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Biological Basis of Infectious Disease Epidemiology

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> When a physician is called to work in a place, his first problem is to study the hygienic potentialities which affect the state of health of the inhabitants. It is, in fact, these hygienic conditions which contribute towards the development and frequency of some diseases and the improbability and rarity of others, and which more or less modify the symptoms of every disease.
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> —Peter Ludwig Panum
> Observations made during the epidemic of measles on the Faroe Islands in the year 1846

An understanding of infectious disease epidemiology cannot be distilled to a discussion of an infectious agent inflicting disease on susceptible human hosts. Although understanding infectious pathogens is important, other factors involving the host and the environment contribute to the transmission of infectious agents, disease production, and the outcome of an infection. Infection represents a complex interplay between host factors, characteristics of the infectious agent, and environmental influences. This complex interaction has been modeled as a triangle (Jackson 1996) (Fig. 1–1), a wheel (Fig. 1–2, Jackson 1996), a tetrahedron (Fig. 1–3) (Rothenberg 1990), or a chain (Fig. 1–4) (Jackson 1996). Regardless of which model one uses to describe the interaction of humans with infectious agents and their environment, a person's state of health represents a dynamic equilibrium—a balance of forces.

This chapter reviews the important biologic factors relevant to the study of infectious disease epidemiology. Readers interested in a more detailed description of the following topics are referred to several excellent volumes on basic microbiology (Murray 1999), clinical infectious diseases (Reese 1996, Evans 1997, Evans 1998, Feigin 1998, Mandell 2000), and immunology (Paul 1999). *The Control of Communicable Diseases Manual*, published by the American Public Health Association, provides a brief description of the major infectious diseases with an emphasis on prevention and control measures (Chin 2000).

CHAIN OF INFECTION

In order for infection to occur, a chain of events must take place (Tables 1–1 and 1–2). First, there must be a susceptible host. Although people live in a sea of microorganisms, they generally stay healthy because of nonspecific (intrinsic) and specific host defenses (see Chapter 2). Second, an infectious agent capable of causing infection must be present. Third, the pathogenic microorganism must have a reservoir where it can propagate (i.e., live, reproduce, and die in the natural state). Potential reservoirs

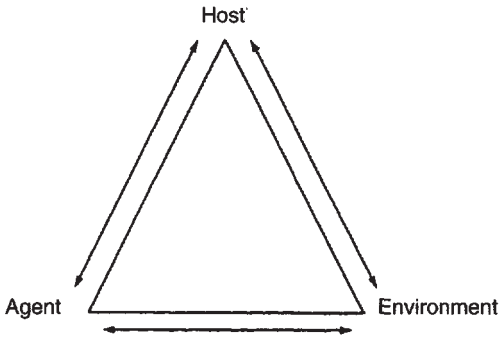

Figure 1–1. Triangle model of infectious diseases.
Source: Adapted from Jackson 1996.

include humans, animals, and the environment. Fourth, there must be portal of exit from the reservoir and portal of entry into a susceptible host. The portals of exit from a human or animal reservoir are the respiratory tract, the genitourinary tract, the gastrointestinal tract, skin and mucous membranes, transplacental (i.e., mother to fetus), and blood. Microbes gain entrance via these same portals, although blood-borne transmission requires percutaneous injury or mucous membrane contamination. As illustrated in Table 1–1, the route of agent shedding often predicts the portal of entry to the subsequent host. Some agents only cause disease when presented to the host by specific means. *Shigella dysentery*, which causes severe diarrhea, must be ingested; other agents such as *Staphylococcus aureus* can cause disease via multiple portals of entry, including respiratory tract (pneumonia), skin (furuncle), gastrointestinal tract (food poisoning), and blood (bacteremia). Fifth, an organism must be transmitted, directly or indirectly, from one place to another.

TRANSMISSION

Infections may result from either exogenous flora (i.e., microorganisms having an animal, human, or environmental reservoir) or endogenous flora. Endogenous flora may be either normal commensals of skin, respiratory tract, gastrointestinal tract, or genitourinary tract or present in relatively inactive forms within the body (i.e., latent infections). Endogenous microflora represent a frequent source of infection when the delicate balance between agent and host is disturbed (e.g., by chemotherapy for cancer). Relatively few pathogens are able to evade host defenses and cause latent infection. The most common of these are the herpes viruses (*Herpes simplex*, *Varicella zoster*, cytomegalovirus, Epstein-Barr virus), human immunodeficiency viruses (HIV-1 and HIV-2), *Mycobacterium tuberculosis*, and some fungi (*Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis*).

Transmission generally refers to the mechanism by which exogenous pathogens reach

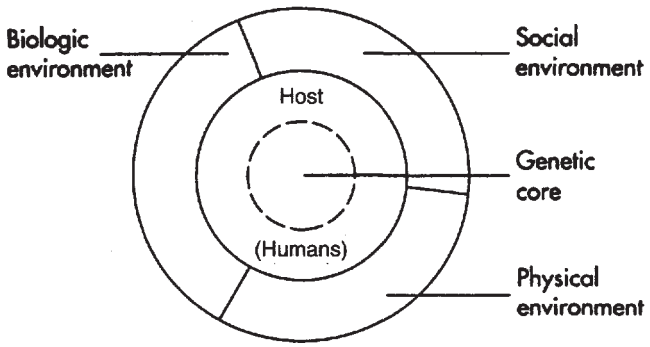

Figure 1–2. Wheel model of infectious diseases.
Source: Adapted from Jackson 1996.

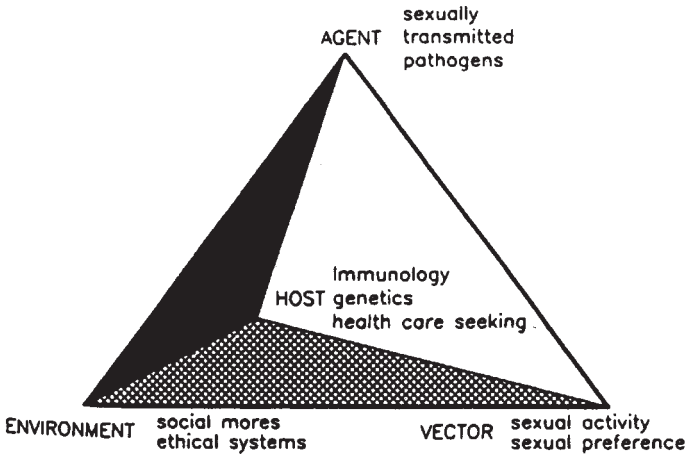

Figure 1–3. Tetrahedron model of infectious diseases. *Source*: Adapted from Rothenberg 1990.

and infect a susceptible host. Transmission may occur by one or more of four routes: contact, common vehicle, airborne, or vector-borne (Tables 1–1 and 1–3). In contact spread, the host has contact with the source that is either direct, indirect, or droplet. Direct contact includes such activities as touching, kissing, and sexual activity. Indirect contact requires an intermediate object, which is usually inanimate, in the transmission of the pathogen from the source to the patient. Droplet spread refers to transmission by respiratory droplets and requires relative proximity (<3 feet). Vertical transmission or transmission from an infected mother to fetus (i.e., in utero transmission) is considered either a category of contact transmission or a separate mode of transmission (see later). Common vehicles may include the following: ingested water or food, medical instruments, or infused products such as blood. Airborne transmission refers to passage of a pathogen through the air for long distances. Such pathogens may have a human

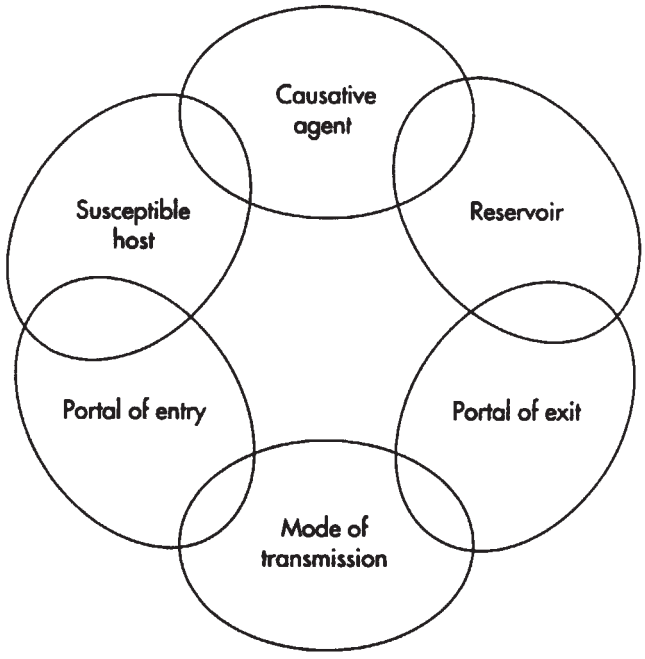

Figure 1–4. Chain model of infectious diseases. *Source*: Adapted from Jackson 1996.

Table 1–1 Key Terms in Understanding the Cycle of Infection

Infectious Agent	Viruses, Bacteria, Fungi, Protozoa, Helminths
Portals of exit	Skin/blood, respiratory secretions, urine, feces, semen/cervical secretions
Means of transmission	Contact (direct, indirect, droplet, vertical), common vehicle, airborne, vector-borne
Portals of entry	Skin, respiratory tract, gastrointestinal tract, genitourinary tract, in utero (transplacental)
Source	Human, animal, environment
Susceptible host	Specific (B- or T-cell mediated) immunity not present, immune compromised host, defects in specific and/or nonspecific host defense mechanisms

or environmental reservoir. Vector-borne spread refers to the transmission of an infectious agent by an arthropod. This transmission may simply be mechanical transfer of microorganisms on the external appendages of the vector. Alternatively, the vector may internalize the agent requiring subsequent regurgitation, defecation (e.g., riduviid bug, which is the vector for *Trypanosoma cruzi*, the causative agent of Chagas' disease), or penetration of the skin or mucosal surface (e.g., mosquito, which is the vector for *Plasmodium vivax*, a causative agent of malaria). Vector-borne infectious agents, in general, are highly adapted to their vector host. The infectious agent may be harbored by the vector without biologic interaction between the vector and the agent (e.g., yellow fever virus) or there may be biologic transmission in which the pathogen undergoes biologic changes within the vector (e.g., malaria).

Direct contact between humans may lead to transmission of an infectious agent via several mechanisms. Close contact may result in transmission of external parasites such as scabies or mites. Exchange of saliva via kissing may transmit such diseases as mononucleosis and oral Herpes simplex. Sexual activity is an efficient means for transmitting several diseases such as gonorrhea, syphilis, and chancroid. Vertical transmission (i.e., from an infected mother to her fetus or child) may occur via in utero transmission, at the time of birth via passage through a contaminated birth canal, or postnatally via breast milk. In utero transmission of infectious agents is fortunately uncommon. However, several infectious agents may be transmitted from an infected mother to her fetus transplacentally. These include syphilis, toxoplasmosis, rubella, cytomegalovirus, and human immunodeficiency virus. Other agents may be transmitted to the fetus by its passage through a contaminated birth canal, including group B streptococcus, *Listeria*, *Neisseria gonorrhoeae*, *Chlamydia*, and various gram-negative bacilli. Finally, some infectious agents may be transmitted to neonates via breast milk (e.g., HIV).

While some infectious agents are transmitted by only a single route, others may be transmitted by multiple routes. In general, the most common diseases transmitted by sexual activity such as gonorrhea and syphilis have no other significant routes of transmission. Tularemia provides an example of a disease transmitted by multiple routes. The causative agent, *Francisella tularensis*, may be transmitted from its animal reservoirs to human by cutaneous contact with infected animal products (e.g., rabbit skins), ingestion of contaminated food or water, ocular contact with infected animal products, inhalation of dust from contaminated soil, bites from infected animals such as the cat or squirrel, and by biting arthopods such as the wood tick, dog tick, deerfly, or mosquito.

In describing the transmission of an infectious agent, vague terms such as person-to-person, household, horizontal, and intimate contact should be avoided, as they may include both physical contact such as handshaking and embracing as well as droplet spread and contact with recently contaminated surfaces.

For some infectious diseases, the route(s) of transmission remain largely unknown, such as *Helicobacter pylori*. Identification

Table 1–2 Importance of Understanding the Cycle of Infection for Control of Infectious Diseases

Pathogen	Disease	Portal of Exit	Transmission	Portal of Entry	Control
Influenza virus	Pneumonia	Respiratory secretions	Airborne	Respiratory tract (inhalation)	Vaccine, tissue to decrease airborne particles
Polio virus	Polio	Stool	Contact: Fecal-oral Common vehicle: Water	Gastrointestinal tract (ingestion)	Vaccine
Rabies virus	Rabies	NR	Contact: Animal bite	Skin (animal bite)	Immunize cats, dogs; immunize at risk humans; postexposure prophylaxis for humans after an animal bite or other exposure
Bordetella pertussis	Whooping cough	Respiratory secretions	Droplet	Respiratory tract (inhalation)	Vaccine; postexposure prophylaxis
Clostridium tetani	Neonatal tetanus	NR	Contact	Skin: umbilical cord (toxin)	Maternal immunization; sterile transection of umbilical cord
Neisseria gonorrhoeae	Gonorrhea	Genital secretions	Sexual	Genital tract	Screening of high-risk and symptomatic persons, followed by treatment
Mycobacterium tuberculosis	Tuberculosis	Respiratory secretions	Airborne	Respiratory tract (inhalation)	Contact tracing with treatment; screening with treatment of latent infection
Rickettsia rickettsii	Rocky Mountain spotted fever	Skin (via tick bite)	Tick-borne	Skin (via tick bite)	Prevention and early removal of ticks
Salmonella typhi	Enteric fever	Stool	Contact: Fecal-oral Common vehicle: Food	Gastrointestinal tract (ingestion)	Vaccine; separation of fecal waste from water supply; good hygiene
Treponema pallidum	Syphilis	Genital secretions	Sexual	Genital tract	Screening of high-risk and symptomatic persons, followed by treatment
Cryptosporidium sp.	Diarrhea	Stool	Contact: Fecal-oral Common vehicle: Water; food	Gastrointestinal tract (ingestion)	Separation of fecal waste from water supply; filter water supply; pasteurize juice
Plasmodium falciparum	Malaria	Skin (mosquito bite)	Vector (mosquito)	Skin (mosquito bite)	Mosquito spraying; reduce mosquito bites (netting, insect repellant); antimalarial prophylaxis

NR, not relevant for humans.

Table 1–3 Mechanisms of Disease Transmission, Examples

Airborne	Direct	Indirect	Droplet	Vertical	Vector-Borne	Common Vehicle
Influenza	HIV (sexual)	Papilloma virus (warts via contaminated surfaces)	Rhinovirus	HIV	Eastern equine encephalitis (mosquito)	Hepatitis A (food)
Measles	Rabies (via bite)	Hepatitis B (via needle sharing)	Pertussis	Rubella	Rocky Mountain spotted fever (tick)	Salmonellosis (food, water)
Tuberculosis	Gonorrhea (sexual)	*Clostridium difficile*	Meningococcal infection	Syphilis	Lyme disease (tick)	Cryptosporidiosis (food, water)
Cryptococcosis	Syphilis (sexual)			Toxoplasmosis	Malaria (mosquito)	

of the route of transmission from the source to the host may provide crucial information for designing control measures.

UNDERSTANDING A PATHOGEN'S LIFE CYCLE

Understanding the life cycle of pathogens is crucial to developing an appropriate study or intervention strategy. Prior to describing the various possible life cycles several key terms must be defined. The *reservoir* is the niche which the pathogen normally inhabits (i.e., where it lives, reproduces). Reservoirs of human infection may be humans, animals, insects, or the environment. The *source* is the means by which the pathogen is directly transmitted to humans. Sources may be animate or inanimate and may include other humans, animals, insects, food or water, medications, or medical devices. The reservoir and the source may be identical (e.g., as with most sexually transmitted agents) or different. For example, the reservoir of *Salmonella typhi* is always humans, but sources of infection are usually contaminated food or water. The reservoir of *Salmonella enteritidis* is animals, but like *S. typhi* they usually pass to humans via contaminated food or water. However, *S. enteritidis* may be transmitted by direct contact with infected animals such as turtles. Within the life cycle of a pathogen, humans may serve as an essential link (e.g., most sexually transmitted agents, *Mycobacterium tuberculosis*, or *Plasmodium vivax* [malaria]) or may represent a dead end host, in which case human infection is accidental (e.g., rabies, Eastern equine encephalitis, tetanus).

Interrupting the life cycle of a pathogen is often an effective means to control the disease (Table 1–4). In general, one may interrupt the life cycle at multiple points. How best to intervene depends on many factors including the effectiveness of the planned intervention strategies, immediate benefits to infected humans, cost, rapidity with which the intervention will reduce infection and/or disease incidence, and environmental concerns. One can use schistosomiasis as an example of the importance of understanding the life cycle for guiding intervention strategies. The life cycle of *Schistosoma* spp. is complex. Humans pass eggs via the stool or urine. These eggs hatch into miracidia when exposed to fresh water and seek out a snail intermediate host. Following a developmental stage in the snail, cercaria are released into the water where they seek out a human host and initiate infection by penetrating

Table 1–4 Possible Life Cycles of Pathogens

Life Cycle	Examples
Human → Human	*Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhea), *Mycobacterium tuberculosis* (tuberculosis)
Human → Environment → Human	*Ascaris lumbricoides* (roundworm), (whipworm)
Human → Arthropod → Human	*Plasmodium vivax* {intermediate host, mosquitoes} (malaria), Dengue virus (breakbone fever)
Human → Animal → Human	*Schistosoma* spp. {intermediate host, snails} (schistosomiasis)
Human → Animal → Animal → Human	*Paragonimus westermani* {intermediate hosts, snails and then crabs or crayfish}
Environment └Human (accidental)	*Sporothrix schenckii* (sporotrichosis, rose pruner's disease), *Coccidioides immitis* (coccidioidomycosis, valley fever)
Animal → Animal └Human (accidental)	Rabies virus (rabies), *Pasteurella multocida* (pasteurellosis)
Animal → Environment → Animal └Human (accidental)	*Cryptosporidium* sp., *Toxoplasma gondii* (toxoplasmosis)
Animal → Arthropod → Animal └Human (accidental)	*Rickettsia rickettsii* {intermediate host, ticks} (Rocky Mountain spotted fever), Eastern equine encephalitis {intermediate hosts, mosquitoes} (arboviral encephalitis)

the skin. The life cycle of this pathogen can be interrupted by treating infected humans thereby eliminating the pathogen, by providing safe sewage disposal thereby preventing the eggs from hatching and/or the miracidia from reaching their snail host, by eliminating the host snails (e.g., via the use of molluscacides, introduction of predators, elimination of snail habitat), or by providing safe water for drinking and bathing thereby preventing the cercaria from finding a human host and initiating infection.

Several epidemiologic tools may be useful in guiding the decision on where to intervene to interrupt the life cycle of a pathogen including modeling disease transmission, decision analysis, and cost-effectiveness analysis. In general, interventions that do not rely on volitional changes in human behavior (e.g., mosquito control) are likely to be more successful than interventions requiring behavior modification (e.g., condom use for sexually transmitted disease prevention).

THE KEY TRIANGLE

As stated earlier, infection results from a complex interaction of the host, the agent, and the environment. Infectious disease epidemiologists must understand these factors and assess their individual importance in the transmission of specific infectious diseases (Table 1–5).

THE HOST

Humans are simultaneously dependent on and threatened by the microorganisms that surround them. Host factors often dictate which individuals exposed to an infectious agent will become infected, develop disease, resolve the infection, or die as a result of infection.

Characterization of Host Defenses

Host resistance may be divided into specific and nonspecific immunity. Specific immune mechanisms include humoral (antibodies) and cell-mediated immunity (see Chapter 2). Nonspecific host defense mechanisms include the skin and mucous membranes, which provide barrier protection; the mucous membranes, which secrete destructive enzymes such as lysozyme, immunoglobulins, and other compounds with antimicrobial properties; the complement system, a protein cascade, which leads to initiation of the inflammatory response, clearance of immune complexes, opsonization of microorganisms, and killing of certain gram-negative bacilli; leukocytes, which are granulocytic white blood cells capable of phagocytosis and killing of microorganisms; cytokines (e.g., interleukins 1 and 2, tumor necrosis factor, interferons), which are able to induce fever, T- and B-cell proliferation, immunoglobulin synthesis, and to interfere with viral synthesis.

Defects of host defenses are a major predisposing factor for infection. Specific defects are often associated with specific infectious agents (Table 1–6). Host defense abnormalities may be congenital (e.g., sickle cell anemia), acquired (e.g., Hodgkin's disease, malnutrition), or due to an infectious agent (e.g., human immunodeficiency virus). Iatrogenic breaches of morphologic integrity, such as the placement of an intravenous catheter for medications, are a major cause of hospital-acquired infections.

Immunosuppression due to medication is increasingly common owing to the increase of solid organ transplantation (e.g., heart, lung, kidney) that requires the administration of immunosuppressive medications to prevent rejection of the "foreign" organ, and more aggressive chemotherapy for malignant tumors. The risk of infection developing in an immunocompromised patient is a result of an interaction between two major factors: the patient's exposure to pathogens and the patient's net state of immunosuppression. Factors influencing the exposure to pathogens include other persons (especially important are children), pets, occupational exposures, travel exposure, and habits (e.g., swimming, hiking, fishing, hunting, camping). Factors influencing the net state of immunosuppression include the underlying disease; the effects of therapy; the presence or absence of granulocytopenia (i.e., <1000 granulocytic white blood cells); presence or absence of injury to the primary host defense

Table 1–5 Understanding the Key Triangle: Host, Pathogen, and Environment

Host Factors			Environmental Factors	
Intrinsic Factors	Behavior Factors/Extrinsic Factors	Pathogen Factor	Physical Environment	Social Environment
Age	Habits (smoking, alcohol consumption, drug use)	Pathogenicity	Urban vs. rural	Sexual network
Gender	Diet	Infectivity	Tropical vs. temperate	Crowding
Race	Sexual activities	Infective dose	Climate	Medical availability
Genetic makeup	Occupation	Immunogenicity	Remoteness	Education
Physiology	Recreational activities	Evasiveness	Vector presence	Public health resources
Immune responsiveness	Animal exposure Chemotherapy Immunosuppressive medications Immunizations	Environmental stability		

Table 1–6 Impact of Specific Host Defense Abnormalities

Host Defense	Defect	Pathogens with Increased Incidence	Disease(s)
Skin	Disruption (e.g., wound)	*Streptococcus pyogenes*	Cellulitis
Skin	Disruption (e.g., wound)	*Staphylococcus aureus*	Cellulitis, furuncle, abscess
Skin	Disruption (e.g., wound)	*Clostridium tetani*	Tetanus
Gastric acid	Achlorhydria	*Salmonella* sp.	Enteric fever
Genital mucosa	Disruption (e.g., from sexually transmitted disease)	HIV	AIDS
Neutrophils	Neutropenia	*Staphylococcus aureus* Gram-negative bacilli	Sepsis Sepsis
Complement	Deficient levels (late components)	*Neisseria* sp. infections	Sepsis
Spleen	Splenectomy	*Streptococcus pneumoniae*	Sepsis
Immunoglobulin (IgG)	Deficient levels	*Streptococcus pneumoniae*	Sepsis
Cell-mediated immunity	Underlying disease (HIV), immunosuppressive medications	*Mycobacterium tuberculosis*	Tuberculosis
Cell-mediated immunity	Underlying disease (HIV), immunosuppressive medications	*Pneumocystis carinii*	Pneumonia
Cell-mediated immunity	Underlying disease (HIV), immunosuppressive medications	*Listeria monocytogenes*	Listeriosis

barrier to infection, the intact mucocutaneous surfaces; metabolic factors such as state of nutrition; and the immunomodulating effects of certain microbial invaders, particularly viruses (Kontoyiannis 1995). The latter includes cytomegalovirus, Epstein-Barr virus, hepatitis viruses, HIV, *Capnocytophaga*, *Plasmodium* spp., and *Histoplasma capsulatum*. The chronic administration of immunosuppressive medications not only increases the incidence and severity of acute infection, but also results in chronic, progressive disease of a form essentially unknown in normal hosts even though the invading microorganisms are common in all populations.

Age

Age is an important predictor of disease incidence for two major reasons: First, exposure is often highly related to age. Figure 1–5 displays the age distribution by gender of the human immunodeficiecy virus (HIV) infection. As with other sexually transmitted diseases, the age-specific incidence peaks between 20 and 40 years of age. A small peak is apparent in childhood corresponding to vertically (mother-to-child) transmitted cases. Although this disease is more prevalent in males in some countries due to the initial association with unsafe sexual practices by gay men, the incidence in male and female children who acquire infection from their infected mothers is equal. Second, immunity to disease is highly correlated with age (see Chapter 2). In general, both extremes of age have a higher incidence of infectious diseases. Young children are partially protected against acquiring many infectious agents by maternally derived antibody transferred via the placenta. However, this immunity wanes over 6 to 15 months. The relationship between young age and in-

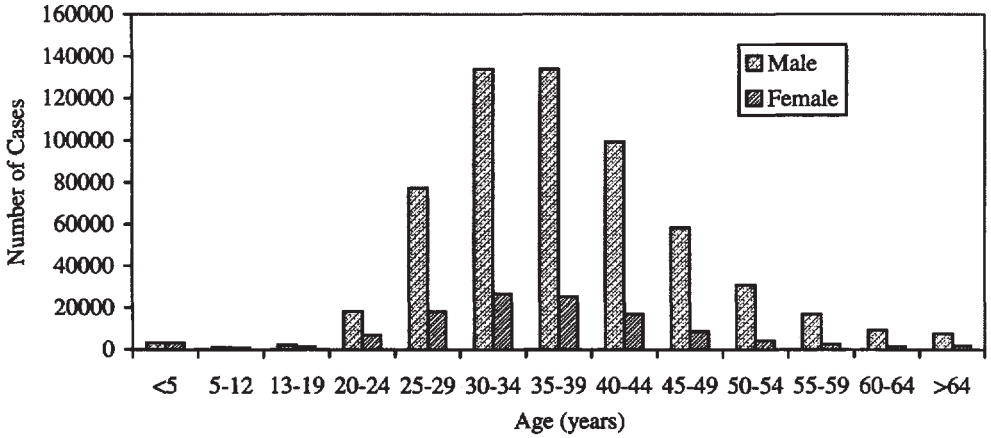

Figure 1–5. HIV infection cases by sex and age at diagnosis.
Source: Adapted from CDC 1999.

fection is clearly illustrated by the classic childhood exanthems; measles, rubella, and varicella (chickenpox). These viral infections occur predominantly in young children who lack immunity and are exposed to infected peers. Older individuals are more likely immune and less likely to become exposed. Older individuals have a higher frequency of infectious diseases due to comorbid states (e.g., diabetes), waning immunity, longer exposure time for latent infections (e.g., tuberculosis), and altered immune state. Tuberculosis is an example of a disease dramatically more frequent among older persons (Fig. 1–6). In describing the relationship between age and disease incidence it is important that age-specific incidence rates be calculated.

The relationship between age and infection is not always simple. For example, age enters into both the incidence of bacterial meningitis and the relative contribution of different organisms at different ages (Schuchat 1997, Wenger 1990). Young children have both a higher incidence of bacterial meningitis and a different set of pathogens. Neonatal meningitis is most commonly due to group B streptococcus, *E. coli*, and *Listeria*. Meningitis among older children and adults is most commonly due to *Streptococcus pneumoniae* and *Neisseria meningitidis*. This evolution of relative risk represents poorly understood interactions between immunity, exposure, and associated medical conditions.

Age also affects the outcome of infection, as exemplified by the common childhood viral illnesses of the past. Measles, varicella (Wharton 1996), mumps, and hepatitis A are more likely to cause significant morbidity with increased age of acquisition. The age-specific incidence of Rocky Mountain spotted fever and case-fatality rate illustrate the important point that age-specific incidence and age-specific mortality may not be colinear (Bernard 1982). The highest incidence of Rocky Mountain spotted fever is among older children and younger adults but the highest mortality is among older adults. Again, in general, individuals at the extremes of life tend to have a higher case fatality rate (i.e., proportion of persons dying as a function of all persons infected).

The use of vaccines and other interventions may significantly alter the age-specific incidence of disease. The introduction of pertussis vaccine has resulted in less disease in younger individuals but a relatively increased frequency of disease in young adults. Immunization may substitute a generally benign childhood illness for disease with sig-

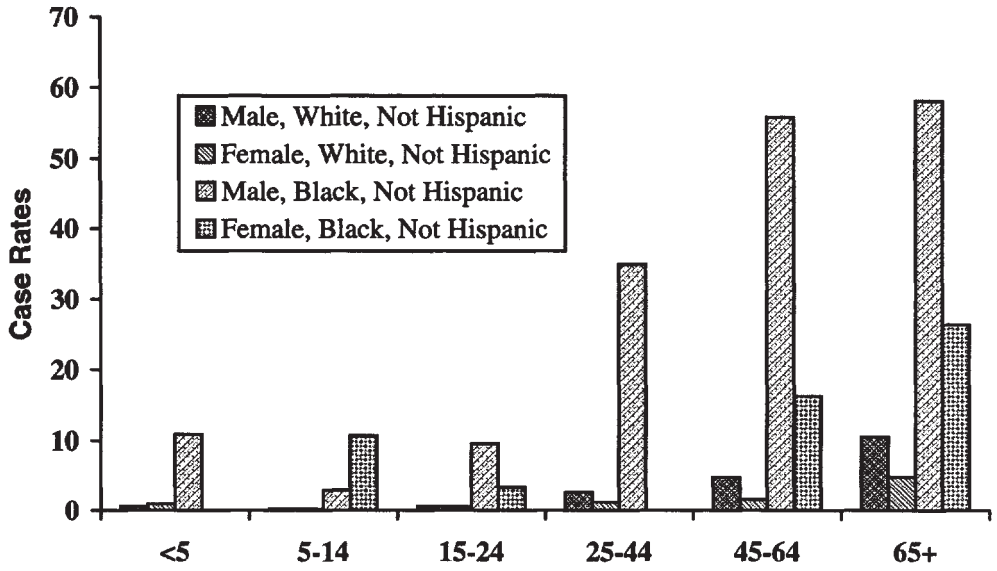

Figure 1–6. Tuberculosis case rates per 100,000 population by race/ethnicity, sex, and age: United States, 1997.
Source: Adapted from Centers for Disease Control and Prevention. Reported Tuberculosis in the United States 1997.

nificant sequelae among a susceptible older population with waning vaccine associated immunity. This issue needs to be considered as newer vaccines such as varicella and hepatitis A are introduced.

Although age is commonly considered a risk factor for infectious disease acquisition and/or morbidity, age may merely serve as a marker for the presence of physiologic factors causally related to disease acquisition. For example, Saviteer and colleagues (1988) showed that the incidence of hospital acquired pneumonia increased with age. However, careful investigations of some infectious diseases has revealed that age per se was not associated with an increased incidence of infection but rather older individuals were more likely to have risk factors associated with disease acquisition. For example, Hanson and colleagues (1992) demonstrated that when all the important risk factors for nosocomial pneumonia were assessed, age was not an independent risk factor; rather the higher incidence in the elderly was due to a greater frequency of risk factors (e.g., smoking, chronic lung disease, decreased mental status). Increasingly, we are coming to realize that physiologic age, not chronologic age, is the important predictor of infection risk.

Gender

Almost all infectious diseases occur more frequently among individuals of one sex versus the other. Sex-specific differences in disease frequency may represent differences in exposure, anatomy and physiology, or as yet unknown factors. Diseases related to out-of-doors exposures such as the tick-transmitted diseases Rocky Mountain spotted fever and tularemia are more common in males than females. While anatomy obviously dictates the risk of pelvic inflammatory disease and epididymitis caused by *Neisseria gonorrhoeae*, disseminated gonorrhea is more common in women, perhaps because of prolonged asymptomatic infection or because local defenses in the female genital tract are not as effective in containing infection to local tissues.

Acquisition of schistosomiasis, a parasitic infection harbored by snails, is related to exposure to contaminated water. Cultural dicta may govern exposure, since such tasks as gathering water for cooking and drinking, laundering of clothing, harvesting rice, and fishing may be gender-specific.

In some cases the reason for sex differences is unclear. Thus the incidence of tuberculous diseases is similar in men and women up to age 24, but thereafter men are increasingly likely to develop tuberculosis mainly as a result of reactivation (Fig. 1–6). Whether this represents a cohort effect with differential exposure in the distant past or a more significant waning of immune surveillance (i.e., ability of host defenses to contain viable tubercule bacilli within local granuloma) among men is unclear. Patterns of tuberculosis in populations also demonstrate that various host factors can act independently as risk factors. Independent risk factors for tuberculosis include older age, male sex, and nonwhite race (Fig. 1–6).

Ethnicity

Although the incidence of many infectious diseases is greater among certain races or ethnic groups, these differences are often explained by differences in socioeconomic status that dictate differences in exposure, immunity, and access to medical care, including vaccines. Selective pressures brought on by centuries of exposure may explain the relative resistance of Caucasians to tuberculosis and Africans to malaria. Certain genetic traits that may enhance or retard the acquisition of infectious agents may be more prevalent in certain ethnic groups (see below). Different immune response gene haplotypes may be present in different ethnic groups and affect the susceptibility to infectious agents.

Genetics

The relationship between heredity and infectious disease susceptibility and pathophysiology is also complex. Genetic traits may result in reduced or enhanced susceptibility to infection or disease if infected. Terminal complement deficiencies (C5, C6, C7, or C8), for instance, may predispose to recurrent infection with *Neisseria gonorrhoeae* and *N. meningitidis* (Lokki 1995). Individuals who lack both Duffy blood group antigens (a and b) are resistant to *Plasmodium vivax* malaria, since these antigens are required for attachment of the agent (Hadley 1997). Other genetically acquired disorders may present with seemingly unrelated manifestations yet have an altered risk of developing disease. Individuals with sickle cell trait (heterozygotes) have less severe infections with *Plasmodium falciparum* (Gendrel 1991) malaria, but persons with sickle cell disease (homozygotes) are at higher risk of serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* (Onwubalili 1983). Growing evidence suggests an association between certain histocompatibility antigen classes and increased risk for tuberculosis, paralytic poliomyelitis, leprosy, and chronic hepatitis B antigenemia. The gene, HLA B27, has been strongly linked to reactive arthropathy following certain gastrointestinal infections (Gonzalez 1999).

Physiology

Besides age, gender, and ethnicity, the dynamic equilibrium represented by health status may be tipped by both subtle and not so subtle influences. Diabetics are at increased risk for respiratory, urinary tract, and skin infections (Joshi 1999). They have a higher frequency of infections with group B streptococcus, *Salmonella enteritidis* (gastroenteritis), *Mycobacterium tuberculosis* (pneumonia), *Candida* sp. (infections of the vagina and mouth), *Pseudomonas aeruginosa* (aggressive infections of the outer ear canal with invasion of adjacent bone), and Mucor (invasive fungal infection of the paranasal sinuses) when ketoacidosis is present. Subtle body temperature differences may ordain the site of agent replication and disease manifestations. Heat sensitivity limits leprosy caused by *Mycobacterium leprae* to the skin and nasal mucosal membrane. Indeed,

inducement of fever by infecting the host with malaria has been used with variable success in the therapy of tertiary syphilis and Lyme disease.

Diet and Nutrition

Specific dietary habits may influence the host's risk of infection. *Diphyllobothrium latum* or fish tapeworm, for instance, occurs only in individuals who ingest raw or undercooked fish (Ruttenber 1984). Other infections are endemic but may be more common in persons eating certain foods. For example, ingestion of raw shellfish is associated with several infections including hepatitis A and viral gastroenteritis (Wanke 1987); *Mycobacterium bovis* infection is associated with ingestion of unpasteurized cow's milk in lesser developed countries (Cosivi 1998); and brucellosis is associated with ingestion of unpasteurized cheese made from goat's milk (Young 1983).

Good nutritional status is critical to the maintenance of good health. Malnutrition contributes significantly to infectious disease–related morbidity in developing countries. Only recently has malnourishment been recognized as a contributing cause of postoperative sepsis and death. Vitamin A deficiency may impair maturation of T lymphocytes, diminish secretory immune responses to polysaccharide antigens, diminish complement activity, and impair the antimicrobial action of phagocytic cells leading to increased morbidity due to measles (Semba 1994). Zinc deficiency has been linked to an increased risk of diarrhea, pneumonia, and malaria (Black 1998).

Intercurrent or Preexisting Infections

Certain infections occur more frequently or even exclusively in hosts who are recovering from or currently infected with another infectious agent. Viral infections of the upper respiratory tract may damage the mucous membranes with destruction of the cilia-bearing epithelial cells resulting in an increased risk of pneumonia caused by two common respiratory pathogens, *Streptococcus pneumoniae* or *Staphylococcus aureus*. *Schistosoma haematobium*, a fluke that causes urinary bladder wall abnormalities, predisposes the host to other urinary tract infections including those with *Salmonella*, an unusual urinary tract pathogen (Lambertucci 1998). Hepatitis delta agent replication is dependent on a simultaneous infection with hepatitis B virus that provides the delta agent with its surface antigen coat (Taylor 1999). Without concomitant hepatitis B replication, the delta agent cannot replicate or cause disease.

Human Behavior

The host's actions are not always in his or her best interest. Neonatal tetanus may result from cord contamination of the umbilical stump due to use of nonsterile instruments to cut the cord (Gurkan 1999) or placing materials such as "ghee" (clarified butter) on an umbilical wound (Bennett 1999). Customs including circumcision, scarification, ear piercing, and tattooing may lead to tetanus unless appropriate sterile techniques are used (Sow 1993). Smoking induces airway inflammation and significantly predisposes to both upper and lower respiratory tract disease. Smoking is one of the major risk factors for chronic bronchitis (Niroumand 1998), and environmental smoke (passive smoking) is an important risk factor for upper respiratory tract infections in children (Gryczynska 1999, Hajnal 1999). A wide spectrum of viral (e.g., HIV, hepatitis B, C, D), bacterial (e.g., endocarditis due to *Staphylococcus aureus* or cellulitis due to group A streptococci), and fungal (e.g., endocarditis due to *Candida* sp.) infections complicate injecting drug use (Contoreggi 1998). Even mundane activities such as maintaining proper hygiene, careful trimming of toe nails, and appropriate care of contact lenses are important in reducing the host's risk of infection.

Human activities are the only significant risk factors for sexually transmitted diseases. Factors associated with an increased risk of sexually transmitted diseases (including HIV infection) include such activities as multiple partners, failure to use condoms,

exchange of sex for money, and receptive anal intercourse. Behavioral interventions are therefore crucial to the control of these infections.

AGENT

Classification

Infectious agents range from self-replicating proteinaceous materials (prions), to subviral particles (the viroid/virusoid-like delta hepatitis agent), viruses, bacteria (including *Chlamydia, Rickettsia,* and *Mycoplasma*), fungi (yeast and molds), protozoans, helminths (flukes, worms), and ectoparasites (lice, fleas, mites, bedbugs, and ticks). Detailed classification is based on morphology, growth requirements, antigenic character, and, increasingly, nucleic acid organization and sequence. When new syndromes or new agents are recognized, hypothesis generation is based on the characteristics of well-recognized disease processes or agents. Important clues regarding route of transmission, pathophysiology, treatment, laboratory diagnosis (antigenicity, immune response, culture techniques, nucleic acid sequence), potential role of vectors and/or reservoirs, and control measures may be surmised. For example, initial investigation and public health recommendations for the illness in the Southwest United States caused by a Hantaan virus-like agent were based on knowledge about other similar viral infections.

Intrinsic characteristics of the agent

Each infectious agent has intrinsic characteristics that may dictate host range, mode of transmission, and ability to produce disease that are independent of any host interaction. Such basic considerations include size, requirements for replication (intracellular versus extracellular, nutrients), as well as temperature, humidity, and pH tolerance. Susceptibility to temperature, detergents, and desiccants varies widely and obviously influences potential modes of transmission. While *N. gonorrhoeae* and HIV do not survive for prolonged periods outside the host, the spores of *Bacillus anthracis*, the agent causing anthrax, can survive in soil for years and *Clostridium botulinum* spores can endure boiling for hours.

Agents produce substances that either help avert host defenses mechanisms or directly cause disease manifestations. Toxins are responsible for the symptoms experienced with diphtheria, tetanus, scarlet fever, and some types of food poisoning including *Clostridia botulinum*, *Clostridia perfringes*, and *Staphylococcus aureus*. Diphtheria toxin production requires the agent to possess a lysogenic phage that encodes the toxin. Vaccines directed at toxin-produced diseases generally comprise inactivated toxin stimulating a protective immune response. Serious host injury may result from the circulating toxins produced by *Staphylococcus aureus* (Staphylococcal toxic shock syndrome) or group A *Streptococcus pyoge*nes (streptococcal toxic shock syndrome) that function as super-antigens (Stevens 1996, Manders 1998), and the effects of local toxins on the colonic mucosa produced by *Clostridium difficile* (necrotizing enterocolitis) (Taege 1999).

Other agents synthesize and secrete one or more substances that aid in the survival of the agent or combine to produce pathologic changes. Enzymes may be produced that destroy red and white blood cells (hemolysins and leukocidins, respectively), disrupt connective tissue (hyaluronidase, collagenase), cleave nucleic acids (nuclease), avert killing of the agent by leukocytes (catalase), or stimulate either clot formation or lysis (coagulase and streptokinase, respectively). Nonenzymatic products such as siderophores, which scavenge for iron, allow the agent to compete in the host environment.

Other structural components of the agent also contribute to pathogenicity. Motility, for instance, may be an important factor in infection and disease production. The presence of a polysaccharide capsule may help the agent avoid phagocytosis. Fingerlike projections on bacterial surfaces called fimbriae may enhance the adherence of the bacteria to host membranes (e.g., *E. coli* strains causing urinary tract infections). Endotoxins refer to the integral lipopolysaccharide

component of certain bacterial cell walls that can trigger a complex series of cascades including complement activation, alteration in vascular tone and permeability, as well as coagulation and fibrinolysis producing fever, inflammation, and sometimes shock.

Susceptibility to available antibiotics may be genetically determined. Unfortunately, selection pressures, mutations, genetic recombination, and plasmid exchange between bacteria have lead to resistance to antibiotics. Antibiotic resistance may result from production of enzymes that degrade the antibiotics, altered cell surface permeability, enhanced efflux pumps, or alteration in the antibiotic target sites, which reduces or prevents binding (Hawkey 1998, Gold 1996). The growing tide of antibiotic resistance among the most common community- and hospital-acquired microorganisms is alarming and carries potentially grave public health consequences (Hawkey 1998, Gerberding 1999, Virk 2000).

Thus mere identification of an agent by genus and species may inadequately define the pathogen without additional description of serotype, genotype, phenotype, phage type, toxin production, or antibiotic resistance pattern. *Staphylococcus aureus* may produce an array of distinct clinical presentations, from local skin infections to food poisoning, endocarditis, toxic shock syndrome, depending on the location of infection and production of specific virulence factors.

Extrinsic characteristics of the agent

The host agent relationship may be *symbiotic*, *commensal*, or *parasitic* depending on the agent, the host, the environment, and the circumstances. *Escherichia coli*, for instance, may be commensal in the vaginal tract, may establish a symbiotic relationship in the gastrointestinal tract synthesizing vitamin K, but may be parasitic in the urinary and respiratory tracts.

Certain characteristics of the agent are best described in relationship to a specific host. The identical strain of *Streptococcus pneumoniae*, for instance, may pose vastly different consequences in mice and humans, for instance. Host specificity refers to limited host range of some agents. *Salmonella typhi* has a predilection for humans, while *S. dublin* infects predominantly cattle. *Clostridia botulinum* types A, B, E, and F may cause human disease, whereas types C and D infect other animals. Smallpox, hepatitis B, polio, and measles are examples of diseases whose causative agents exclusively infect humans.

Several terms define the interaction between agent and host. *Infection and infectivity* refers to the ability of the agent to invade and multiply in a host. The *infective dose* refers to the theoretical number of organisms required to establish an infection in a group of hosts of the same species. Even such a seemingly simplistic concept is complicated by the multitude of host and agent factors discussed previously as well as mode of transmission. The infective dose of *Staphylococcus aureus*, for example, is dependent on the virulence factors produced. Even a virulent organism presents variable risks when presented to intact skin, a clean wound, a clean wound with a foreign body (suture), a necrotic wound, the respiratory tract, or the bloodstream. In the laboratory, infective dose is described by the minimum number of agents required to cause infection in 50% of hosts (ID_{50}). Stomach acidity adversely affects the survival of some bacteria (*Salmonella*) more than others (*Shigella*). Thus neutralization of gastric acid by disease, medication, or diet may affect on the host's susceptibility to *Salmonella* more than *Shigella*. From a practical standpoint, a gauge of infectivity is estimated by the *secondary attack rate*—the proportion of exposed susceptible hosts who develop disease. Infectivity represents a continuous spectrum from measles and chickenpox, which are highly infectious, to rubella and the common cold, which are of intermediate infectivity, and tuberculosis, leprosy, and Creutzfeldt-Jakob disease, which are of low infectivity.

Clinical presentation may (tuberculosis, syphilis, Herpes simplex) or may not (hepatitis A, *Salmonella*, polio) influence infectivity. The number, size, and degree of inflam-

mation and healing of syphilis and *H. simplex* genital ulcers presumably influence the level of infectivity. Severity of illness, however, does not alter the risk of transmission of such infectious agents as hepatitis C or polio.

Colonization is the persistence, often with multiplication, of an agent on a mucosal surface without an apparent host reaction. *Contamination*, on the other hand, generally refers to the presence of an agent on the surface of the body or an inanimate object (i.e., fomite) such as an eating utensil, toy, or handkerchief that may serve as a source of infection. While the distinction between infection and colonization or contamination is important, it is not always simple. Intubated patients on a respirator often develop colonization of their upper respiratory tract with gram-negative organisms that are also the most common cause of lower respiratory tract disease. Identification of these organisms in respiratory secretions is not synonymous with infection and disease.

Pathogenicity represents the proportion of infections that result in clinically apparent infection or *disease*. Again, host factors, infecting dose, route of transmission contribute to this continuous spectrum. Highly pathogenic agents include rabies, measles, chickenpox, and the common cold while polio and tuberculosis are of low pathogenicity.

Virulence can be conceptualized as the proportion of clinically apparent cases resulting in significant clinical manifestations. Measurement might include days absent from work/school, specific sequelae, or mortality referred to as *case fatality rate*. When death is used as the measurement of virulence, the difference between pathogenicity and virulence becomes apparent. Rabies is both highly pathogenic and virulent; the common cold is highly pathogenic but rarely virulent, and poliovirus might be classified as moderately virulent despite having a low pathogenicity.

The pathogenesis or mechanism by which an agent causes disease is often multifactorial but may include: (1) direct tissue invasion, (2) induction of an inflammatory response, (3) direct cellular destruction, (4) toxin production, (5) immune perturbation, hypersensitivity, or allergic reaction (post Strepococcal glomerulonephritis, dengue hemorrhagic fever), (6) immune suppression, and (7) obstruction or mass effect.

The characteristics of the agent, the host, and the environment interact in a complex manner to determine the natural history of an infectious disease. This interaction determines the latent period, incubation time, and period of infectivity.

ENVIRONMENTAL FACTORS

The "environment" encompasses all areas in which the host and agent interact. This milieu has been categorized into three areas: physical, describing the geography and the climate; biologic, made up of plants, animals, and other life forms; and socioeconomic, which describes the interactions of host species. Such classification oversimplifies the identification and the characterization of the complex interplay of environmental factors.

As discussed previously, the environment modifies or dictates host, agent, reservoir and vector ranges, and behaviors. In this current age of jet travel, bodies of water, mountain ranges, and deserts no longer represent barriers to the dissemination of plants, animals, microbes, or disease. Influenza has caused pandemics spreading around the globe during a single season. Plants and animals may be transported either inadvertently (rodents, insects) or purposefully (kudzu, tropical fish) from indigenous areas to locations without natural predators, disease, or competition for food, allowing for unrestricted spread. Humans may also change their environment through travel or directly such as deforestation, building water reservoirs, or introducing new fauna or flora to their surroundings. Many of the recently recognized human pathogens have been associated with changes to our environment.

Temperature (average and range), humidity, precipitation, as well as altitude and latitude, which affect solar radiation and ultraviolet exposure, directly and indirectly

affect the risk of infection. Agents, reservoirs, and vectors generally tolerate a limited range of conditions. Hookworm ova deposited in the soil require both warmth and humid conditions for maturation and hatching. The temperature tolerance of malarial parasites and their mosquito vectors may not be identical with the parasites requiring relatively warmer temperatures for maturation. Thus some areas may be infested with the mosquito yet not be plagued by malaria. Global warming poses the theoretical spread of both the vector and the parasite to higher latitudes and altitudes.

The incidence of respiratory infections tends to be higher during the colder months in temperate areas and during the rainy season in the tropics. Even within the colder months, the relative incidence of many viral pathogens fluctuates. Rhinoviruses tend to cause outbreaks in the early fall and spring, while coronaviruses and influenza are more prominent in the winter. Increased crowding indoors during colder months presumably contributes to this seasonality, but changes in relative humidity may also be important. Viruses surrounded by a lipid bilayer (envelope) survive better under lower relative humidity conditions found in the coldest months.

Climate and geography and human manipulation also dictate the distribution of plant and animal life, which in turn, influences recreation, agriculture, occupational pursuits, diet, behavior, and economy. Plague, caused by the bacterium *Yersinia pestis*, has caused multiple pandemics devastating the human population and altering the course of history. Crowding and poor sanitation provided a suitable environment when in 1346 the black death rode into Europe from Central Asia in the guise of *Y. pestis*–infected rodents and their fleas transported by the returning Mongols. A more recent example is the emergence of Lyme disease caused by a spirochetal organism, *Borrelia burgdorferi*. Reclamation of farmland in the northeast United States for forest and housing communities has led to a juxtaposition of humans and deer, mice, and ticks, creating ideal conditions for disease transmission.

Socioeconomic factors are strongly linked with the risk of infectious agents transmitted by fecal-oral, respiratory, vertical, and sexual routes, but dissecting the etiology of this association are problematic. Housing, sanitation, population density, diet, level of education, occupation, availability of health services, and cultural attributes are just a few of the variables that contribute to these "socioeconomic" differences.

GEOGRAPHIC DISTRIBUTION OF DISEASE

The host, agent, vector, reservoir, and route of transmission all affect the geographic distribution of an infectious disease. Host behaviors (e.g., communal bathing), rituals (e.g., scarification), occupation (e.g., hunting, fishing), water supply, diet (e.g., raw fish), as well as pet and domestic animal exposure influence the geographic distribution of disease. Even population density and size influence disease persistence. A small, closed population of individuals previously infected by measles, which induces lifelong immunity, will not support further infection.

Geologic differences can also be attributed to temperature, humidity, and rainfall, as discussed earlier. The distribution of West African and East African trypanosomiasis is related to the breeding habits of the tsetse fly vectors. Most dramatically, the distribution of bartonellosis is limited by the range of the vector sandflies confined to the river valleys of the Andes Mountains at altitudes between 2000 and 8000 feet.

THE NATURAL HISTORY OF INFECTIOUS DISEASES

A variety of host responses may occur when a susceptible host is exposed to an infectious agent (Friis 1999) (Fig. 1–7). These are often depicted as an iceberg, with the largest number of responses occurring subclinically. Host responses are very variable, ranging from exposure without multiplication of the pathogen (e.g., response in a person who has received live polio vaccine to a challenge with wild polio) to colonization without infection

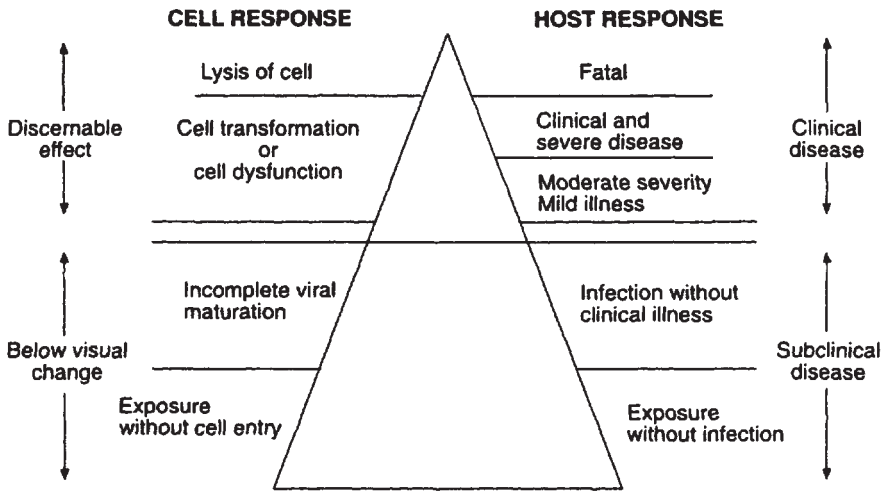

Figure 1–7. Iceberg concept of infection.
Source: Adapted from Friis and Sellers 1999.

(i.e., replication of the pathogen without invasion or host response) to illness (ranging from mild to severe). The severity of disease varies tremendously among infectious disease pathogens, being very low for some agents such as rhinoviruses (i.e., common cold) and very high for others such as smallpox (Fig. 1–8).

Clinical Infection

The factors that affect whether a person exposed to a pathogen will develop clinical illness include nonspecific and specific (i.e., antibody and cell-mediated) immunity, route of exposure, inoculum (i.e., dose of pathogen), and pathogenicity of the microbe. Once the microbe successfully invades the host, a period of replication occurs before clinical symptoms develop. The latent period is defined as the time from infection until the infectious period starts (Fig. 1–9).

The period of time from exposure to a source of infection to the first signs of symptoms of clinical illness is called the incubation

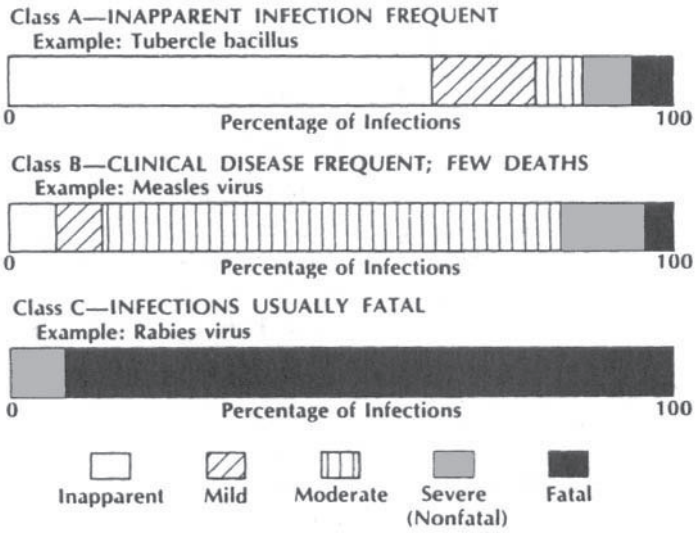

Figure 1–8. Distribution of clinical severity for different infectious diseases.
Source: Adapted from Mausner and Kramer 1985.

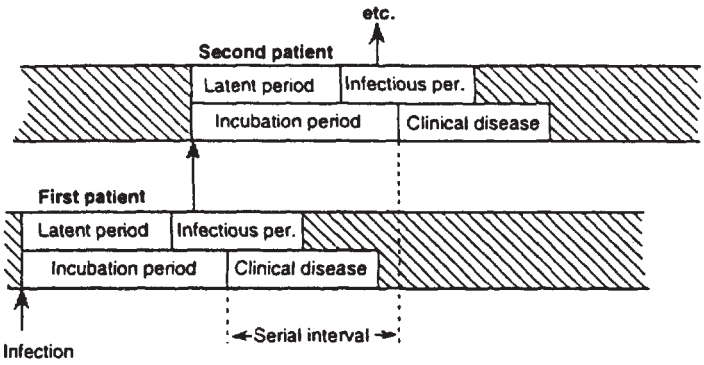

Figure 1–9. The relationship of some important time periods. *Source*: Adapted from Giesecke 1994.

period. The factors influencing the incubation period include the specific pathogen, inoculum dose, portal of entry, mechanism of tissue injury, and immune response. The incubation period may be calculated if the source of exposure is known (e.g., contaminated food source) or if multiple generations of infection occur via person-to-person transmission (Fig. 1–9). The incubation period is useful in infectious disease epidemiology because it helps define the agent causing an outbreak, aids in differentiating common-source from person-to-person transmission, impacts on the window of time during which postexposure prophylaxis (if available) may be effective, determines the time during which an exposed person is at risk for developing infection, and assists in determining the time during which the person is infectious.

The incubation period must be differentiated from the communicable period (i.e., the time during which the infected person may transmit infection) (Table 1–7). Persons infected with many viral agents become infectious prior to development of symptoms such as rash including such childhood illnesses as varicella, measles, and parvovirus B-19 (fifth disease). The communicable period may last only a few days or may persist for years (e.g., tuberculosis) or through the person's lifetime (e.g., human immunodeficiency virus, cytomegalovirus). It is important to note that not all infectious diseases are communicable (i.e., can be transmitted via person-to-person spread). This includes vector-borne diseases (e.g., malaria, Rocky Mountain spotted fever, Lyme disease) and some diseases acquired from the environment (e.g., tetanus, cryptococcal infection).

The infectiousness of an infected person refers to how likely that person is to transmit infection and is best measured by the secondary attack rate. Diseases such as measles and varicella have secondary attack rates above 80% among susceptible exposed persons. A disease such as leprosy is only rarely ($<<1\%$) communicable. The virulence of the pathogen refers to how likely the agent is to cause severe disease. Examples of diseases with low virulence include rhinoviruses (i.e., common cold) and parvoviruses (i.e., warts). Examples of diseases with mortality greater than 50% include smallpox, Ebola virus infection, and rabies. Infectiousness and virulence are not linked and infectious agents may be of low infectivity and low virulence (e.g., parvovirus), low infectivity and high virulence (e.g., leprosy), high infectivity and low virulence (e.g., rhinoviruses), and high infectivity and high virulence (e.g., smallpox).

PREVENTING INFECTIOUS DISEASES

The ultimate goal of studying infectious diseases is to implement interventions that prevent infection or ameliorate infection. In

Table 1–7 Incubation Periods and Period of Communicability for Selected Infectious Diseases

Disease	Average Incubation Period (range)	Period of Communicability
Diphtheria	2–5 d (occasionally longer)	Variable, <2 weeks to >4 weeks
Hepatitis A	28–30 d (15–50 d)	Latter half of incubation period till a few days after onset of jaundice
Hepatitis B	60–90 d (45–180 d)	Weeks prior to symptoms till clearance of HbsAg (days to lifelong)
Influenza	1–3 d	3–5 days from clinical onset in adults
Lyme disease	7–10 d (3–32 d)	No person-to-person transmission
Measles	~10 d (7–18 d)	1 day prior to prodromal period to 4 days after rash
Pertussis	7–20 d	Onset of cough till ~3 weeks
Rocky Mountain spotted fever	7–10 d (3–14 d)	No person-to-person transmission
Rubella	14–17 d (14–21 d)	1 week prior to rash till 4 days after onset of rash
Syphilis	~3 weeks (10 d–3 months)	During time when skin lesions of primary and secondary syphilis present
Typhoid fever	8–14 d (3 d–1 month)	As long as viable bacteria in excreta (usually from first week through convalescence, 2%–5% become chronic carriers)
Varicella	14–16 d (8–21 d)	1–2 days before rash till all lesions dried and crusted

Source: Adapted from Chin J., 2000.

this regard, it is important to remember that although many infections are successfully treated with antimicrobials, prevention is superior to therapy. Mausner and Kramer (1985) define several levels of prevention (Fig. 1–10). Primary prevention (appropriate in the stage of susceptibility) is prevention of disease by altering susceptibility or reducing exposure for susceptible individuals. Secondary prevention (applied in early disease, i.e., preclinical and clinical stages) is the early detection and treatment of disease. Tertiary prevention (appropriate in the stage of advanced disease or disability) is the alleviation of disability resulting from disease and attempts to restore effective functioning.

Primary Prevention

Prevention of the occurrence of disease consists of measures that fall into two major categories: general health promotion and specific protective measures (Mausner and Kramer 1985). General health promotion includes provision of conditions at home, work, and school that favor healthy living (e.g., good nutrition, adequate clothing, shelter, rest, and recreation). It also includes health education such as safe sex, preventive medicine, and personal hygiene. Specific health measures include immunizations, environmental sanitation (e.g., purification of water supplies), and protection against accidents and occupational hazards.

Immunizations are the best example of a successful primary intervention technique. Immunizations have been listed as the greatest public health achievement of the twentieth century (CDC 1999b). Vaccines currently recommended for universal use in the United States include mumps, measles, rubella, varicella, polio, *Haemophilus influenzae* type b, hepatitis B, diphtheria, pertussis, tetanus, and conjugate pneumococcal vaccine (CDC 2000). The universal use of vaccines in the United States has resulted in a dramatic decrease in vaccine preventable diseases (CDC 1999c) (Table 1–8). Smallpox has been eradicated from the world. Polio is likely to be eradicated in the next decade.

Prophylactic therapy of persons exposed

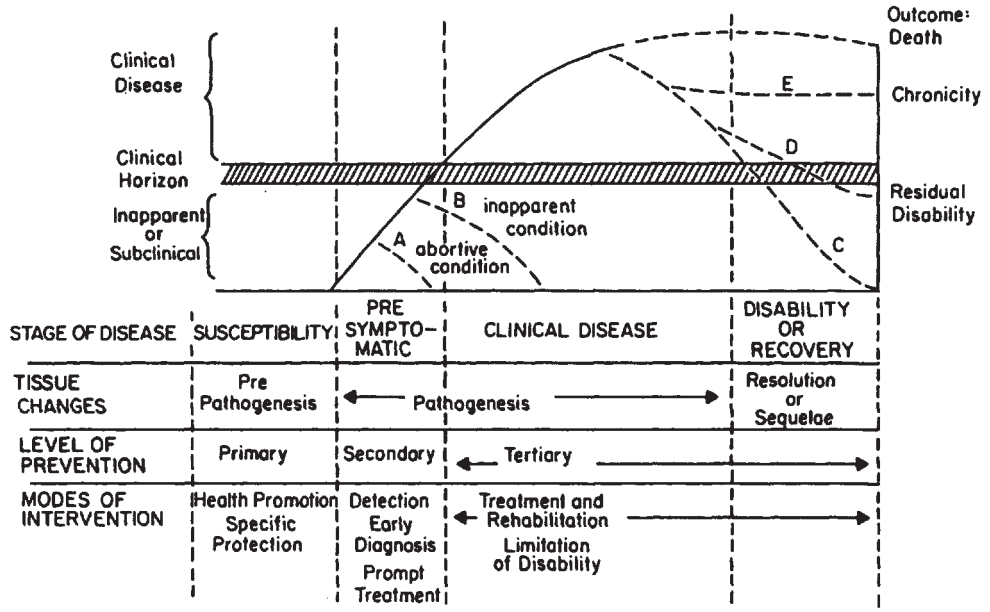

Figure 1–10. Schematic representation of the natural history of infection.
Source: Adapted from Mausner and Kramer 1985.

to infections who are in the incubating stage of illness has been highly successful in reducing the risks of disease transmission. Examples of infections for which postexposure prophylaxis is available and has been highly successful include hepatitis A, rabies, invasive meningococcal infection, and pertussis.

Secondary Prevention

Secondary prevention refers to the early detection and prompt treatment of disease. Infectious diseases represent the best example of the successful therapy of disease preventing morbidity and mortality. In addition to benefiting the sick infected person, treatment with antibiotics reduces the risk of contacts. For example, detection of chronic infections such as syphilis and tuberculosis and appropriate therapy may dramatically decrease the overall incidence of these diseases.

Tertiary Prevention

Tertiary prevention consists of limitation of disability and rehabilitation where disease has already occurred and left residual damage. For example, the use of artificial respirators saved many persons with paralytic polio in the era before polio vaccine. Rehabilitative services have improved the lives of persons with congenital infections such as rubella and syphilis.

SUMMARY

The examples provided are not intended to suggest that host, agent, and environmental factors contribute only to the epidemiology of unusual agents, transmitted by curious vectors in some isolated environmental niche. For example, the epidemiology of urinary tract infections, a common infection in adult women, exemplifies the complex interplay between host, agent, and environment.

The environment (community-acquired versus nosocomial or hospital-acquired) is a critical determinant in the incidence and relative contribution of various urinary pathogens. While *E. coli* and *Staphylococcus saprophyticus* are the predominant pathogens in an outpatient population, *Klebsiella*, *Enterobacter*, *Enterococcus*, and *Pseudomonas* are

Table 1–8 Impact of Vaccines Recommended Before 1990 for Universal Use in Children—United States

Disease	Baseline 20th Century Annual Morbidity	1998 Morbidity	% Decrease
Smallpox	48,164	0	100
Diphtheria	175,885	1	100
Pertussis	147,271	7405	95.0
Tetanus	1314	41	96.9
Poliomyelitis (paralytic)	16,316	0	100
Measles	503,282	100	100
Mumps	152,209	666	99.6
Rubella	47,745	364	99.2
Rubella (congenital)	823	7	99.1
Haemophilus influenzae type b	20,000	1194	94.0

Source: Adapted from the Centers for Disease Control and Prevention, 1999c.

more often isolated from hospitalized patients. Cross-infection, especially between patients with indwelling Foley catheters on broad spectrum antibiotics, contributes to this phenomenon.

Many host related factors affect the risk of urinary tract infections. The incidence of infection is greater in women than in men, who are more often affected as children and in old age. Women who inherit the P blood group have a receptor allowing for the adherence of certain fimbriated *E. coli.* Physiologic considerations include pregnancy, diabetes mellitus, and menopause, which increase the risk of infection. Compromised immune status and possibly altered inflammatory responses contribute to risk. For example, damage to the bladder epithelium by schistosomiasis may predispose to infection as may conditions that impair urinary flow such as catheters, prostatic enlargement, stones, and strictures from previous gonococcal infections. Sexual activity and instrumentation (i.e., use of indwelling catheters) of the urinary tract increase the risk of infection.

The most common urinary pathogens have virulence factors that contribute to their pathogenicity. Specific fimbriae, adhesions, motility, and urease production are factors that may confer virulence. Alteration in the normal flora may predispose to yeast infection, and broad spectrum antibiotic exposure may lead to infection with an antibiotic resistant organism.

In conclusion, the goal of public health is to alter the natural history of disease in order to prevent or ameliorate the disease. Infectious disease epidemiologists use an understanding of the biology of infectious diseases and the principles of epidemiology to design and conduct studies that ultimately will aid in the control of infections.

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