Major Factors in the Development of Infection

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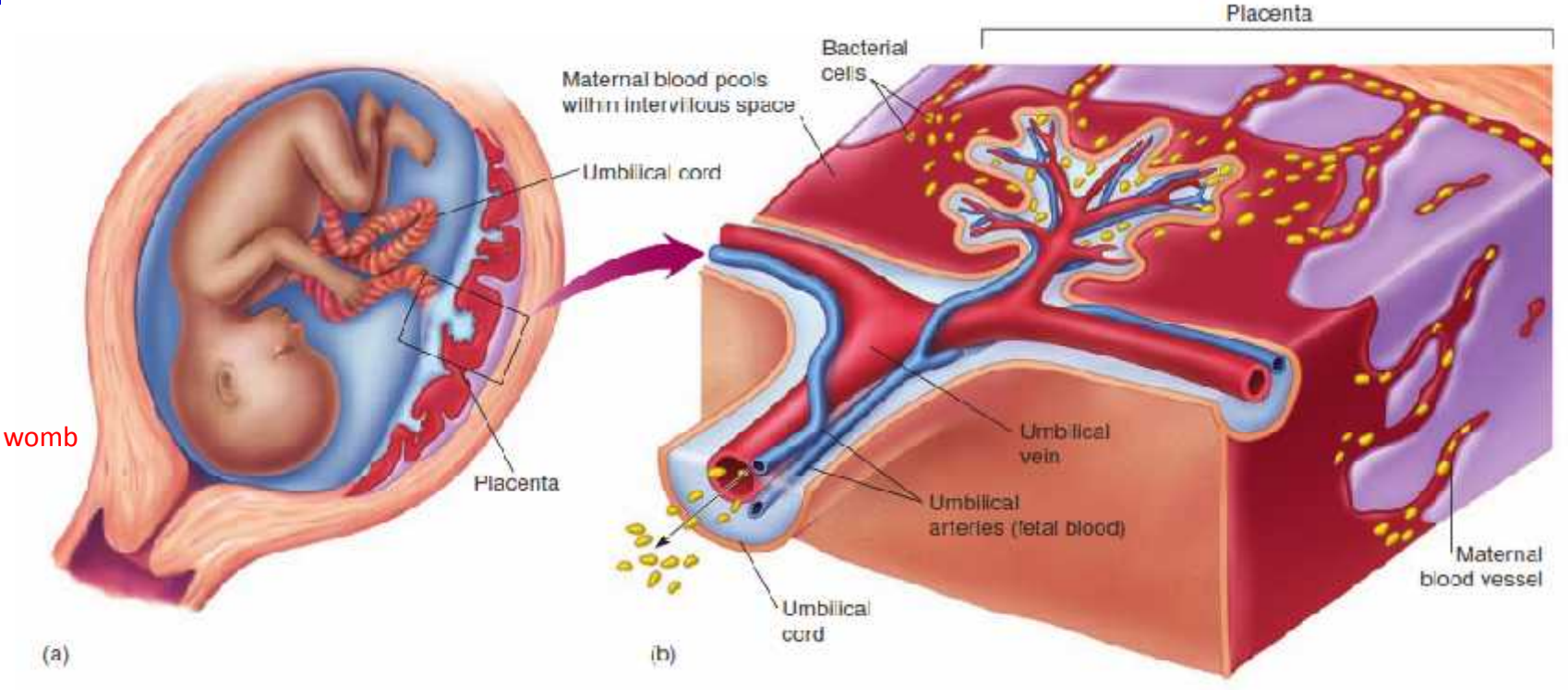
Transplacental Infection of The Fetus

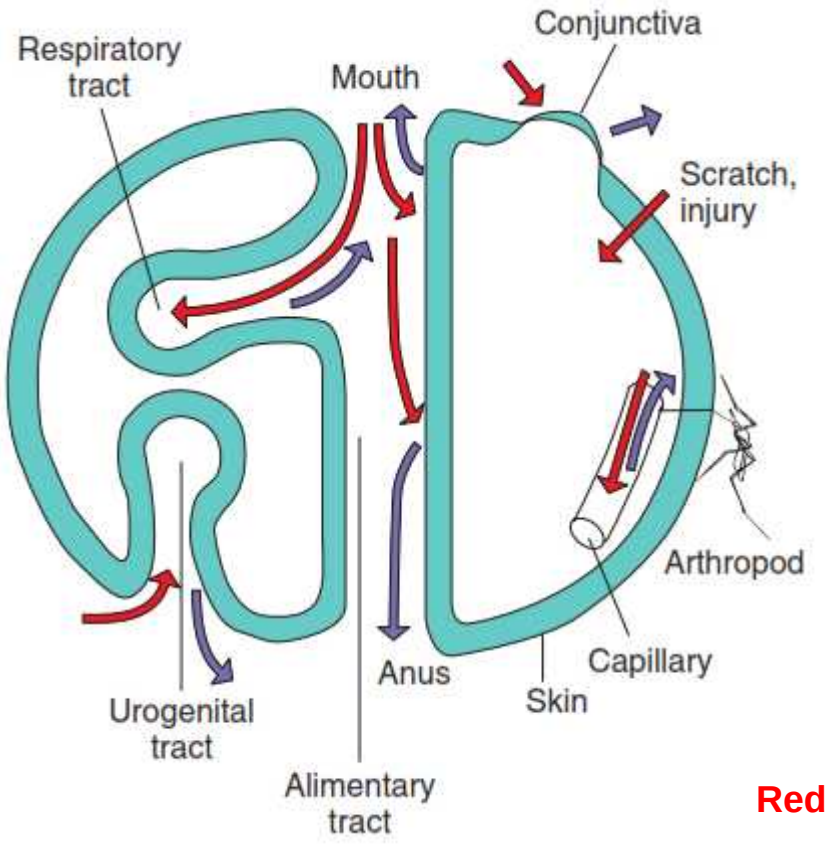


Fetus in the womb

Microbes are penetrating the **maternal blood vessels** and entering the blood pool of the **placenta**. They then invade the **fetal circulation** by way of the umbilical vein

STORCH: **S**yphilis, **T**oxoplasmosis, **O**ther diseases (hepatitis B, AIDS, and chlamydia), **R**ubella, **C**ytomegalovirus, **H**erpes simplex virus.
The most serious complications of STORCH infections are **spontaneous abortion, congenital abnormalities, brain damage, prematurity, & stillbirths**

Body Surfaces as Sites of Microbial Infection & Shedding

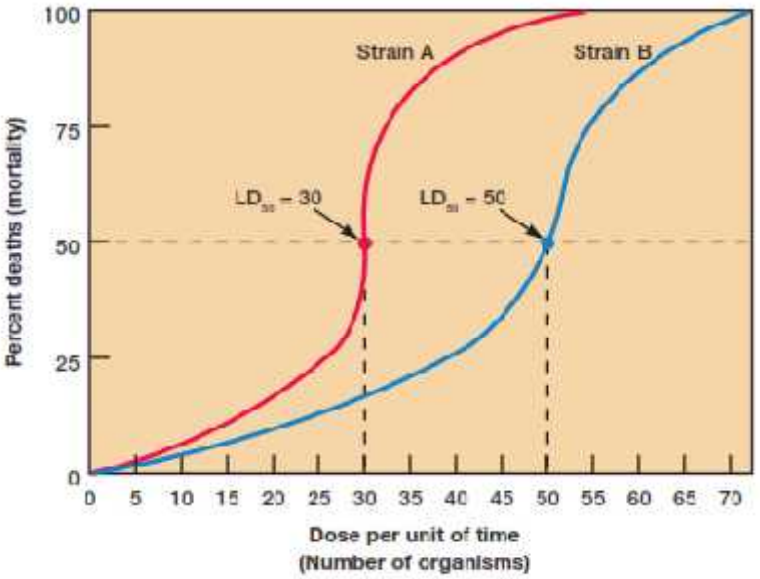


Red arrows indicate infection; **purple arrows indicate shedding**.

Estimated Infectious Doses (ID) of Selected Pathogens*

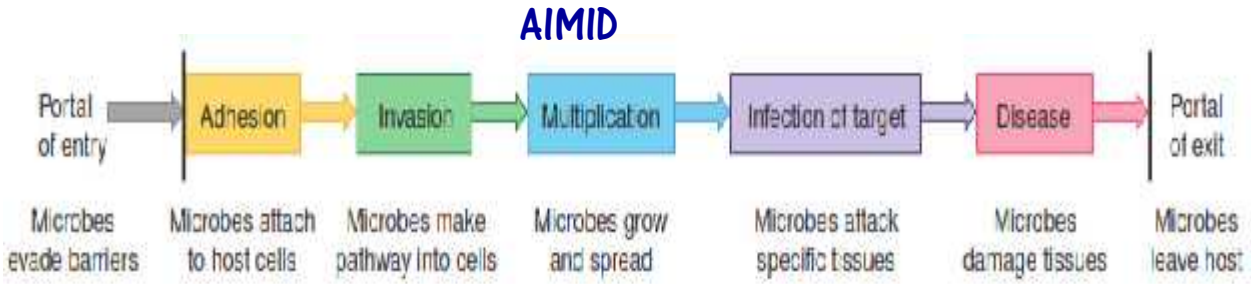
Agent of	Infectious Dose Estimate	Primary Route of Infection
Measles	1 virus	Respiratory
Q fever	1–10 cells	Respiratory
Tularemia	10–50 cells	Various
Smallpox	10–100 viruses	Respiratory
Brucellosis	10–100 cells	Various
Viral encephalitis	10–100 viruses	Mosquito bite
Plague	100–500 cells	Flea bite
Gonorrhea	1,000 cells	Sexual contact
Anthrax	8,000–50,000 spores	Respiratory, cutaneous
Typhoid	10,000 cells	Ingestion
Cholera	100,000,000 cells	Ingestion

*Several of these agents are considered potential bioterror pathogens.

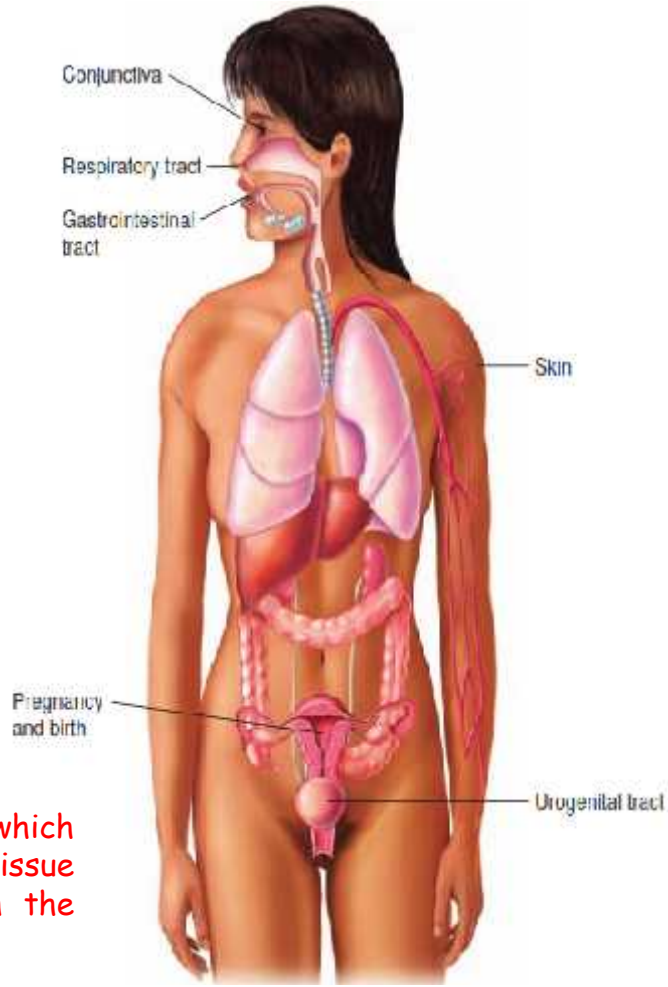


LD_{50} & ID_{50}: Dose or number of pathogens that will either kill or infect, respectively, 50% of an experimental group of hosts within a specified period

Events In Entry, Establishment, & Exit of Infectious Agents



Portals of Entry



Factors that Weaken Host Defences & Increase Susceptibility to Infection

- Old age and extreme youth (infancy, prematurity)
- Genetic defects in immunity and acquired defects in immunity
- Surgery and organ transplants
- Organic disease: cancer, liver malfunction, diabetes
- Chemotherapy/immunosuppressive drugs
- Physical and mental stress
- Other infections

Note: Organic disease is the term used to describe any health condition in which there is an observable & measurable disease process, such as inflammation or tissue damage. An org disease is one that can be validated & quantified through the standardized biological measures known as biomarkers.

Bacterial Disease Production

Bacterial Virulence Mechanisms

Adherence
Invasion
Byproducts of growth (gas, acid)
Toxins
Degradative enzymes
Cytotoxic proteins
Endotoxin
Superantigen
Induction of excess inflammation
Evasion of phagocytic and immune clearance
Capsule
Resistance to antibiotics
Intracellular growth

✓Disease is caused by damage produced by the bacteria plus the consequences of innate and immune responses to the infection.

✓The signs and symptoms of a disease are determined by the function and importance of the affected tissue.

✓The length of the incubation period is the time required for the bacteria and/or the host response to cause sufficient damage to initiate discomfort or interfere with essential functions.

Microbial Factors Contributing to Adhesion/Colonization of Host Surfaces

Survival Against Environmental Conditions

- Localization in moist areas
- Protection in ingested or inhaled debris
- Expression of specific metabolic characteristics (e.g., salt tolerance)

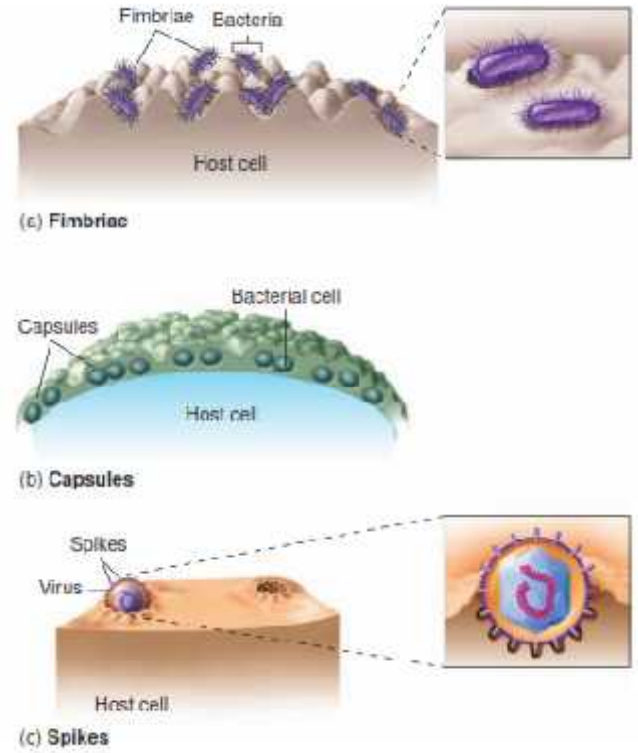
Achieving Attachment and Adherence to Host Cell Surfaces

- Pili
- Adherence proteins
- Biofilms
- Various protein adhesins

Other Factors

- Motility
- Production of substances that compete with host for acquisition of essential nutrients (e.g., siderophores for capture of iron)
- Ability to coexist with other colonizing microorganisms

Mechanisms of Adhesion by Pathogens



Adhesion Properties of Microbes

Microbe	Disease	Adhesion Mechanism
Neisseria gonorrhoeae	Gonorrhea	Fimbriae attach to genital epithelium.
Escherichia coli	Diarrhea	Well-developed fimbrial adhesin
Shigella and *Salmonella*	Gastroenteritis	Fimbriae can attach to intestinal epithelium.
Vibrio	Cholera	Glycocalyx anchors microbe to intestinal epithelium.
Treponema	Syphilis	Tapered hook embeds in host cell.
Mycoplasma	Pneumonia	Specialized tip at ends of bacteria fuses tightly to lung epithelium.
Pseudomonas aeruginosa	Burn, lung infections	Fimbriae and slime layer
Streptococcus mutans, S. sobrinus	Dental caries	Dextran slime layer glues cocci to tooth surface.
Influenza virus	Influenza	Viral spikes react with receptor on respiratory surface.
Poliovirus	Polio	Capsid proteins attach to receptors on susceptible cells.
HIV	AIDS	Viral spikes adhere to white blood cell receptors.
Giardia lamblia (protozoan)	Giardiasis	Small suction disc on underside attaches to intestinal surface
Trypanosoma (protozoan)	African and S. American trypanosomiasis	Flagellum is needed to penetrate and stay alive.

(a) Fimbriae, minute bristlelike appendages.
(b) Adherent extracellular capsules made of slime or other sticky substances
(c) Viral envelope spikes.

Factors Contributing to Invasion/Disruption of the Skin and Mucosal Surface

Trauma
- Penetrating wounds
- Abrasions
- Burns (chemical and fire)
- Surgical wounds
- Needle sticks

Inhalation
- Noxious or toxic gases
- Particulate matter
- Smoking

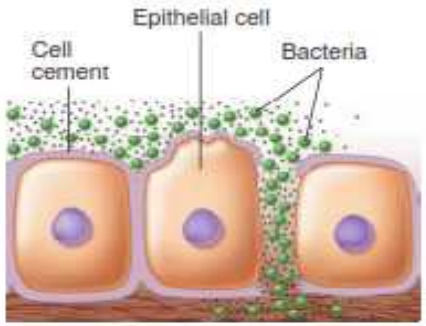
Implantation of Medical Devices

Other Diseases
- Malignancies
- Diabetes
- Previous or simultaneous infections
- Alcoholism and other chemical dependencies

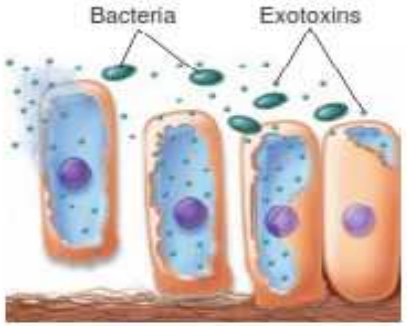
Childbirth

Overuse of Antibiotics

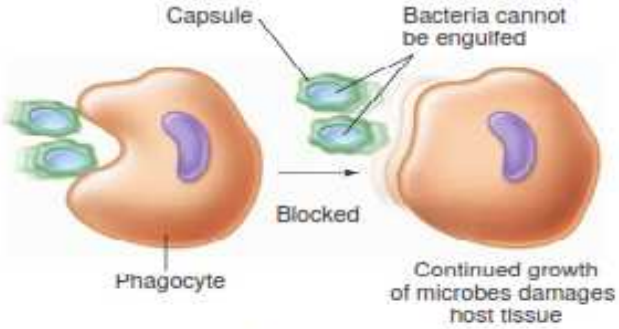
Invading the Host & Becoming Established



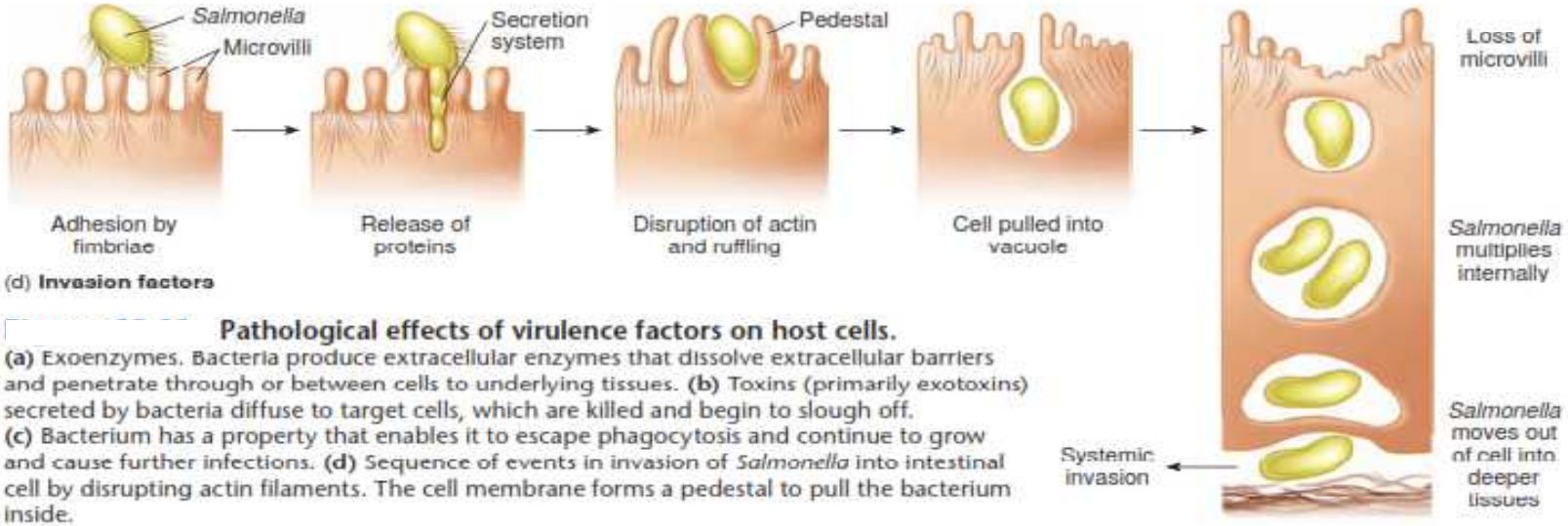
(a) **Exoenzymes**



(b) **Toxins**



(c) **Blocked phagocytic response**



(d) **Invasion factors**

Pathological effects of virulence factors on host cells.
(a) Exoenzymes. Bacteria produce extracellular enzymes that dissolve extracellular barriers and penetrate through or between cells to underlying tissues. **(b)** Toxins (primarily exotoxins) secreted by bacteria diffuse to target cells, which are killed and begin to slough off. **(c)** Bacterium has a property that enables it to escape phagocytosis and continue to grow and cause further infections. **(d)** Sequence of events in invasion of *Salmonella* into intestinal cell by disrupting actin filaments. The cell membrane forms a pedestal to pull the bacterium inside.

Microbial Strategies for Surviving Inflammation

Avoid Killing by Phagocytes (Polymorphonuclear Leukocytes)

- Producing a capsule, thereby inhibiting phagocytes' ability to ingest them

Avoid Phagocyte-Mediated Killing

- Inhibiting phagosome-lysosome fusion
- Being resistant to destructive agents (e.g., lysozyme) released by lysosomes
- Actively and rapidly multiplying within a phagocyte
- Releasing toxins and enzymes that damage or kill phagocytes

Avoid Effects of the Complement System

- Using a capsule to hide surface molecules that would otherwise activate the complement system, including the formation of a complex protein polysaccharide matrix referred to as a biofilm
- Producing substances that inhibit the processes involved in complement activation
- Producing substances that destroy specific complement proteins

Continue

Microbial Strategies for Surviving Inflammation

- Pathogen multiplies and invades so quickly that damage to host is complete before immune response can be fully activated, or organism's virulence is so great that the immune response is insufficient.
- Pathogen invades and destroys cells involved in the immune response.
- Pathogen survives unrecognized in host cells and avoids detection by immune system.
- Pathogen covers its antigens with a capsule or biofilm so that an immune response is not activated.
- Pathogen changes antigens so that immune system is constantly fighting a primary encounter (i.e., the memory of the immune system is neutralized).
- Pathogen produces enzymes (proteases) that directly destroy or inactivate antibodies.

Some Bacterial Enzymes that Contribute to Virulence

Enzyme	Source	Action	Effect
Coagulase	*Staphylococcus aureus*	Forms a fibrin clot	Provides resistance to phagocytosis
Streptokinase	Streptococci Staphylococci	Dissolves a fibrin clot	Prevents isolation of infection
Hyaluronidase	Streptococci Staphylococci	Digests hyaluronic acid	Allows tissue penetration
Leukocidin	Staphylococci Streptococci Pneumococci	Destroys phagocytes	Limits phagocytosis
Hemolysins	Clostridia Staphylococci Streptococci	Lyses red blood cells	Provides pathogens with source of iron for growth

Avoiding Immediate Destruction by Host Defense System:

- **Anti-phagocytic surface components** (inhibit phagocytic uptake):
  - **Capsules**/slime layers:
    ***Streptococcus pyogenes* M protein**
    ***Neisseria gonorrhoeae* pili**
    ***Staphylococcus aureus* A protein**
- **IgA proteases,** destruction of mucosal IgA: *Neisseria, Haemophilus, S. pneumoniae*

"Hunting and Gathering" Needed Nutrients:

- **Siderophores** steal (chelate) and import iron.

Ability to Survive Intracellularly

- **Evading intracellular killing by professional phagocytic cells** allows intracellular growth:
  - *M. tuberculosis* survives by inhibiting phagosome-lysosome fusion.
  - *Listeria* quickly escapes the phagosome into the cytoplasm **before** phagosome-lysosome fusion.
- **Invasins**: surface proteins that allow an organism to bind to and invade normally non-phagocytic human cells, escaping the immune system. Best studied invasin is on *Yersinia pseudotuberculosis* (an organism causing diarrhea).
- Damage from viruses is largely from intracellular replication, which either kills cells, transforms them or, in the case of latent viruses, may do no noticeable damage.

Type III Secretion Systems

- Tunnel from the bacteria to the host cell (macrophage) that delivers bacterial toxins directly to the host cell
- Have been demonstrated in many pathogens: *E. coli, Salmonella* species, *Yersinia* species, *P. aeruginosa*, and *Chlamydia*

Note

Mnemonic

***S**treptococcus pneumoniae*
***K**lebsiella pneumoniae*
***H**aemophilus influenzae*
***P**seudomonas aeruginosa*
***N**eisseria meningitidis*
***C**ryptococcus neoformans*

(**S**ome **K**illers **H**ave **P**retty **N**ice **C**apsules)

Note

Intracellular organisms

- Elicit different immune responses
- Different pathology
- Different antibiotics
- Different culture techniques

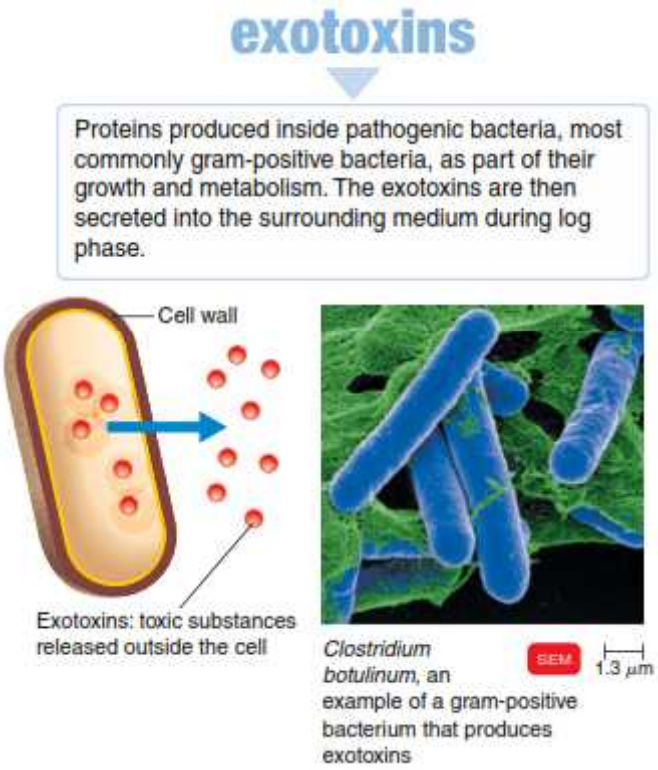
Antigenic Variation

- Changing surface antigens to avoid immune destruction
- *N. gonorrhoeae*—pili and outer membrane proteins
- *Trypanosoma brucei rhodesiense* and *T. b. gambiense*—phase variation
- Enterobacteriaceae: capsular and flagellar antigens may or may not be expressed
- HIV—antigenic drift

Bacterial Toxins

Exotoxins

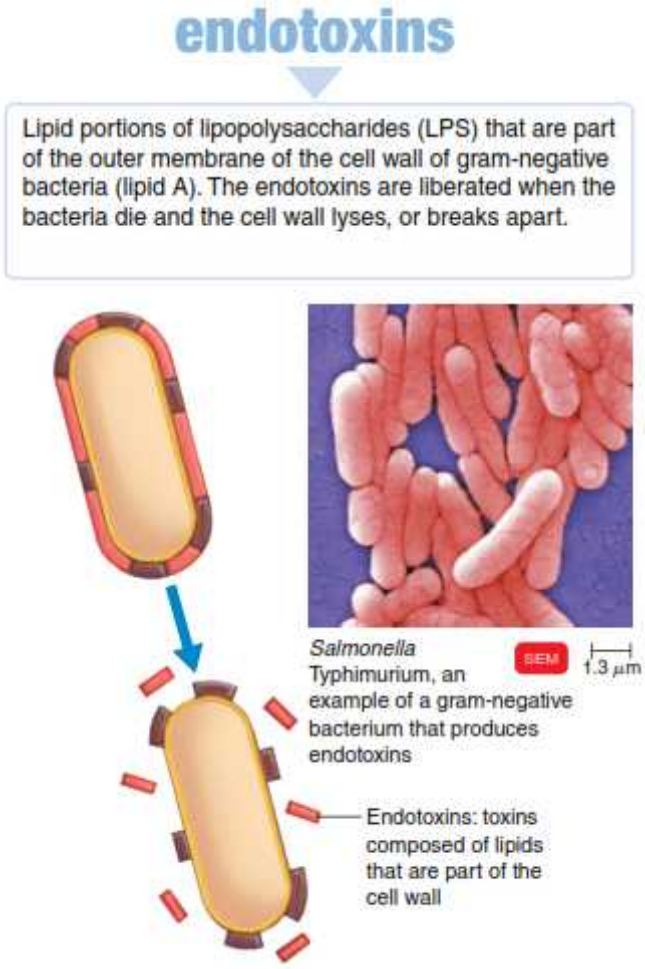
- Most commonly associated with gram-positive bacteria
- Produced and released by living bacteria; do not require bacterial death for release
- Specific toxins target specific host cells; the type of toxin varies with the bacterial species.
- Some kill host cells and help spread bacteria in tissues (e.g., enzymes that destroy key biochemical tissue components or specifically destroy host cell membranes).
- Some destroy or interfere with specific intracellular activities (e.g., interruption of protein synthesis, interruption of internal cell signals, or interruption of neuromuscular system).



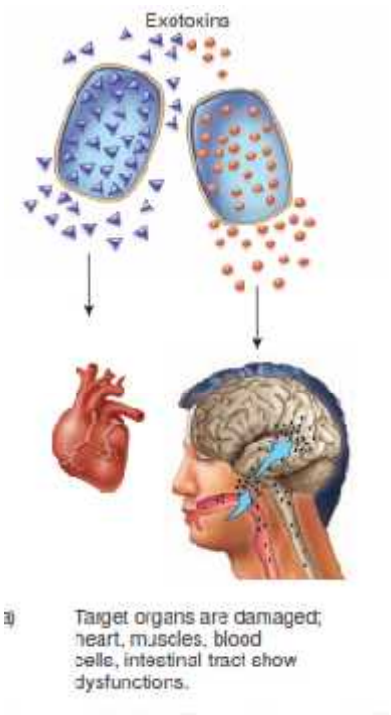
Bacterial Toxins

Endotoxins

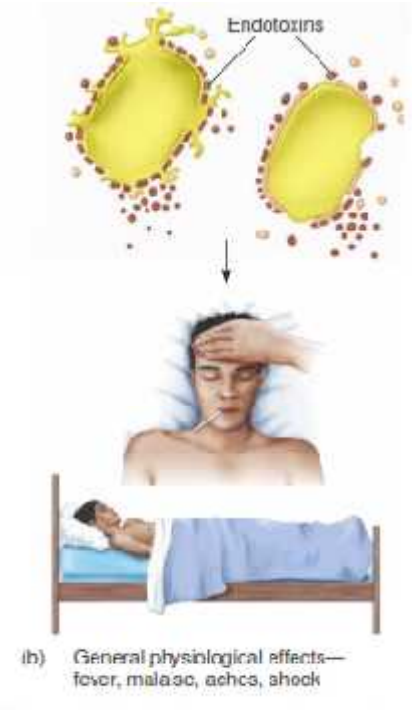
- General toxin common to almost all gram-negative bacteria
- Composed of lipopolysaccharide portion of cell envelope
- Released when gram-negative bacterial cell is destroyed
- Effects on host include:
  - Disruption of clotting, causing clots to form throughout the body (i.e., disseminated intravascular coagulation [DIC])
  - Fever
  - Activation of complement and immune systems
  - Circulatory changes that lead to hypotension, shock, and death



The Origins & Effects of Circulating Bacterial Exotoxins & Endotoxins



Exotoxins, given off by live cells, have highly specific targets and physiological effects



Endotoxin, given off when the cell wall of gram-negative bacteria disintegrates, has more generalized physiological effects

Differential Characteristics of Bacterial Exotoxins and Endotoxin

Property	Exotoxins	Endotoxins
		
Bacterial Source	Gram-positive and gram-negative bacteria	Gram-negative bacteria
Relation to Microorganism	Metabolic product of growing cell	Present in LPS of outer membrane of cell wall and released with destruction of cell or during cell division
Chemistry	Proteins, usually with two parts (A-B)	Lipid portion (lipid A) of LPS of outer membrane
Pharmacology (Effect on Body)	Specific for a particular cell structure or function in the host (mainly affects cell functions, nerves, and gastrointestinal tract)	General, such as fever, weaknesses, aches, and shock; all produce the same effects
Heat Stability	Unstable; can usually be destroyed at 60–80°C (except staphylococcal enterotoxin)	Stable; can withstand autoclaving (121°C for 1 hour)
Toxicity (Ability to Cause Disease)	High	Low
Fever-Producing	No	Yes
Immunology (Relation to Vaccines)	Can be converted to toxoids to immunize against toxin; neutralized by antitoxin	Not easily neutralized by antitoxin; therefore, effective toxoids cannot be made to immunize against toxin
Lethal Dose	Small	Considerably larger
Representative Diseases	Gas gangrene, tetanus, botulism, diphtheria, scarlet fever, cyanobacterial intoxication	Typhoid fever, urinary tract infections, and meningococcal meningitis

Bacterial Exotoxins

Disease	Bacterium	Type of Exotoxin	Mechanism
Botulism	*Clostridium botulinum*	A-B	Neurotoxin prevents transmission of nerve impulses; flaccid paralysis results.
Tetanus	*Clostridium tetani*	A-B	Neurotoxin blocks nerve impulses to muscle relaxation pathway; results in uncontrollable muscle contractions.
Diphtheria	*Corynebacterium diphtheriae*	A-B	Cytotoxin inhibits protein synthesis, especially in nerve, heart, and kidney cells.
Scalded skin syndrome	*Staphylococcus aureus*	A-B	Exotoxin causes skin layers to separate and slough off.
Cholera	*Vibrio cholerae*	A-B	Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.
Traveler's diarrhea	Enterotoxigenic *Escherichia coli* and *Shigella* spp.	A-B	Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.
Anthrax	*Bacillus anthracis*	A-B	Two A components enter the cell via the same B. The A proteins cause shock and reduce the immune response.
Gastric (stomach) cancer	*Helicobacter* spp.	A-B toxin	Genotoxin causes breaks in DNA.
Skin and soft tissue infection	Methicillin-resistant *S. aureus*	Membrane-disrupting	The Panton-Valentine leukocidin found in the community-acquired strain of MRSA makes pores in WBC membranes.
Gas gangrene and food poisoning	*Clostridium perfringens* and other species of *Clostridium*	Membrane-disrupting	One exotoxin (cytotoxin) causes massive red blood cell destruction (hemolysis); another exotoxin (enterotoxin) is related to food poisoning and causes diarrhea.
Antibiotic-associated diarrhea	*Clostridium difficile*	Membrane-disrupting	Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea; cytotoxin disrupts host cytoskeleton.
Food poisoning	*S. aureus*	Superantigen	Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea.
Toxic shock syndrome (TSS)	*S. aureus*	Superantigen	Toxin causes secretion of fluids and electrolytes from capillaries that decreases blood volume and lowers blood pressure.

Determinants of Viral Disease

Nature of the Disease

Target tissue
Portal of entry of virus
Access of virus to target tissue
Tissue tropism of virus
Permissiveness of cells for viral replication
Pathogenic activity (strain)

Severity of Disease

Cytopathic ability of virus
Immune status (naïve or immunized)
Competence of the immune system
Prior immunity to the virus
Immunopathology
Virus inoculum size
Length of time before resolution of infection
General health of the person
Nutrition
Other diseases influencing immune status
Genetic makeup of the person
Age

Progression of Viral Disease

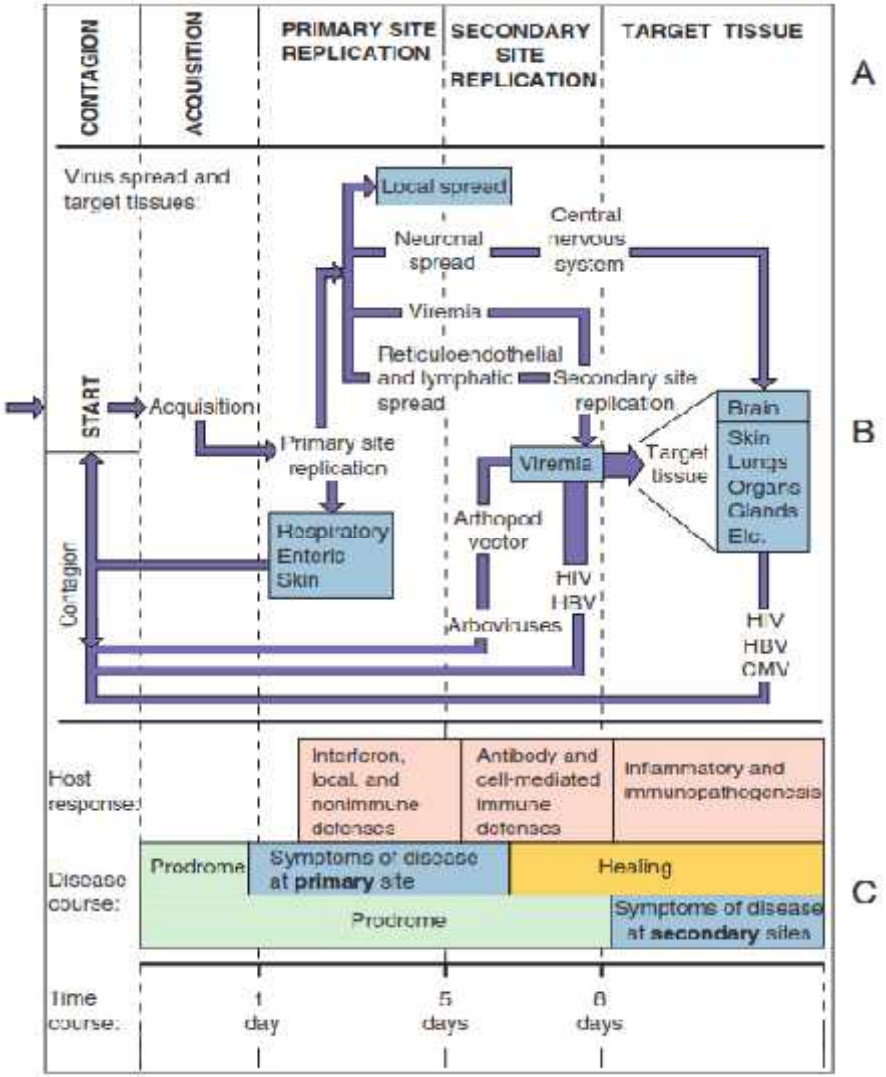
1. **Acquisition** (entry into the body)
2. Initiation of infection at a primary site
3. Activation of innate protections
4. An **incubation period,** when the virus is amplified and may spread to a secondary site
5. Replication in the **target tissue,** which causes the characteristic disease signs
6. **Host responses** that limit and contribute (immunopathogenesis) to the disease
7. Virus production in a tissue that releases the virus to other people for **contagion**
8. **Resolution** or **persistent infection/chronic disease**

Basic Steps in Viral Disease

A, The stages of viral infection.
The virus is released from one person, is acquired by another, replicates, and initiates a primary infection at the site of acquisition. Depending on the virus, it may then spread to other body sites and finally to a target tissue characteristic of the disease.

B, The cycle starts with acquisition, as indicated, and proceeds until the release of new virus.
The thickness of the arrow denotes the degree to which the original virus inoculum is amplified on replication. The boxes indicate a site or cause of symptoms.

C, Time course of viral infection.
The time course of symptoms and the immune response correlate with the stage of viral infection and depend on whether the virus causes symptoms at the primary site or only after dissemination to another (secondary) site.



CMV, Cytomegalovirus; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

Determinants of Viral Pathogenesis

Interaction of Virus with Target Tissue

Access of virus to target tissue
Stability of virus in the body
- Temperature and dryness
- Acid and bile of the gastrointestinal tract

Ability to cross skin or mucosal epithelial cells (e.g., cross the gastrointestinal tract into the bloodstream)
Ability to establish viremia
Ability to spread through the reticuloendothelial system
Target tissue
- Specificity of viral attachment proteins
- Tissue-specific expression of receptors

Host Protective Responses

Antigen-nonspecific antiviral responses
- Interferon and cytokines
- Natural killer cells and macrophages

Antigen-specific immune responses
- T-cell responses
- Antibody responses

Viral mechanisms of escape of immune responses

Cytopathologic Activity of the Virus

Efficiency of viral replication in the cell
- Optimum temperature for replication
- Permissiveness of cell for replication

Cytotoxic viral proteins
Inhibition of cell's macromolecular synthesis
Accumulation of viral proteins and structures (inclusion bodies)
Altered cell metabolism (e.g., cell immortalization)

Immunopathology

Interferon: flulike systemic symptoms
T-cell responses: cell killing, inflammation
Antibody: complement, antibody-dependent cellular cytotoxicity, immune complexes
Other inflammatory responses

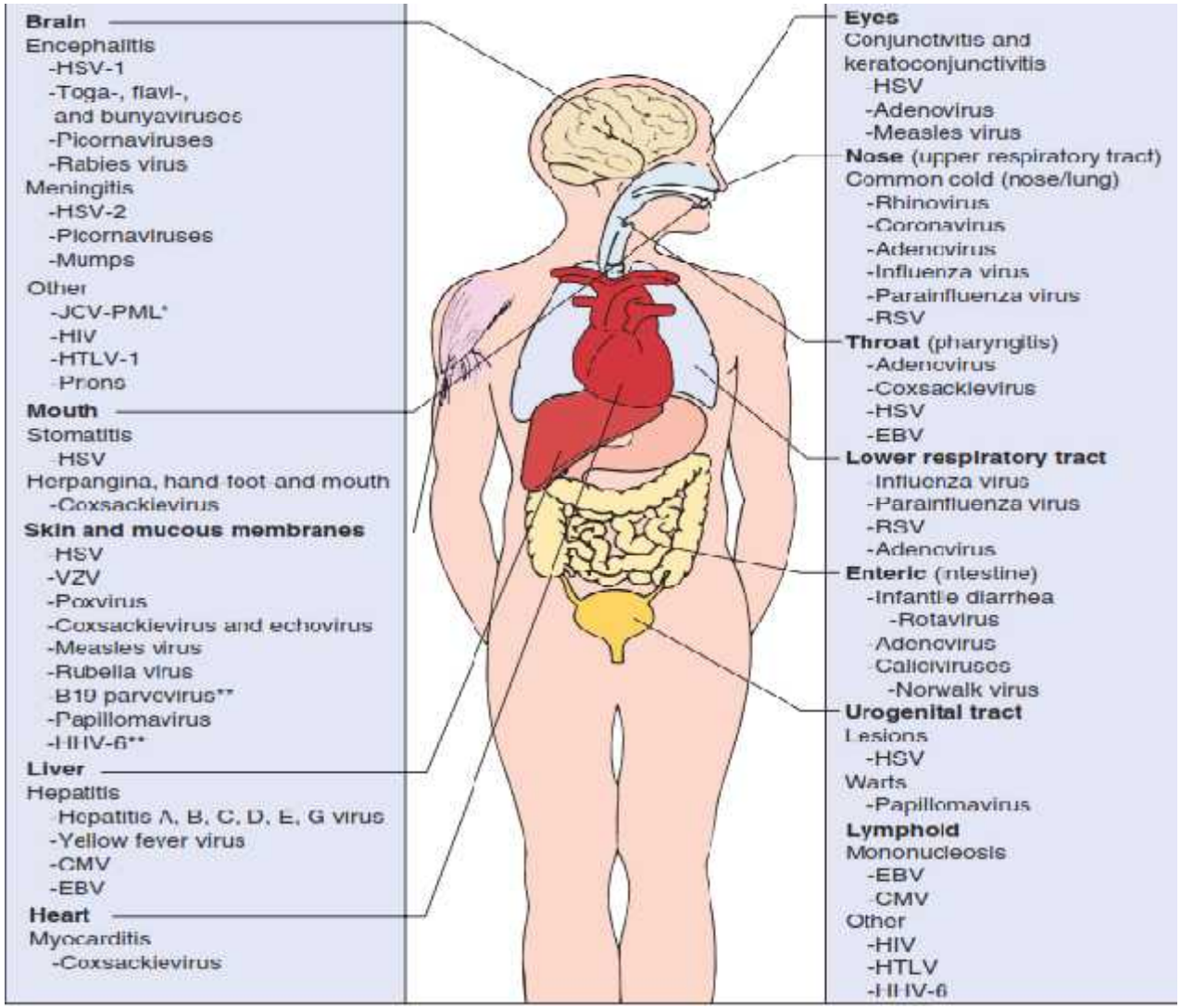
Types of Viral Infections at the Cellular Level

Type	Virus Production	Fate of Cell
Abortive	–	No effect
Cytolytic	+	Death
Persistent		
Productive	+	Senescence
Latent	–	No effect
Transforming		
DNA viruses	–	Immortalization
RNA viruses	+	Immortalization

Mechanisms of Viral Cytopathogenesis

Mechanism	Examples
Inhibition of cellular protein synthesis	Poliovirus, herpes simplex virus (HSV), togaviruses, poxviruses
Inhibition and degradation of cellular DNA	Herpesviruses
Alteration of cell membrane structure	Enveloped viruses
Viral glycoprotein insertion	All enveloped viruses
Syncytia formation	HSV, varicella-zoster virus, paramyxoviruses, human immunodeficiency virus
Disruption of cytoskeleton	Nonenveloped viruses (accumulation), HSV
Permeability	Togaviruses, herpesviruses
Toxicity of virion components	Adenovirus fibers, reovirus NSP4 protein
Inclusion Bodies	**Examples**
Negri bodies (intracytoplasmic)	Rabies
Intranuclear basophilic (Owl's eye)	Cytomegalovirus (enlarged cells), adenoviruses
Cowdry type A (intranuclear)	HSV, subacute sclerosing panencephalitis (measles) virus
Intracytoplasmic acidophilic	Poxviruses
Perinuclear cytoplasmic acidophilic	Reoviruses

Major Target Tissues of Viral Disease



Asterisk (*) indicates progressive multifocal leukoencephalopathy (PML).

Infection by viruses indicated by double asterisks (**) results in an immune-mediated rash.

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus; JCV, JC virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

Primary Biosafety Levels (BSL) & Agents of Disease

Personnel handling infectious agents in the laboratory must be protected from possible infection through special risk management or containment procedures.

Biosafety Level	Facilities and Practices	Risk of Infection and Class of Pathogens
1	Standard, open bench, no special facilities needed; typical of most microbiology teaching labs; access may be restricted.	Low infection hazard; class 1 microbes not generally considered pathogens and will not invade the bodies of healthy persons; *Micrococcus luteus, Bacillus megaterium, Lactobacillus, Saccharomyces.*
2	At least Level 1 facilities and practices; plus personnel must be trained in handling pathogens; lab coats and gloves required; safety cabinets may be needed; biohazard signs posted; access restricted.	Agents with moderate potential to infect; class 2 pathogens can cause disease in healthy people but can be contained with proper facilities; pathogens that belong to class 2 include *Staphylococcus aureus, Escherichia coli, Salmonella* sp.; pathogenic helminths; hepatitis A, B, and rabies viruses; *Cryptococcus* and *Blastomyces;* HIV
3	Minimum of Level 2 facilities and practices; manipulation performed in safety cabinets with special containment features; only personnel require protective clothing; no unsterilized materials can leave the lab; personnel are, monitored and vaccinated.	Agents can cause severe or lethal disease, especially when inhaled; class 3 microbes include *Mycobacterium tuberculosis, Francisella tularensis, Yersinia pestis, Brucella* sp., *Coxiella burnetii, Coccidioides immitis,* and yellow fever, and western equine encephalitis.
4	Minimum of Level 3 facilities and practices; facilities have highest levels of controlled access; clothing changes and showers required for all people entering and leaving; materials must be autoclaved or gas sterilized prior to entering and leaving lab.	Agents being handled are highly virulent microbes that pose extreme risk for morbidity and mortality when inhaled in droplet or aerosol form; class 4 microbes include flaviviruses; arenaviruses (Lassa fever virus) and filoviruses (Ebola and Marburg viruses).