Microbiology Overview

- Bacteria
- Mycobacteria
- Fungi
- Protozoa
- Viruses
- Prions

Interaction of Host, Organism, & Environment

HOST

Virulence Factors

Isolation

Mode of Transmission

ORGANISM

(Strain)

Antimicrobials

Contamination

ENVIRONMENT

Sanitation, Sterilization

(Reservoir)

Immunity

Vector control

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†

* Per 100,000 population per year.
**Differentiation of Infectious Organisms**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Visual</th>
<th>Nucleic Acids</th>
<th>Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro-parasite</td>
<td>Eye</td>
<td>Both (Nucleus)</td>
<td>Organ</td>
</tr>
<tr>
<td>Micro-parasite</td>
<td>Low power</td>
<td>Both (Nucleus)</td>
<td>Organ</td>
</tr>
<tr>
<td>Fungus</td>
<td>Low power</td>
<td>Both (Nucleus)</td>
<td>Media</td>
</tr>
<tr>
<td>Bacteria</td>
<td>High power</td>
<td>Both</td>
<td>Media</td>
</tr>
<tr>
<td>Virus</td>
<td>EM</td>
<td>One</td>
<td>Cell line</td>
</tr>
</tbody>
</table>

**Dr. Hans Christian Jaochim Gram: Inventor of the Gram Stain 1884**

- **1884** While examining lung tissue from patients who had died of pneumonia
  - discovered that certain stains were preferentially taken up and retained by bacterial cells
- Over the course of the next few years, Gram developed a staining procedure which divided almost all bacteria into two large groups - the Gram stain.

**Diagram:**
- **Gram Positive**
  - Fixation
  - Crystal violet
  - Iodine treatment
  - Decolorization
  - Counter stain safranin

- **Gram Negative**
Viruses: Structure

Interaction of Organisms with Hosts

- Organism Strain
- Exposure
- Virulence Factors
  - Attachment
  - Protection from Host Defenses
  - Toxins
    - Fimbriae Attachment Proteins Receptors
    - Intracellular Growth Capsules Resistance Genes Cytolytic Enzymes
    - Exotoxins Endotoxins
  - Host Defenses
  - Disease

The life of a virus

Modes of Transmission

- Contact
  - Indirect- infected fomite, blood, or body fluid
  - Direct- skin or sexual contact
- Food- or water-borne
  - Ingestion of contaminated food
- Airborne
  - Inhalation of contaminated air
- Vector-borne
  - Dependent on biology of the vector (mosquito, tick, snail) and infectivity of organism
- Perinatal
Infection Requires Exposure

**RESERVOIR** (Organisms)  ➔ **HOST**

**Exposure**

**Mode of**

**Transmission**

Methods of Prevention of Infection

**RESERVOIR** (Organisms)  ➔ **HOST**

**Exposure**

**Mode of**

**Transmission**

- Eliminate
- Transmission
- Enhance Immunity
- Antimicrobial Prophylaxis
- Sanitation, Vector control

Stages of Infection in Populations

- Case
- Cluster
- Outbreak
  - (Same)
- Endemic
  - Expected Rate
- Epidemic
- Regional
- Pandemic
- Global

Media Can Distort Public’s Views on Infectious Diseases

- Media coverage of infectious diseases such as avian influenza can create the impression that the conditions are more of a threat than they really are
- Researchers compared reader impressions (undergraduate psychology students and medical students) of 10 infectious diseases—frequent in print media: anthrax, SARS, West Nile virus, Lyme disease, avian influenza;
  - rarely mentioned: tularemia, human babesiosis, yellow fever, Lassa fever, hantavirus
- Findings: rated “high media frequency” diseases as more serious

Bacteria Run Wild, Defying Antibiotics

“A new chapter in the continuing story of antibiotic resistance is being written in doctors' offices across the country, as a group of common bacteria rapidly becomes resistant to the antibiotics that have been used to treat them for decades.”

Cytolytic Proteins

- **Hemolysins:**
  - \( \alpha, \beta, \delta, \gamma \)
  - Red cell lysis
    - Beta Hemolysis
  - Tissue damage

- **Panton-Valentine Leucocidin**
  - White cell lysis
  - Protection from phagocytosis
  - Invasive Skin Disease

Relationship of staphylococcal virulence factors and resultant diseases

- **S. aureus**
  - Many Strains with Multiple Virulence Factors
  - Localization Factors
    - Coagulase Clumping Factor Protein A
    - Focal Infection Abscesses
    - Bacteremia
  - Toxins
    - Exfoliatin
    - TSST-1
    - Enterotoxins
    - Food Poisoning
    - Disseminated Infection
    - Deep Localized Infection
  - Localizing Factors
    - Scalded Skin Syndrome
    - Staphylococcal Scarlet Fever
    - Toxic Shock Syndrome

Staphylococcus

- Aerobic
- Gram-positive
- Cocci
- Pairs & groups
- **Staphylo** = grape-like
- **Coccus** = coccus
S. aureus Skin Infections

- Furuncles (boils)
- Cellulitis
  - Mild
  - Severe

Staphylococcus aureus periorbital cellulitis

Lymphadenitis due to S. aureus

S. aureus Scalded Skin
Toxic Shock Syndrome

Staph Toxic Shock Syndrome

CA-MRSA Pyomyositis

Organism Strains Evolve Over Time

Neonatal Sepsis (Phage type 80/81)
Scalded Skin Syndrome (Phage group II strains)
Toxic Shock Syndrome (Phage group I strains)

MRSA+ (PVL)

80/81 increasing

Ongoing Evolution of MRSA

- HA-MRSA
  - Hospital-acquired
  - Mono-resistant
  - Soft-tissue

- CA-MRSA
  - Community-associated
  - Poly-resistant
  - Superficial and Invasive

MRSA+
- Any locale
- Poly-resistant

**Microbiology of Streptococcus pyogenes**

- Gram positive spherical bacteria; pairs and chains
- Cell size form 0.5 μm to 1.0 μm
- Catalase negative (distinguishes them from staphylococci)
  \[ 2\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + 2\text{H}_2\text{O} \]
- No bubbles
- Facultative anaerobes

**Microbiology of Streptococcus pyogenes: Classification**

**Hemolysis patterns**
- α-hemolysis: *S. pneumoniae*
- β-hemolysis: *S. pyogenes*
- γ-hemolysis:

**Antigenic composition**
- Lancefield Groups A, B, C, G, etc based on cell-wall carbohydrate antigens
  - A: *S. pyogenes*
  - B: *S. agalactiae*
- M, T and R proteins
  - M protein a major virulence factor in *S. pyogenes*

**Multiple Faces of Streptococcal Disease**

- Noninvasive Strains
  - Impetigo
  - Pharyngitis
  - Pyogenic Exotoxins
  - Hyaluronic Acid Capsule
  - Proteinase
  - Spreading Factors

- Invasive Strains
  - Scarlatina
  - Septicemia
  - Necrotizing Cellulitis/Fasciitis
  - Cellulitis Erysipelas

- Poststreptococcal Glomerulonephritis
- Rheumatic Fever
- Toxic Shock Syndrome
Clinical Pharyngitis

Virulence Factors: M-protein -> attachment

Symptoms referable to the throat - 6th most frequently mentioned principal reason for visit.

Over 10 million cases of acute pharyngitis diagnosed in physician's offices annually.

Streptococcus pyogenes - most common cause of bacterial pharyngitis.

Rheumatic Fever

• Incidence
  - 1935  40 per 100,000
  - 1960  65 per 100,000
  - 1980s 0.23-1.88 per 100,000
  - 1985-90 Several major outbreaks of ARF throughout the US.

• Worldwide prevalence of chronic rheumatic heart disease ranges from 4.9 to 30 million children and young adults.

Rheumatic Fever

MODIFIED JONES CRITERIA FOR THE DIAGNOSIS OF ACUTE RHEUMATIC FEVER

• Major manifestations
  - Carditis
  - Polyarthritis
  - Chorea
  - Erythema marginatum
  - Subcutaneous nodules

• Minor manifestations
  - Clinical Arthralgia
  - Fever

Laboratory findings:
- Increased acute phase reactants: Increased erythrocyte sedimentation rate, Increased C-reactive protein
- Prolonged P-R interval

• If there is evidence of antecedent group A streptococcal infection, two major manifestations or one major and two minor manifestations indicate a high probability of acute rheumatic fever. If not an initial attack, then murmurs are not a reliable sign of carditis unless new mitral or aortic involvement is proven. In addition, pure chorea, insidious or late-onset carditis, or recurrences of rheumatic fever should raise a strong suspicion of rheumatic fever. Adapted from American Heart Association Guidelines, 1992.

Risk Factors

• Only certain strains of strep
• Only certain families
Pathogenesis of Rheumatic Fever

Cross-reacting immune response with Strep antigen that causes inflammation of heart, joints, skin
**Impetigo**

- Only certain strains of Strep (DNAase producing)
- May cause antibody response that leads to antigen/antibody complexes that cause glomerulonephritis

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**American Civil War: The “Scourge of the Hospital Ward”**

- “Erysipelas was a scourge of the hospital wards rather than the regimental camps”

  - Rate per thousand men: 13.2 per 1000
  - Fatality Rate: 10.2%

- “Contagious nature undoubted:
  - “special wards provided for erysipelas”
  - “few of the nurses escaped attack”
  - “the surgeon dreaded the presence of erysipelas among his wounded”

  *Medical and Surgical History of the Civil War*

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**Strep Cellulitis**

- Only certain strains (spreading factors: Hyaluronidase, DNAase B, Streptokinase)

**S. pyogenes “Spreading” Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>Activates plasminogen Lyses fibrin</td>
</tr>
<tr>
<td>DNAase</td>
<td>Dissolves DNA</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Dissolves ground substance</td>
</tr>
<tr>
<td>Protease</td>
<td>Proteolytic destruction</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle necrosis</td>
</tr>
<tr>
<td></td>
<td>Hyaluronate-protein cleavage</td>
</tr>
</tbody>
</table>
"The doctor came. It was pneumonia, and, he said, a peculiar erysipelas, which had started under the chin where the collar chafed, and was spreading over the face. He hoped it would not get to the brain .... but the young man’s face grew more discoloured, in the night she struggled with him. He raved, and raved, and would not come to consciousness. At two o’clock, in a dreadful paroxysm, he died."

Denver Zoo Komodo Dragon Exhibit
January 1996

- Case-control study
  - Identified 65 patients with *Salmonella enteritidis*
  - Median age 7 years (range, 3 mths to 48 yrs)
  - 56% had bloody diarrhea

- No patients and two controls reporting touching a dragon—however, 83% of pts touched the wooden barrier surrounding the dragon pen
- Washing hands after exhibit highly protective \((OR=0.14, 95\% CI 0.03 to0.7)\)
- Cultures from patients, one dragon, and exhibit barriers positive for *S. enteritidis*


Epi Curve of Salmonella Outbreak

Pertussis

*Whooping Cough* (Also Called "Pertussis")

A child with whooping cough has coughing spells which end in vomiting and a gasp for breath.

A baby with whooping cough has a runny nose.

The cough can last a long time (about 3 months).
Pertussis Through the Ages

- First reference in England 1540
  - “100 day cough”
- Guillaume de Baillou described 1578 Paris epidemic
- 1679 Sydenham used name “pertussis” (violent cough)
  - Scotland “the Kink” – fit, paroxysms
  - Northern Europe “Kindhoest” – child’s cough
  - Hooping cough, tussis perennis, tussis epidemica infantum, tussis puerorum convulsiva, tussis quinta, tussis quintana
- 1906 cultured from patient
  - “le microbe de la coqueluche” – Jules Bordet and O. Gengou
- 1930s first experimental pertussis vaccines
- 1944 Council on Pharmacy and Chemistry of AMA endorses immunization


Pertussis (Whooping Cough)

- *Bordetella pertussis* – gm-neg pleomorphic bacillus
- Humans only known host
- Transmission via contact with respiratory secretions (droplet precautions)
- Incubation period 6-20 days (usually 7-10 days)
  - **Catarrhal stage** (mild URI sx- most contagious) → Paroxysmal stage (severe cough, whoop) → Convalescent stage
- Duration 6-10 weeks

When Is Pertussis Communicable?

- Persons with pertussis become highly infectious during the catarrhal stage.
- Some individuals, especially infants, may be infectious for a longer period than shown above.

Reference:
Dramatic Growth in Reports of Adult and Adolescent Pertussis

Reasons for Increased Pertussis Incidence

- Increased reporting
  - Improved recognition of cases in adults and adolescents
  - Reporting criteria changed in 1995
    - Confirmation through PCR
    - Epidemiologic links
  - Serology
- Increasing incidence
  - Waning protection from childhood vaccination or prior infection
  - Delay or refusal of vaccines

Transmission of Pertussis

- Pertussis is transmitted to and from all age groups.
- Highly contagious, with 80% secondary attack rate among susceptible household contacts. Transmission of pertussis to household members has been documented.
- Young infants get pertussis primarily from family members, and are at high risk of morbidity and mortality.
- Adolescents get pertussis from household contacts and schoolmates.
- Adults get pertussis from work and household contacts; parents (adult and adolescent) give pertussis to their infants.

References:
Craft your governance text here. This text should be concise and clear, focusing on the key points of the document. It should be written in a way that is easy for a human reader to understand and follow.
### National Pertussis Rates

States with incidence of pertussis the same or higher than the national incidence (as of July 5, 2012), which is 5.24/100,000 persons

<table>
<thead>
<tr>
<th>State</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin</td>
<td>50.7</td>
</tr>
<tr>
<td>Washington</td>
<td>39.2</td>
</tr>
<tr>
<td>Montana</td>
<td>32.7</td>
</tr>
<tr>
<td>Vermont</td>
<td>23.7</td>
</tr>
<tr>
<td>Minnesota</td>
<td>23.4*</td>
</tr>
<tr>
<td>Iowa</td>
<td>21.0</td>
</tr>
<tr>
<td>Utah</td>
<td>14.2</td>
</tr>
<tr>
<td>Maine</td>
<td>14.1</td>
</tr>
<tr>
<td>Oregon</td>
<td>13.4</td>
</tr>
<tr>
<td>New Mexico</td>
<td>11.7</td>
</tr>
<tr>
<td>Arizona</td>
<td>8.3</td>
</tr>
<tr>
<td>Colorado</td>
<td>8.2</td>
</tr>
<tr>
<td>Idaho</td>
<td>5.7</td>
</tr>
<tr>
<td>Alaska</td>
<td>5.2</td>
</tr>
<tr>
<td>New York State</td>
<td>7.3</td>
</tr>
<tr>
<td>Illinois</td>
<td>6.7</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>6.3</td>
</tr>
<tr>
<td>Missouri</td>
<td>5.8</td>
</tr>
<tr>
<td>Idaho</td>
<td>5.7</td>
</tr>
<tr>
<td>Iowa</td>
<td>21.0</td>
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<tr>
<td>Colorado</td>
<td>8.2</td>
</tr>
<tr>
<td>Alaska</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Provisional counts of pertussis cases nationally as of July 12, 2012: >17,000 cases

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### Emergence of New Viral Diseases

- Hantavirus
- Ebola Virus
- Prions: Mad Cow Disease/BSE
- Human Immunodeficiency Virus
- West Nile Virus
- SARS CoV

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Duke team passed on rare virus

Bad turkey sandwiches disrupted 43 players, staff

By the middle of the second quarter, several (Duke) players, including three of the defensive starters, were on IVs in the locker room.

Duke team member sickened (vomiting or diarrhea) after eating box lunch

Duke team member sickened who did not eat box lunch

Florida State team member sickened

A virus makes a tough offensive play

During a 1998 college football game, a food- and waterborne virus spread among players in an unprecedented way. Members of the losing team -- Duke -- caught the virus from a pregame turkey lunch, fell ill, and then passed the virus to teammates and members of the opposing team -- Florida State -- through contact during the game.

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What Is West Nile Virus and Where Did It Come From?

- Flavivirus
  - Similar to Japanese Encephalitis virus and St Louis Encephalitis virus
- First isolated and identified in an infected person in the West Nile district of Uganda in 1937
- Widely distributed in Africa, Asia, the Middle East and Europe
- 1999 appeared in New York City and has been spreading westward since that time

West Nile Virus

- Summer 1999: Outbreak of viral encephalitis in New York State – 62 human cases/7 deaths
- Bronx Zoo Exotic birds dead; NYC Crows dead
- Arbovirus isolated: DNA analysis revealed West Nile Virus – first time isolated in Western hemisphere
- Mosquito vector: Surveillance of mosquito pools
- Mass-spraying campaign to eradicate vector and control spread
- But......

West Nile Virus Transmission Cycle

- Mosquito vector
- Incidental infection
- Bird reservoir hosts

WNV Human Infection “Iceberg”

- <1% CNS disease
- ~20% “West Nile Fever”
- ~80% Asymptomatic
- ~10% fatal (<0.1% of total infections)

Dead End Hosts
No High Level Viremia

Very crude estimates
Influenza Virus

- **15th Century Italians**
  - “to influence”; illness influenced by the stars and planets

- **Family Orthomyxoviridae**
  - “myxo” mucus
  - Segmented, single-stranded RNA

- **Influenza A** first isolated 1933; Influenza **B** 1940

- **15 hemagglutinin (HA) and 9 neuraminidase (NA) subtypes**
  - Only H1N1, H2N2, H3N2 subtypes associated with widespread epidemics in humans

**Diseases of Infancy and Childhood Textbook**
L. Emmett Holt 1906

Chapter XII  Influenza

**synonym:** la grippe

- Influenza is an infectious, communicable disease, which is now generally admitted to be due to the bacillus described by Pfeiffer in 1892.

- Treatment....The fumigation of apartments after attacks should be regularly practiced, preferably with formalin gas; this with isolation will do much to control house epidemics...The cough which persists after influenza is best controlled by cod-liver oil and creosote, used as after acute bronchitis.
Influenza: A Continuously Changing Virus

Polymerase Proteins (PP)

Hemagglutinin (HA) *cell entry
Neuraminidase (NA) *cell escape
M1, M2
Nucleoprotein (NP)


Antigenic Drift (A & B)

Antigenic Shift (A only)
Timeline of Emergence of Influenza Viruses in Humans


H1
H2
H3
H5
H6
H7
H8
H9
Spanish Influenza
Asian Influenza
Russian Influenza
Hong Kong Influenza

Transmission of Influenza

- Person to person
- Droplet spread:
  - small particle aerosols
- Fomite contamination:
  - Steel and plastic 24-48 hrs
  - Cloth, paper, tissues 8-12 hrs
  - Hands 5 min (high viral titer)
- Principal site of replication: columnar epithelium
- Incubation period: 18 hrs to 5 or more days (avg 2-3 days)
- Virus shedding 3-7 days
- Viral titers are generally higher in young children with shedding lasting 10 days or longer

Influenza Disease Burden in the US in an Average Year

- Hospitalizations: 117,000 - 816,000
- Deaths*: 25,000-72,000
- Physician visits: ~25 million
- Infections and illnesses: 50-60 million

* All-cause hospitalization and mortality associated with influenza virus infection

Reported Influenza Activity

Week ending October 18, 2003
Week ending November 29, 2003
Week ending December 20, 2003
Week ending January 31, 2004

No Report  No Activity  Sporadic  Local  Regional  Widespread
Definition of a Pandemic

Global outbreak occurring when:

1. A new influenza A virus appears/emerges in the global immunologically naïve human population
   - New subtype
   - Subtype that has never circulated among humans
   - Or has not circulated for a long time

2. Infection results in serious illness and high mortality

***3. Effective person-to-person transmission

20th Century Influenza Pandemics

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Strain</th>
<th>Worldwide Deaths</th>
<th>US Deaths</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>1918-1919</td>
<td>Spanish flu</td>
<td>*H1N1</td>
<td>25-50 million</td>
<td>&gt;500,000</td>
<td>Unclear Human-adapted animal virus</td>
</tr>
<tr>
<td>1957</td>
<td>Asian flu</td>
<td>H2N2</td>
<td>&gt; 1 million</td>
<td>70,000</td>
<td>Reassortment with avian virus</td>
</tr>
<tr>
<td>1968</td>
<td>Hong Kong flu</td>
<td>*H3N2</td>
<td>&gt; 1 million</td>
<td>34,000</td>
<td>Reassortment with avian virus</td>
</tr>
<tr>
<td>1977</td>
<td>Russian flu</td>
<td>H1N1</td>
<td>low</td>
<td>low</td>
<td>1950’s H1N1 (frozen stock?)</td>
</tr>
</tbody>
</table>

All spread around the world within 1 year of being detected

Committee of American Public Health Association

- Disease extremely communicable
- Advocated legislation that would prevent the use of common cups and utensils and ban public coughing and sneezing
- Good handwashing
- Nervous and physical exhaustion should be avoided
- Encouraged exposure to fresh air
- Gargling with elixirs (chlorinated soda, mixture of sodium bicarb and boric acid)
Obey the laws
And wear the gauze
Protect your jaws
From Septic Paws.

**Influenza Type A (H5N1)**
- Fatal epidemic among Hong Kong poultry in 1997
- Two months later appeared in humans in Hong Kong, 1997
- Primarily associated with avian species
- 18 total confirmed cases, with 6 deaths
  - Each human case caused by independent transmission from birds in poultry markets


**Why H5N1 is of Particular Concern**
- Known to rapidly reassort and mutate: 2004 strain different from 1997
- Documented propensity to acquire genes from viruses infecting other animal species
- Severe disease in humans documented on three occasions: 1997, 2003 and current epidemic
- Surviving birds excrete for >10 days (oral and fecal) facilitating spread in poultry markets and migratory birds
- Spread of infection in birds increases opportunity for direct infection of humans
- Person-to-person spread documented in 1997, 2003 outbreaks (but only in limited number of cases)
- Further adaptation to humans: The start of a pandemic

**Avian Influenza: Sick Chickens**
- Blue Comb
- Congestion and Blood Spots on Hocks and Shanks
- Vesicles on comb
- Swollen Wattle
Novel H1N1 aka “Swine Flu”

- H1N1 declared pandemic by WHO 06/11/09
- Current H1N1 involves a new strain that appears to be a result of reassortment of human influenza, avian and swine influenza viruses
What Does the 2008 Measles Outbreak Mean?

Spread of measles has been controlled or limited due to:

1. high vaccination coverage in the U.S.
2. excellent two-dose vaccine performance
3. rapid and effective public health responses

These cases and outbreaks resulted primarily from failure to vaccinate, many because of personal or religious belief exemption.

This fact highlights:

- the ongoing risk of measles in unvaccinated persons
- the risk that unvaccinated persons transmitting measles to others, including infants too young to be vaccinated
- the importance of maintaining high levels of vaccination
Vaccines: Basic Strategy

- Expose vaccinee to weakened, inactivated or small piece of the infectious agent
- Trigger a protective immune response
- Maintain this immune response for a lifetime of possible re-encounters

Principles of Vaccination

1. Active immunity produced by vaccine
2. Produce protection without producing disease

Key Vaccine Attributes:
- Tolerability- incidence, severity, and duration of local reactions
- Safety- systemic side effects
- Immunogenicity
- Efficacy
- Persistence of Immunity

Influenza Vaccine (TIV)

Manufacturing Schedule

- 1 year before production- order chickens
- 3 mths before production- hens moved into laying houses
- Early spring- inoculate eggs
- Strain selection
  - First strain- late Jan
  - Second strain- Mar
  - Third strain- early April
- Purification is by centrifugation
- Neutralized by chemical
- Inactive vaccine preparation only
- Production cycle = 70 weeks

Factors Influencing Evolution of New Diseases and Spread of Old Ones

Organism

Political - Economic

Social

Personal

Vaccination

Cancer

Cronic
Factors Influencing Evolution of New Diseases and Spread of Old Ones

**Organism**
- New Organism
- Resistant Organism

**Political - Economic**
- Poverty
- Famine/Malnutrition
- Territorial conflict
- Natural Disaster

**General Health Care**
- Poor Sanitation
- Inadequate immunization
- Unsafe blood supply
- Poor public health system

**Social**
- Age extremes
- Illiteracy
- Global Travel

**Personal**
- Sexual Activity
- IV Substance abuse
- Immune suppression
- Cancer
- Chronic Disease