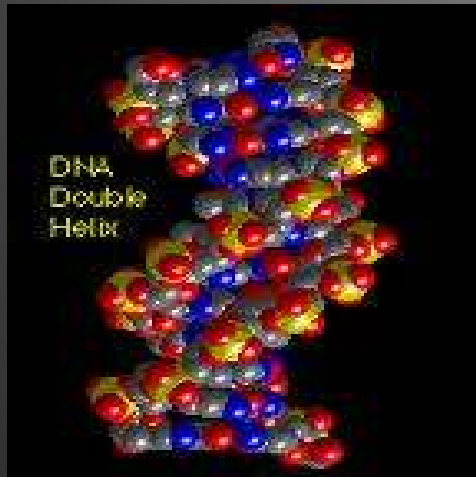


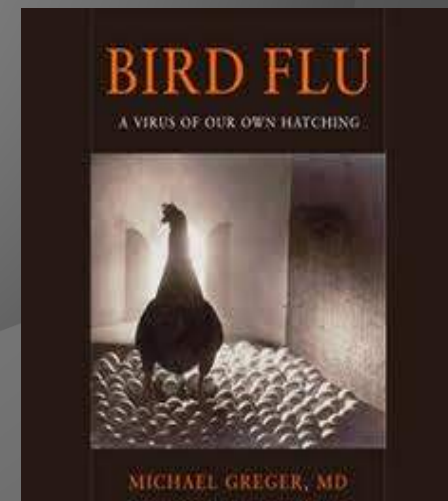
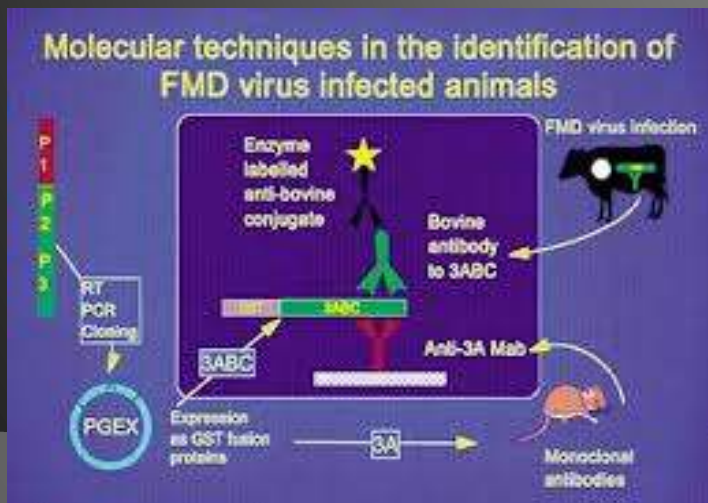
EMERGING HEALTH THREATS OF THE 21ST CENTURY & BEYOND: Biological Mechanisms & Biomedical Countermeasures

Frank G. Rando



Introduction

- While we live in a multi-threat /"all hazards" environment, this presentation will be limited to an overview of biological (organisms) and biochemical (toxin) threat agents of interest to global public health ,safety and security (biodefense ,biosafety & biosecurity).



**“Nature isn’t benign.
The survival of the human species
is *not* a preordained evolutionary
program.”**



- Joshua Lederberg, Nobel laureate at age 33

The Threat Spectrum

- ⦿ Natural
Epidemics/Pandemics
Natural Disasters

EPIDEMIC AND PANDEMIC THREATS ARE OF GREAT CONCERN DUE TO INCREASED GLOBALIZATION AND A RISE IN MICROBIAL DRUG RESISTANCE AND VIRULENCE.

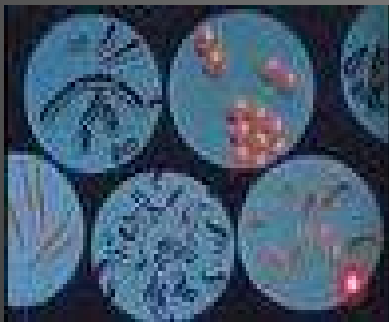
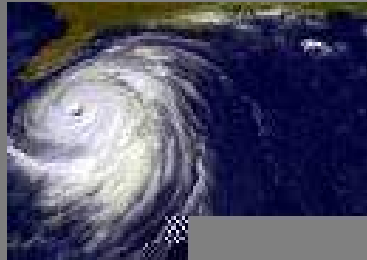
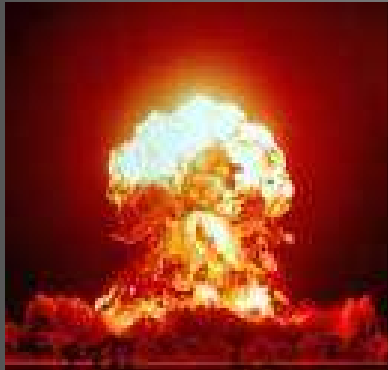
Natural disasters can create secondary technological ,epidemiological and environmental disasters, impact and overwhelm critical infrastructure

- ⦿ Anthropogenic
 - ⦿ Biowarfare/Bioterrorism
 - ⦿ Chemowarfare/Terrorism
 - ⦿ Radiological-Nuclear Warfare/Terrorism
 - ⦿ Technological Disasters
 - ⦿ BIOTHREAT AGENTS.
- ESPECIALLY,INFECTIOUS DISEASES, ARE A GLOBAL HEALTH & SECURITY PRIORITY.

Anthropogenic disasters may generate complex acute and chronic health effects, overwhelm and impact critical infrastructure, including health systems /public health ,resist and evade detection and biomedical countermeasures.

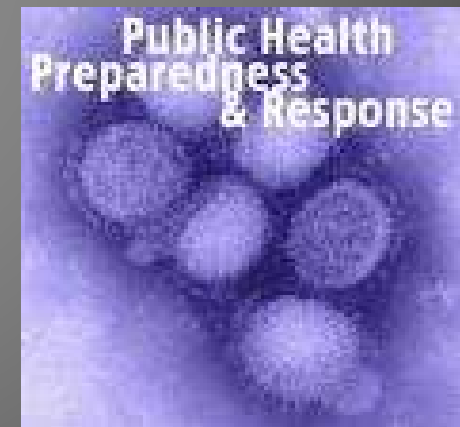
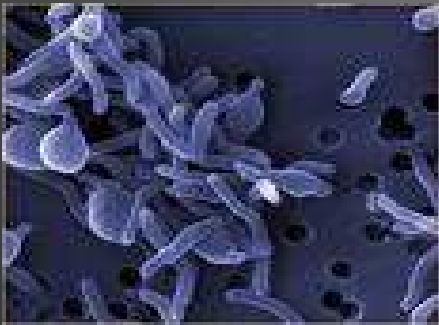
“Run, Forrest...RUN!!

- Multi-threat environment



An Evolving Paradigm: Medical Threats of the 21 st Century

- Emerging Infectious Diseases
- Pandemics and Biowarfare/Bioterrorism
- Biothreats a top priority concern for global health and international security!



A Global Call to Action



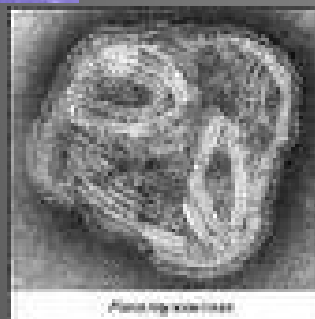
"Emerging infections, the re-emergence of infectious diseases previously considered to be under control, and the alarming trend of antibiotic resistance... require an immediate and appropriate response."

**Dr. Gall Cassell, Past President,
American Society of Microbiology, May 1994**

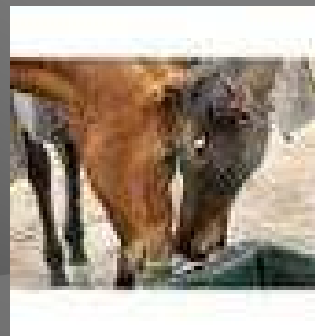
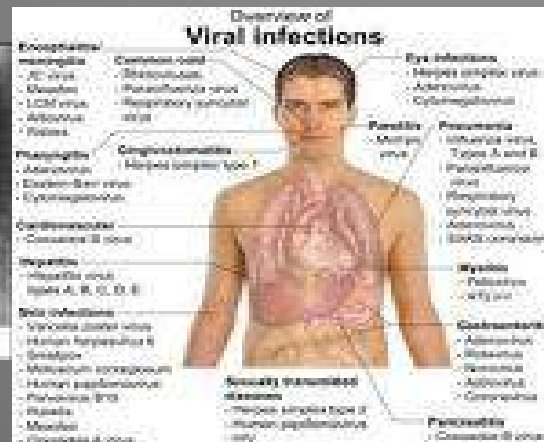
An Evolving Paradigm: Medical Threats of the 21st Century

- ⦿ Emerging/Re-emerging Infections
- ⦿ “The single greatest threat to man’s predominance on the planet is the virus”-Joshua Lederberg, Nobel laureate
- ⦿ High infectivity/pathogenicity
- ⦿ Zoonotic infections
- ⦿ Drug resistance
- ⦿ Evolutionary adaptations
- ⦿ Many can cause severe respiratory illness
- ⦿ ALI-ARDS/ARF, pandemic threats

Viral Threats



Flamingo adenovirus



An Evolving Paradigm: Medical Threats of the 21st century

- ⊙ Avian Influenza (H5N1)/HPAI
- ⊙ Human Influenza (1918 severity)
- ⊙ SARS-CoV
- ⊙ Nipah & Hendra viruses
- ⊙ Viral Hemorrhagic Fevers

NOTE: Selected pathogens have
“weaponization potential”.

Spanish Flu 1918: Will it happen again, or worse?



Pandemic Influenza

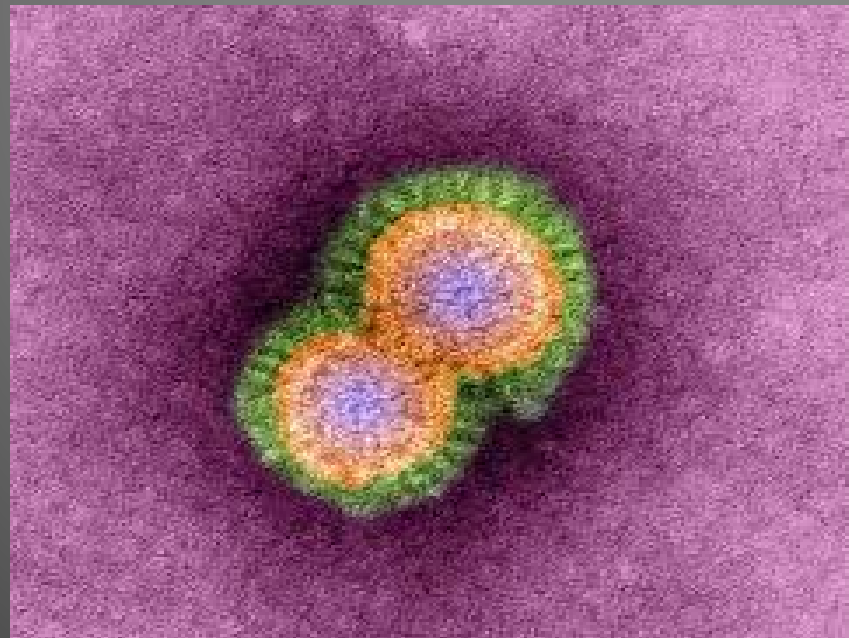
- Populations:
- Susceptible
- Exposed
- Sick & Contagious-Resource Allocation

H1N1: Epidemiology & Pathophysiology

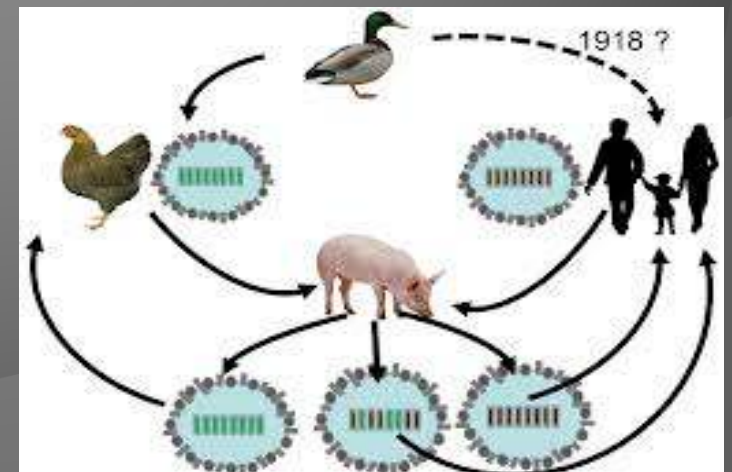
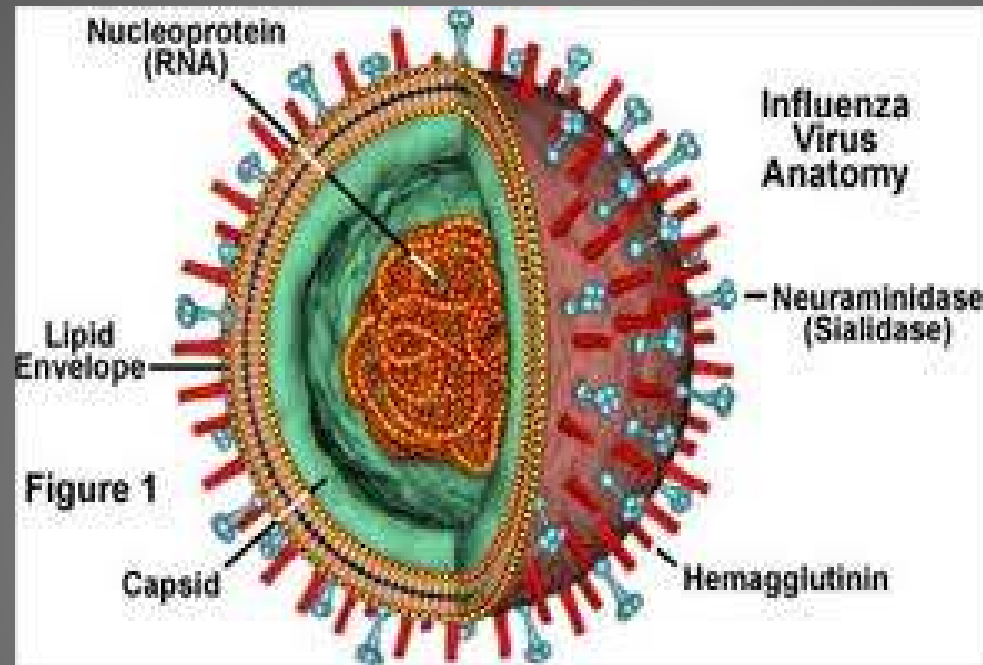
- ⦿ Epidemiology/Demographics:
- ⦿ Young, “healthy” population
- ⦿ Pregnant women
- ⦿ Immunocompromised
- ⦿ Pre-existing co-morbidities eg. asthma

THE H5N7 STRAIN

- ⦿ Emerging avian influenza subtype
- ⦿ Genetic reassortment of highly pathogenic genes

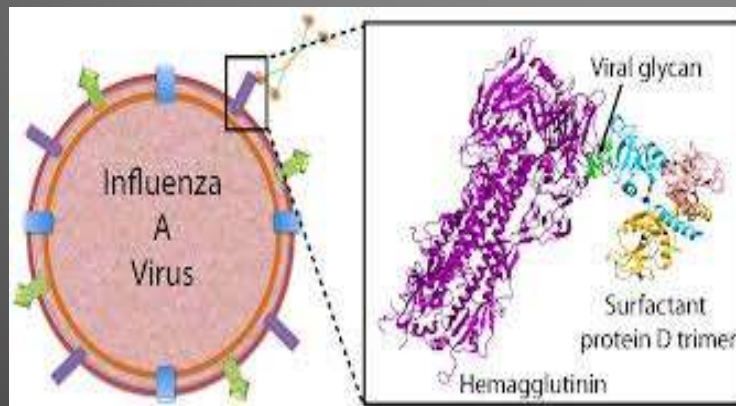


The Biology of Influenza



Biological Mechanisms: Influenza

- Genome- 8 helices of RNA
- Each RNA encodes a single gene
- Each bound by nucleoprotein
- Nucleoprotein determines type (A,B,or C)



Biological Mechanisms: Influenza

- ⦿ Spherical surface-lipid bilayer (envelope)
- ⦿ Envelope contains *hemagglutinin(H)* & *neuraminidase (N)*
- ⦿ *H & N* determine viral *subtypes* (*H1N1,H5N7,etc.*)
- ⦿ *Antigenic drift*- Viral mutations occur which involve *H & N* and allows for virus to escape host defenses ,specifically antibodies.
- ⦿ *Pandemics* may occur when both *H&N are replaced via recombination of RNA segments.,ie. antigenic shift.*

Biological Mechanisms: Influenza

● GENETIC REASSORTMENT= NOVEL STRAIN

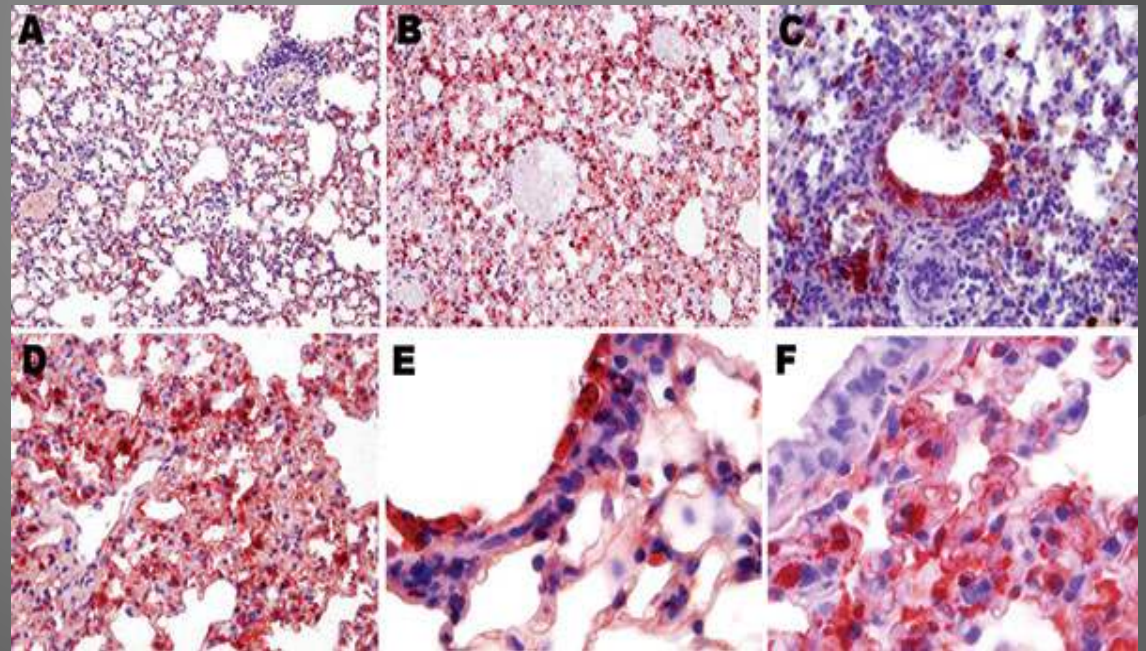
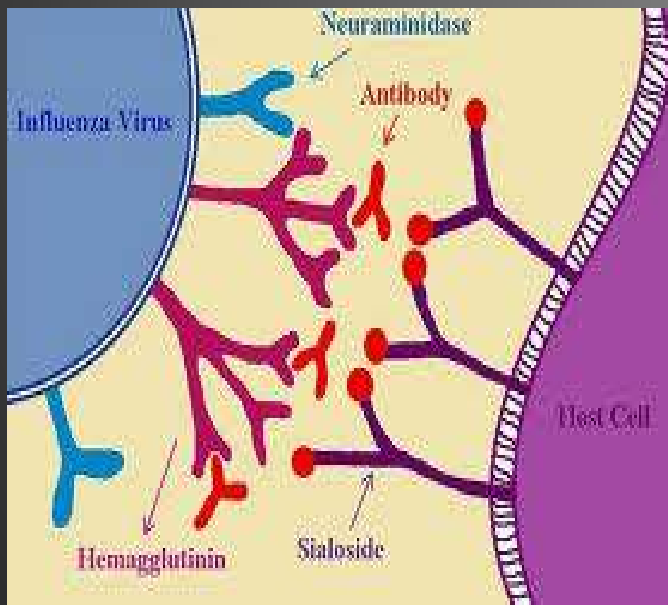
Antigenic Shift = Pandemic Potential

- Profound variation in hemagglutinin or neuraminidase
 - reassortment of genomic material
- Influenza type A only
- New virus with novel antigenic profile
- Influenza virus transmitted from aquatic birds (center) directly (solid lines) to fowl and pigs, who transmit to humans



How does the influenza virus attack cells ?....

- ⦿ Depiction of host cell infection (L)
- ⦿ H5N1&H1N1 virus infected mouse pneumocytes (R)



General Mechanisms of Viral – Induced Injury

Viruses are adept at directly damaging cells via invasion of host cells and viral replication.

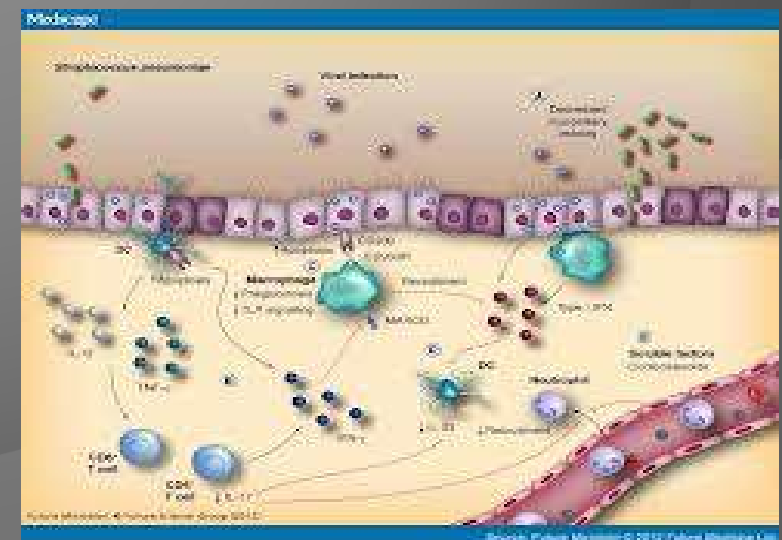
DETERMINANT FACTORS:

Host cell receptors need to be present (specific cell surface proteins, eg. glycoproteins).

Presence of transcription factors.

Anatomic barriers?

Local temperature, pH and host defenses.



General Mechanisms of Viral-Induced Cell Injury (cont'd)

- *Direct cytopathic effects*-Inhibit synthesis of macromolecules(e.g.,host cell DNA,RNA or proteins) by producing enzymes,toxic proteins,apoptosis)
- *Antiviral immune responses*-Viral proteins on cell surface of host cells “recognized” by immune system. Cytotoxic T-lymphocytes are important for *immune defense* ,but may result in cellular /tissue injury,as in accelerated liver failure during Hepatitis B infection.

General Mechanisms of Viral – Induced Cell Injury (cont'd)

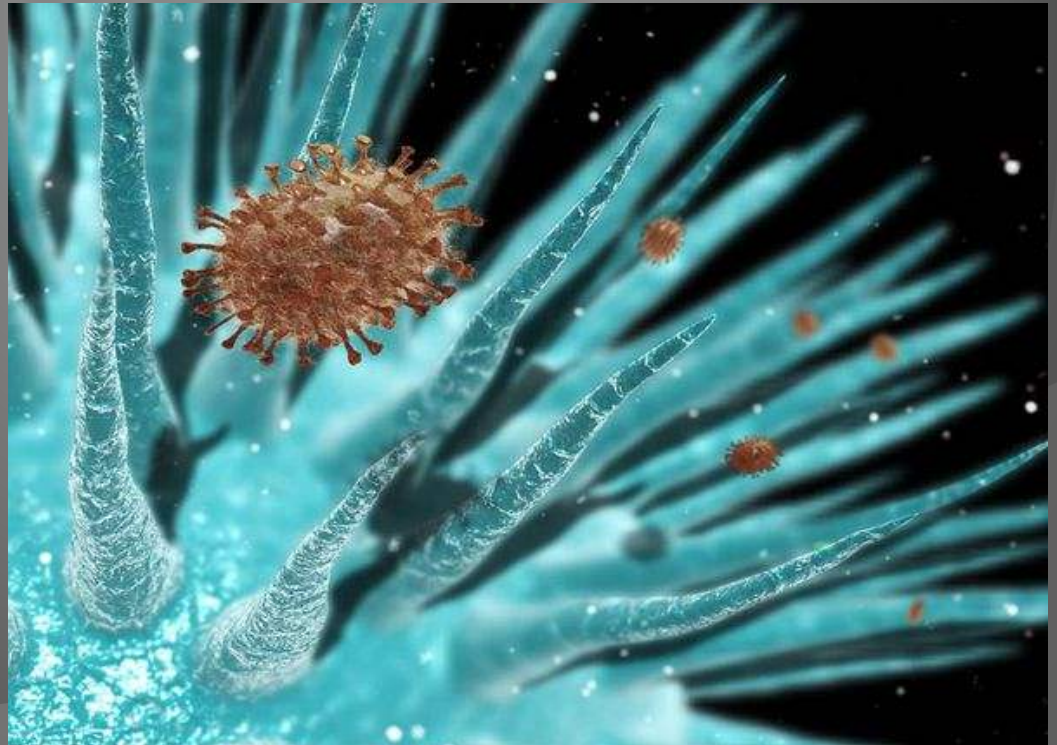
- *Transformation of infected cells into benign or malignant tumor cells by oncogenic viruses via expression of oncogenes, anti-apoptosis factors, or insertional mutagenesis-ie., host genes are altered by viral genes inserted into the host genome.*

Influenza: Pathophysiology

- ⦿ The *pathogenicity* of influenza results from the virus' ability to cause systemic infection
- ⦿ *H & N structure are related to pathogenicity of the strain.*
- ⦿ Highly pathogenic strains increase morbidity & mortality via cytokine storm, tissue necrosis, organ failure and Acute Respiratory Distress Syndrome (ARDS) which leads to severe alveolar flooding , hypoxia and Acute Respiratory Failure (ARF).

Target Organ: Lung

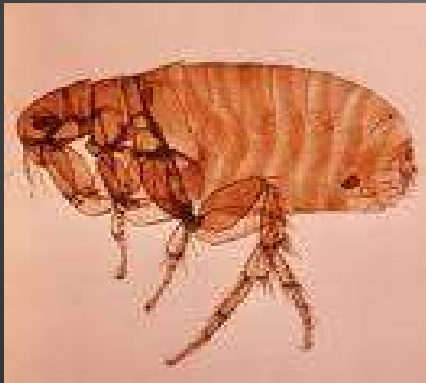
- ⦿ Gross pathology of chicken lung infected with HPAI
- ⦿ Influenza virus attacking cilia in the human lung
- ⦿ Lung is hemorrhagic& edematous, cilia gets ‘denuded’



Pandemic/Emerging Infectious Diseases: Implications

- ⦿ Severe febrile respiratory illness.
- ⦿ ICU patient surge requiring mechanical ventilation in many instances.
- ⦿ Overtaxed healthcare resources including “staff, stuff and space”.
- ⦿ Infection Control issues, PPE.
- ⦿ Health workforce absenteeism.
- ⦿ Disruptions in supply chain, eg. Medical gases.
- ⦿ Availability of vaccines and antivirals.

Natural Vectors OR Weapon Systems??... Maybe both??....



Bioterrorism (CDC Definition)

“Bioterrorism is the intentional or threatened use of viruses, bacteria, fungi, toxins from living organisms or other chemicals to produce death or disease in humans, animals or plants.”

Potential Bioterrorism Agents

⊙ Bacterial Agents

- Anthrax
- Brucellosis
- Cholera
- Pneumonic plague
- Tularemia
- Q Fever

⊙ Viruses

- Smallpox
- Venezuelan Equine Encephalitis
- Viral Hemorrhagic Fever

⊙ Biological Toxins

- Botulinum
- Staph Entero-B
- Ricin
- T-2 Mycotoxins

CDC Category Definitions of Diseases/Agents

◎ Category A - Highest priority

- Can be easily disseminated or transmitted from person to person
- Results in high mortality rates and have the potential for major public health impact
- Might cause public panic and social disruption
- Require special action for public health preparedness

◎ Category A – Agents

- Anthrax (*Bacillus anthracis*); Botulism (*Clostridium botulinum* toxin); Plague (*Yersinia pestis*); Smallpox (variola major); Tularemia (*Francisella tularensis*); and Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

CDC Category Definitions of Diseases/Agents (cont)

- ⦿ **Category B** – Second highest priority
 - Moderately easy to disseminate
 - Result in moderate morbidity rates and low mortality rates
 - Require special enhancements of CDC's diagnostic capacity and enhanced disease surveillance
- ⦿ **Category B** – Agents
 - Brucellosis (*Brucella* species); Epsilon toxin of *Clostridium perfringens*; Food safety threats (e.g., *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*); Glanders (*Burkholderia mallei*); Melioidosis (*Burkholderia pseudomallei*); Psittacosis (*Chlamydia psittaci*); Q fever (*Coxiella burnetii*)

CDC Category C Definitions of Diseases/Agents (cont)

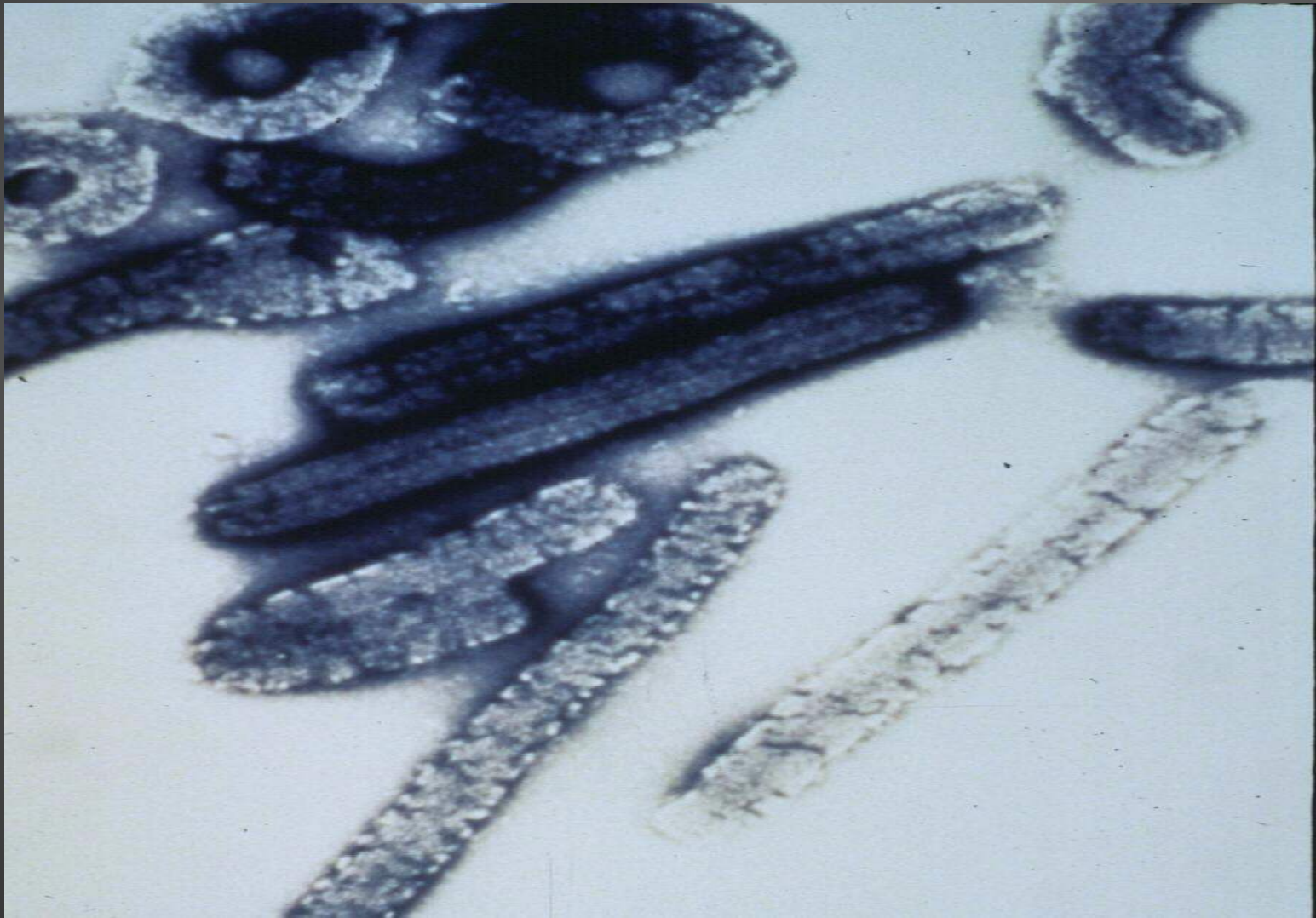
- ◎ **Category C – Third highest priority**
 - Includes emerging pathogens that could be engineered for mass dissemination in the future because of
 - > availability
 - > ease of production and dissemination
 - > potential for high morbidity/mortality rates and major health impact
- ◎ **Category C – Agents**
 - Nipah virus and hantavirus

CDC Category Definitions of Diseases/Agents (cont'd)

◎ Category B – Agents (Cont)

- Ricin toxin from *Ricinus communis* (castor beans); Staphylococcal enterotoxin B»Typhus fever (*Rickettsia prowazekii*); Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis]); and Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)

Viral Threats

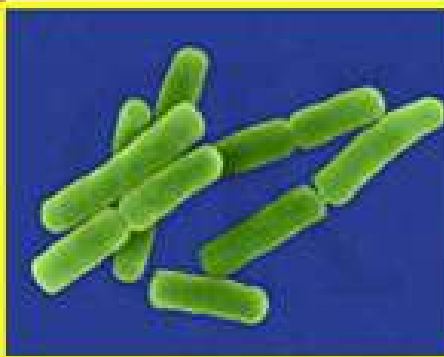


Myxoviruses: Nipah & Hendra

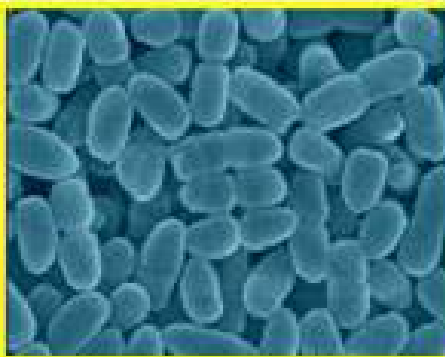
- Origin: Naturally infect fruit bats and cause severe disease when transmitted to humans and other animals .
- Hendra virus was first described in 1994 and Nipah in 1998-1999.
- Transmission: Mostly by respiratory secretions and inhalation.
- Portal of entry : Upper respiratory tract
- Incubation period: 4 days to 2 mo.(but usually < 2 weeks) for Nipah virus.
- Case fatality rate : 40- 70 % No vaccine or cure .
Ribavirin? Encephalitis, severe LRTI, pneumonia

Microbial Threats

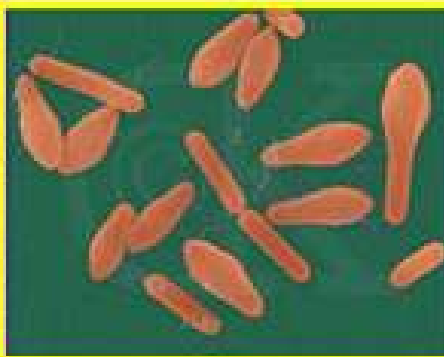
Bacillus



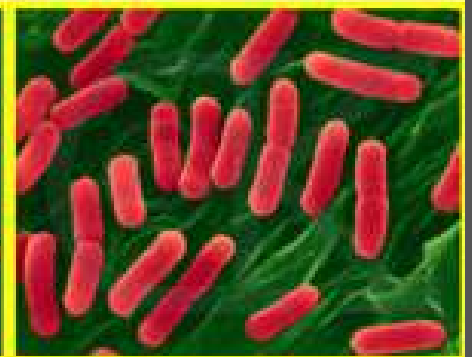
Bordetella



Clostridium



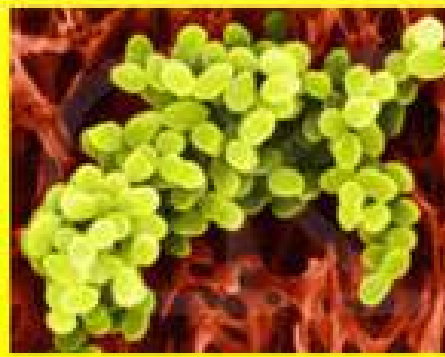
Escherichia



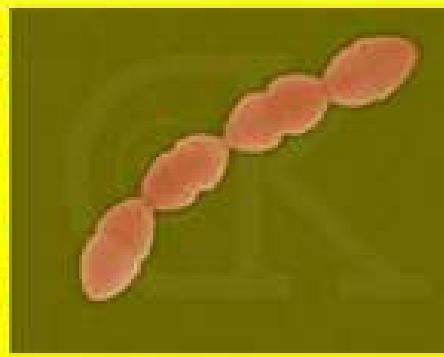
Spirulina



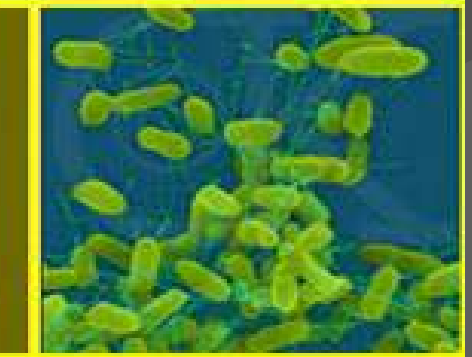
Staphylococcus



Streptococcus

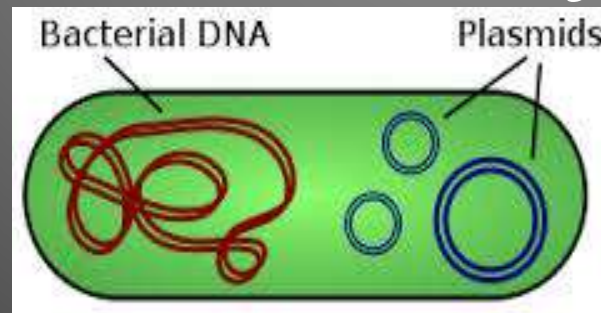


Salmonella



Bacterial Mechanisms

- *Virulence- Pathogenic bacteria must be able to adhere to host cells,invade cells/tissues,or deliver toxins (virulence genes).*
- *Plasmids and bacteriophages (viruses) are “mobile”genetic elements that spread between bacteria and confer (encode) virulence factors(e.g. toxins,or enzymes that can confer antibiotic resistance*



Bacterial Mechanisms (cont'd)

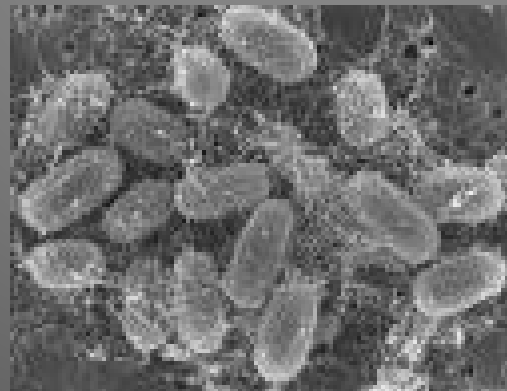
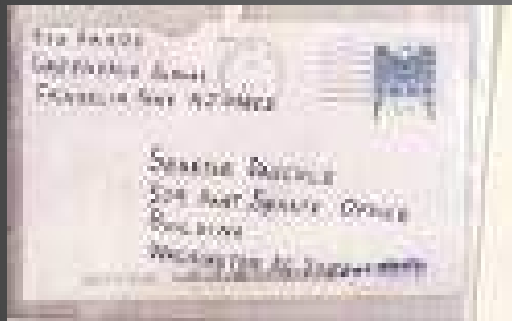
- *Bacterial adherence to host cells-Adhesins are surface molecules that bind to host cells or extracellular matrix (ECM)*
- *Bacterial toxins- Any bacterial substance that contributes to pathogenicity& illness can be considered a toxin.*
- *Endotoxins-components of bacterial cell (lipopolysaccharides)*
- *Exotoxins- Proteins that are secreted by bacteria-induce cellular injury & disease via enzymes,toxins,superantigens.*

Anthrax: Mail-borne Bioterrorism



Mailborne Bioterrorism

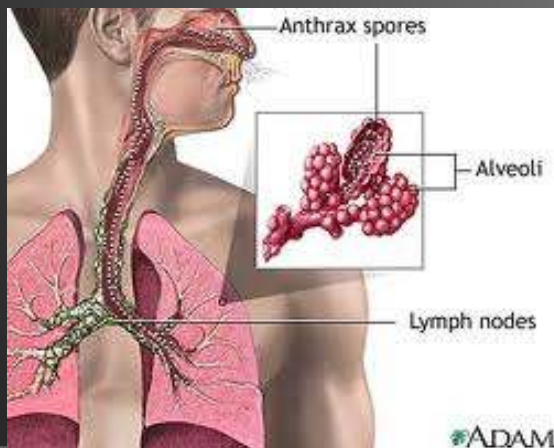
◎ The Anthrax Letters-October 2001



Bacillus anthracis: High threat “select agent”

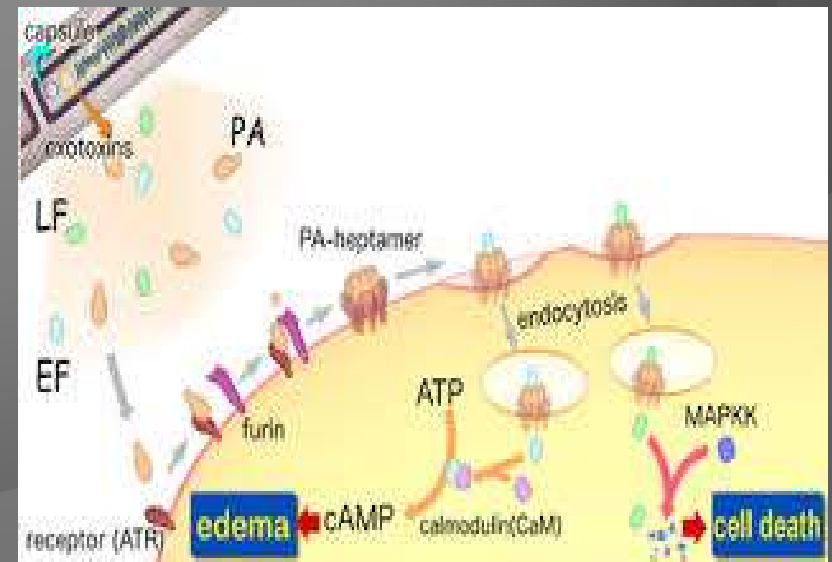
Large, spore-forming Gram-positive rod –shaped bacterium.

Common in farm and wild animals–



Anthrax Toxins: Mechanisms of Action

- Protective antigen (PA)-binds to cell surface protein
- Polyglutamyl capsule -antiphagocytic
- Edema factor (EF)-binds to Ca^{++} & calmodulin to eventually convert ATP to cAMP>signals for efflux of H_2O from cell causing interstitial edema
- Lethal factor (LF)-
- LF destroys mitogen-activated protein kinases (MAPKKs) – leads to cytotoxicity/cell death.

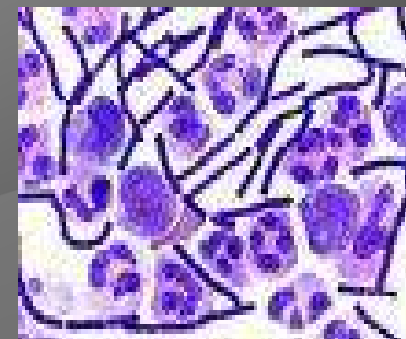
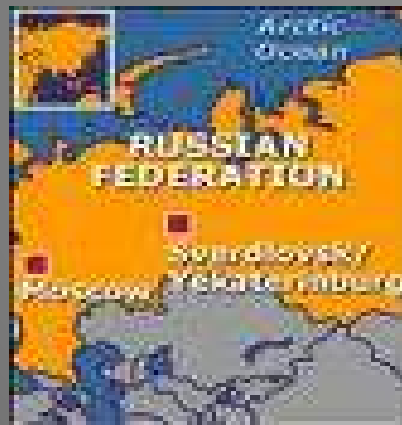


Anthrax: Some Facts

- ◉ Inhalational (pulmonary)
- ◉ Gastrointestinal
- ◉ Cutaneous
- ◉ Bacillus anthracis-releases toxin/lethal factor and edema factor
- ◉ Toxin is cytotoxic and causes edema
- ◉ Weaponized form behaves like a gas/aerosol and is “energetic”
- ◉ Particles are capable of being inhaled ,deposited and retained in lung
- ◉ Inhalation form-high mortality-inhaled spores travel to mediastinum ,liberate toxin & causes hemorrhage and toxic shock ,may cause secondary hemorrhagic meningitis
- ◉ Post-9/11-Oct. 2001-22 victims exposed in mailborne attack-5 deaths.

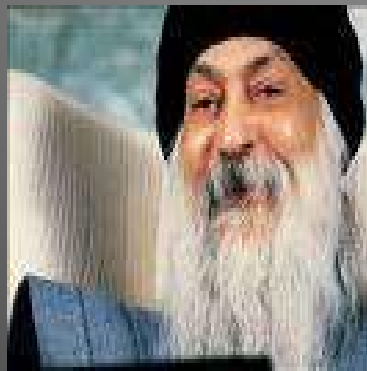
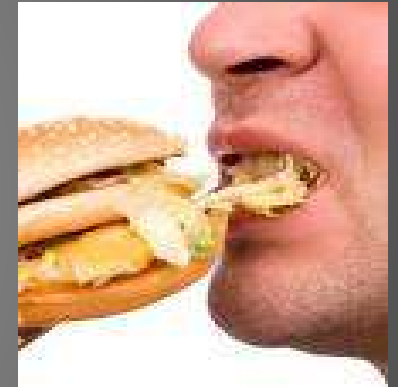
Lessons from Sverdlovsk

- April-May 1979- Accidental anthrax release from (former) Soviet military research & production facility-66 fatalities-bioengineered strain



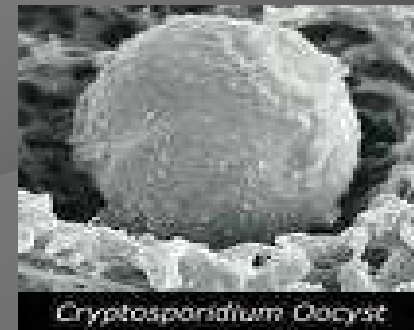
Foodborne Illness...or Bioterrorism?

- Food supply and distribution-biosecurity and safety issues



Waterborne Biothreats

- ⦿ Water distribution systems possible (intentional)
- ⦿ Reservoirs-highly unlikely to succeed
- ⦿ Water purification, dilution and natural forces minimize or eliminate threat
- ⦿ Unpolluted sources a challenge for many poor and developing nations



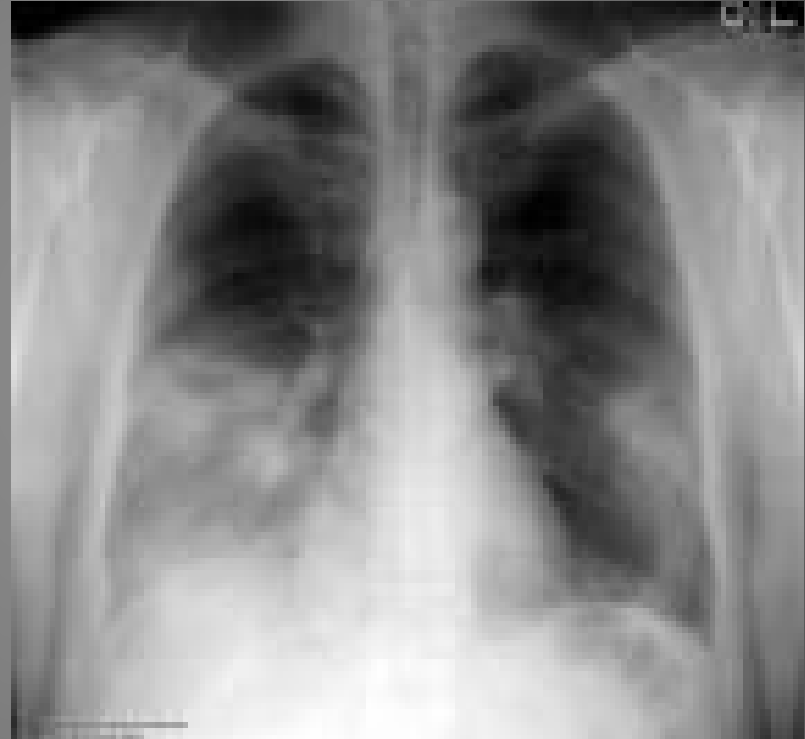
Bubonic Plague: The “Black Death”

Inguinal bubo on upper thigh of person with bubonic plague.

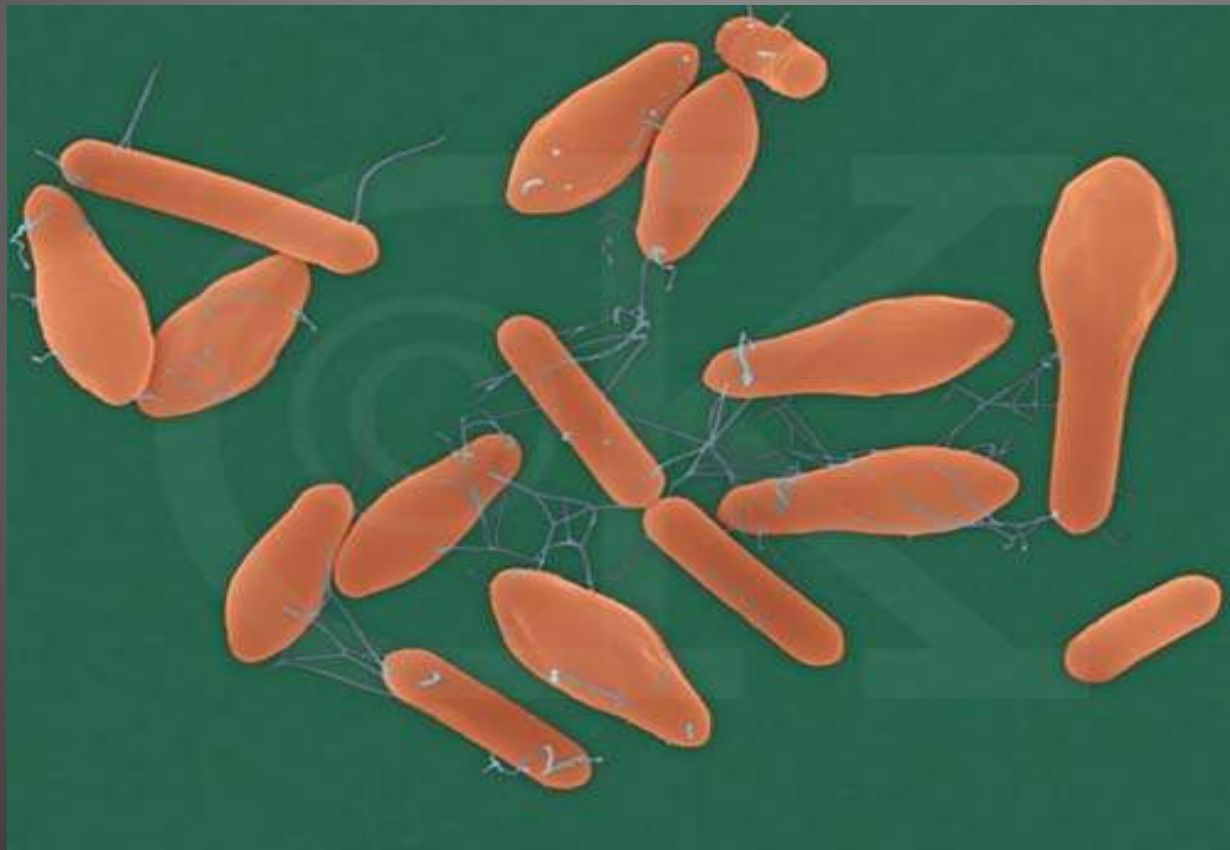


p5.jpg

Tularemia: Cutaneous vs. Pulmonary



Botulinum Toxin:Natural Outbreak OR Toxin Weapon? LD50= 0.001 ug/kg



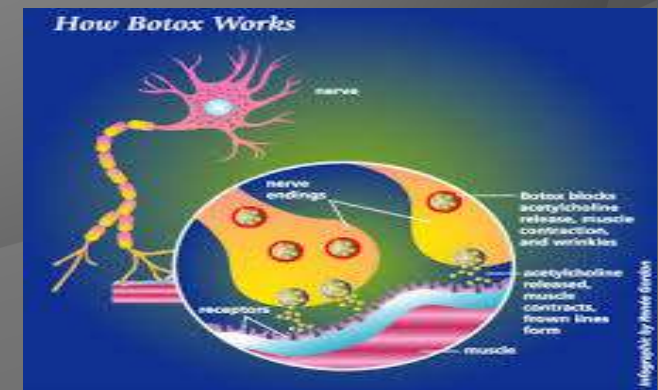
Botulinum Toxin: Mechanisms

Clostridium botulinum- Anaerobic Gram-positive bacilli which produces botulinum toxin, a highly toxic neurotoxin that blocks synaptic release of acetylcholine (neurotransmitter) and causes a severe flaccid, descending paralysis of respiratory and skeletal muscles. **ONLY** toxin on CDC “A” List.

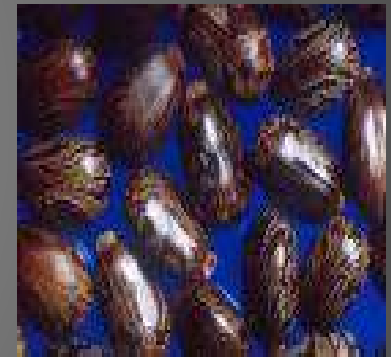
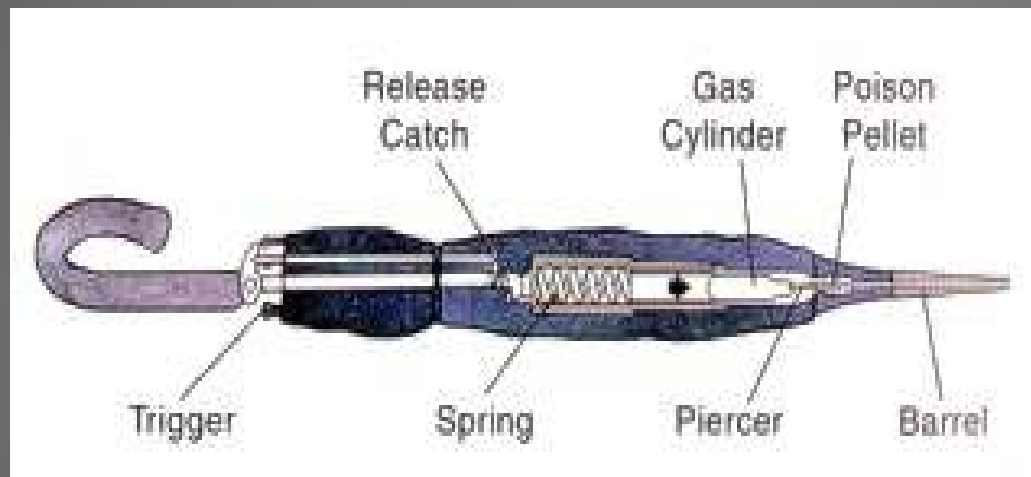
Acetylcholine may require prolonged time for adequate regeneration leading to ventilator dependency

Antitoxins are available.

BT attack may be food-borne or aerosolized for inhalation.

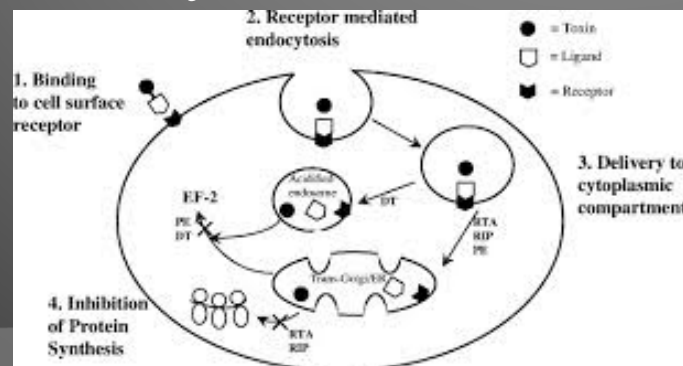


RICIN: The Assassination of Georgi Markov-CIA Depiction



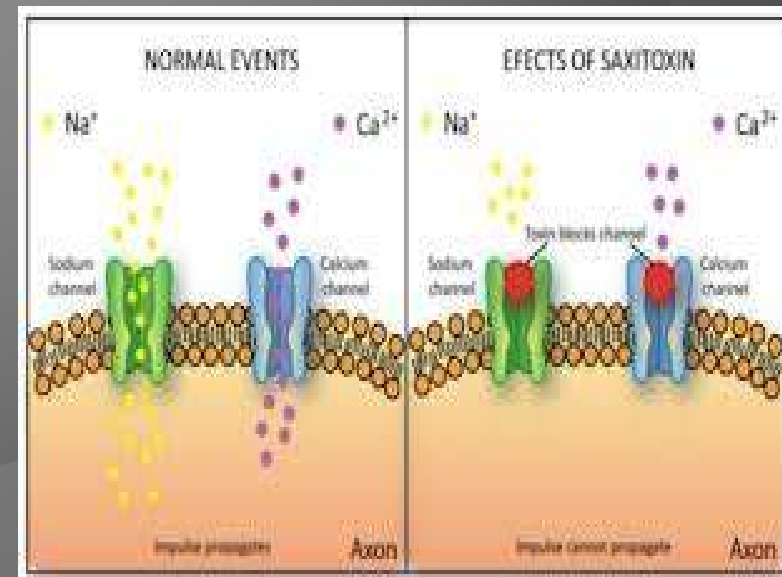
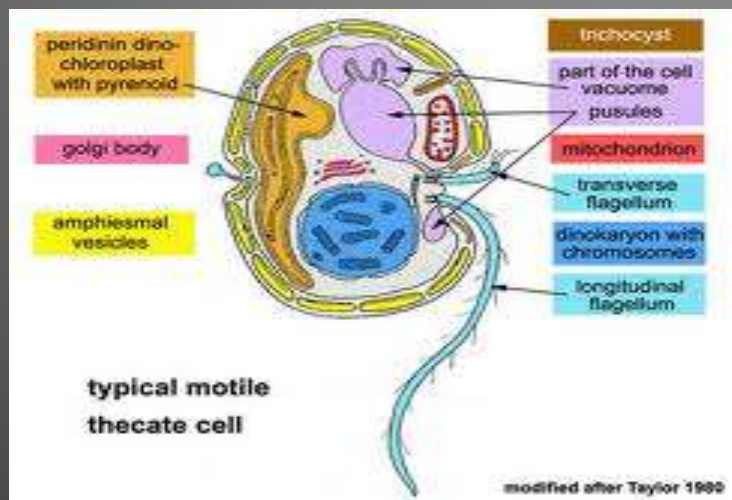
Ricin: Mechanism(s)

- *Toxin extracted from waste mash of castor beans from the plant, Ricinus communis, which grows ubiquitously (toxinalbumin)- Category 'B' CDC select agent .Recently used as a bioweapon.*
- *Toxicodynamics- Molecular structure allows it to bind onto mammalian cell surfaces and inhibits nucleic acid synthesis by specifically & irreversibly inactivating eukaryotic ribosomes.*



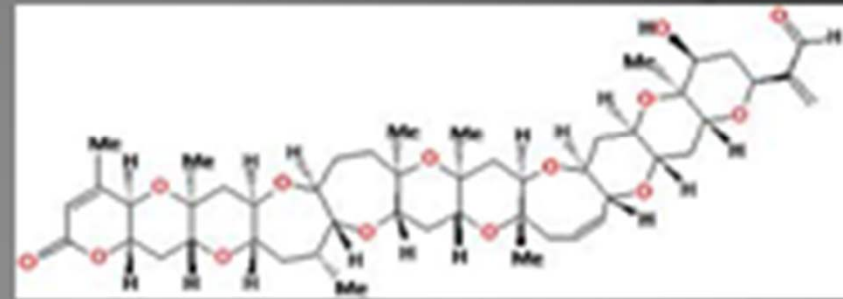
“EXOTIC” BIOTOXINS

- Marine & freshwater aquatic dinoflagellate neurotoxins (toxic phytoplankton, “red tide” algal blooms)
- Saxitoxin & gonyautotoxins* result in *Paralytic Shellfish Poisoning (PSP)* via blockade of Na^+ channels which disrupts nerve conduction.



More Biotoxins...

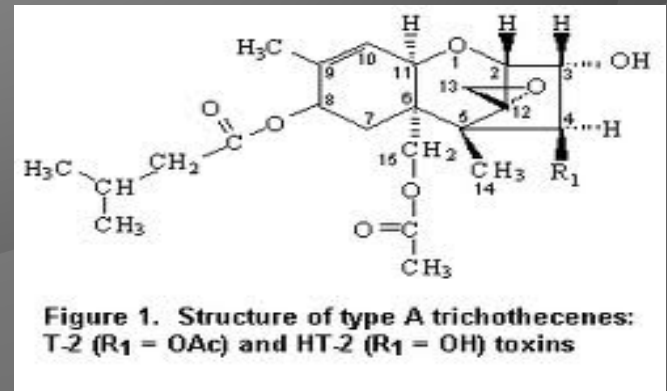
⊙ *Brevetoxins- found in toxic algal blooms & also act upon sodium channel blockers*
Aerosolized form has been shown to initiate & exacerbate asthma attacks



Tetrodotoxin (TTX)-Potent neurotoxin w/o antidote found in puffer fish and other animals such, certain amphibians. Na^+ channel blocker leads to respiratory paralysis (disrupts nerve conduction)

And...even more biotoxins

- *T-2 Mycotoxins (fungal toxins), aka tricothecene mycotoxins, eg. Fusarium, Stachybotrys atra, etc.*
- *Allegedly used in Laos , Kampuchea and Afghanistan by (former) Soviet Forces according to medical intelligence and reports (“yellow rain attack”)*
- *Low-molecular weight(250-500 daltons) nonvolatile compounds produced by over 350 species of fungi.*



T-2 Mycotoxins: Mechanisms

- *NOTE: “Yellow rain” was purported to have been fecal matter of honey bees. (NOT conclusive!!)*
- *T-2 EXPOSURES IN 1991 GULF WAR.*
- *T-2 mycotoxins are dermally active.*
- *Cytotoxic and immunosuppressive. “radiomimetic” mechanism, similar to ionizing radiation. Blistering effects and action similar to military “mustard” agents. Rapid action/potent protein/nucleic acid synthesis inhibitors.*
- *T-2 toxin thought to disrupt DNA polymerases, MAO, and several proteins involved in the coagulation pathway.*

AFLATOXINS:MECHANISMS

- *Naturally occurring mycotoxins produced by many species of Aspergillus, (eg. Aspergillus flavus) which may contaminate grains and other agricultural products such as peanuts.*
- *Mortality associated with consuming contaminated foodstuffs (poor & developing nations).*
- *Hepatotoxic, highly carcinogenic, can alkylate DNA bases. Can affect domestic and farm animals.*



Biological “Mystery” Threat: Prions

- *What are prions?- An infectious agent composed of misfolded protein that cause a group of invariably fatal neurodegenerative diseases by a novel mechanism. (Derivation:PROteinaceous and INfectious).*
- *Bovine spongiform encephalopathy (BSE”mad cow”disease), scrapie of sheep, and variant Crutzfeldt-Jacob (CJD) of humans are prion diseases. They are transmissible particles devoid of nucleic acids and composed of modified protein (PrPSc).*
- *Formerly known as a “slow virus”.*
- *The disease kuru seen in tribes known to consume raw monkey brain tissue.*

AGROTERRORISM

- *Agroterrorism-Malevolent intent to disrupt or destroy agricultural industry/productivity and /or food supply and distribution systems of a population via the malicious use of plant or animal pathogens to cause devastating damage and disease in the agricultural sectors.*

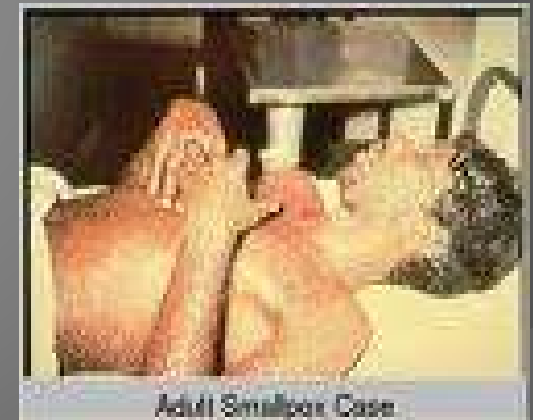


AGROTERRORISM (CONT'D)

- *Insect vectors-possibly “disguised” among invasive species to spread pathogens*
- *Anti-crop agents, eg. wheat rust, rice blast (weaponized for biowarfare by U.S. military and others)*
- *Defoliant/herbicidal agents (“Agent Orange”)*
- *Animal pathogens: prions, foot and mouth disease (FMD), brucellosis, glanders, anthrax, etc.*
- *Contamination of food web, supply, distribution system with biotoxins, heavy metals, dioxin, radionuclides, toxic industrial chemicals (TICs), chemical warfare agents.*

Most Common Syndromes in Biological Events

- ⦿ Flu-like illnesses
- ⦿ Acute respiratory symptoms with fever
- ⦿ Gastrointestinal symptoms/syndromes
- ⦿ Skin lesions (small pox)
- ⦿ Acute neuromuscular syndromes



BT Event: Some Types and Characteristics

- ◎ Four types of BT events
- ◎ Biological *toxin* dispersal, eg mycotoxins, ricin, botox-
Can be considered a chemical *or (biochemical)* event, if suspected or known contamination of patients has occurred. Toxins profoundly more toxic than CWAs or TICs/TIMs.
- ◎ Biological (*infectious*) agent release that is announced or immediately recognizable, eg suspect powder letter. Decon of patients in proximity of primary aerosol & prophylaxis of those exposed to source device.

BT Events: Some Types and Characteristics (cont'd)

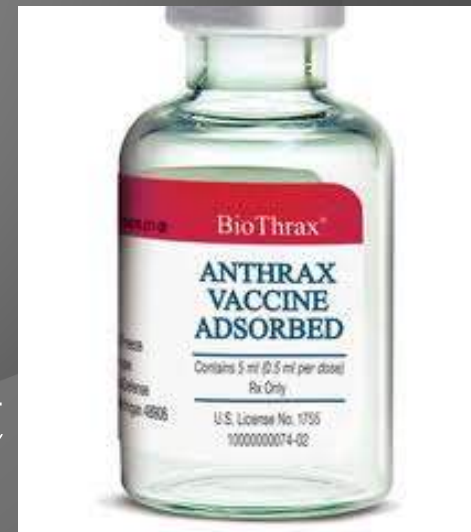
- ◎ Four Types of BT events
- ◎ Biological agent released and detected after its incubation period. Decon is NOT a significant issue. Tx of affected populations and determination of potentially exposed populations can be difficult. Airborne or droplet transmission of the agent and isolation /quarantine issues must be addressed, eg smallpox (*Variola major*)-airborne threat)
- ◎ Biological hoax. A letter , other material, substance or object is portrayed as a biothreat agent, and is determined not to be a threat.

Clues to Biological Events

- ⦿ Increase in the number of patients with similar symptoms
- ⦿ Large number of deaths
- ⦿ Cluster of an illness from single area
- ⦿ Infection that is not endemic to area
- ⦿ Common infections in unusual seasons
- ⦿ Increase/large number of sick/dead animals
- ⦿ Intelligence from law enforcement
- ⦿ Stated threat

Biological Therapeutics/Countermeasures

- Antibiotics-bacteria, eg doxycycline
- Antivirals-viruses, eg ribavirin
- Antitoxins- botulinum antitoxin
- Antifungals-mycotic infections
- Immunoprophylaxis-vaccines
- Chemoprophylaxis-drugs
- Supportive medical therapies, eg ventilators, vasopressors, IV fluids
- Veterinary/agricultural expertise & support



And ...Just a few words about..

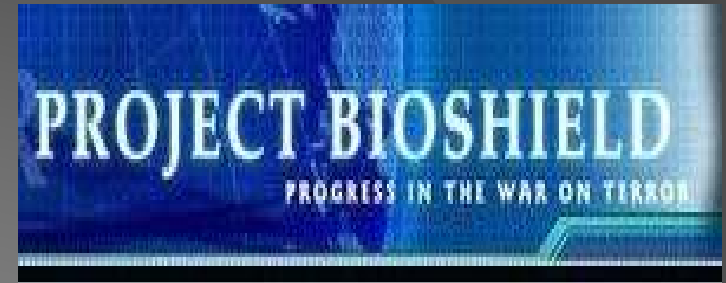
- ⊙ Nanoparticles
- ⊙ Microplastics
- ⊙ Endocrine and immune disruptors
- ⊙ Wildfire smoke
- ⊙ Biotechnology – double sword

Implications of above

- Can affect neuro,endocrine and immune systems ,as well as respiratory and cardiac functions
- Can effect development of organ systems in utero , - Can result in novel,pathogenic organisms or influence biochemical – genetic mechanisms resulting in disease (biotech ,endocrine disruptors)



SUMMARY



- *Biological threat agents are ubiquitous, and present a clear and present danger to humans, plants, animals, ecosystems and global health and security.*
- *Understanding biological mechanisms is key to optimizing prevention, mitigation and therapeutic/ response strategies. Continued research is essential.*
- *Biotechnology is a double-edged sword: It has the ability to facilitate therapies and diagnostics and create novel life forms that may be deleterious AND used to induce disease, death and destruction of other life forms.*
- **BIODEFENSE NEEDS TO BE A GLOBAL PRIORITY**

Thank You !!

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