UNIT – V APPLICATIONS OF MICROBIOLOGY

SATHYABAMA UNIVERSITY **FACULTY OF BIO AND CHEMICAL ENGINEERING**

SBT1103	MICROBIOLOGY	L	T	P	Credits	Total Marks
		3	0	0	3	100

COURSE OBJECTIVES

- To enable students to learn about the principles of Microbiology to emphasize structure and biochemical aspects of various micro organisms.
- To know the control and preventive measures of microbial infections and environmental pollutions.

UNIT 1 INTRODUCTION TO MICROBIOLOGY **11 Hrs.**

Introduction, History and scope of microbiology, Contributions of Leewenhoek, Pasteur, Koch, Jenner and Fleming, Microbial classification: Classical and Current systems, Methods of identifying microbes.

Basics of Microscopy, Staining: simple, differential (Gram staining, Acid fast staining), special staining (flagella,capsule,endospore)

UNIT 2 MICROBIAL STRUCTURE AND REPRODUCTION **9 Hrs.**

Morphology and Reproduction: Bacteria - General structure and forms, Reproduction methods - Fission, budding and sporulation, Virus - TMV, HIV & T4 bacteriophage - lytic, lysogenic cycle, Fungi - Fungal morphology - Mycelial and yeast forms - sexual and asexual Reproduction, Actinomycete

UNIT 3 MICROBIAL GROWTH AND PHYSIOLOGY **7 Hrs.**

Microbial Growth and Nutrition, Types of media - Based on Consistency, Nutritional components, Funtional uses and application, Microbial types based on nutrition, Growth of microbes in culture - Pure culture techniques, Batch & Continous - Growth curve - Enumeration methods , Types of fungal growth media. Aerobic and Anaerobic metabolism of sugars, mixed acid fermentation.

UNIT 4 CONTROL OF MICROORGANISMS **9 Hrs**

Definitions of frequently used terms - Pattern or Rate of Microbial Death, Physical methods of Microbial Control: Heat (Moist & Dry), Low temperature, Filtration, High pressure, Desiccation, Osmotic pressure, Radiation. Chemical methods of Microbial Control: Liquids - Alcholos, Aldehydes, Phenolics, Halogens - Heavy metals, Surface active agents & Dyes, Gases - Formaldehyde, Ethylene Oxide, Plasma - Physico-chemical methods - Chemotherapeutic agents - Evaluation of effectiveness of antimicrobial agents. Difference between cleaning - sanitizing - sterilizing agents. Moist heat sterilization: D, Z and F Values and significance.

UNIT 5 APPLICATIONS OF MICROBIOLOGY **9 Hrs.**

Microbial ecology: Microbe-Microbe interaction - Mutualism, Commensalism, Altruism, Microbe - host interactions - Colonization and Infection- Causes and Transmission of Infectious Diseases, Emerging and re-emerging infectious diseases - Mechanism and examples, Multidrug resistance - MRSA, Diagnostic Microbiology, Childhood and adult vaccinations - MMR, Polio, Rabies etc, bioterrorism agents, Biofilm - Quorum sensing,

Max. 45 Hours.

TEXT / REFERENCE BOOKS

1. Pelczar, Jr E.C.S Chan and noel R.Krieg, Microbiology, 5th edition Tata McGrawHill -2006
2. Joanne M. Willey, Linda Sherwood, Christopher J. Woolverton, Prescott's Microbiology, 8th Edition, McGraw-Hill Higher Education, 2008
3. Jawetz, Melnick and Adelberg's Medical Microbiology . McGraw-Hill Medical, 2007
4. University of South Carolina School of Medicine (http://pathmicro.med.sc.edu/book/bact-sta.htm)

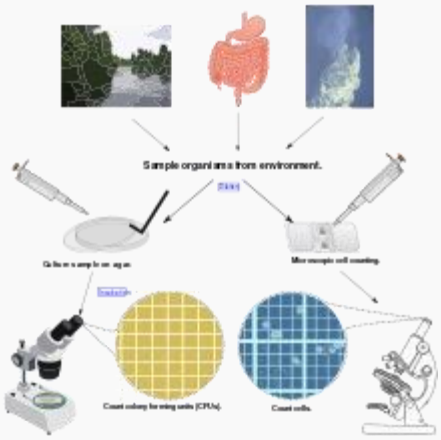
END SEMESTER EXAMINATION QUESTION PAPER PATTERN

Max Marks : 80 **Exam Duration : 3 Hrs.**

PART A : 10 questions of 2 marks each - No choice **20 Marks**

PART B : 2 questions from each unit of internal choice; each carrying 12 marks **60 Marks**

Microbial ecology



The great plate count anomaly. Counts of cells obtained via cultivation are orders of magnitude lower than those directly observed under the microscope. This is because microbiologists are able to cultivate only a minority of naturally occurring microbes using current laboratory techniques, depending on the environment.[1]

Microbial ecology (or **environmental microbiology**) is the ecology of microorganisms: their relationship with one another and with their environment. It concerns the three major domains of life—Eukaryota, Archaea, and Bacteria—as well as viruses.

Microorganisms, by their omnipresence, impact the entire biosphere. Microbial life plays a primary role in regulating biogeochemical systems in virtually all of our planet's environments, including some of the most extreme, from frozen environments and acidic lakes, to hydrothermal vents at the bottom of deepest oceans, and some of the most familiar, such as the human small intestine.[3][4] As a consequence of the quantitative magnitude of microbial life (Whitman and coworkers calculated 5.0×10^{30} cells, eight orders of magnitude greater than the number of stars in the observable universe[5][6]) microbes, by virtue of their biomass alone, constitute a significant carbon sink.[7] Aside from carbon fixation, microorganisms' key collective metabolic processes (including nitrogen fixation, methane metabolism, and sulfur metabolism) control global biogeochemical cycling.[8] The immensity of microorganisms' production is such that, even in the total absence of eukaryotic life, these processes would likely continue unchanged.[9]

History

While microbes have been studied since the seventeenth-century, this research was from a primarily physiological perspective rather than an ecological one.[10]Martinus Beijerinck invented the enrichment culture, a fundamental method of studying microbes from the environment. He is often incorrectly credited with framing the microbial ecology idea that "everything is everywhere, but, the environment selects", which was stated by Lourens Baas Becking.[11] Sergei Winogradsky was one of the first researchers to attempt to understand microorganisms outside of the medical context—making him among the first students of microbial ecology and environmental microbiology—discovering chemosynthesis, and developing the Winogradsky column in the process.[12]:644

Beijerinck and Windogradsky, however, were focused on the physiology of microorganisms, not the microbial habitat or their ecological interactions.[10] Modern microbial ecology was launched by Robert Hungate and coworkers, who investigated the rumen ecosystem. The study of the rumen required Hungate to develop techniques for culturing anaerobic microbes, and he also pioneered a quantitative approach to the study of microbes and their ecological activities that differentiated the relative contributions of species and catabolic pathways.[10]

Symbiosis

Microbes, especially bacteria, often engage in symbiotic relationships (either positive or negative) with other organisms, and these relationships affect the ecosystem. One example of these fundamental symbioses are chloroplasts, which allow eukaryotes to conduct photosynthesis. Chloroplasts are considered to be endosymbiotic cyanobacteria, a group of bacteria that are thought to be the origins of aerobic photosynthesis. Some theories state that this invention coincides with a major shift in the early earth's atmosphere, from a reducing atmosphere to an oxygen-rich atmosphere. Some theories go as far as saying that this shift in the balance of gases might have triggered a global ice-age known as the Snowball Earth.

Roles

Microorganisms are the backbone of all ecosystems, but even more so in the zones where photosynthesis is unable to take place because of the absence of light. In such zones, chemosynthetic microbes provide energy and carbon to the other organisms.

Other microbes are decomposers, with the ability to recycle nutrients from other organisms' waste products. These microbes play a vital role in biogeochemical cycles.[13] The nitrogen cycle, the phosphorus cycle, the sulphur cycle and the carbon cycle all depend on microorganisms in one way or another. For example, thenitrogen gas which makes up 78% of the earth's atmosphere is unavailable to most organisms, until it is converted to a biologically available form by the microbial process of nitrogen fixation.

Due to the high level of horizontal gene transfer among microbial communities,[14] microbial ecology is also of importance to studies of evolution.[15]

Microbial resource management

Biotechnology may be used alongside microbial ecology to address a number of environmental and economic challenges. For example, molecular techniques such as community fingerprinting can be used to track changes in microbial communities over time or assess their biodiversity. Managing the carbon cycle to sequeste rcarbon dioxide and prevent excess methanogenesis is important in mitigating global warming, and the prospects of bioenergy are being expanded by the development of microbial fuel cells. Microbial resource management advocates a more progressive attitude towards disease, whereby biological control agents are favoured over attempts at eradication. Fluxes in microbial communities has to be better characterized for this field's potential to be realised.[16]

Microbe – Microbe interactions

Microbial cooperation

Microorganisms engage in a wide variety of social interactions, including cooperation. A cooperative behavior is one that benefits an individual (the recipient) other than the one performing the behavior (the actor).[1] This article outlines the various forms of cooperative interactions (mutualism and altruism) seen in microbial systems, as well as the benefits that might have driven the evolution of these complex behaviors.

Introduction

Microorganisms, or microbes, span all three domains of life, including bacteria, archaea, viruses, and many unicellular eukaryotes (e.g., some fungi and protists). Typically defined as unicellular life forms that can only be observed with a microscope, microorganisms were the first cellular life forms, and were critical for creating the conditions for the evolution of more complex multicellular forms.

History

Table 1: Hamilton's classification of the four types of social behaviors.[1]

		Effect on recipient	
		+	−
Effect on actor	+	Mutual benefit	Selfishness
	−	Altruism	Spite

From an evolutionary point of view, a behavior is social if it has fitness consequences for both the individual that performs that behavior (the actor) and another individual (the recipient). Hamilton first categorized social behaviors according to whether the consequences they entail for the actor and recipient are beneficial (increase direct fitness) or costly (decrease direct fitness).[2] Based on Hamilton's definition, there are four unique types of social interactions:mutualism (+/+), selfishness (+/−), altruism (−/+), and spite (−/−) (Table 1). Mutualism and altruism are considered cooperative interactions because they are beneficial to the recipient, and will be the focus of this article.

Explaining cooperation remains one of the greatest challenges for evolutionary biology, regardless of whether the behavior is considered mutually beneficial or altruistic. According to classical evolutionary theory, an organism will only behave in ways that maximize its own fitness. Therefore, the origin of cooperative interactions, or actions by individuals that result in other individuals receiving fitness benefits, seems counterintuitive.

Theoretical explanations for the evolution of cooperation can be broadly classified into two categories: direct fitness benefits or indirect fitness benefits. This follows from Hamilton's 1964 insight that individuals gain inclusive fitness directly through their impact on their own reproduction (direct fitness effects), as well as through their impact on the reproduction of individuals with related genes (indirect fitness effects).[2]

Types of co-operation

Recently, Griffin et al. (2004) investigated the social nature of the production of siderophores in *Pseudomonas aeruginosa*.[6] When cells were grown in pure culture were placed in an iron-limiting environment, populations of cells that secreted siderophores (wild-type) outcompeted a population of mutant non-secretors. Therefore, siderophore production is beneficial when iron is limiting. However, when the same populations were placed in an iron-rich environment, the mutant population outcompeted wild-type population, demonstrating that siderophore production is metabolically costly. Finally, when both wild type and mutant bacteria were placed in the same mixed population, the mutants can gain the benefit of siderophore production without paying the cost, and hence increase in frequency. This concept is commonly referred to the tragedy of the commons.

1. Altruism

The second type of cooperative interactions is altruistic, or interactions that are beneficial to the recipient but costly to the actor (-/+). Justifying the evolutionary benefit of altruistic behavior is a highly debated topic. A common justification for the presence of altruistic behaviors is that they provide an indirect benefit because the behavior is directed towards other individuals who carry the cooperative gene.[2] The simplest and most common reason for two individuals to share genes in common is for them to be genealogical relatives (kin), and so this is often termed kin selection.[12] According to Hamilton, an altruistic act is evolutionarily beneficial if the relatedness of the individual that profits from the altruistic act is higher than the cost/benefit ratio this act imposes. This rationale is referred to as Hamilton's rule.

Natural selection normally favors a gene if it increases reproduction, because the offspring share copies of that gene. However, a gene can also be favored if it aids other relatives, who also share copies. Therefore, by helping a close relative reproduce, an individual is still passing on its own genes to the next generation, albeit indirectly. Hamilton pointed out that kin selection could occur via two mechanisms: (a) kin discrimination, when cooperation is preferentially directed toward relatives, and (b) limited dispersal (population viscosity), which keeps relatives in spatial proximity to one another, allowing cooperation to be directed indiscriminately toward all neighbors (who tend to be relatives).[2] In microbial systems, these two mechanisms are equally important. For example, most microbial populations often begin from a small number of colonizers. Because most microbes reproduce asexually, close genetic relatives will surround cells as the population grows. These clonal populations often result in an extremely high density, especially in terrestrial systems. Therefore, the probability that a cells altruistic behavior will benefit a close relative is extremely high.

While altruistic behaviors are most common between individuals with high genetic relatedness, it is not completely necessary. Altruistic behaviors can also be evolutionarily beneficial if the cooperation is directed towards individuals who share the gene of interest, regardless of whether this is due to coancestry or some other mechanism.[5] An example of this is known as the "green beard" mechanism, and requires a single gene (or a number of tightly linked genes) that both causes the cooperative behavior and can be recognized by other individuals due to a distinctive phenotypic marker, such as a green beard.[2]

The most studied slime mold from this perspective is *Dictyostelium discoideum*, a predator of bacteria that is common in the soil. When starving, the usually solitary single-celled amoebae aggregate and form a multicellular slug that can contain 10^4–10^6 cells. This slug migrates to the soil surface, where it transforms into a fruiting body composed of a spherical tip of spores and a stalk consisting of nonviable stalk cells that hold the spores aloft (Figure 2). Roughly 20% of the cells develop into the non-reproductive stalk, elevating the spores and aiding their dispersal.[13]

Programmed cell death (PCD) is another suggested form of microbial altruistic behavior. Although programmed cell death (also known as apoptosis or autolysis) clearly provides no direct fitness benefit, it can be evolutionary adaptive if it provides indirect benefits to individuals with high genetic relatedness (kin selection). Several altruistic possibilities have been suggested for PCD, such as providing resources that could be used by other cells for growth and survival in *Saccharomyces cerevisiae*.[14][15] While using kin selection to explain the evolutionary benefits of PCD is common, the reasoning contains some inherent problems. Charlesworth (1978) noted that it is extremely hard for a gene causing suicide to spread because only relatives that do NOT share the gene would ultimately benefit.[16] Therefore, the possible solution to this problem in microbes is that selection could favor a low probability of PCD among a large population of cells, possibly depending upon individual condition, environmental conditions, or signaling.

A. A **symbiont** is any microorganism that spends all or a portion of its life associated with another organism of a different species

B. Symbiosis is the living together in close physical association of two or more different organisms

1. Ectosymbiosis organisms remain outside each other

2. Endosymbiosis one organism is found within the other

II. Types of Symbiosis, Functions, and Examples

2. Commensalism

The microorganism (commensal) benefits, while the host is neither harmed nor helped

1. The microorganism shares the same food source with the host

2. The microorganism is not directly dependent on the metabolism of the host

3. The microorganism causes no particular harm to host

4. Example The common nonpathogenic strain of *Escherichia coli* lives in the human colon; this facultative anaerobe uses oxygen creating an anaerobic environment in which obligate anaerobes (e.g. *bacteroids*) can grow. The bacteroids benefit but the *E. coli* derives no obvious benefit or harm.

There are numerous examples of species of bacteria that interact in a commensal manner. For example*Acetobacter oxydans* produces fructose by oxidising mannitol; in turn, a species such as *Saccharomyces carlsbergensis* that can metabolise fructose, but cannot metabolise mannitol. In another instance,*Mycobacterium vaccae* is able to draw on propane as its energy intake and co-metabolise cyclohexane to the corresponding alcohol, cyclohexanol; subsequently certain *Pseudomonas* species are able to use cyclohexanol and become the beneficiaries of this commensal association.

3. Mutualism

1. There is some reciprocal benefit to both partners. Perhaps the most common cooperative interactions seen in microbial systems are mutually beneficial (+/+). Mutually beneficial social interactions provide a direct fitness benefit to the individual that performs the behavior, which outweighs the cost of performing the behavior.[3] Most of the time, individuals partaking in the behaviors have a shared interest in cooperation. In microbial systems, this is most often seen as the production of public goods. Many microbes, especially bacteria, produce numerous factors that are released into the environment beyond the cell membrane.

2. The microorganism (mutualist) and host are metabolically dependent upon each other

3. Syntropism is a mutually beneficial relationship in which each organism provides one or more growth factors, nutrients or substrates for the other organism; also referred to as cross-feeding or the satellite phenomenon.

4. Examples

One very popular example of mutually beneficial microbial interactions involves the production of siderophores. Siderophores are iron-scavenging molecules produced by many microbial taxa, including bacteria and fungi. Iron is a major limiting factor for bacterial growth because most iron in the environment is in the insoluble Fe(III) form. In order for bacteria to access this limiting factor, cells will manufacture these enzymes, and then secrete them into the extracellular space.[4]Once released, the siderophore will sequester the iron, making it metabolically accessible for the bacteria.

a. Protozoan-termite relationship protozoa live in the guts of insects which ingest but cannot metabolize cellulose; the protozoa secrete cellulases, which metabolize cellulose, releasing nutrients that the insects can use

b. Lichens an association between a fungus (ascomycetes) and an alga (green algae) or cyanobacteria

(1) Fungal partner (mycobiont) obtains nutrients from alga by hyphal projections (haustoria) that penetrate the algal cell wall

(2) Algal partner (phycobiont) is protected from excess light intensity and is provided with water, minerals, and a firm substratum in which it can grow protected from environmental stress

c. Zooxanthellae algae harbored by marine invertebrates; reef-building (hermatypic) corals are unable to utilize zooplankton as food and rely heavily on endosymbiotic zooxanthellae; the coral pigments protect the algae from ultraviolet radiation

d. The tube worm-bacterial relationship

(1) Exist in hydrothermal vent communities where the vent fluids are anoxic, with high concentrations of hydrogen sulfide and temperatures up to 350EC

(2) The surrounding seawater reaches temperatures 10E to 20EC above the normal temperature of 2.1EC

(3) Free living and endosymbiotic chemolithotrophic bacteria provide the main energy source in the community through the oxidation of hydrogen sulfide

(4) Chemolithotrophic endosymbiotic bacteria are maintained in a specialized tissue (trophosome) of giant (less than one meter in length), red, gutless tube worms

(5) The tube worm binds hydrogen sulfide to hemoglobin and transports it to the bacteria; the bacteria use the energy from hydrogen sulfide oxidation to synthesize reduced organic material that is supplied to the tube worms

e. Rumen ectosymbiosis bacteria in the rumen anaerobically metabolize cellulose, and then normal digestion occurs; microorganisms produce the majority of vitamins that are needed by the ruminant; methane is also produced in the process

G. Gnotobiotic animals are unusually susceptible to pathogens but may be resistant to some diseases caused by protozoa that use bacteria as a food source (e.g. *Entamoeba histolytica*)

IV. Distribution of the Normal Microbiota of the Human Body

A. Reasons to acquire knowledge of normal human microbiota and its distribution

1. It provides greater insight into possible infections resulting from injury to these areas

2. It gives perspective on the possible sources and significance of microorganisms isolated from an infection site

3. It increases understanding of the causes and consequences of overgrowth of microorganisms normally absent from a specific body site

4. It aids awareness of the role these indigenous microorganisms play in stimulating the immune response that provides protection against potential pathogens

B. Skin

1. Resident microbiota multiply on or in the skin

a. They vary from one part of the body to another

b. They experience periodic drying in a slightly acidic, hypertonic environment

2. Transient microbiota are found on the skin for a short time and do not multiply there; they usually die in a few hours

3. One species, *Propionibacterium acnes*, is associated with acne vulgaris

C. Nose and nasopharynx

1. NoseCjust inside the nares; contains the same organisms as skin, including *Staphylococcus epidermidis* and *S. aureus*

2. NasopharynxCabove the level of the soft palate; contains nonencapsulated strains of some of the same species that may cause clinical infection; other species also are found

D. OropharynxCbetween the soft palate and upper edge of the epiglottis; houses many different species

E. Respiratory tractCno normal microbiota due to mucociliary blanket, the enzyme *lysozyme* in mucus, and the phagocytic action of alveolar macrophages

F. Oral cavity (mouth)Ccontains those organisms that survive mechanical removal by adhering to gums (anaerobes) and teeth (aerobes); organisms contribute to the formation of dental plaque, dental caries, gingivitis, and periodontal disease

G. Eye aerobic commensals are found on the conjunctiva

H. External ear resembles microbiota of the skin with some fungi

I. StomachCmost microorganisms are killed by acidic conditions unless they pass through very quickly; the number of microorganisms present increases immediately after a meal, but decreases quickly

J. Small intestine

1. DuodenumCfew microorganisms present because of stomach acidity and inhibitory action of bile and pancreatic secretions

2. JejunumC*Enterococcus fecalis*, diphtheroids, lactobacilli, and *Candida albicans*

3. IleumCmicrobiota resemble that of the colon as the pH becomes more alkaline

K. Large intestine (colon)Clargest microbial population of the body

1. Over 300 different species have been isolated from human feces

2. Most are anaerobes or facultative organisms growing anaerobically

3. Ratio of anaerobes to facultatives is approximately 300:1

4. They are excreted by peristalsis, segmentation, desquamation, and movement of mucus

5. They are replaced rapidly because of their high reproductive rate

6. This is a self-balancing (self-regulating) microbial ecology

7. The balance may change with: stress, altitude, starvation, diet, parasite infection, diarrhea, use of antibiotics or probiotics (microorganisms orally administered that promote health)

L. Genitourinary tract

1. Kidneys, ureter, and bladder are normally free of microorganisms

2. Males - a few microorganisms are found in distal portions of the urethra

3. Females complex microbiota in a state of flux due to menstrual cycle; Döderlein=s bacilli are primarily *Lactobacillus acidophilus* that forms lactic acid and thereby maintains the pH of the vagina and cervical os between 4.4 and 4.6

Microbe – host interactions

Introduction

Microbial **pathogenicity** has been defined as the structural and biochemical mechanisms whereby microorganisms cause disease. Pathogenicity in bacteria may be associated with unique structural components of the cells (e.g. capsules, fimbriae, LPS or other cell wall components) or active secretion of substances that either damage host tissues or protect the bacteria against host defenses. Hence, there are two broad qualities of pathogenic bacteria that underlie the means by which they cause disease: **invasiveness** and **toxigenesis**.

Toxigenesis is the **ability to produce toxins.** Toxic substances produced by bacteria, both soluble and cell-associated, may be transported by blood and lymph and cause cytotoxic effects at tissue sites remote from the original point of invasion or growth.

Invasiveness is the **ability of a pathogen to invade tissues.** Invasiveness encompasses (1) mechanisms for colonization (adherence and initial multiplication), (2) production of extracellular substances ("invasins"), that promote the immediate invasion of tissues and (3) ability to bypass or overcome host defense mechanisms which facilitate the actual invasive process. This chapter deals with the first two aspects of of invasiveness: colonization and invasion.

COLONIZATION

The first stage of microbial infection is **colonization**: the establishment of the pathogen at the appropriate portal of entry. Pathogens usually colonize host tissues that are in contact with the external environment. Sites of entry in human hosts include the urogenital tract, the digestive tract, the respiratory tract and the conjunctiva. Organisms that infect these regions have usually developed tissue adherence mechanisms and some ability to overcome or withstand the constant pressure of the host defenses at the surface.

Bacterial Adherence to Mucosal Surfaces. In its simplest form, bacterial adherence or attachment to a eucaryotic cell or tissue surface requires the participation of two factors: a **receptor** and a **ligand**. The receptors so far defined are usually specific carbohydrate or peptide residues on the eucaryotic cell surface. The bacterial ligand, called an **adhesin**, is typically a macromolecular component of the bacterial cell surface which interacts with the host cell receptor. Adhesins and receptors usually interact in a complementary and specific fashion with specificity comparable to enzyme-substrate relationships and antigen-antibody reactions. Table 1 is a list of terms that are used in medical microbiology to refer to microbial adherence to surfaces or tissues.

TABLE 1. TERMS USED TO DESCRIBE ADHERENCE FACTORS IN MICROBIOLOGY

ADHERENCE FACTOR	DESCRIPTION
Adhesin	A surface structure or macromolecule that binds a bacterium to a specific surface
Receptor	A complementary macromolecular binding site on a (eucaryotic) surface that binds specific adhesins or ligands
Lectin	Any protein that binds to a

	carbohydrate
Ligand	A surface molecule that exhibits specific binding to a receptor molecule on another surface
Mucous	The mucopolysaccharide layer of glucosaminoglycans covering animal cell mucosal surfaces
Fimbriae	Filamentous proteins on the surface of bacterial cells that may behave as adhesins for specific adherence
Common pili	Same as fimbriae
Sex pilus	A specialized pilus that binds mating procaryotes together for the purpose of DNA transfer
Type 1 fimbriae	Fimbriae in *Enterobacteriaceae* which bind specifically to mannose terminated glycoproteins on eucaryotic cell surfaces
Type 4 pili	Pili in certain Gram-positive and Gram-negative bacteria. In *Pseudomonas*, thought to play a role in adherence and biofilm formation
Biofilm	exopolysaccharide or slime produced by bacteria that attaches imbedded cells to a surface
	Proteins that form the outermost cell envelope component of a

S-layer	broad spectrum of bacteria, enabling them to adhere to host cell membranes and environmental surfaces in order to colonize.
Glycocalyx	A layer of exopolysaccharide fibers on the surface of bacterial cells which may be involved in adherence to a surface. Sometimes a general term for a bacterial capsules.
Capsule	A detectable layer of polysaccharide (rarely polypeptide) on the surface of a bacterial cell which may mediate specific or nonspecific attachment
Lipopolysaccharide (LPS)	A distinct cell wall component of the outer membrane of Gram-negative bacteria with the potential structural diversity to mediate specific adherence. Probably functions as an adhesin
Teichoic acids and lipoteichoic acids (LTA)	Cell wall components of Gram-positive bacteria that may be involved in nonspecific or specific adherence

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Symptoms and causes

Symptoms

Each infectious disease has its own specific signs and symptoms. General signs and symptoms common to a number of infectious diseases include:

- Fever , Diarrhea, Fatigue , Muscle aches and Coughing

Causes

Infectious diseases can be caused by:

- **Bacteria.** These one-cell organisms are responsible for illnesses such as strep throat, urinary tract infections and tuberculosis.
- **Viruses.** Even smaller than bacteria, viruses cause a multitude of diseases — ranging from the common cold to AIDS.
- **Fungi.** Many skin diseases, such as ringworm and athlete's foot, are caused by fungi. Other types of fungi can infect your lungs or nervous system.
- **Parasites.** Malaria is caused by a tiny parasite that is transmitted by a mosquito bite. Other parasites may be transmitted to humans from animal feces.

Disease Transmission Overview

Infectious diseases are those that are transmitted from person to person by direct or indirect contact. Viruses, bacteria, parasites, and fungi all cause infectious disease. Malaria, measles, and respiratory illnesses are examples of infectious diseases.
Simple preventative measures, like frequent hand washing, can cut down on disease transmission.

Direct contact

An easy way to catch most infectious diseases is by coming in contact with a person or animal who has the infection. Three ways infectious diseases can be spread through direct contact are:

- **Person to person.** A common way for infectious diseases to spread is through the direct transfer of bacteria, viruses or other germs from one person to another. This can occur when an individual with the bacterium or virus touches, kisses, or coughs or sneezes on someone who isn't infected.

  These germs can also spread through the exchange of body fluids from sexual contact. The person who passes the germ may have no symptoms of the disease, but may simply be a carrier.

Droplet Spread

The spray of droplets during coughing and sneezing can spread infectious disease. You can even infect another person through the droplets created when you speak. Droplets fall to the ground within a few feet, so this type of transmission requires close proximity.

Animal to person. Being bitten or scratched by an infected animal — even a pet — can make you sick and, in extreme circumstances, can be fatal. Handling animal waste can be hazardous, too. For example, you can acquire a toxoplasmosis infection by scooping your cat's litter box.
The *Toxoplasma* parasite can be found in cat feces. Pregnant women and people with compromised immune systems should take extra care (disposable gloves and good hand washing) when changing cat litter, or avoid it altogether.

- **Mother to unborn child.** A pregnant woman may pass germs that cause infectious diseases to her unborn baby. Some germs can pass through the placenta. Germs in the vagina can be transmitted to the baby during birth.

Indirect Contact

Infectious diseases can also be spread indirectly through the air and other mechanisms.

Airborne Transmission Some infectious agents can travel long distances and remain suspended in the air for an extended period of time. You can catch a disease like measles by entering a room well after someone with measles has departed.

Contaminated Objects

Some organisms can live on objects for a short time. If you touch an object, such as a doorknob, soon after an infected person, you are exposed to infection. Transmission occurs when you touch your mouth, nose, or eyes before thoroughly washing your hands. Germs can also be spread through contaminated blood products and medical supplies.

Insect Bites (Vector-borne Disease)

Some infectious agents are transmitted by insects, especially those that suck blood. These include mosquitos, fleas, and ticks. The insects become infected when they feed on infected hosts, such as birds, animals, and humans. The disease is then transmitted when the insect bites a new host. **Malaria**, **West Nile virus (WNV)**, and **Lyme** disease are all spread this way.

Food and Drinking Water

Infectious diseases can be transmitted via contaminated food and water. *E. coli* is often transmitted through improperly handled produce or undercooked meat. Improperly canned foods can create an environment ripe for *Clostridium botulinum*, which causes **botulism**.

Animal Reservoirs

Animal-to-animal disease transmission can sometimes transfer to humans. **Zoonosis** occurs when diseases are transferred from vertebrate animals to people. Zoonotic diseases include **anthrax** (from sheep), **rabies** (from rodents and other mammals), and WNV (from birds). **Plague** is transmitted through rodents.

Environmental Reservoirs

Soil, water, and vegetation containing infectious organisms can also be transferred to people. **Hookworm**, for example, is transmitted through contaminated soil. According to the United States Centers for Disease Control and Prevention (CDC), **Legionnaires' disease** is an example of a disease that can be spread by water that supplies cooling towers and evaporative condensers (CDC, 2013).

Risk factors

While anyone can catch infectious diseases, you may be more likely to get sick if your immune system isn't working properly. This may occur if:

- You're taking steroids or other medications that suppress your immune system, such as anti-rejection drugs for a transplanted organ
- You have HIV or AIDS
- You have certain types of cancer or other disorders that affect your immune system

In addition, certain other medical conditions may predispose you to infection, including implanted medical devices, malnutrition and extremes of age, among others.

Complications

Most infectious diseases have only minor complications. But some infections — such as pneumonia, AIDS and meningitis — can become life-threatening. A few types of infections have been linked to a long-term increased risk of cancer:

- Human papillomavirus is linked to cervical cancer
- Helicobacter pylori is linked to stomach cancer and peptic ulcers
- Hepatitis B and C have been linked to liver cancer

In addition, some infectious diseases may become silent, only to appear again in the future — sometimes even decades later. For example, someone who's had a chickenpox infection may develop shingles much later in life.

How to Prevent Disease Transmission

A few simple precautions can prevent some disease transmission. The most important of these is to **wash your hands thoroughly and often.**

Illness

When you have a contagious illness, try to avoid direct contact with other people. **Cover your nose and mouth when you sneeze and cough.** When caring for an ill person, use disposable gloves and wash your hands frequently.

Foodborne Illness

Dangerous organisms can thrive in improperly prepared food. Avoid cross-contamination by keeping raw meats and produce separate. Use different preparation surfaces and wash surfaces and utensils thoroughly.

Freeze or refrigerate perishable foods and leftovers promptly. According to the United States Department of Agriculture (USDA), you should set your refrigerator to 40°F or below and your freezer to 0°F or below. Cook meats to a minimum internal temperature of 145°F. Cook ground meats to 160°F and poultry to 165°F (USDA, 2011).

Be careful about sources of food when visiting foreign countries.

Insects and Animals When camping or enjoying wooded areas, wear long pants and long sleeves. Use insect repellent and mosquito netting. Don't touch animals in the wild.

Vaccinations

Stay up to date on vaccinations, especially when traveling. Don't forget to keep your pet's vaccinations current, too.

Emerging and Re-emerging Infectious Diseases

Fifty years ago many people believed the age-old battle of humans against infectious disease was virtually over, with human kind the winners. The events of the past two decades have shown the foolhardiness of that position. At least a dozen "new" diseases have been identified (such as AIDS, Legionnaire disease, and hantavirus pulmonary syndrome), and traditional diseases that appeared to be "on their way out" (such as malaria and tuberculosis) are resurging. Globally, infectious diseases remain the leading cause of death, and they are the third leading cause of death in the United States. Clearly, the battle has not been won.

Emerging infectious diseases are diseases that (1) have not occurred in humans before (this type of emergence is difficult to establish and is probably rare); (2) have occurred previously but affected only small numbers of people in isolated places (AIDS and Ebola hemorrhagic fever are examples); or (3) have occurred throughout human history but have only recently been recognized as distinct diseases

due to an infectious agent (Lyme disease and gastric ulcers are examples). Figure 7 lists several examples of infectious diseases that have emerged in the last three decades.

Disease	Infectious Agent	Year Recognized*	Contributing Factors
Lassa fever	*Arenaviridae* family (virus)	1969	urbanization and other conditions that favor the rodent host; nosocomial transmission
Ebola hemorrhagic fever	*Filoviridae* family (virus)	1977	unknown natural reservoir; nosocomial transmission
Legionnaire disease	*Legionella pneumophila* (bacterium)	1977	cooling and plumbing systems
hemolytic uremic syndrome	*Escherichia coli* 0157:H7 (bacterium)	1982	mass food production systems
Lyme borreliosis	*Borrelia burgdorferi* (bacterium)	1982	conditions favoring the tick vector and deer, such as reforestation near homes
AIDS	human immunodeficiency virus	1983	migration to cities, global travel, trans-fusions, organ transplants, intravenous drug use, multiple sexual partners
gastric ulcers	*Helicobacter pylori* (bacterium)	1983	newly recognized as due to infectious agent
cholera	*Vibrio cholerae* 0139 (bacterium)	1992	evolution of new strain of bacteria combining increased virulence and long-term survival in the environment
hantavirus pulmonary syndrome	*Bunyaviridae* family (virus)	1993	environmental changes favoring contact with rodent hosts
pandemic influenza	*Orthomyxoviridae* family (virus)	new viral strains emerge periodically	pig-duck agriculture (possibly)

Figure 7 Examples of Emerging Infectious Diseases Sources: Morse, S.S. 1995. Factors in the emergence of infectious diseases. *Emerging Infectious Diseases* [Serial online], 1(1). Available http://www.cdc.gov/ncidod/EID/index.htm. June 1999; Satcher, D. 1995. Emerging (more...)

A review of Figure 7 reveals that environmental changes are related to the emergence of many infectious diseases. For example, Lyme disease, hantavirus pulmonary syndrome (HPS), and Lassa fever all emerged when humans began encountering the insect vector (for Lyme disease) or rodent host (for HPS and Lassa fever) of the causative agents in greater numbers than ever before. Factors related to the emergence of infectious diseases such as Legionnaire disease and hemolytic uremic syndrome include changing technologies: air conditioning systems for the former disease and mass food production for the latter.

Re-emerging infectious diseases are diseases that once were major health problems globally or in a particular country, and then declined dramatically, but are again becoming health problems for a significant proportion of the population (malaria and tuberculosis are examples). Many specialists in infectious diseases include re-emerging diseases as a subcategory of emerging diseases. Figure 8 lists examples of re-emerging infectious diseases.

Disease	Infectious Agent	Contributing Factors
cryptosporidiosis	*Cryptosporidium parvum* (protozoa)	inadequate control in water supply; international travel; increased use of child-care facilities
diphtheria	*Corynebacterium diptheriae* (bacterium)	interruption of immunization program due to political changes
malaria	*Plasmodium* species (protozoon)	drug resistance; favorable conditions for mosquito vector
meningitis, necrotizing fasciitis (flesh-eating disease), toxic shock syndrome, and other diseases	Group A *Streptococcus* (bacterium)	uncertain
pertussis (whooping cough)	*Bordetella pertussis* (bacterium)	refusal to vaccinate based on fears the vaccine is not safe; other possible factors: decreased vaccine efficacy or waning immunity among vaccinated adults
rabies	*Rhabdovirus* group (virus)	breakdown in public health measures; changes in land use; travel
rubeola (measles)*	*Morbillivirus* genus (virus)	failure to vaccinate; failure to receive second dose of vaccine
schistosomiasis	*Schistosoma* species (helminth)	dam construction; ecological changes favoring snail host
tuberculosis	*Mycobacterium tuberculosis* (bacterium)	antibiotic-resistant pathogens; immunocompromised populations (malnourished, HIV-infected, poverty-stricken)
yellow fever	*Flavivirus* group (virus)	insecticide resistance; urbanization; civil strife

Figure 8 Examples of Re-emerging Infectious Diseases Sources: Krause, R.M. 1992. The origin of plagues: Old and new. *Science, 257*: 1073–1078; Measles—United States, 1997. April 17, 1998. *Morbidity and Mortality Weekly Report, 47*(14): 273–276; (more...)

A review of Figure 8 reveals some explanations for the re-emergence of infectious diseases. Tuberculosis has re-emerged due to evolution of the causative bacteria. The pathogen has acquired resistance to the antibiotics used to treat tuberculosis (either through mutation or genetic exchange) and the long-term use of antibiotics (both within one individual and across the population) has selected for the pathogen's proliferation. Malaria has also become drug resistant, and the vector mosquito has acquired resistance to pesticides as well. The re-emergence of diseases such as diphtheria and whooping cough (pertussis) is related to inadequate vaccination of the population. When the proportion of immune individuals in a population drops below a particular threshold, introduction of the pathogen into the population leads to an outbreak of the disease.

Despite the challenges of emerging and re-emerging infectious diseases, the results of basic research, such as that sponsored by NIH, show that there is reason for hope. AIDS was first described in 1981, and it took two years to identify the retrovirus that causes AIDS, which was named the human immunodeficiency virus. In contrast, less than four months elapsed between the description of hantavirus pulmonary syndrome (HPS) in 1993 and the identification of the previously unknown viral

agent, now called Sin Nombre virus. One difference between these two cases is that the years that intervened between the advent of AIDS and the advent of HPS saw the development of polymerase chain reaction, a powerful new research technique that allows rapid identification of causative agents. Recommendations for avoiding and/or treating of new infectious diseases become possible when new techniques, developed through basic research, are applied to the problem of disease emergence.

Other examples of the benefits of basic research include the development of HIV protease inhibitors by researchers funded by NIH and others. These drugs, when used in combination with other anti-HIV drugs, are responsible for the dramatic decrease in deaths from AIDS in the United States. One active area of research at NIH is the development of new types of vaccines based on our new understanding of the immune system. In addition, basic research on the immune system and host pathogen interactions has revealed new points at which vaccines could work to prevent diseases.

Finally, basic research on the ecology of disease organisms—their reservoirs, modes of transmission, and vectors, if any—reveals points at which preventive measures can be used to interrupt this cycle and prevent the spread of disease. For example, research supported by NIAID delineated the mechanism of Lyme disease transmission and how disease results: The tick vector was identified and the life cycle of the causative bacterium was traced through deer and rodent hosts. Understanding this ecology has led to predictions about the regions where and years when the threat of Lyme disease is greatest, as well as recommendations to the public for avoiding infection. These examples and others demonstrate that investment in basic research has great long-term payoffs in the battle against infectious diseases.

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (**MRSA**) is a bacterium responsible for several difficult-to-treat infections in humans. It is also called **oxacillin-resistant *Staphylococcus aureus*** (**ORSA**).[1] MRSA is any strain of *Staphylococcus aureus* that has developed, through the process of natural selection, resistance to beta-lactam antibiotics, which include the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins. Strains unable to resist these antibiotics are classified as methicillin-sensitive *Staphylococcus aureus*, or MSSA. The evolution of such resistance does not cause the organism to be more intrinsically virulent than strains of *S. aureus* that have no antibiotic resistance, but resistance does make MRSA infection more difficult to treat with standard types of antibiotics and thus more dangerous.

MRSA is especially troublesome in hospitals, prisons, and nursing homes, where patients with open wounds, invasive devices, and weakened immune systems are at greater risk of nosocomial infection than the general public. MRSA began as a hospital-acquired infection, but has developed limited endemic status and is now sometimes community-acquired and livestock-acquired. The terms **HA-MRSA** (healthcare-associated MRSA), **CA-MRSA** (community-associated MRSA) and LA-MRSA (livestock-associated) reflect this distinction.

Signs and symptoms

S. aureus most commonly colonizes under the anterior nares (the nostrils).[2] The rest of the respiratory tract, open wounds, intravenous catheters, and the urinary tract are also potential sites for infection. Healthy individuals may carry MRSA asymptomatically for periods ranging from a few weeks to many years. Patients with compromised immune systems are at a significantly greater risk of symptomatic secondary infection.

In most patients, MRSA can be detected by swabbing the nostrils and isolating the bacteria found inside the nostrils. Combined with extra sanitary measures for those in contact with infected patients, swab screening patients admitted to hospitals has been found to be effective in minimizing the spread of MRSA in hospitals in the United States,[3] Denmark, Finland, and the Netherlands.[4]

MRSA may progress substantially within 24–48 hours of initial topical symptoms. After 72 hours, MRSA can take hold in human tissues and eventually become resistant to treatment. The initial presentation of MRSA is small red bumps that resemble pimples, spider bites, or boils; they may be accompanied by fever and, occasionally, rashes. Within a few days, the bumps become larger and more painful; they eventually open into deep, pus-filled boils.[5] About 75 percent of community-associated (CA-) MRSA infections are localized to skin and soft tissue and usually can be treated effectively.[6] Some CA-MRSA strains display enhanced virulence, spreading more rapidly and causing illness much more severe than traditional HA-MRSA infections, and they can affect vital organs and lead to widespread infection (sepsis), toxic shock syndrome, and necrotizing pneumonia. This is thought to be due to toxins carried by CA-MRSA strains, such as PVL and PSM, though PVL was recently found not to be a factor in a study by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. It is not known why some healthy people develop CA-MRSA skin infections that are treatable while others infected with the same strain develop severe infections or die.[7]

People are occasionally colonized with CA-MRSA and are completely asymptomatic. The most common manifestations of CA-MRSA are simple skin infections, such as impetigo, boils, abscesses, folliculitis, and cellulitis. Rarer, but more serious, manifestations can occur, such as necrotizing fasciitis and pyomyositis (most commonly found in the tropics), necrotizing pneumonia, and infective endocarditis (which affects the valves of the heart), and bone and joint infections.[8] CA-MRSA often results in abscess formation that requires incision and drainage. Before the spread of MRSA into the community, abscesses were not considered contagious, because infection was assumed to require violation of skin integrity and the introduction of staphylococci from normal skin colonization. However, newly emerging CA-MRSA is transmissible (similar, but with very important differences) from HA-MRSA. CA-MRSA is less likely than other forms of MRSA to cause cellulitis.

Risk factors

Some of the populations at risk:

- People who are frequently in crowded places, especially with shared equipment and skin-to-skin contact[9]

- People with weak immune systems (HIV/AIDS, lupus, or cancer sufferers; transplant recipients, severe asthmatics, etc.)
- Diabetics[10]
- Intravenous drug users[11][12]
- Users of quinolone antibiotics[13]
- The elderly[14]
- College students living in dormitories[9]
- Women with frequent urinary tract or kidney infections due to infections in the bladder
- People staying or working in a health care facility for an extended period of time[9]
- People who spend time in coastal waters where MRSA is present, such as some beaches in Florida and the west coast of the United States[15][16]
- People who spend time in confined spaces with other people, including occupants of homeless shelters and warming centers, prison inmates, military recruits in basic training,[17] and individuals who spend considerable time in changing rooms or gyms[*citation needed*]
- Veterinarians, livestock handlers, and pet owners.

Diagnostic Microbiology

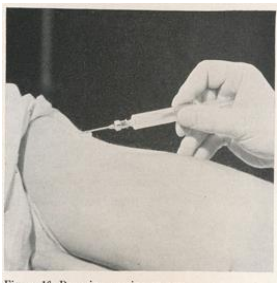
Diagnostic medical microbiology is concerned with the etiologic diagnosis of infection. Laboratory procedures used in the diagnosis of infectious disease in humans include the following:

1. Morphologic identification of the agent in stains of specimens or sections of tissues (light and electron microscopy).
2. Culture isolation and identification of the agent.
3. Detection of antigen from the agent by immunologic assay (latex agglutination, enzyme immunoassay [EIA], etc) or by fluorescein-labeled (or peroxidase-labeled) antibody stains.
4. DNA-DNA or DNA-RNA hybridization to detect pathogen- specific genes in patients'specimens.
5. Detection and amplification of organism nucleic acid in patients'specimens.
6. Demonstration of meaningful antibody or cell-mediated immune responses to an infectious agent.

In the field of infectious diseases, laboratory test results depend largely on the quality of the specimen, the timing and the care with which it is collected, and the technical proficiency and experience of laboratory personnel. Although physicians should be competent to perform a few simple, crucial microbiologic tests—make and stain a smear, examine it microscopically, and streak a culture plate—technical details of the more involved procedures are usually left to the bacteriologist or virologist and the technicians on the staff. Physicians who deal with infectious processes must know when and how to take specimens, what laboratory examinations to request, and how to interpret the results. Diagnostic microbiology encompasses the characterization of thousands of agents that cause or are associated with infectious diseases. The techniques used to characterize infectious agents vary greatly depending on the clinical syndrome and the type of agent being considered, be it virus, bacterium, fungus, or parasite. Because no single test will permit isolation or characterization of all potential pathogens, clinical information is much more important for diagnostic microbiology than it is for clinical chemistry or hematology. The clinician must make a tentative diagnosis rather than wait until

laboratory results are available. When tests are requested, the physician should inform the laboratory staff of the tentative diagnosis (type of infection or infectious agent suspected). Proper labeling of specimens includes such clinical data as well as the patient's identifying data (at least two methods of definitive identification) and the requesting physician's name and pertinent contact information. Many pathogenic microorganisms grow slowly, and days or even weeks may elapse before they are isolated and identified. Treatment cannot be deferred until this process is complete. After obtaining the proper specimens and informing the laboratory of the tentative clinical diagnosis, the clinician should begin treatment with drugs aimed at the organism thought to be responsible for the patient's illness. As the laboratory staff begins to obtain results, they inform health care providers, who can then reevaluate the diagnosis and clinical course of the patient and perhaps make changes in the therapeutic program. This "feedback" information from the laboratory consists of preliminary reports of the results of diseases.

Childhood and adult Vaccination



The Historical Medical Library of The College of Physicians of Philadelphia

First step in multiple puncture technique of TB vaccination

Vaccines are most often discussed in the context of childhood, where they're given according to a recommended schedule to prevent common (and not-so-common) childhood illnesses. Frequent and routine "well child" visits to the doctor help ensure that children are kept up-to-date on their vaccines.

With fewer doctor visits as we age, however, the percentage of the population that is up-to-date on recommended vaccines wanes. Data from the U.S. Centers for Disease Control and Prevention show that only about half of all teenagers have received the recommended meningococcal vaccine, which protects against bacterial infections that may lead to amputation of infected limbs and death. Similarly, only about half of adolescents received the recommended influenza vaccine during the 2010-2011 flu season. By adulthood, many of us have forgotten that vaccines are available – and important – for everyone, not just kids.

Apart from protecting themselves, adults should consider the benefits of vaccination to the family and community. In most cases, a person who is vaccinated against a disease cannot spread that disease to other people. High rates of vaccination help protect those around us who cannot be immunized for health reasons (such as illness, age, or allergy). This principle is known as herd immunity, or community immunity.

Following are vaccines typically recommended for adults. Note that younger adults may have received vaccines that were more recently developed, such as those against chickenpox or hepatitis A, as children. If so, they *may* not need to receive the vaccines again.

If you think you may need to receive one or more of these vaccines, consult your doctor.

Pneumococcal Vaccine

Pneumococcal disease includes a variety of illnesses caused by the bacterium *Streptococcus pneumoniae.* Different types of pneumococcal disease include pneumococcal bacteremia, meningitis, and pneumonia.

The pneumococcal vaccine is recommended for adults based on a variety of risk factors. It is recommended for the following groups:

- Anyone who is **65 or older**
- Anyone between 19 and 65 years of age with **asthma**, or who is a **smoker**
- Anyone between the ages of 2 and 65 with one of the following long-term health problems: **heart disease, lung disease, sickle cell disease, diabetes, alcoholism, cirrhosis, leaks of cerebrospinal fluid,** or **cochlear implant**
- Anyone between the ages of 2 and 65 with a condition that lowers resistance to infection, including **lymphoma, leukemia, HIV or AIDS, kidney failure, a damaged or missing spleen,** or **organ transplant**
- Anyone between the ages of 2 and 65 receiving a treatment that lowers resistance to infection, including **radiation therapy,** some **cancer drugs**, or **long-term steroids**
- Anyone living in a **nursing home** or **long-term care facility**

Human papillomavirus (HPV) Vaccine

HPV vaccines protect against multiple strains of HPV that cause cervical, vaginal, and vulvar cancer. One of the two HPV vaccines also provides protection against genital warts.

HPV vaccination is recommended for children as part of the routine childhood immunization schedule, but is also recommended for adults who were not vaccinated as children.

- **Women who are 26 years old or younger** can receive either version of the HPV vaccine for protection against cervical, vaginal, and vulvar cancer. The vaccine may also provide protection against oral and anal cancer, and the quadrivalent version of the vaccine protects against genital warts.
- **Men who are 26 years old or younger** can receive the quadrivalent vaccine, which offers protection against genital warts and may protect against oral, anal, and penile cancer caused by HPV.

Influenza Vaccine

Seasonal influenza vaccination is recommended **yearly for all adults**; in fact, it is recommended for everyone over the age of 6 months. The vaccine protects against respiratory illness caused by influenza viruses. Because new strains of influenza appear frequently, the seasonal flu vaccine usually changes each year. Each season's vaccine is designed to protect against three strains of influenza. Influenza vaccine is available as an injected or inhaled vaccine, but for adults 50 years of age and older, only the injectable vaccine is recommended.

Tetanus/Diphtheria and Tetanus/Diphtheria/Pertussis Booster Vaccines

A combination vaccine against tetanus, diphtheria, and pertussis (whooping cough) is given in childhood in a series of shots called DTaP. After that, **everyone needs a booster shot for tetanus and diphtheria every 10 years**, given in the form of a vaccine called Td. One of those boosters, however, should be replaced with a shot of the Tdap vaccine (which provides protection against tetanus, diphtheria, and pertussis). A Tdap booster is particularly recommended for **health care workers** and anyone who has **contact with an infant**. (This is because infants are too young to receive their own vaccination against whooping cough, which can be fatal in young children. Therefore, it is important that anyone in contact with the child be protected against whooping cough so as not to expose the child to the disease.) Pregnant women are recommended to take the Tdap vaccine during the last trimester of each pregnancy in order to protect the baby via maternal antibody until age 2 months. At two months of age, the baby can receive DTaP.

Separate from routine boosters given every 10 years, Td is also given to individuals who have suffered injuries or wounds that may have exposed them to tetanus bacteria. Tdap can also be used in this instance, to provide protection against pertussis.

Hepatitis A Vaccine

Hepatitis A vaccines were added to the routine childhood immunization schedule in 2006, but are also recommended for adults who are at an increased risk for hepatitis A. This includes the following groups:

- Anyone **traveling to developing countries**
- **Men who have sex with men**
- Anyone who **uses illegal drugs**
- Anyone who **works with non-human primates infected with hepatitis A,** or who **works with hepatitis A in a research setting**
- Anyone with **chronic liver disease**
- Anyone with **clotting factor disorders**

Separately, hepatitis A vaccination may be considered for food handlers because of their potential to transmit the virus to others.

Hepatitis B Vaccine

Hepatitis B vaccines were added to the routine childhood immunization schedule in 1991, but are also recommended for adults who are at an increased risk for hepatitis B. This includes the following groups:

- Anyone **living with or having sex with a hepatitis B-infected person**
- Anyone having **sex with multiple partners**
- Anyone **seeking treatment for sexually transmitted diseases, HIV testing (or treatment), or drug treatment**
- **Men who have sex with men**
- Anyone who **uses illegal drugs**
- Anyone with a **job that involves direct contact with human blood**
- Anyone who **works in facilities for the developmentally disabled**
- Anyone who **receives hemodialysis** or has **end-stage kidney disease**
- Anyone who **has HIV**
- Anyone who **receives dialysis**
- Anyone with **chronic liver disease**
- Anyone who is a **prisoner in a correctional facility**
- Anyone who is **traveling to a country where the virus is common**

Measles, Mumps, and Rubella (MMR) Vaccine

Any adult born in the United States before 1957 is considered immune to both measles and mumps because the diseases were so widespread in the pre-vaccine era.

Individuals who were born after 1957 *may* need to receive booster shots or be revaccinated with MMR if they are members of one of the following groups:

- Anyone who is a **college student**
- Anyone who is a **health care worker**
- Anyone **traveling internationally** (particularly to countries with high rates of measles, mumps or rubella – a travel clinic can provide additional information)
- Anyone who **received the killed measles vaccine, or a measles vaccine of unknown type, from 1963 to 1967**. (The immunity provided by the killed vaccine was not adequate, and individuals immunized with this vaccine may not be protected against measles. Your doctor can provide more information.)
- **Women of childbearing age who want to become pregnant** and have no evidence of immunity against rubella

Chickenpox (varicella) Vaccine

The chickenpox vaccine was added to the recommended childhood immunization schedule in 1996, but is also recommended for adults with no evidence of chickenpox immunity.

Anyone born in the United States before 1980 is considered immune to chickenpox. (Note: health care workers and pregnant women born before 1980 are *not* considered immune for the purposes of determining whether the vaccine should be administered. Health care workers should receive the vaccine; pregnant women should receive the first dose of the vaccine *after* the completion of their pregnancies.)

Anyone born in 1980 or later should receive the varicella vaccine unless they can provide documentation of having received two doses of the vaccine at least one month apart, or of having had a case of chickenpox or herpes zoster diagnosed by a doctor and/or confirmed by a laboratory.

Shingles (zoster) Vaccine

The shingles vaccine is licensed by the Food and Drug Administration for individuals who are 50 years of age or older. The vaccine is recommended for **anyone who is 60 years of age or older**, even if they have reported a previous case of shingles.

Meningococcal Vaccine

Meningococcal disease includes a variety of illnesses caused by the bacterium, *Neisseria meningitidis.* Different types of meningococcal disease include meningococcal meningitis and meningococcemia (blood infection).

The meningococcal vaccine is recommended for adults based on a variety of risk factors. It is recommended for the following groups:

- Anyone who is a **member of the military**
- Anyone with a **damaged or removed spleen**
- Anyone doing **research that exposes him/her to** *Neisseria meningitidis*
- Anyone **traveling to a country where meningococcal disease is common**
- Anyone with **terminal complement deficiency**
- Anyone **starting college** who has not received a dose of the vaccine during the past five years

Travel Vaccines

In addition to the vaccines listed above, some of which are recommended if you are traveling to an area with a large number of cases of the diseases they prevent, other vaccines may be recommended if you are traveling internationally.

In addition, some vaccines may be **required** before you are allowed to enter a particular country or region. For example, if you are traveling to certain countries in tropical South America or sub-Saharan Africa, international health regulations require that you be vaccinated against yellow fever. (These requirements made national news in 2011, when the World Cup was held in South Africa. South Africa requires proof of yellow fever vaccination before issuing travel visas, and fans in Uganda, where there was a shortage of the vaccine, scrambled to be immunized in time to travel.)

Vaccines that may be recommended before traveling internationally, particularly to developing countries, include those against **typhoid**, **rabies**, and **Japanese encephalitis**. More information can be found on the Centers for Disease Control and Prevention's Travelers' Health website, where you can search by destination or locate a clinic that specializes in travel health. In addition to vaccines, travel medicine centers can advise on important issues such as the prevention of malaria and the prevention and potential treatment of travel related illnesses such as diarrhea.

Polio vaccine

Polio vaccines, are vaccines used to prevent poliomyelitis (polio).[1] One type uses inactivated poliovirus and is given by injection (IPV), while the other type uses weakened poliovirus and is given by mouth (OPV). The World Health Organization recommends all children be vaccinated against polio.[1] The two vaccines have eliminated polio from most of the world,[2][3] and reduced the number of cases each year from an estimated 350,000 in 1988 to 359 in 2014.[4]

The inactivated polio vaccines are very safe. Mild redness or pain may occur at the site of injection. Oral polio vaccines result in vaccine-associated paralytic poliomyelitis in about three per million doses. Both are generally safe to give during pregnancy and in those who have HIV/AIDS but are otherwise well.[1]

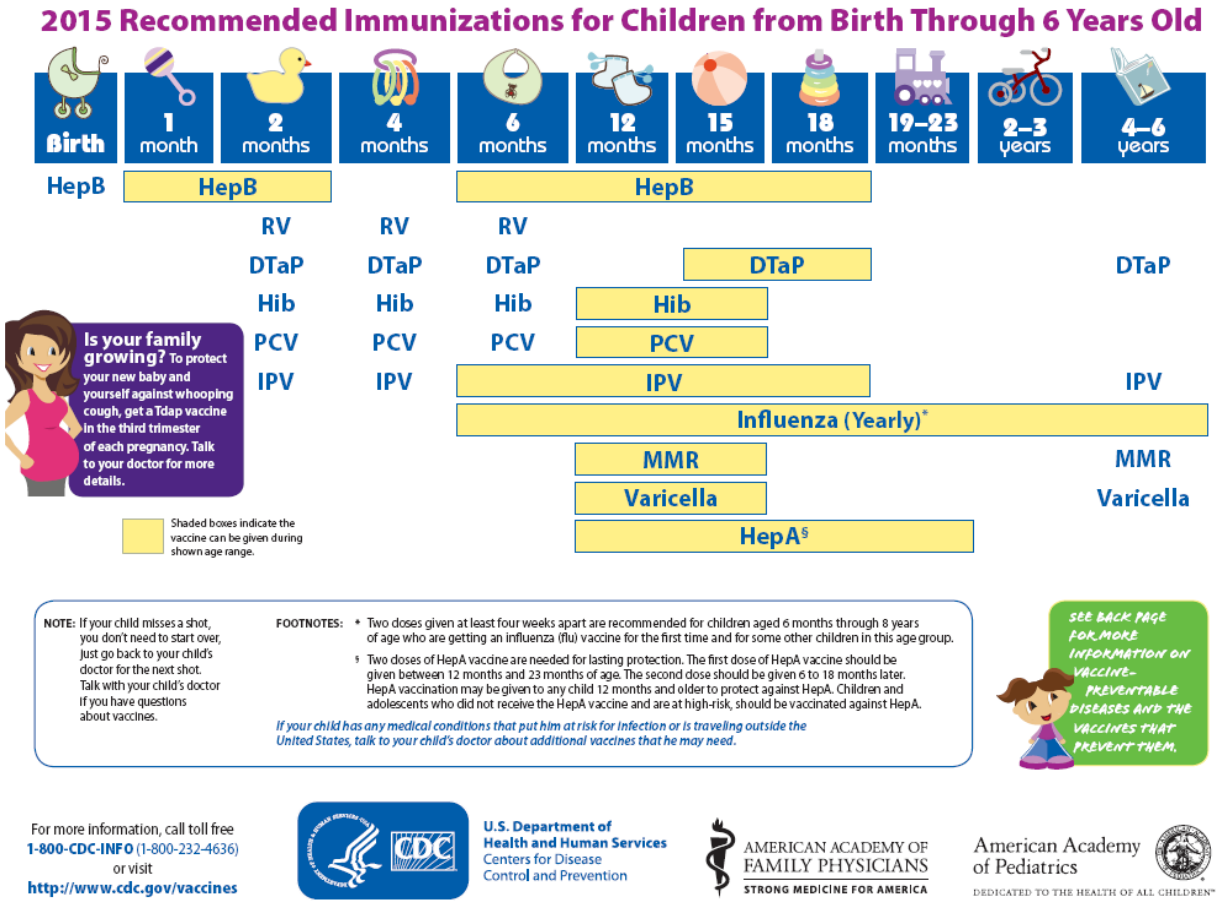
The first polio vaccine was the inactivated polio vaccine. It was developed by Jonas Salk and came into use in 1955.[1] The oral polio vaccine was developed by Albert Sabin and came into commercial use in 1961.[1][5] They are on the World Health Organization's List of Essential Medicines, the most important medication needed in a basic health system.[6] The wholesale cost is about 0.25 USD per dose for the oral form as of 2014.[7] In the United States it costs between 25 and 50 USD for the inactivated form.

Rabies vaccine

Rabies vaccine is a vaccine used to prevent rabies.[1] There are a number of vaccines available that are both safe and effective. They can be used to prevent rabies before and for a period of time after exposure to the virus such as by a dog or bat bite. The immunity that develops is long lasting after three doses. Doses are usually given by injection into the skin or muscle. After exposure vaccination is typically used along with rabies immunoglobulin. It is recommended that those who are at high risk of exposure be vaccinated before potential exposure. Vaccines are effective in humans and other animals. Vaccinating dogs is very effective in preventing the spread of rabies to humans.[1]

Rabies vaccines may be safely used in all age groups. About 35 to 45 percent of people develop a brief period of redness and pain at the injection site. About 5 to 15 percent of people may have fever, headaches, or nausea. After exposure to rabies there is no contraindication to its use. Most vaccines do not contain thimerosal. Vaccines made from nerve tissue are used in a few countries, mainly in Asia and Latin America, but are less effective and have greater side effects. Their use is thus not recommended by the World Health Organization.[1]

The first rabies vaccine was introduced in 1885, which was followed by an improved version in 1908.[2] Millions of people globally have been vaccinated and it is estimated that this saves more than 250,000 people a year.[1] It is on the World Health Organization's List of Essential Medicines, the most important medication recommended for a basic health system.[3] The wholesale cost is between 44 and 78 USD for a course of treatment as of 2014.[4] In the United States a course of rabies vaccine is more than 750 USD.[5]

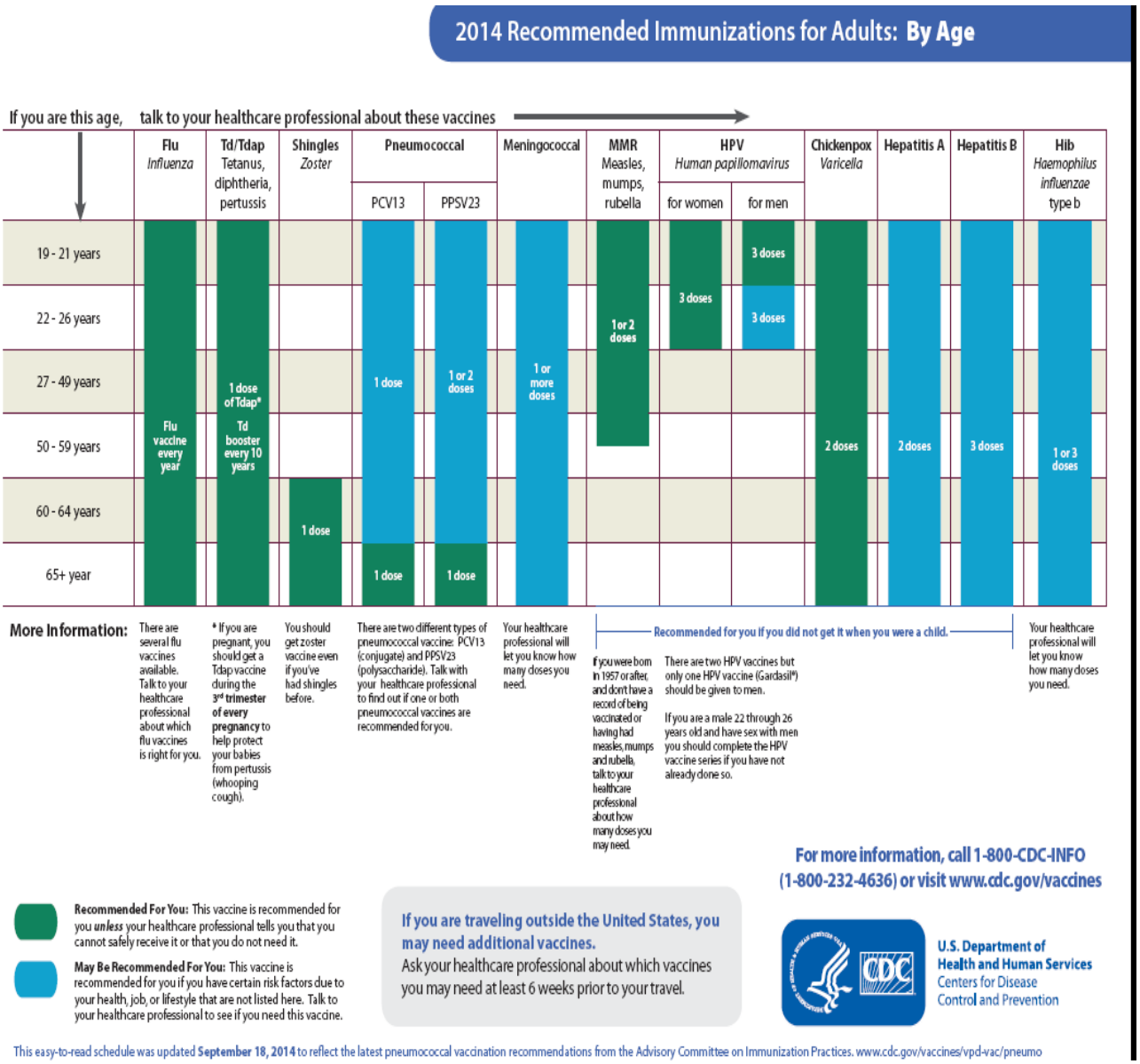


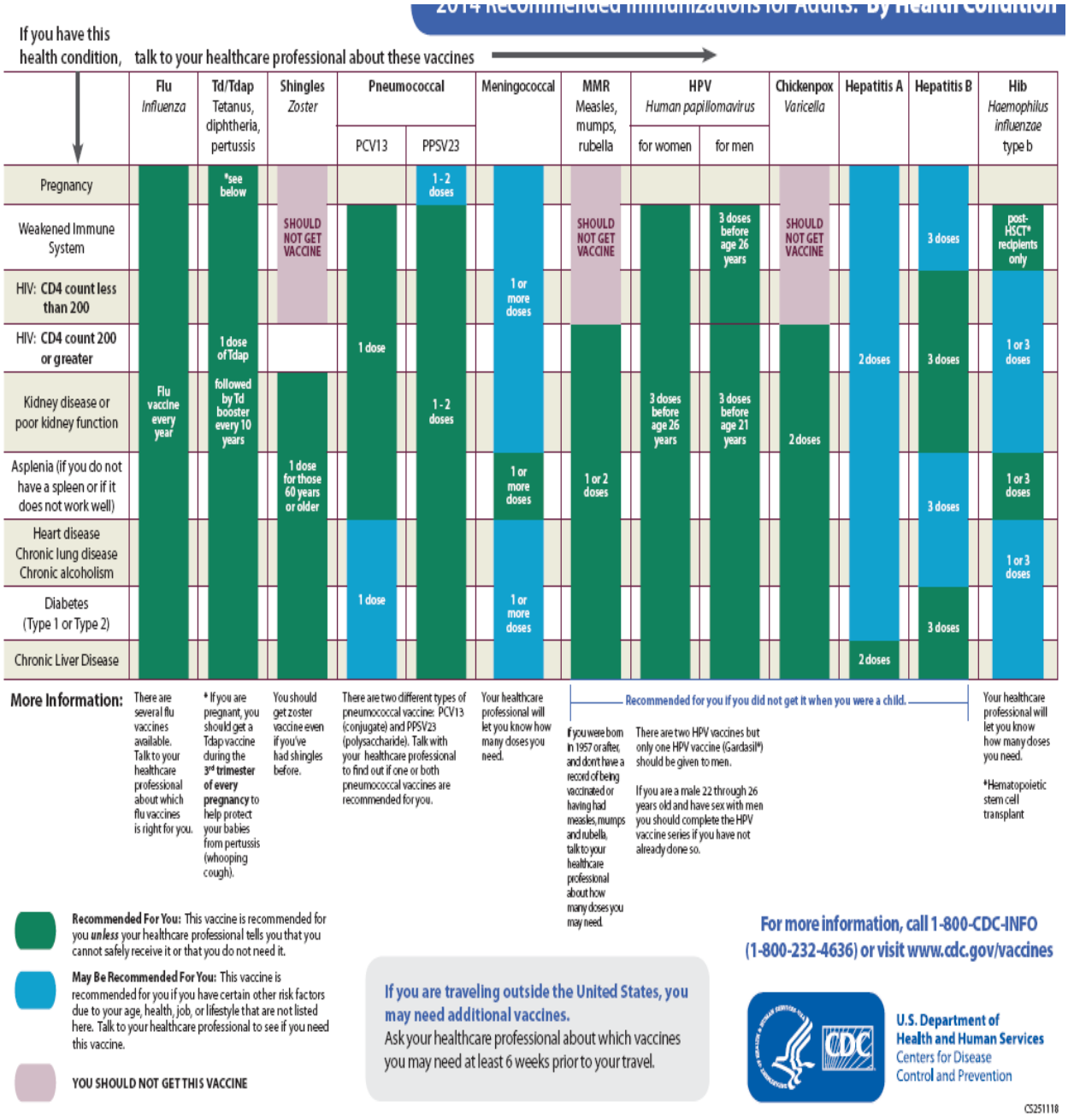
Vaccine-Preventable Diseases and the Vaccines that Prevent Them

Disease	Vaccine	Disease spread by	Disease symptoms	Disease complications
Chickenpox	Varicella vaccine protects against chickenpox.	Air, direct contact	Rash, tiredness, headache, fever	Infected blisters, bleeding disorders, encephalitis (brain swelling), pneumonia (infection in the lungs)
Diphtheria	DTaP* vaccine protects against diphtheria.	Air, direct contact	Sore throat, mild fever, weakness, swollen glands in neck	Swelling of the heart muscle, heart failure, coma, paralysis, death
Hib	Hib vaccine protects against *Haemophilus influenzae* type b.	Air, direct contact	May be no symptoms unless bacteria enter the blood	Meningitis (infection of the covering around the brain and spinal cord), intellectual disability, epiglottitis (life-threatening infection that can block the windpipe and lead to serious breathing problems), pneumonia (infection in the lungs), death
Hepatitis A	HepA vaccine protects against hepatitis A.	Direct contact, contaminated food or water	May be no symptoms, fever, stomach pain, loss of appetite, fatigue, vomiting, jaundice (yellowing of skin and eyes), dark urine	Liver failure, arthralgia (joint pain), kidney, pancreatic, and blood disorders
Hepatitis B	HepB vaccine protects against hepatitis B.	Contact with blood or body fluids	May be no symptoms, fever, headache, weakness, vomiting, jaundice (yellowing of skin and eyes), joint pain	Chronic liver infection, liver failure, liver cancer
Flu	Flu vaccine protects against influenza.	Air, direct contact	Fever, muscle pain, sore throat, cough, extreme fatigue	Pneumonia (infection in the lungs)
Measles	MMR** vaccine protects against measles.	Air, direct contact	Rash, fever, cough, runny nose, pinkeye	Encephalitis (brain swelling), pneumonia (infection in the lungs), death
Mumps	MMR**vaccine protects against mumps.	Air, direct contact	Swollen salivary glands (under the jaw), fever, headache, tiredness, muscle pain	Meningitis (infection of the covering around the brain and spinal cord) , encephalitis (brain swelling), inflammation of testicles or ovaries, deafness
Pertussis	DTaP* vaccine protects against pertussis (whooping cough).	Air, direct contact	Severe cough, runny nose, apnea (a pause in breathing in infants)	Pneumonia (infection in the lungs), death
Polio	IPV vaccine protects against polio.	Air, direct contact, through the mouth	May be no symptoms, sore throat, fever, nausea, headache	Paralysis, death
Pneumococcal	PCV vaccine protects against pneumococcus.	Air, direct contact	May be no symptoms, pneumonia (infection in the lungs)	Bacteremia (blood infection), meningitis (infection of the covering around the brain and spinal cord), death
Rotavirus	RV vaccine protects against rotavirus.	Through the mouth	Diarrhea, fever, vomiting	Severe diarrhea, dehydration
Rubella	MMR** vaccine protects against rubella.	Air, direct contact	Children infected with rubella virus sometimes have a rash, fever, swollen lymph nodes	Very serious in pregnant women—can lead to miscarriage, stillbirth, premature delivery, birth defects
Tetanus	DTaP* vaccine protects against tetanus.	Exposure through cuts in skin	Stiffness in neck and abdominal muscles, difficulty swallowing, muscle spasms, fever	Broken bones, breathing difficulty, death

* DTaP combines protection against diphtheria, tetanus, and pertussis.
** MMR combines protection against measles, mumps, and rubella.

Last updated January 26, 2015 - CS245366-A -


2014 Recommended Immunizations for Adults: By Age
If you are this age, talk to your healthcare professional about these vaccines
Flu Influenza
Td/Tdap Tetanus, diphtheria, pertussis
Shingles Zoster
Pneumococcal
PCV13
PPSV23
Meningococcal
MMR Measles, mumps, rubella
HPV Human papillomavirus
for women
for men
Chickenpox Varicella
Hepatitis A
Hepatitis B
Hib Haemophilus influenzae type b
19 - 21 years
22 - 26 years
27 - 49 years
50 - 59 years
60 - 64 years
65+ year
Flu vaccine every year
1 dose of Tdap*
Td booster every 10 years
1 dose
1 dose
1 or 2 doses
1 dose
1 or more doses
1 or 2 doses
3 doses
3 doses
2 doses
2 doses
3 doses
1 or 3 doses
More Information:
There are several flu vaccines available. Talk to your healthcare professional about which flu vaccines is right for you.
* If you are pregnant, you should get a Tdap vaccine during the 3rd trimester of every pregnancy to help protect your babies from pertussis (whooping cough).
You should get zoster vaccine even if you've had shingles before.
There are two different types of pneumococcal vaccine: PCV13 (conjugate) and PPSV23 (polysaccharide). Talk with your healthcare professional to find out if one or both pneumococcal vaccines are recommended for you.
Your healthcare professional will let you know how many doses you need.
Recommended for you if you did not get it when you were a child.
If you were born in 1957 or after, and don't have a record of being vaccinated or having had measles, mumps and rubella, talk to your healthcare professional about how many doses you may need.
There are two HPV vaccines but only one HPV vaccine (Gardasil®) should be given to men.
If you are a male 22 through 26 years old and have sex with men you should complete the HPV vaccine series if you have not already done so.
Your healthcare professional will let you know how many doses you need.
For more information, call 1-800-CDC-INFO (1-800-232-4636) or visit www.cdc.gov/vaccines
Recommended For You: This vaccine is recommended for you unless your healthcare professional tells you that you cannot safely receive it or that you do not need it.
May Be Recommended For You: This vaccine is recommended for you if you have certain risk factors due to your health, job, or lifestyle that are not listed here. Talk to your healthcare professional to see if you need this vaccine.
If you are traveling outside the United States, you may need additional vaccines.
Ask your healthcare professional about which vaccines you may need at least 6 weeks prior to your travel.
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
This easy-to-read schedule was updated September 18, 2014 to reflect the latest pneumococcal vaccination recommendations from the Advisory Committee on Immunization Practices. www.cdc.gov/vaccines/vpd-vac/pneumo


2014 Recommended Immunizations for Adults: By Health Condition
If you have this health condition, talk to your healthcare professional about these vaccines
Flu Influenza
Td/Tdap Tetanus, diphtheria, pertussis
Shingles Zoster
Pneumococcal
PCV13
PPSV23
Meningococcal
MMR Measles, mumps, rubella
HPV Human papillomavirus
for women
for men
Chickenpox Varicella
Hepatitis A
Hepatitis B
Hib Haemophilus influenzae type b
Pregnancy
*see below
1 - 2 doses
Weakened Immune System
SHOULD NOT GET VACCINE
1 dose
1 - 2 doses
1 or more doses
SHOULD NOT GET VACCINE
3 doses before age 26 years
SHOULD NOT GET VACCINE
3 doses
post-HSCT* recipients only
HIV: CD4 count less than 200
HIV: CD4 count 200 or greater
1 dose of Tdap
2 doses
3 doses
1 or 3 doses
Kidney disease or poor kidney function
Flu vaccine every year
followed by Td booster every 10 years
3 doses before age 26 years
3 doses before age 21 years
2 doses
Asplenia (if you do not have a spleen or if it does not work well)
1 dose for those 60 years or older
1 or more doses
1 or 2 doses
3 doses
1 or 3 doses
Heart disease Chronic lung disease Chronic alcoholism
1 dose
1 or 3 doses
Diabetes (Type 1 or Type 2)
1 or more doses
3 doses
Chronic Liver Disease
2 doses
More Information:
There are several flu vaccines available. Talk to your healthcare professional about which flu vaccines is right for you.
* If you are pregnant, you should get a Tdap vaccine during the 3rd trimester of every pregnancy to help protect your babies from pertussis (whooping cough).
You should get zoster vaccine even if you've had shingles before.
There are two different types of pneumococcal vaccine: PCV13 (conjugate) and PPSV23 (polysaccharide). Talk with your healthcare professional to find out if one or both pneumococcal vaccines are recommended for you.
Your healthcare professional will let you know how many doses you need.
Recommended for you if you did not get it when you were a child.
If you were born in 1957 or after, and don't have a record of being vaccinated or having had measles, mumps and rubella, talk to your healthcare professional about how many doses you may need.
There are two HPV vaccines but only one HPV vaccine (Gardasil®) should be given to men.
If you are a male 22 through 26 years old and have sex with men you should complete the HPV vaccine series if you have not already done so.
Your healthcare professional will let you know how many doses you need.
*Hematopoietic stem cell transplant
Recommended For You: This vaccine is recommended for you unless your healthcare professional tells you that you cannot safely receive it or that you do not need it.
May Be Recommended For You: This vaccine is recommended for you if you have certain other risk factors due to your age, health, job, or lifestyle that are not listed here. Talk to your healthcare professional to see if you need this vaccine.
YOU SHOULD NOT GET THIS VACCINE
If you are traveling outside the United States, you may need additional vaccines.
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U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
CS251118

Bioterrorism

Bioterrorism is terrorism involving the intentional release or dissemination of biological agents. These agents are bacteria, viruses, or toxins, and may be in a naturally occurring or a human-modified form. For the use of this method in warfare, see biological warfare.

According to the U.S. Centers for Disease Control and Prevention a *bioterrorism* attack is the deliberate release of viruses, bacteria, toxins or other harmful agents used to cause illness or death in people, animals, or plants. These agents are typically found in nature, but it is possible that they could be mutated or altered to increase their ability to cause disease, make them resistant to current medicines, or to increase their ability to be spread into the environment. Biological agents can be spread through the air, water, or in food. Terrorists tend to use biological agents because they are extremely difficult to detect and do not cause illness for several hours to several days. Some bioterrorism agents, like the smallpox virus, can be spread from person to person and some, like anthrax, cannot.[1]

Bioterrorism is an attractive weapon because biological agents are relatively easy and inexpensive to obtain, can be easily disseminated, and can cause widespread fear and panic beyond the actual physical damage.[2] Military leaders, however, have learned that, as a military asset, bioterrorism has some important limitations; it is difficult to employ a bioweapon in a way that only the enemy is affected and not friendly forces. A biological weapon is useful to terrorists mainly as a method of creating mass panic and disruption to a state or a country. However, technologists such as Bill Joy have warned of the potential power which genetic engineering might place in the hands of future bio-terrorists.[3]

The use of agents that do not cause harm to humans but disrupt the economy have been discussed.[*citation needed*] A highly relevant pathogen in this context is the foot-and-mouth disease (FMD) virus, which is capable of causing widespread economic damage and public concern (as witnessed in the 2001 and 2007 FMD outbreaks in the UK), whilst having almost no capacity to infect humans.

History

20th century

By the time World War I began, attempts to use anthrax were directed at animal populations. This generally proved to be ineffective. Shortly after the start of World War I, Germany launched a biological sabotage campaign in the United States, Russia, Romania, and France.[4] At that time, Anton Dilger lived in Germany, but in 1915 he was sent to the United States carrying cultures of glanders, a virulent disease of horses and mules. Dilger set up a laboratory in his home in Chevy Chase, Maryland. He used stevedores working the docks in Baltimore to infect horses with glanders while they were waiting to be shipped to Britain. Dilger was under suspicion as being a German agent, but was never arrested. Dilger eventually fled to Madrid, Spain, where he died during the Influenza Pandemic of 1918.[5] In 1916, the Russians arrested a German agent with similar intentions. Germany and its allies infected French cavalry horses and many of Russia's mules and horses on the Eastern Front. These actions hindered artillery and troop movements, as well as supply convoys.[4]

In 1972 police in Chicago arrested two college students, Allen Schwander and Stephen Pera, who had planned to poison the city's water supply with typhoid and other bacteria. Schwander had founded a terrorist group, "R.I.S.E.", while Pera collected and grew cultures from the hospital where he worked. The two men fled to Cuba after being released on bail. Schwander died of natural causes in 1974, while Pera returned to the U.S. in 1975 and was put on probation.[6]

1984 Rajneeshee bioterror attack: In Oregon in 1984, followers of the Bhagwan Shree Rajneesh attempted to control a local election by incapacitating the local population. This was done by infecting salad bars in 11 restaurants, produce in grocery stores, doorknobs, and other public domains with *Salmonella typhimurium* bacteria in the city of The Dalles, Oregon. The attack infected 751 people with severe food poisoning. There were no fatalities. This incident was the first known bioterrorist attack in the United States in the 20th century.[7]

Aum Shinrikyo anthrax release in Kameido : In June 1993 the religious group Aum Shinrikyo released anthrax in Tokyo. Eyewitnesses reported a foul odor. The attack was a total failure, infecting not a single person. The reason for this, ironically, is that the group used the vaccine strain of the bacterium. The spores recovered from the attack showed that they were identical to an anthrax vaccine strain given to animals at the time. These vaccine strains are missing the genes that cause a symptomatic response.[8]

21st century

2001 - USA and Chile - Anthrax Attacks: In September and October 2001, several cases of anthrax broke out in the United States in the 2001 anthrax attacks, apparently caused deliberately. Letters laced with infectious anthrax were concurrently delivered to news media offices and the U.S Congress, alongside an ambiguously related case in Chile. The letters killed 5.CNN

Types of agents

Under current United States law, bio-agents which have been declared by the U.S. Department of Health and Human Services or the U.S. Department of Agriculture to have the "potential to pose a severe threat to public health and safety" are officially defined as "select agents". The CDC categorizes these agents (A, B or C) and administers the Select Agent Program, which regulates the laboratories which may possess, use, or transfer select agents within the United States. As with US attempts to categorize harmful recreational drugs, designer viruses are not yet categorized and avian H5N1 has been shown to achieve high mortality and human-communication in a laboratory setting.

Category A

These high-priority agents pose a risk to national security, can be easily transmitted and disseminated, result in high mortality, have potential major public health impact, may cause public panic, or require special action for public health preparedness.

Tularemia or "rabbit fever"

[9] has a very low fatality rate if treated, but can severely incapacitate. The disease is caused by the *Francisella tularensis* bacterium, and can be contracted through contact with the fur, inhalation, ingestion of contaminated water or insect bites. *Francisella tularensis* is very infectious. A small number (10–50 or so organisms) can cause disease. If *F. tularensis* were used as a weapon, the bacteria would likely be made airborne for exposure by inhalation. People who inhale an infectious aerosol would generally experience severe respiratory illness, including life-threatening pneumonia and systemic infection, if they are not treated. The bacteria that cause tularemia occur widely in nature and could be isolated and grown in quantity in a laboratory, although manufacturing an effective aerosol weapon would require considerable sophistication.[10]

Anthrax

Anthrax is a non-contagious disease caused by the spore-forming bacterium *Bacillus anthracis*. An anthrax vaccine does exist but requires many injections for stable use. When discovered early, anthrax can be cured by administering antibiotics (such as ciprofloxacin).[11] Its first modern incidence in biological warfare were when Scandinavian "freedom fighters" supplied by the German General Staff used anthrax with unknown results against the Imperial Russian Army in Finland in 1916.[12] In 1993, the Aum Shinrikyo used anthrax in an unsuccessful attempt in Tokyo with zero fatalities.[8] Anthrax was used in a series of attacks on the offices of several United States Senators in late 2001. The anthrax was in a powder form and it was delivered by the mail.[13] Anthrax is one of the few biological agents that federal employees have been vaccinated for. The strain used in the 2001 anthrax attack was identical to the strain used by the USAMRIID.[14]

Smallpox

[15] Smallpox is a highly contagious virus. It is transmitted easily through the atmosphere and has a high mortality rate (20–40%). Smallpox was eradicated in the world in the 1970s, thanks to a worldwide vaccination program.[16] However, some virus samples are still available in Russian and American laboratories. Some believe that after the collapse of the Soviet Union, cultures of smallpox have become available in other countries. Although people born pre-1970 will have been vaccinated for smallpox under the WHO program, the effectiveness of vaccination is limited since the vaccine provides high level of immunity for only 3 to 5 years. Revaccination's protection lasts longer.[17] As a biological weapon smallpox is dangerous because of the highly contagious nature of both the infected and their pox. Also, the infrequency with which vaccines are administered among the general population since the eradication of the disease would leave most people unprotected in the event of an outbreak. Smallpox occurs only in humans, and has no external hosts or vectors.

Botulinum toxin

[18] The neurotoxin [19] Botulinum is one of the deadliest toxins known, and is produced by the bacterium *Clostridium botulinum*. Botulism causes death by respiratory failure and paralysis.[20] Furthermore, the toxin is readily available worldwide due to its cosmetic applications in injections.

Bubonic plague

[21] Plague is a disease caused by the *Yersinia pestis* bacterium. Rodents are the normal host of plague, and the disease is transmitted to humans by flea bites and occasionally by aerosol in the form of pneumonic plague.[22] The disease has a history of use in biological warfare dating back many centuries, and is considered a threat due to its ease of culture and ability to remain in circulation among local rodents for a long period of time. The weaponized threat comes mainly in the form of pneumonic plague (infection by inhalation)[23] It was the disease that caused the Black Death in Medieval Europe.

Viral hemorrhagic fevers

[24] This includes hemorrhagic fevers caused by members of the family *Filoviridae* (Marburg virus and Ebola virus), and by the family *Arenaviridae* (for example Lassa virus and Machupo virus). Ebola virus disease, in particular, has caused high fatality rates ranging from 25–90% with a 50% average. No cure currently exists, although vaccines are in development. The Soviet Union investigated the use of filoviruses for biological warfare, and the Aum Shinrikyo group unsuccessfully attempted to obtain cultures of Ebola virus.[*citation needed*] Death from Ebola virus disease is commonly due to multiple organ failure and hypovolemic shock. Marburg virus was first discovered in Marburg, Germany. No treatments currently exist aside from supportive care. The arenaviruses have a somewhat reduced case-fatality rate compared to disease caused by filoviruses, but are more widely distributed, chiefly in central Africa and South America.

Category B

Category B agents are moderately easy to disseminate and have low mortality rates.

- Brucellosis (*Brucella* species)[25]
- Epsilon toxin of *Clostridium perfringens*
- Food safety threats (for example, *Salmonella species*, *E coli* O157:H7, *Shigella*, Staphylococcus aureus*)*
- Glanders[26] (*Burkholderia mallei*)
- Melioidosis (*Burkholderia pseudomallei*)[27][28]
- Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)[29]
- Ricin[30] toxin from *Ricinus communis* (castor beans)

- Abrin toxin from *Abrus precatorius* (Rosary peas)
- Staphylococcal enterotoxin B
- Typhus (*Rickettsia prowazekii*)
- Viral encephalitis (alphaviruses, for example,: Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis)
- Water supply threats (for example, *Vibrio cholerae*,[31] *Cryptosporidium parvum*)

Category C

Category C agents are emerging pathogens that might be engineered for mass dissemination because of their availability, ease of production and dissemination, high mortality rate, or ability to cause a major health impact.

- Nipah virus
- Hantavirus
- SARS
- H1N1 (a strain of influenza)
- HIV/AIDS

Biofilm - Quorum sensing

Quorum sensing is a system of stimuli and response correlated to population density. Many species of bacteria use quorum sensing to coordinate gene expression according to the density of their local population. In similar fashion, some social insects use quorum sensing to determine where to nest. In addition to its function in biological systems, quorum sensing has several useful applications for computing and robotics.

Quorum sensing can function as a decision-making process in any decentralized system, as long as individual components have: (a) a means of assessing the number of other components they interact with and (b) a standard response once a threshold number of components is detected.

Bacteria

Some of the best-known examples of quorum sensing come from studies of bacteria. Bacteria use quorum sensing to coordinate certain behaviors such as biofilm formation, virulence, and antibiotic resistance, based on the local density of the bacterial population. Quorum sensing can occur within a single bacterial species as well as between diverse species, and can regulate a host of different processes, in essence, serving as a simple indicator of population density or the diffusion rate of the cell's immediate environment. A variety of different molecules can be used as signals. Common classes of signaling molecules are oligopeptides in Gram-positive bacteria, N-Acyl Homoserine Lactones (AHL) in Gram-negative bacteria, and a family of autoinducers known as autoinducer-2 (AI-2) in both Gram-negative and Gram-positive bacteria.[1]

Mechanism

Bacteria that use quorum sensing constitutively produce and secrete certain signaling molecules (called *autoinducers* or *pheromones*). These bacteria also have a receptor that can specifically detect the signaling molecule (inducer). When the inducer binds the receptor, it activates transcription of certain genes, including those for inducer synthesis. There is a low likelihood of a bacterium detecting its own secreted inducer. Thus, in order for gene transcription to be activated, the cell must encounter signaling molecules secreted by other cells in its environment. When only a few other bacteria of the same kind are in the vicinity, diffusion reduces the concentration of the inducer in the surrounding medium to almost zero, so the bacteria produce little inducer. However, as the population grows, the concentration of the inducer passes a threshold, causing more inducer to be synthesized. This forms a positive feedback loop, and the receptor becomes fully activated. Activation of the receptor induces the up-regulation of other specific genes, causing all of the cells to begin transcription at approximately the same time. This coordinated behavior of bacterial cells can be useful in a variety of situations. For instance, the bioluminescent luciferase produced by *Vibrio fischeri* would not be visible if it were produced by a single cell. By using quorum sensing to limit the production of luciferase to situations when cell populations are large, *V. fischeri* cells are able to avoid wasting energy on the production of useless product.

Aliivibrio fischeri

Quorum sensing was first observed in *Aliivibrio fischeri*, a bioluminescent bacterium that lives as a mutualistic symbiont in the photophore (or light-producing organ) of the Hawaiian bobtail squid.[2] When *A. fischeri* cells are free-living (or planktonic), the autoinducer is at low concentration, and, thus, cells do not luminesce. However, when they are highly concentrated in the photophore (about 10^{11} cells/ml), transcription of luciferase is induced, leading to bioluminescence.

Escherichia coli

In the Gram-negative bacterium *Escherichia coli* (*E. coli*), cell division may be partially regulated by AI-2-mediated quorum sensing. This species uses AI-2, which is produced and processed by the *lsr* operon. Part of it encodes an ABC transporter, which imports AI-2 into the cells during the early stationary (latent) phase of growth. AI-2 is then phosphorylated by the LsrK kinase, and the newly produced phospho-AI-2 can be either internalized or used to suppress LsrR, a repressor of the *lsr* operon (thereby activating the operon). Transcription of the *lsr* operon is also thought to be inhibited by dihydroxyacetone phosphate (DHAP) through its competitive binding to LsrR. Glyceraldehyde 3-phosphate has also been shown to inhibit the *lsr* operon through cAMP-CAPK-mediated inhibition. This explains why, when grown with glucose, *E. coli* will lose the ability to internalize AI-2 (because of catabolite repression). When grown normally, AI-2 presence is transient.

E. coli and *Salmonella enterica* do not produce AHL signals commonly found in other Gram-negative bacteria. However, they have a receptor that detects AHLs from other bacteria and change their gene expression in accordance with the presence of other "quorate" populations of Gram-negative bacteria.[3]

Salmonella enterica

Salmonella encodes a LuxR homolog, SdiA, but does not encode an AHL synthase. SdiA detects AHLs produced by other species of bacteria including *Aeromonas hydrophila*, *Hafnia alvei*, and *Yersinia enterocolitica*.[4] When AHL is detected, SdiA regulates the *rck* operon on the *Salmonella* virulence plasmid (*pefI-srgD-srgA-srgB-rck-srgC*) and a single gene horizontal acquisition in the chromosome *srgE*.[5][6] *Salmonella* does not detect AHL when passing through the gastrointestinal tracts of several animal species, suggesting that the normal microbiota does not produce AHLs. However, SdiA does become activated when *Salmonella* transits through turtles colonized with *Aeromonas hydrophila* or mice infected with *Yersinia enterocolitica*.[7][8] Therefore, *Salmonella* appears to use SdiA to detect the AHL production of other pathogens rather than the normal gut flora.

Pseudomonas aeruginosa

The opportunistic pathogen *Pseudomonas aeruginosa* uses quorum sensing to coordinate the formation of biofilms, swarming motility, exopolysaccharide production, virulence, and cell aggregation.[9] These bacteria can grow within a host without harming it, until they reach a threshold concentration. Then they become aggressive, developing to the point at which their numbers are sufficient to overcome the host's immune system, and form a biofilm, leading to disease within the host as the biofilm is a protective layer encasing the bacteria population. Another form of gene regulation that allows the bacteria to rapidly adapt to surrounding changes is through environmental signaling. Recent studies have discovered that anaerobiosis can significantly impact the major regulatory circuit of quorum sensing. This important link between quorum sensing and anaerobiosis has a significant impact on production of virulence factors of this organism.[10] Garlic and ginseng experimentally block quorum sensing in *Pseudomonas aeruginosa*.[11] It is hoped that the therapeutic enzymatic degradation of the signaling molecules will prevent the formation of such biofilms and possibly weaken established biofilms. Disrupting the signalling process in this way is called *quorum sensing inhibition*.

Acinetobacter *sp.*

It has recently been found that *Acinetobacter* sp. also show quorum sensing activity. This bacterium, an emerging pathogen, produces AHLs.[12] Interestingly, *Acinetobacter* sp. shows both quorum sensing and quorum quenching activity. It produces AHLs and also, it can degrade the AHL molecules as well.[12]

Aeromonas *sp.*

This bacterium was previously considered a fish pathogen, but it has recently emerged as a human pathogen.[13] *Aeromonas* sp. have been isolated from various infected sites from patients (bile, blood, peritoneal fluid, pus, stool and urine). All isolates produced the two principal AHLs, N-butanoylhomoserine lactone (C4-HSL) and N-hexanoyl homoserine lactone (C6-HSL). It has been documented that Aeromonas sobria has produced C6-HSL and two additional AHLs with N-acyl side chain longer than C6.[14]

Yersinia

The YenR and YenI proteins produced by the gammaproteobacterium *Yersinia enterocolitica* are similar to *Aliivibrio fischeri* LuxR and LuxI.[15][16] YenR activates the expression of a small non-coding RNA, YenS. YenS inhibits YenI expression and acylhomoserine lactone production.[17] YenR/YenI/YenS are involved in the control of swimming and swarming motility.[16][17]

Molecules involved in quorum sensing

Three-dimensional structures of proteins involved in quorum sensing were first published in 2001, when the crystal structures of three LuxS orthologs were determined by X-ray crystallography.[18] In 2002, the crystal structure of the receptor LuxP of *Vibrio harveyi* with its inducer AI-2 (which is one of the few biomolecules containing boron) bound to it was also determined.[19] Many bacterial species, including *E. coli*, an enteric bacterium and model organism for Gram-negative bacteria, produce AI-2. A comparative genomic and phylogenetic analysis of 138 genomes of bacteria, archaea, and eukaryotes found that "the LuxS enzyme required for AI-2 synthesis is widespread in bacteria, while the periplasmic binding protein LuxP is present only in Vibrio strains," leading to the conclusion that either "other organisms may use components different from the AI-2 signal transduction system of Vibrio strains to sense the signal of AI-2 or they do not have such a quorum sensing system at all."[20]

A database of quorum-sensing peptides is available under the name Quorumpeps.[21][22]

Certain bacteria can produce enzymes called lactonases that can target and inactivate AHLs. Researchers have developed novel molecules which block the signalling receptors of bacteria. mBTL is a compound that has been shown to inhibit quorum sensing and decrease the amount of cell death by a significant amount.[23] Additionally, researchers are also examining the role of natural compounds (such as caffeine) as potential quorum sensing inhibitors.[24] Research in this area has been promising and could lead to the development of natural compounds as effective therapeutics.

Quorum sensing

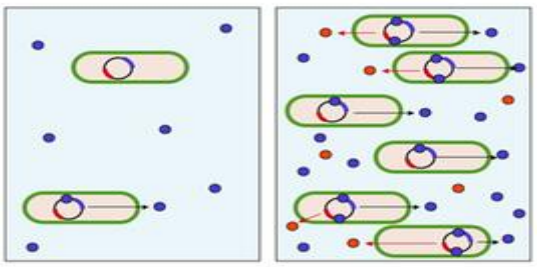

Figure 3: **Diagram of quorum sensing**. (left) In low density, the concentration of the autoinducer (blue dots) is relatively low and the substance production is restricted. (right) In high density, the concentration of the autoinducer is high and the bacterial substances (red dots) are produced.

The integration of cooperative and communicative interactions appear to be extremely important to microbes; for example, 6–10% of all genes in the bacterium *Pseudomonas aeruginosa* are controlled

by cell-cell signaling systems.[17] One way that microbes communicate and organize with each other in order to partake in more advanced cooperative interactions is through quorum sensing. Quorum sensing describes the phenomenon in which the accumulation of signaling molecules in the surrounding environment enables a single cell to assess the number of individuals (cell density) so that the population as a whole can make a coordinated response. This interaction is fairly common among bacterial taxa, and involves the secretion by individual cells of 'signaling' molecules. called autoinducers or pheromones.These bacteria also have a receptor that can specifically detect the signaling molecule. When the inducer binds the receptor, it activates transcription of certain genes, including those for inducer synthesis. There is a low likelihood of a bacterium detecting its own secreted inducer. Thus, in order for gene transcription to be activated, the cell must encounter signaling molecules secreted by other cells in its environment. When only a few other bacteria of the same kind are in the vicinity, diffusion reduces the concentration of the inducer in the surrounding medium to almost zero, so the bacteria produce little inducer. However, as the population grows the concentration of the inducer passes a threshold, causing more inducer to be synthesized. This forms a positive feedback loop, and the receptor becomes fully activated. Activation of the receptor induces the up regulation of other specific genes, causing all of the cells to begin transcription at approximately the same time. In other words, when the local concentration of these molecules has reached a threshold, the cells respond by switching on particular genes. In this way individual cells can sense the local density of bacteria, so that the population as a whole can make a coordinated response.[18]

In many situations, the cost bacterial cells pay in order to coordinate behaviors outweighs the benefits unless there is a sufficient number of collaborators. For instance, the bioluminescent luciferase produced by *Vibrio fischeri* would not be visible if it was produced by a single cell. By using quorum sensing to limit the production of luciferase to situations when cell populations are large, *V. fischeri* cells are able to avoid wasting energy on the production of useless product. In many situations bacterial activities, such as the production of the mentioned public goods, are only worthwhile as a joint activity by a sufficient number of collaborators. Regulation by quorum sensing would allow the cells to express appropriate behavior only when it is effective, thus saving resources under low density conditions. Therefore, quorum sensing has been interpreted as a bacterial communication system to coordinate behaviors at the population level.

The opportunistic bacteria *Pseudomonas aeruginosa* also uses quorum sensing to coordinate the formation of biofilms, swarming motility, exopolysaccharideproduction, and cell aggregation.[19] These bacteria can grow within a host without harming it, until they reach a certain concentration. Then they become aggressive, their numbers sufficient to overcome the host's immune system, and form a biofilm, leading to disease within the host. Another form of gene regulation that allows the bacteria to rapidly adapt to surrounding changes is through environmental signaling. Recent studies have discovered that anaerobiosis can significantly impact the major regulatory circuit of quorum sensing. This important link between quorum sensing and anaerobiosis has a significant impact on production of virulence factors of this organism.[20] It is hoped that the therapeutic enzymatic degradation of the signaling molecules will prevent the formation of such biofilms and possibly weaken established biofilms. Disrupting the signalling process in this way is called quorum inhibition.

Implications

The advantage of the Colonial Theory hypothesis is that it has been seen to occur independently numerous times (in 16 different protoctistan phyla). For instance, during food shortages *Dictyostelium discoideum* cells group together in a colony that moves as one to a new location. Some of these cells then slightly differentiate from each other. Other examples of colonial organisation in protozoa are Volvocaceae, such as Eudorina and Volvox. However, it can often be hard to separate colonial protists from true multicellular organisms, as the two concepts are not distinct. This problem plagues most hypotheses of how multicellularisation could have occurred. However, most scientists accept that multicellular organisms, from all phyla, evolved by the colonial mechanism.