

Overview of Vaccines

Osher Lifelong Learning Institute

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Leopoldo Mendez (Mexico). *Recepción*, 1935 (Philadelphia Museum of Art, accession no. 59-6-11. Given by an Anonymous Donor.)

Overview of Vaccines

Outline:

- Introduction & history
- How vaccines work—Overview of immune system
- Types of vaccines approved in the U.S.
- Pathway for approval: Vaccine development

Vaccine Definition:

- **Vaccine:**
 - A suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae) administered for the prevention, amelioration, or treatment of infectious diseases (**Dorland's Medical Dictionary**)
 - A preparation of the causative agent of a disease, its products, or a synthetic substitute, that has been specially treated for use in vaccination; *originally specifically*, a preparation of vaccinia (cowpox) for inoculation against smallpox (**The New Shorter Oxford English Dictionary**)

Brief History of Human Vaccines

- **1100's** – Variolation in China
- **1798** – Smallpox (live attenuated) – Edward Jenner
- **1885** – Rabies (live attenuated) – Louis Pasteur
- **1896-7** – Typhoid, cholera, plague (killed whole organisms)
- **1923, 1927** – Diphtheria, tetanus (purified protein toxin)
- **1936** – Influenza (killed whole virus)
- **After WWII** –
 - Vaccines produced in cell culture (e.g., measles, mumps, rubella)
 - Purified polysaccharide (e.g., pneumococcus, meningococcus)
 - Recombinant proteins (e.g., hepatitis B)
 - Polysaccharide – protein conjugates (e.g., Hib, pneumococcus)

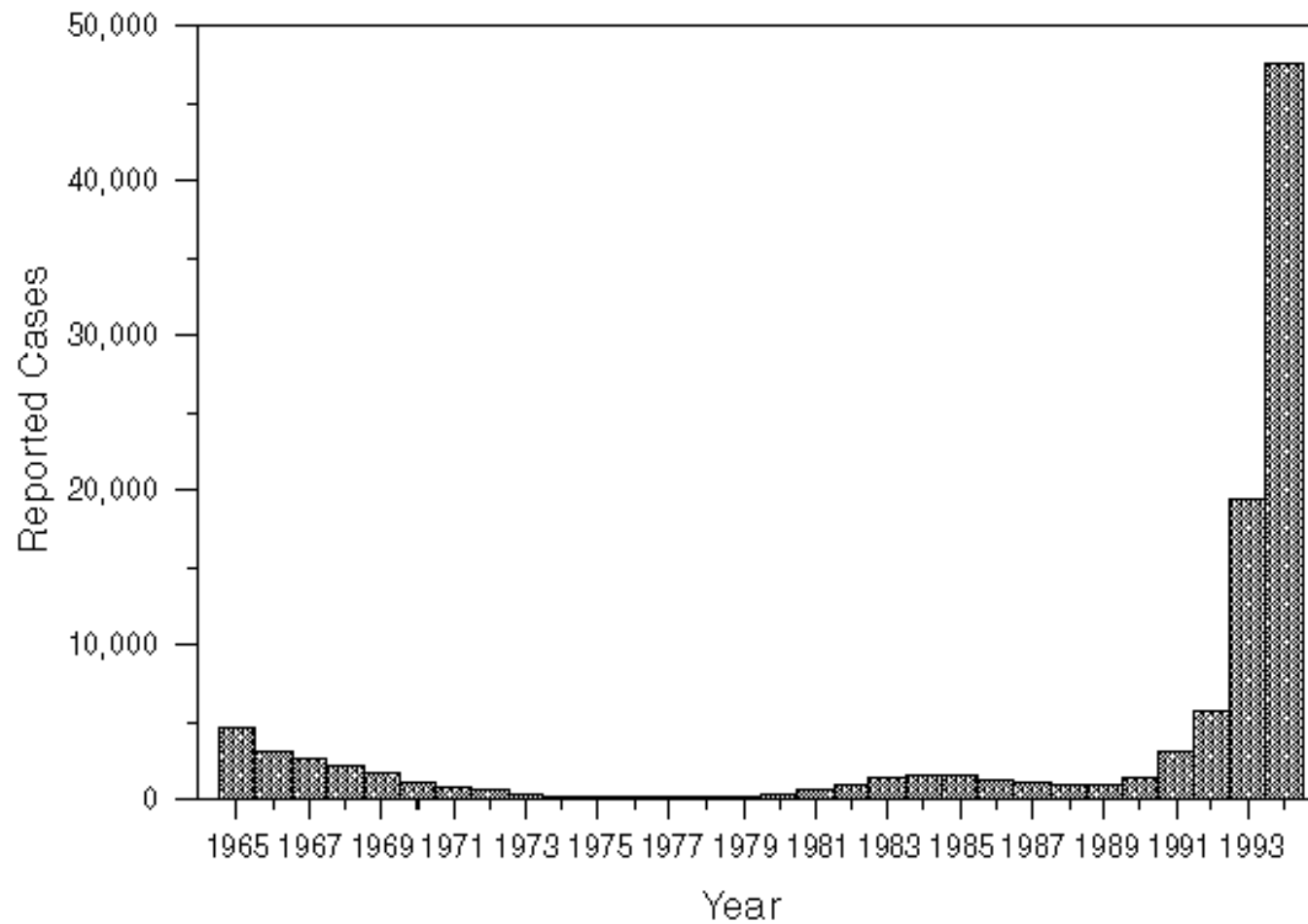
Vaccine Successes in US

<u>Disease</u>	<u>Annual Cases Baseline 20th Cent.</u>	<u># Cases 1998</u>	<u>% Decrease</u>
Smallpox	48, 164	0	100
Diphtheria	175, 885	1	100
Pertussis	147, 271	7405	95
Tetanus	1,314	41	97
Polio	16,316	1	100
Measles	503,282	100	100
Mumps	152,209	666	>99
Rubella	47,745	364	>99
Congenital	823	7	>99
<i>H.influenzae b</i>	<i>20,000</i>	61	>99

Diphtheria in Former Soviet Union

MMWR Mar 17, 1995

FIGURE 1. Reported number of diphtheria cases — New Independent States of the former Soviet Union, 1965–1994*



*Data for 1994 are provisional.

Source: World Health Organization.

How Vaccines Work

Overview of Immune System

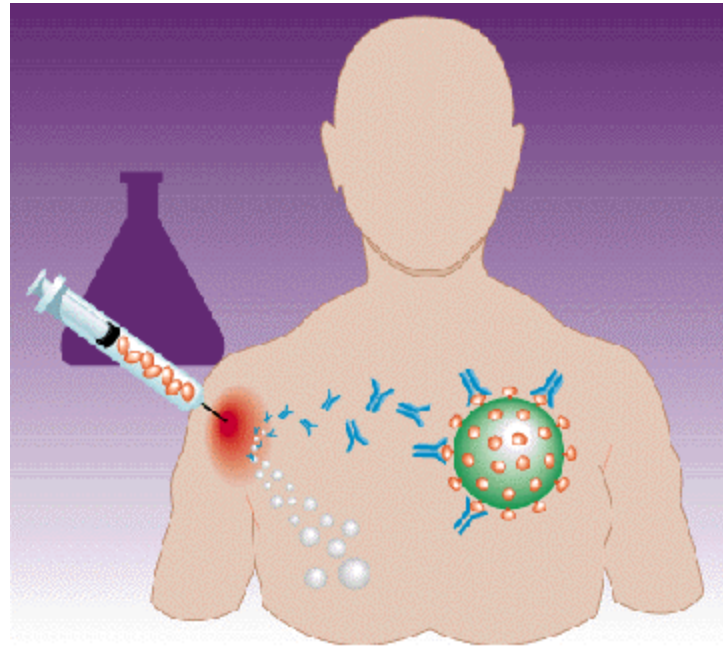
Types Of Infections

- **Bacteria** - Widely distributed group of microscopic prokaryotic mainly single-celled organisms, many of which are symbiotic or pathogenic in animals and plants, **e.g., pneumococcus, anthrax**
- **Virus** - A submicroscopic organism that can multiply only inside living host cells, has a non-cellular structure lacking any intrinsic metabolism and usually comprising a single DNA or RNA molecule inside a protein coat, and is frequently pathogenic, **e.g., influenza, varicella**
- **Parasite** - An animal or plant which lives in or on another and draws its nutriment directly from it, harming it in the process, **e.g., malaria⁸**

Vaccines For Preventive Infectious Disease Indications

- Generally, preparations containing all or a portion of a disease-causing organism or the nucleic acid encoding one or more proteins from that organism
- Vaccines are intended to induce an immune response to prevent an infectious disease

How Vaccines Work



The vaccine is made from an antigen isolated or produced from the disease-causing microorganism. The vaccine is injected into the body. The B cells in the blood stream respond to the antigen by producing antibodies. The antibodies bind to the antigen to "neutralize" or inactivate it. In addition, memory cells are produced and remain ready to mount a quick protective immune response against subsequent infection with the same disease causing agent.

Mammalian Immune System

- **Innate (nonspecific, nonadaptive)**
 - Macrophages, Neutrophils, Natural Killer Cells
 - Cytokines, Interferons, Complement
- **Acquired (specific, adaptive)**
 - Immunoglobulins = Antibodies
 - Produced by **B Lymphocytes** (Plasma Cells)
 - **Cell-Mediated Immune Response**
 - Mediated by **T (thymus-derived) Lymphocytes**
 - **CD4+ Cells** - Help B cells make antibodies
 - **CD8+ Cells** - Cytotoxic T-Lymphocytes (CTLs), recognize and lyse infected target cells
 - **Mucosal Immune System**

Role Of Antibody And Lymphocytes In Preventing, Controlling, And Clearing An Infectious Agent

- Prevent infection: Neutralizing Antibody
- Limit infection
 - Extracellular: Antibody
 - Intracellular: CD4+, CD8+, Antibody
- Reduce infection
 - Extracellular: Antibody
 - Intracellular: CD4+, CD8+, Antibody
- Clear/control infection
 - Extracellular: Antibody
 - Intracellular: CD4+, CD8+

Antibodies To Type-specific Pneumococcal Polysaccharides

Biological Function:

- Bind to surface of bacteria
- Activate complement
- Uptake by phagocytic cells, esp. polymorphonuclear leucocytes (PMN)
- Bacteria killed

Sequence Of Responses During An Infection: e.g, Influenza Virus Infection In The Lungs Of Mice

- 1) CD4+ Cells (Helpers)
- 2) CD8+ Cells (Lytic)
- 3) Antibody Secreting Cells: First IgM, then IgG
- 4) Decrease in lung virus titers begins, which coincides with:
- 5) Increase in CTL activity
- 6) Virus disappears, CTL effector activity no longer detected
- 7) Memory CTLs appear and persist
- 8) Antibody Secreting Cells gradually decline
- 9) Specific B Memory Cells present

Vaccines Approved In The U.S.

Types of Preventive Vaccines

- **Live, attenuated:** Varicella, Influenza, Smallpox
- **Inactivated:** Influenza, Inactivated Polio, Rabies
- **Crude or purified antigens derived from living or killed cells:** Diphtheria and Tetanus Toxoids, Polysaccharides (PS), Anthrax
- **Conjugate vaccines:** Meningococcal, Haemophilus and Pneumococcal PS-Protein Conjugate
- **Recombinant-DNA derived:** Hepatitis B, Human Papillomavirus (HPV) Vaccine
- **Vectored and DNA vaccines:** (*Investigational*)

Vaccines Licensed in the US

- Infants/Toddlers (birth - 6 year):
 - Diphtheria, Tetanus, Acellular Pertussis
 - Haemophilus influenzae type b
 - Pneumococcal Conjugate
 - Meningococcal Conjugate
 - Hepatitis B, Hepatitis A
 - Rotavirus
 - Inactivated polio
 - Measles, Mumps, Rubella
 - Influenza
 - Varicella (Chicken Pox)

Vaccines Licensed in the US (2)

Adolesc/Adults/Travelers/Military/Special Cases*

- Typhoid
- BCG/TB
- Anthrax
- TdaP
- Human Papilloma Virus
- Yellow Fever
- Japanese Encephalitis Virus
- Smallpox
- Rabies

*In addition to booster doses or vaccines not received as a child

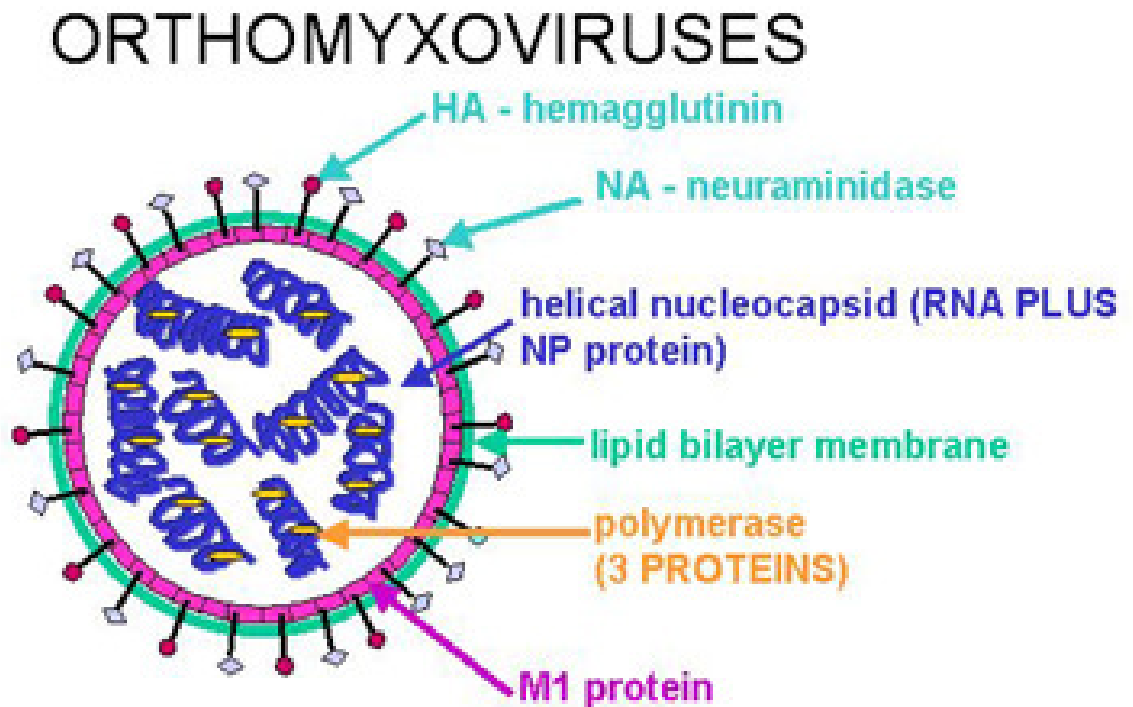
Vaccines Licensed in the US (3)

➤ Seniors:

- Tetanus, Diphtheria
- Pneumococcal Polysaccharide
- Influenza
 - (High Dose)
- Varicella/Zoster – Shingles

Schematic Diagram of Influenza Virus

(<http://pathmicro.med.sc.edu/mhunt/flu.htm>)



type A, B, C : NP, M protein
sub-types: HA or NA protein

Pathway for Approval: Vaccine development

- Regulatory/legal framework
- Development path



Production of diphtheria antitoxin by inoculating horses...From CBER's centennial book titled, "Science and the Regulation of Biological Products – From a Rich History to a Challenging Future." See <http://www.fda.gov/cber/inside/centennial.htm>

Tragedy To Action

- **A horse name Jim: In 1901, 13 children died after receiving diphtheria antitoxin contaminated with tetanus.**
- **At that time, biologics were not subject to federal oversight and lacked standards for quality, safety, purity and potency.**
- **The Biologics Control Act of 1902 established federal authority to regulate biological products and ensure their safety for the American public.**

FDA Legal Framework

Statutes/Laws
(Congress, signed by President)



Regulations (CFR)
(FDA)



Guidance Documents
(FDA – “in the trenches”)

Vaccine Laws and Regulations:

Human vaccines are approved & regulated by Food & Drug Administration

- **Biologics Control Act (1902)**
 - A horse named Jim
- **Food, Drug and Cosmetic Act (1938)**
 - Ethylene glycol in elixir of sulfonilamide (107 deaths)
 - Safety: Pre-market review for safety before approval
- **Public Health Service Act (1944)**
 - Required safety, purity, potency of biologics (drugs)
- **Kefauver-Harris Amendments (1962)**
 - Response to thalidomide incident
 - Efficacy: Required before marketing
- **Prescription Drug User Fee Act (1992)**

Licensed Biological Products, Including Vaccines, Must Be:

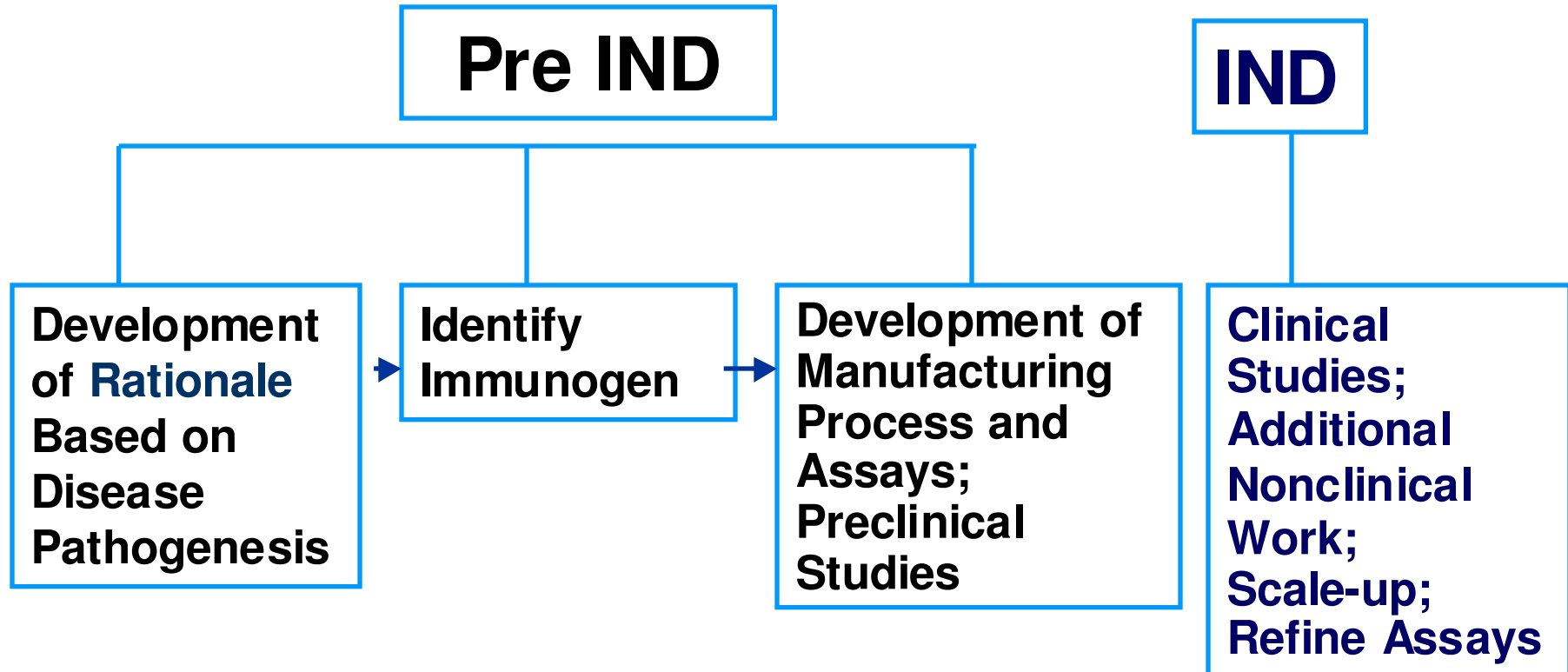
- **Safe:** “relatively free from harmful effect when prudently administered”
- **Pure:** “relatively free from extraneous matter”
- **Potent:** “specific ability of product ... to effect a given result”
- **Manufactured consistently according to current Good Manufacturing Practices**

(21 CFR 600.3 and 21 CFR 210-211)

Stages Of Vaccine Development

- **Pre-clinical**
 - Product chemistry/biology; animal studies; other safety testing (sterility, etc.)
- **Clinical**
 - Studies in human (show safe and effective)
 - Investigational New Drug Application (IND)
- **Biologics License Application (BLA)**
 - Marketing application
- **Post-marketing**
 - Follow up: safety, efficacy, addn'l info

Vaccine Development



IND = Investigational New Drug application

Vaccines Are Developed From A Knowledge Of:

- **Pathogenic mechanisms, e.g., invasion of cells**
- **Virulence factors, e.g., toxins, capsular polysaccharides, attachment proteins**
- **Protective antigens, e.g., viral coat proteins**

Pre-Clinical Studies To Support Clinical Trial

- **Product characterization**
- **Potency**
- **Immunogenicity**
- **Pyrogenicity/Toxicity**
- **Adventitious agents**
- **Safety/Toxicity**

Investigational New Drug Application (IND)

- Collect data in humans to assure vaccine is safe and effective ([ClinicalTrials.gov](https://clinicaltrials.gov))
- **Phase 1** - Safety/Immunogenicity in small number of subjects
- **Phase 2** - Dose-ranging in more subjects (e.g., 100's)
- **Phase 3** - Efficacy and additional safety data (thousands)
- Informed Consent and Institutional Review Board
- Product manufacturing and testing finalized

Biologics License Application (BLA)

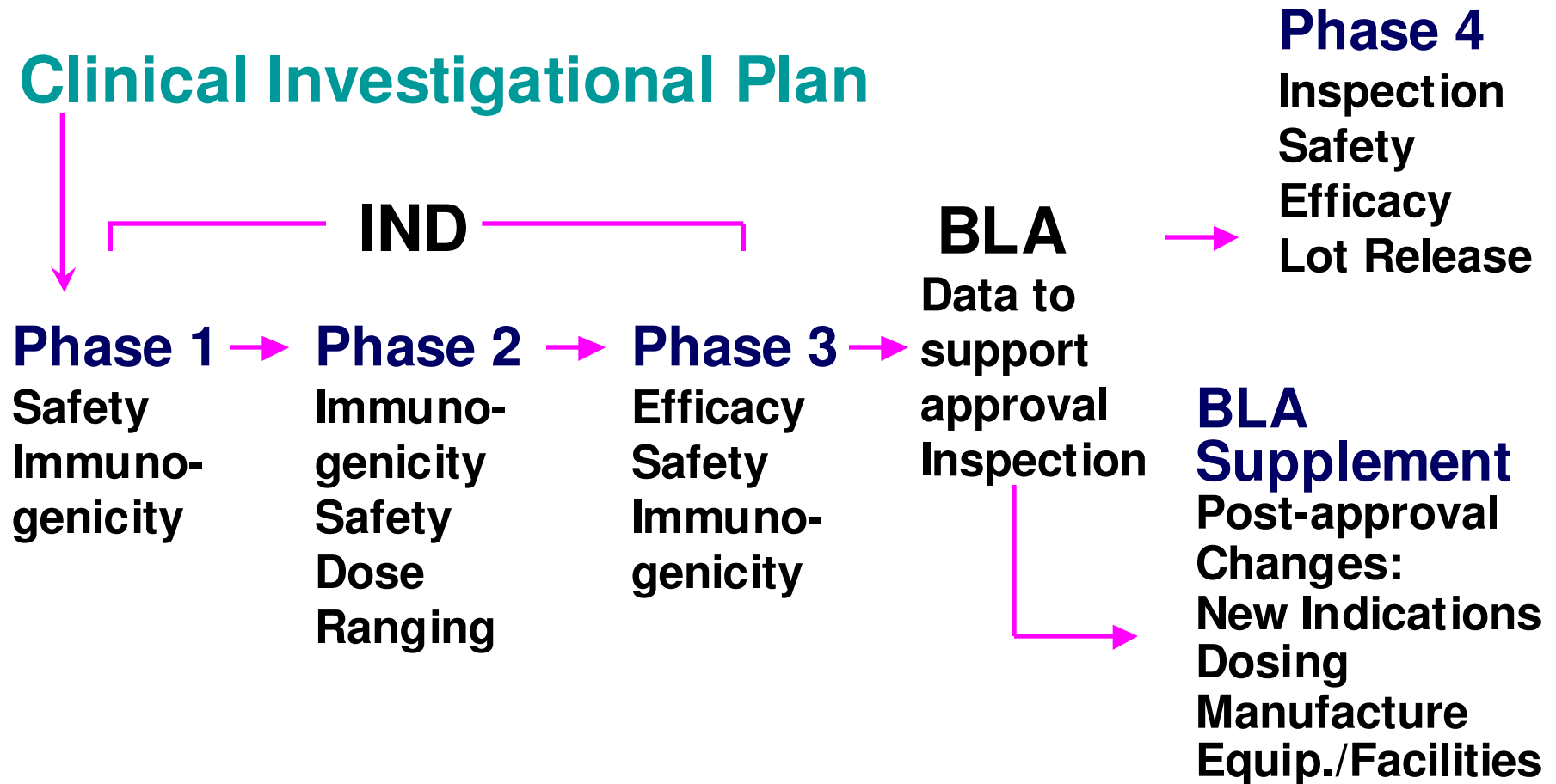
- **Safety and efficacy data evaluated**
- **Manufacturing process and quality control testing evaluated**
- **Labeling is reviewed**
- **Pre-approval inspection of manufacturing facility**
- **Advisory Committee presentation**
- **Approval allows interstate commerce and marketing**

Post-Marketing Activities

- **Continue monitoring vaccine production and safety**
- **Periodic facility inspections**
- **Phase 4 clinical studies**
- **Lots monitored before release**
- **Vaccine Adverse Event Reporting System (VAERS)**
- **Supplement to license for manufacturing or indication changes**

Stages of Review and Regulation

Clinical Investigational Plan



IND = Investigational New Drug Application

BLA = Biologics License Application

Vaccines: Agency Involvement

- ***Food and Drug Administration:***
 - Review and regulation
 - Research
- ***National Institutes of Health:***
 - Research and clinical studies
 - Contracts
- ***Centers for Disease Control & Prevention:***
 - Disease investigations
 - Purchase vaccines for public use/Strategic National Stockpile
 - Advisory Committee on Immunization Practices (ACIP)
- ***Dept. Health & Human Services:***
 - Contracts
 - Coordination
- ***Companies***
 - Manufacture the vaccines

2009 H1N1 Cases (CDC estimates)*

Cases (Total)	~55 million
0-17 years	~18 million
18-64 years	~32 million
65 years and older	~5 million

*http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm#UnderCounting

2009 H1N1 Hospitalizations & Deaths (CDC estimates)

Hospitalizations (Total)	~246,000
0-17 years	~78,000
18-64 years	~145,000
65 years and older	~23,000
Deaths (Total)	~11,160
0-17 years	1,180
18-64 years	8,620
65 years and older	1,360

CDC Recommendations for Seniors

The data confirms that people younger than 65 years of age are more severely affected by this disease relative to people 65 and older compared with seasonal flu. With seasonal influenza, about 60 percent of seasonal flu-related hospitalizations and 90 percent of flu-related deaths occur in people 65 years and older. With 2009 H1N1, approximately 90% of estimated hospitalizations and 88% of estimated deaths from April through December 12, 2009 occurred in people younger than 65 years old. **However, because severe illness and deaths *have* occurred among people 65 and older and because supplies of 2009 H1N1 vaccine have increased dramatically, CDC is now encouraging all people 6 months and older, including people older than 65, to get vaccinated against 2009 H1N1.**

Resources

- **Websites:**

- www.pandemicflu.gov
- www.fda.gov
- <http://www.fda.gov/cber/summaries/sci042006jq.pdf>
- <http://www.fda.gov/cber/vaccine/licvacc.htm>
- www.nih.gov
- www.cdc.gov/mmwr
- www.hhs.gov
- www.bt.cdc.gov
- <http://www.who.int/en/>
- <http://www.fda.gov/cdrh/ppe/fluoutbreaks.html>
(personal protective equipment)