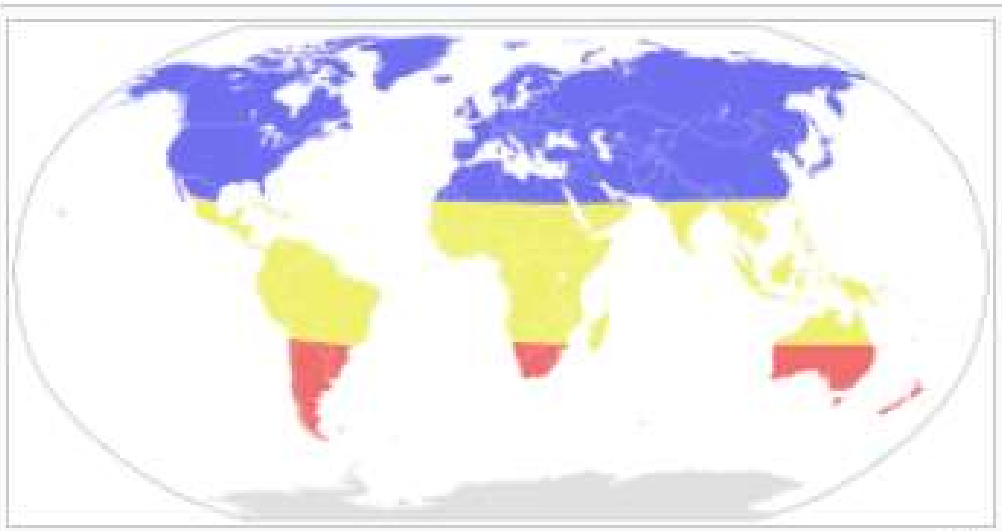
Source: Wikepedia

Flu Vaccine Production



Source: CDC

Influenza



Seasonal risk areas for influenza: November-April (blue), April-November (red), and year-round (yellow).

Source: Wikepedia

Flu Vaccine Production

Methodology for Production:
Current and Future Techniques

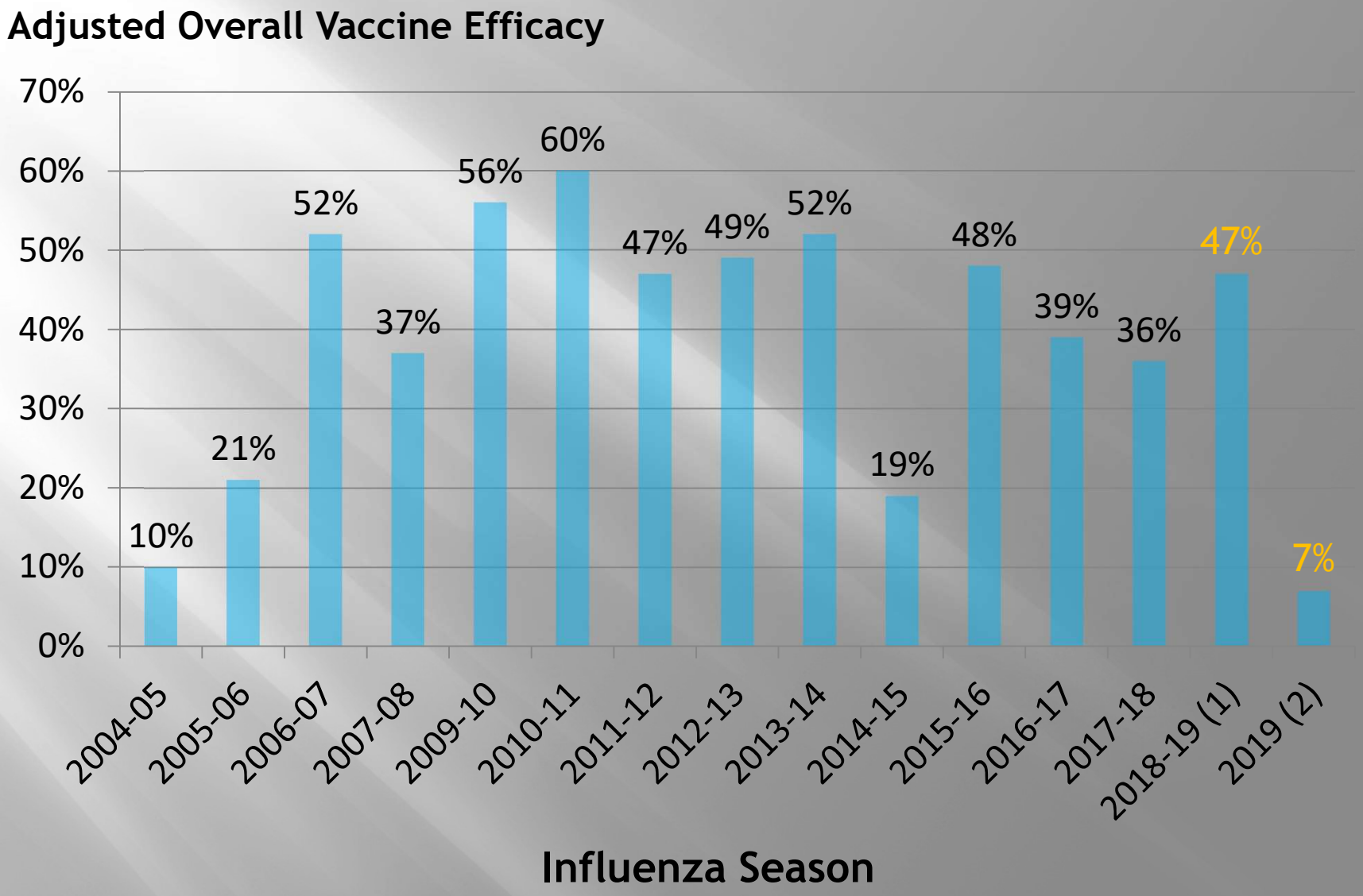
sanofi pasteur
Egg-based Facility
No bioreactors - 600K eggs/day
100M doses/year
140K square feet
$150M
Existing site and infrastructure

From Clone to Commercial®

Ref: J. Trazzino, BIO2010

BioProcess Technology Consultants®

Adjusted Vaccine Efficacy for Flu Vaccine



Source: CDC

Flexible Facilities: The Future?

- **Seqirus/CSL** (Holly Springs, NC)
  - Growing flu vaccine in canine kidney cells
  - Capacity of 200 MM doses in 6 months
  - 20 MM doses to be made this year
  - US HHS contributed $700MM to facility construction
  - *½ the cost* ($3.50 for egg-based) of traditional vaccine
  - Approved by FDA in May 2016 (4 strain vaccine)
- **Protein Sciences** (Rockland County, NY)
  - Cells from caterpillars
  - Faster than egg-based systems
  - However, *5-10X the cost* of egg-based vaccines.
  - Can make 5MM doses this year but expects to sell only 900,000

Methodology for Production:
Current and Future Techniques

sanofi pasteur
Egg-based Facility
No bioreactors - 600K eggs/day
100M doses/year
140K square feet
$150M
Existing site and infrastructure

Novartis
Mammalian Cell Culture Facility
Stainless steel bioreactors
50M doses/year
140K square feet
$600M
New site and infrastructure

Novavax
Insect Cell Culture Facility
Single-use bioreactor
75M doses/year
55K square feet
$40M
New site and infrastructure

From Clone to Commercial®

Ref: J. Trazzino, BIO2010

BioProcess Technology Consultants®

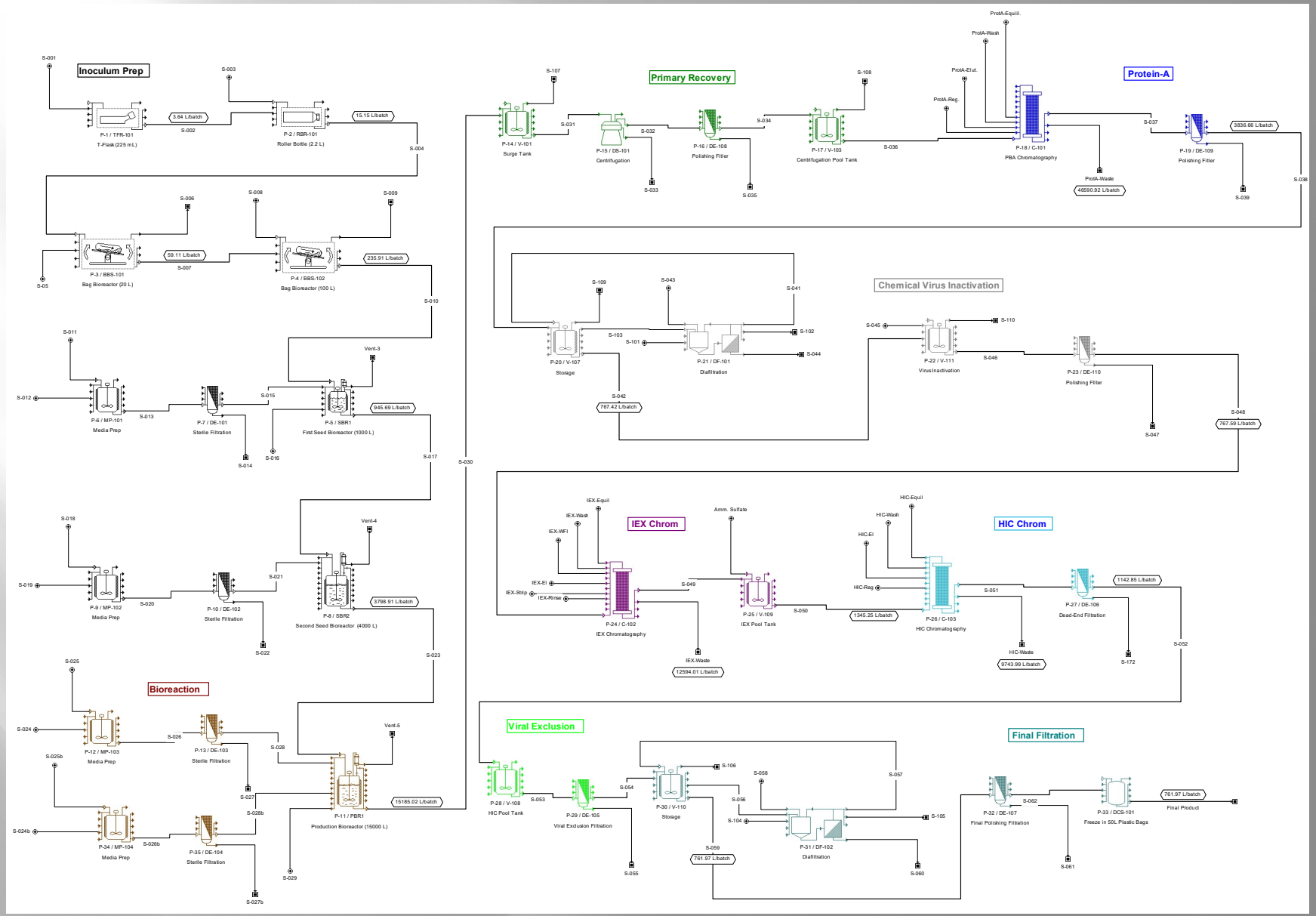
How Do You Make This

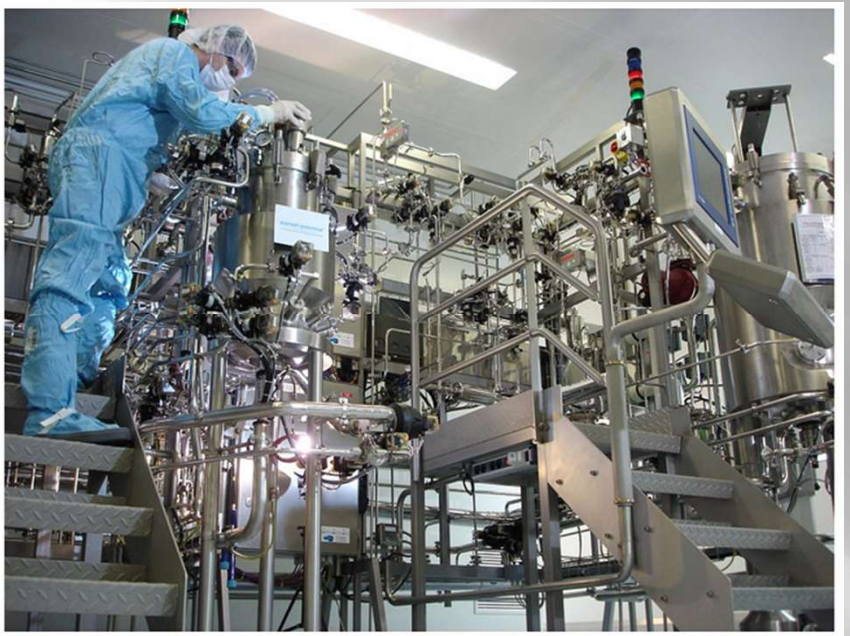
Bioreactor Technologies

- **Small-scale** (<10 L)
  - - Flasks (T-flasks, Erlenmeyer, Spinners)
  - - Roller Bottles

- **Mid-scale** (10 - 250 L)
  - - Roller Bottles (automated handling)
  - - Nunc Cell Factories and Costar Cell cubes
  - - “Small” continuous stirred reactors
  - - Wave Bioreactors

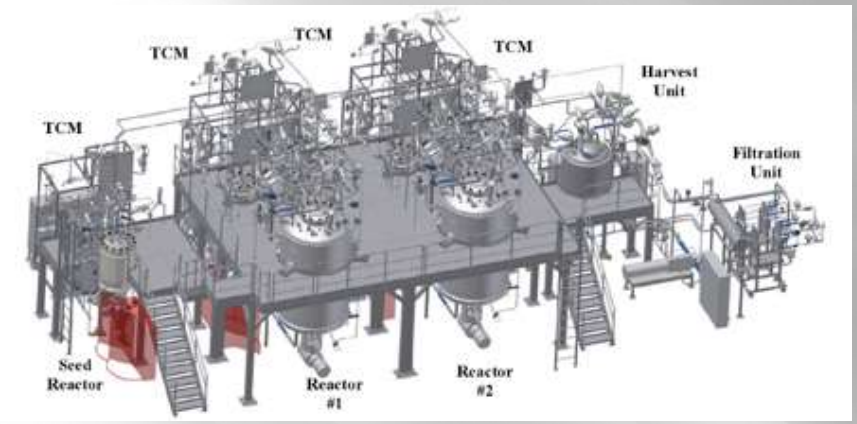
Making a Biologic Product





- **Large scale** (> 250 L) engineered systems.

Images: Copyright Sanofi Pasteur , Amgen, and New York Times


TCM
TCM
TCM
TCM
Harvest Unit
Filtration Unit
Seed Reactor
Reactor #1
Reactor #2

What's Next?

Emerging Diseases

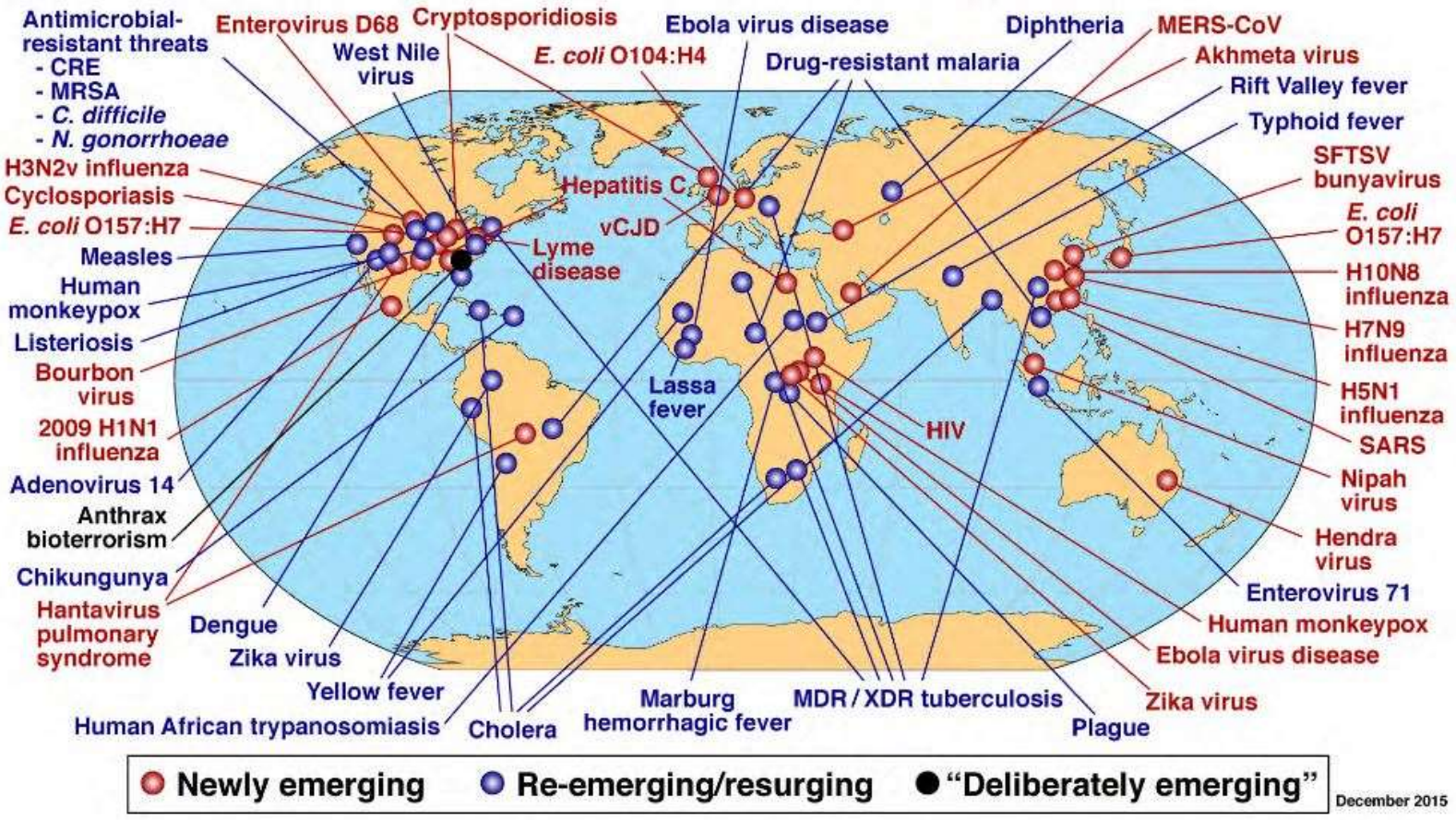
Chinese Authorities Continue Work To Identify Cause Of Pneumonia Outbreak In Wuhan

BloombergQuint: China Pneumonia Outbreak Widens to 59 Amid Hunt for Source
"A pneumonia outbreak in China that's infected 15 more people doesn't appear to be spreading from human to human, officials said, after ruling out SARS as a potential cause of the mysterious disease. As of Sunday morning, 59 people had been diagnosed with pneumonia, the cause of which is unknown, the Wuhan Municipal Health Commission said in a statement late Sunday. That's up from 44 on Friday..." (Gale, 1/6).

Reuters: Chinese authorities say viral pneumonia outbreak is not SARS, MERS or bird flu
"Chinese healthcare authorities in Wuhan said an outbreak of *viral pneumonia was not Severe Acute Respiratory Syndrome (SARS), Middle East respiratory syndrome (MERS), or bird flu, and that they were still working to identify the cause and source*..." (Li/Woo, 1/5).

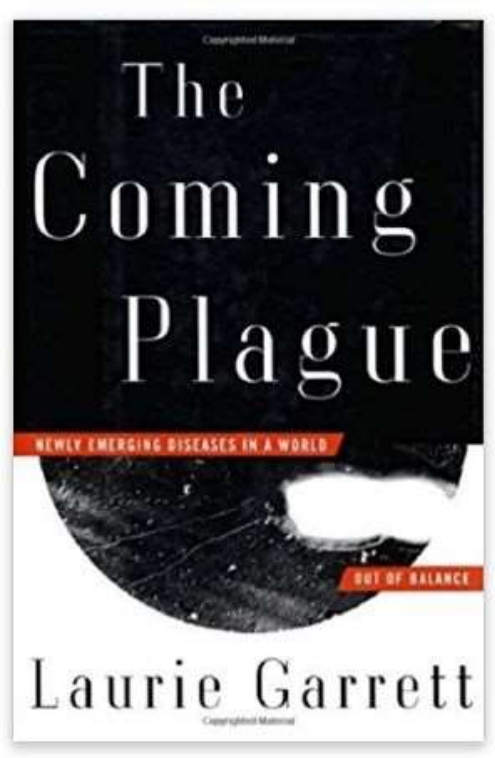
STAT: Experts search for answers in limited information about mystery pneumonia outbreak in China
"...*The infections are linked to a large seafood market where it is believed some exotic animals were also sold for consumption*. The World Health Organization has said little about the outbreak beyond that it is in close contact with China authorities on the issue..." (Branswell, 1/4).

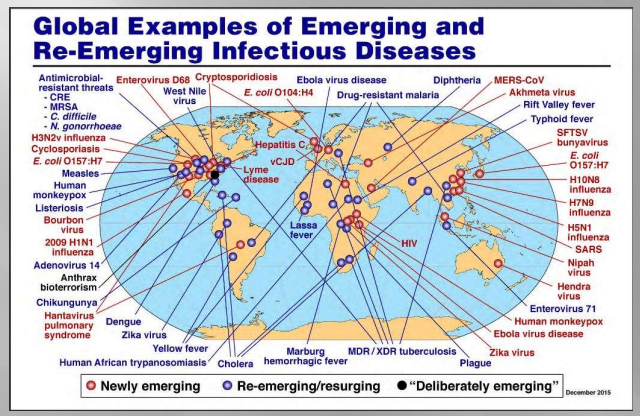
Global Examples of Emerging and Re-Emerging Infectious Diseases

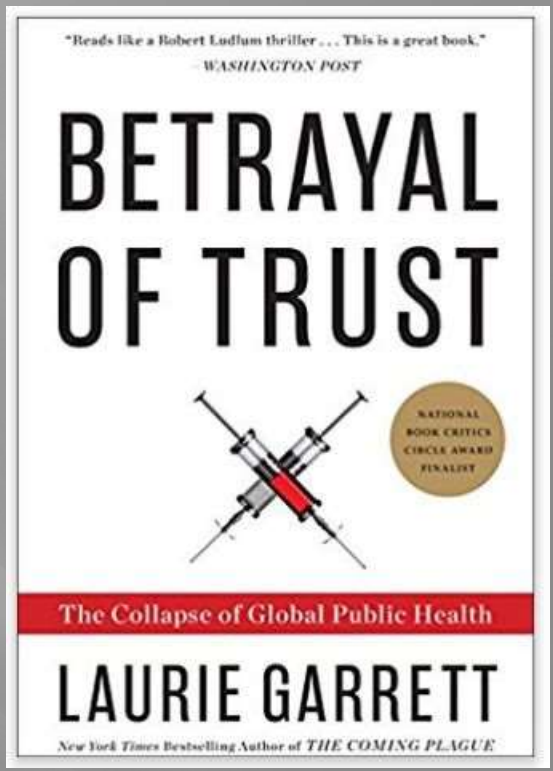


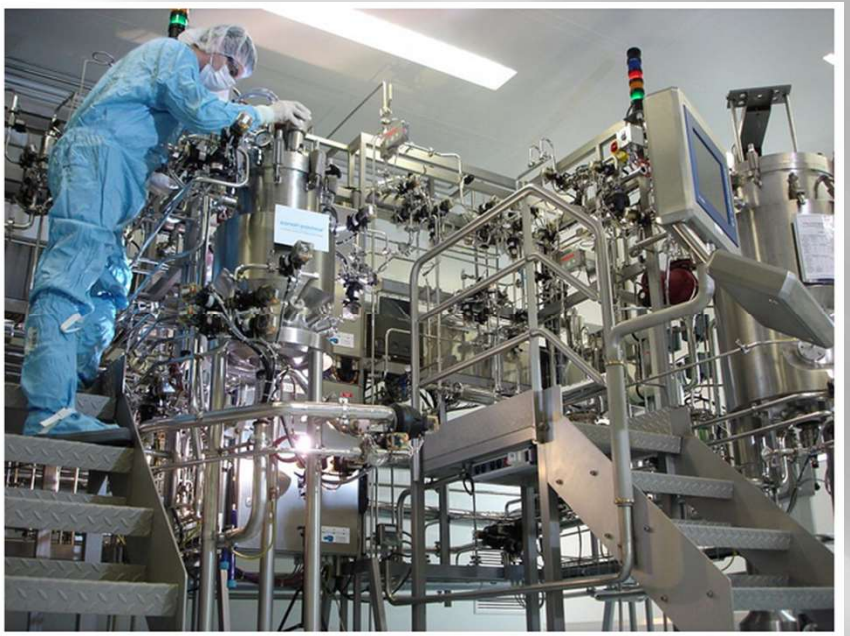
Emerging Diseases

Emerging Diseases









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Images: Copyright Sanofi Pasteur , Amgen, and New York Times

Scaling the Process:
Single Use Systems

Source: Xcellerex, Sartorius, Pall

Flexible Facilities: The Future?

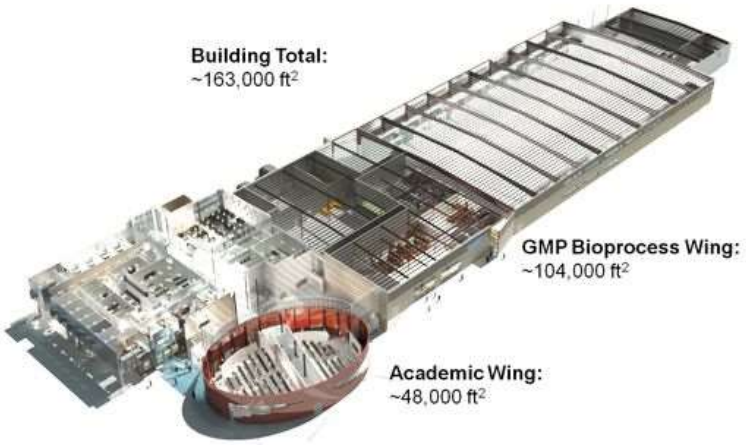


Figure 1. National Center for Therapeutics Manufacturing, designed and built based on Flexible Manufacturing Criteria

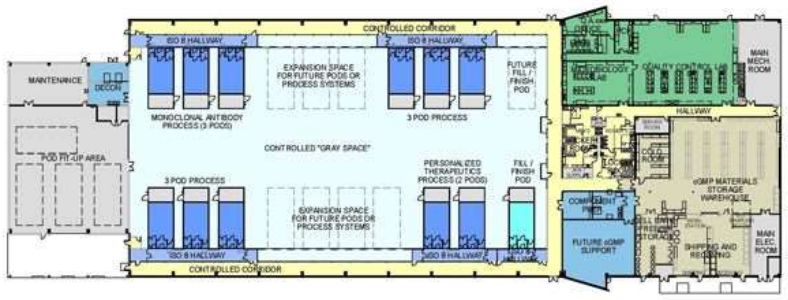


Figure 2. Manufacturing Wing of the NCTM

Figure 4. A downstream processing suite developed as part of Project GreenVAX at NCTM. GreenVAX uses tobacco rather than egg-based vaccine technology.

The Future of Vaccines

"Predictions are difficult to make, especially about the future"

Yogi Berra

The Future of Vaccines

- Vaccine developers are currently under immense pressure as the uptake of vaccines falls in many countries as a result of negative comments in press stories or misinformed social media exchanges.
- This decreasing appreciation of the benefits and the AEs associated with vaccination programs has converged to create the anti-vaxer movement.
- As a consequence, rubella, mumps and especially measles are re-emerging even though we once thought they were on the path to eradication.

Adapted from: A.Wildfire, Contract Pharma, Nov/Dec 2019

The Future of Vaccines

- The public needs to be better informed about the relevant risk & benefit analyses as they have lost their historical knowledge regarding vaccine preventable diseases.
- It is largely due to childhood vaccination programs with wider public health programs that led to smallpox being eradicated and polio on the verge of extinction.

Adapted from: A.Wildfire, Contract Pharma, Nov/Dec 2019

The Future of Vaccines

- The success of vaccination is troublesome as it is difficult to ***celebrate the absence of a disease.***
- This is in sharp contrast to the acceptance and appreciation of antimicrobials as they cure a tangible, frequently visible illness.

Adapted from: A.Wildfire, Contract Pharma, Nov/Dec 2019

The Future of Vaccines

"The Earth is round, gasoline is flammable, and vaccines are safe and effective, all the rest are dangerous lies.“

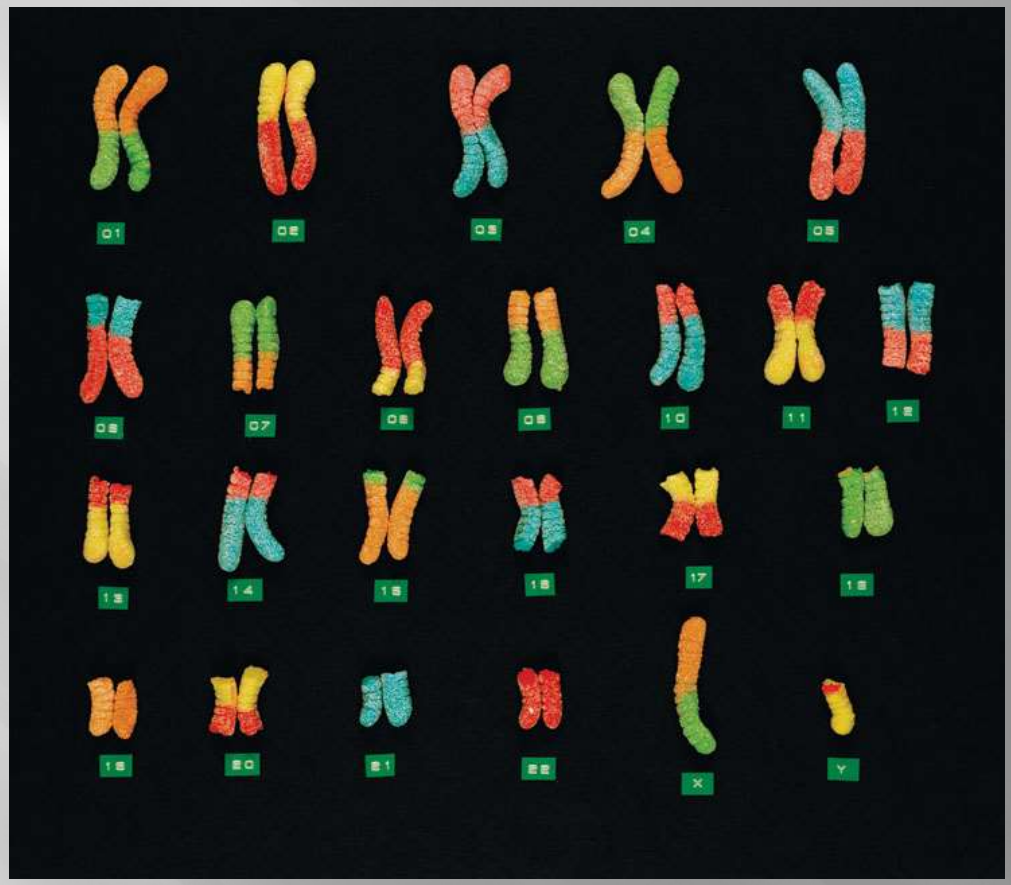
Roberto Burioni, MD, PhD

Vita-Salute San Raffaele University

The Future of Vaccines

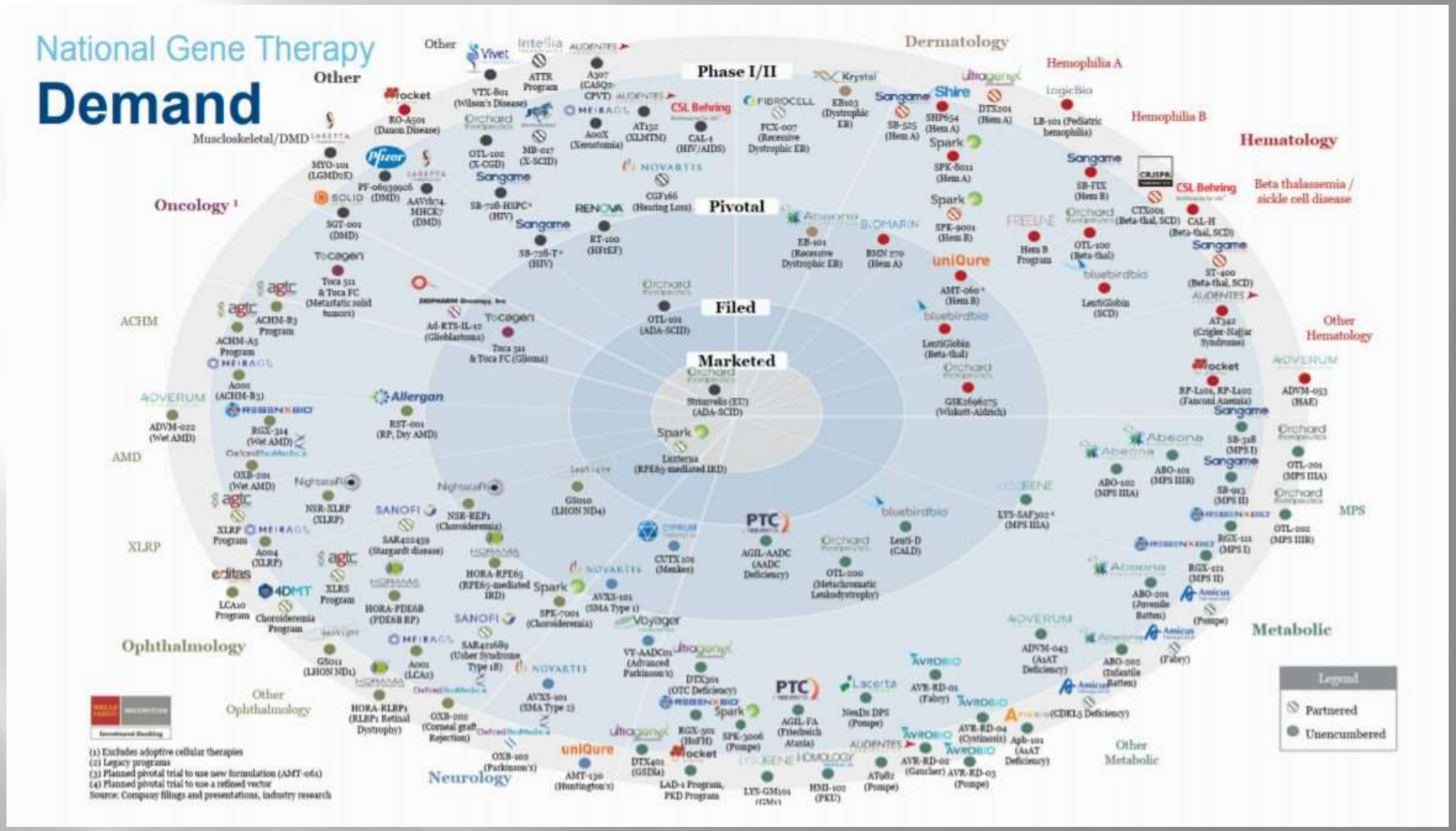
" It is hard to un-ring a bell"

Paul A. Offit, MD
CHOP



dgross@padrugdiscovey.org

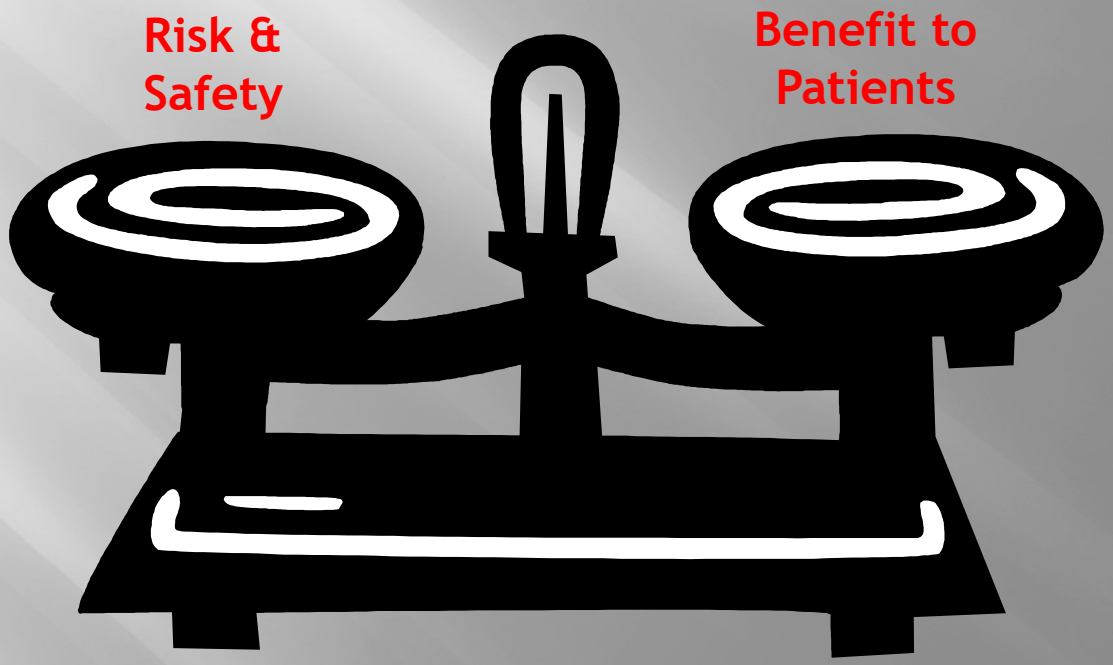
+1.267.893.6777


National Gene Therapy
Demand
Phase I/II
Pivotal
Filed
Marketed
Oncology [1]
Dermatology
Hematology
Ophthalmology
Neurology
Metabolic
Other
Other Ophthalmology
Other Hematology
Other Metabolic
Musculoskeletal/DMD
ACHM
AMD
XLRP
MPS
Hemophilia A
Hemophilia B
Beta thalassemia / sickle cell disease
Legend
Partnered
Unencumbered
(1) Excludes adoptive cellular therapies
(2) Legacy programs
(3) Planned pivotal trial to use new formulation (AMT-061)
(4) Planned pivotal trial to use a refined vector
Source: Company filings and presentations, industry research

Adaptive (acquired) immunity

- Develops in response to microbial contact
- Recognizes features of specific pathogens
- Immunologic memory
- Humoral and cellular arms:
  - Humoral immunity: antibodies
  - Cellular immunity: cytotoxicity
- Characteristic of vertebrates

Agency Responsibility



Differences Between Drugs and Biologics

- **Drugs**

- **Pre-clinical**
  - Toxicology in rodent and something else
  - Hepatic microsome for CYP enzyme metabolism
  - Safety pharmacology *(CNS, cardiovascular, respiratory studies ICH S7)*
  - Carcinogenicity (*Ames Test*)

- **Clinical**
  - Drug-drug interactions
  - Food-drug interactions for oral administration
  - Effect on QT/QTc & arrhythmic potential

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Drugs

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Biologics

- **Pre-Clinical**
  - Toxicology in relevant animal species
  - Very difficult learning curve at the moment
  - Don't always get NOAEL (*No Observed Adverse Event Level*)
- **Clinical**
  - PK and bioavailability but not metabolism
  - Concomitant use (*vaccines*)
  - Off-target incorporation of material (*DNA Vaccines*)

Potential Safety Concerns

- Inherent toxicity of the vaccine
- Toxicity of impurities/contaminants
- Toxicity due to interaction of components
- Toxicity linked to the immune response induced
- Unknown unknowns (*Black Swans*)

Toxicity Assessment: Animal Model

- "Relevant" animal species
  - An animal species susceptible to respond to the test article activity, *e.g.*, development of an immune response after vaccination
    - Ideally, species should be sensitive to the pathogenic organism or toxin
  - One relevant animal species in general is sufficient
    - Exceptions on a case-by-case
    - Non-human primates not generally necessary
  - Group size dependent on the animal model

Toxicity Assessment: ROA/Dosing

- Route of administration (ROA) and dose should correspond to clinically intended ROA and dose(s), *e.g.*, oral, SC, IM, Nasal
- Total number of doses equal to or exceed number of clinically administered doses
  - ["N plus 1"]
- Episodic dosing, *e.g.*, weeks between doses

Clinical Drug Development Process

IND/ CTA 

- **Phase I – *First-into-Human***
  - 20-100 normal healthy volunteers
  - Determine safety and tolerability
- **Phase IIa/IIb – *Therapeutic Exploration***
  - 100-300 patients
  - Evaluate efficacy
  - Determine dose range and adverse events (AEs)
- **Phase III – *Therapeutic Confirmation***
  - 1,000 to 15,000 patients
  - Verify efficacy, monitor AEs and effect in usual therapy and special populations
- **Phase IV – *Post-Approval***
  - Postmarketing surveillance
  - Monitor long term risks and benefits, outcomes and pharmacoeconomics
- **Phase V**
  - Postmarketing studies (Potentially thousands of patients)
  - New indications: “Megatrials”

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IND/ CTA ➡

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NDA/ WMA/ BLA ➡

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IND/ CTA ⇨

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  - Determine dose range and adverse events (AEs)
- **Phase III – *Therapeutic Confirmation***
  - *Possibly 60-70,000 for a vaccine*
  - Verify efficacy, monitor AEs and effect in usual therapy and special populations

NDA/ WMA/ BLA ⇨

- **Phase IV – *Post-Approval***
  - Postmarketing surveillance
  - Monitor long term risks and benefits, outcomes and pharmacoeconomics
- **Phase V**
  - Postmarketing studies (Potentially thousands of patients)
  - New indications: "Megatrials"

CLINICAL POPULATIONS FOR THE DEVELOMENT OF VACCINES

- ROTATEQ® : Rotavirus vaccine- 70,000 patients in the pivotal trials worldwide

- ZOSTAVAX® : Shingles vaccine- 68,000 patients in the pivotal trials worldwide.

EVALUATING A VACCINE

Sources: Clemens et al. *JAMA* 1996;275:390-7
Levine MM. *British Medical Bulletin* 2002;62:1-13

Promising vaccine candidate

IND →

Phase I: Well-tolerated and immunogenic in healthy adults?

Yes

No

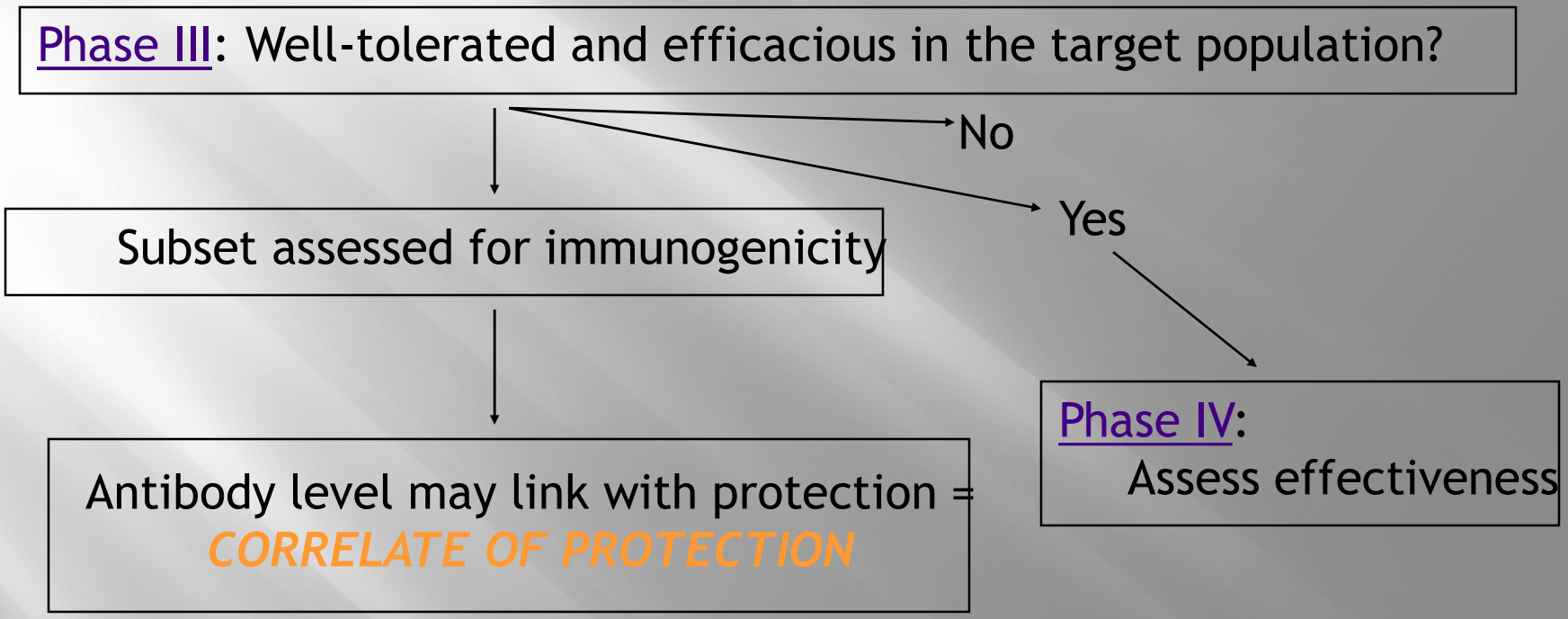
Phase II: Well-tolerated and immunogenic in the target population?

Yes

No

Phase III: Well-tolerated and efficacious in the target population?

EVALUATING A VACCINE



Sources: VacciNews 2002;1(6):1-4 Clemens et al. *JAMA* 1996;275:390-7

Levine MM. *British Medical Bulletin* 2002;62:1-13

EVALUATING A VACCINE

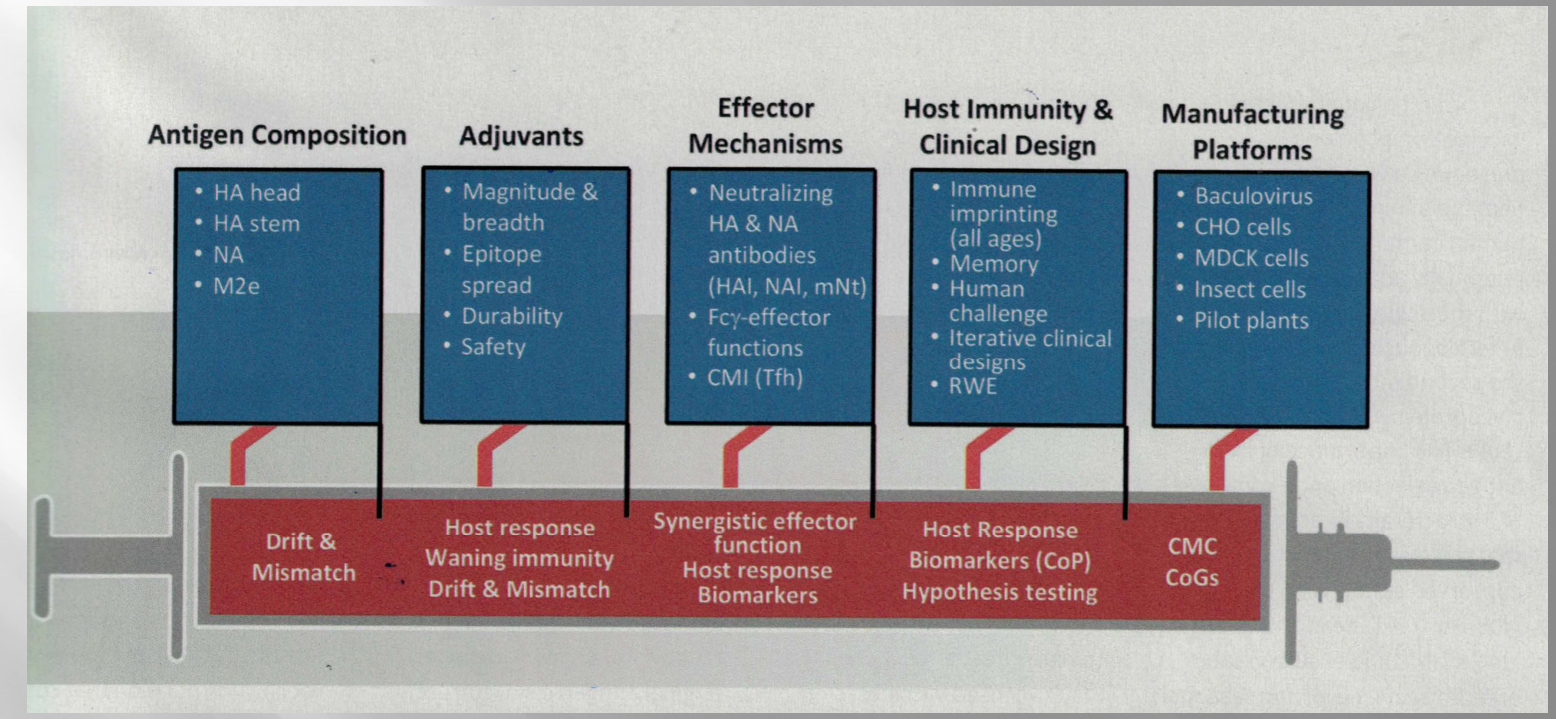
- An Efficacy trial provides a more direct measurement of protection

- Efficacy- the protective effect of a vaccine against the target disease

$$\text{Protective Efficacy} = \left[1 - \left(\frac{\text{incidence of disease in vaccinees}}{\text{incidence of disease in nonvaccinees}}\right)\right] \text{X } 100\%$$

Sources: VacciNews 2002;1(6):1-4 Clemens et al. JAMA 1996;275:390-7

Methodology for Production:
Future Flu Vaccines



Arms of the Immune System