Animal-Related Health Risks

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- Read the enclosed course.
- Complete the questions at the end of the course.
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Faculty

Sharon Holt, DVM, MBA, ADN, graduated from Ohio University with a Bachelor's degree in fine art in 1977. She returned to Greater Hartford Community College and she earned an Associate degree in nursing in 1979. She later received a Master's in business administration in marketing management in 1983 from University of Hartford. She received her doctorate in veterinary medicine from Tufts University School of Veterinary Medicine in 1997. Dr. Holt has been working in wildlife medicine for 15 years and has lectured on the subject at the University of Massachusetts. Her nursing background includes acute care, emergency room, critical care, clinic settings, and case management for a non-profit visiting nurse association. She currently owns her own veterinary practice in Massachusetts and provides veterinary vaccine clinics in western Massachusetts.

Faculty Disclosure

Contributing faculty, Sharon Holt, DVM, MBA, ADN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, nurses, and allied health staff involved in identifying, treating, and preventing zoonotic diseases, including West Nile virus, Lyme disease, and avian influenza.

Accreditations & Approvals

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Course Objective

The purpose of this course is to increase the awareness of zoonotic diseases and their management in both prevention and care. There are many potential diseases that can spread from animals to humans, and with basic precautions, most zoonoses are preventable or at least avoidable. The public has many misconceptions about what to do after a potential exposure to a zoonotic source, and healthcare professionals are often the first to help and answer questions.

Learning Objectives

Upon completion of this course, you should be able to:

1. Reflect on the history of zoonotic diseases.
2. Define the hosts and host characteristics associated with zoonotic diseases.
3. Compare the types of vectors and transmission of zoonotic diseases.
4. Discuss the classification of zoonotic diseases.
5. Identify the common pathogens involved in the spread of infection from animals to humans.
6. Discuss the clinical presentation, diagnosis, and treatment of Lyme disease.
7. Outline characteristics and treatment of other tickborne zoonotic diseases, including tularemia, Rocky Mountain spotted fever (RMSF), and ehrlichiosis.
8. Discuss the clinical presentation, diagnosis, and treatment of West Nile virus infection.
9. Describe the characteristics and treatment of other viral zoonotic diseases, including avian influenza.
10. Discuss the background, clinical presentation, and prevention of bovine spongiform encephalitis (BSE) and its resulting disease in humans, variant Creutzfeldt-Jakob disease (vCJD).
11. Identify some of the common protozoal zoonotic diseases.
12. Describe the characteristics and treatment of anthrax infection.
13. Identify other common bacterial zoonotic diseases, including cholera.
14. Recall the characteristics of common parasitic zoonotic diseases and appropriate treatment.
15. Outline the role of an interpreter in treating non-English-proficient patients.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

In this era of globalization and rapid world travel, diseases that were once localized to a country or region or that were uncommon in developed countries are now found in new or widespread areas. Examples include avian influenza, West Nile encephalitis, plague, "mad cow disease," rabies, and to a lesser extent, Lyme disease. These and many other diseases belong to a category known as zoonoses, or zoonotic diseases.

A zoonosis is an infection transmitted from a vertebrate animal to humans. The animal is the natural host and may simply be a carrier of the infectious agent without suffering any disease from the infection itself. This is the case in many diseases that are persistently difficult to control, such as infection with certain roundworms. The host may act only as the reservoir, with a vector being the actual source of the exposure and subsequent infection. Some diseases, such as Lyme disease, babesiosis, and Rocky Mountain spotted fever (RMSF), are transmitted to humans and other non-target hosts through insect (arthropod) vectors. The animal host may become ill from the infection, but the signs of illness can be quite different in human cases or the organism may target different organ systems when infecting other than the definitive host animal. The environment and degree of susceptibility will also determine whether transmission actually occurs after an exposure. Immunosuppressed individuals, the elderly, children, and pregnant women may have a greater susceptibility to illness caused by some zoonotic infections.

HISTORY

Several zoonoses have been known and documented as animal-to-human diseases from much earlier times. Rabies was known and written of many centuries ago, as were ringworm, tetanus, and plague (*Yersinia pestis*). For example, the bite of a "mad dog" was known to transmit rabies in the 1300s, though obviously the knowledge of the virus came much more recently [1]. The invention of the light microscope by Leeuwenhoek in the late 1600s allowed visualization of the agents of zoonoses for the first time. Bacteria and parasites could be seen, and the connection between a disease and its causative agent could be confirmed.

Tapeworms, liver flukes, and roundworms were readily seen with the early microscopes. Linnaeus began classification in the mid-1700s and was the first to describe many zoonotic parasites in an early edition of *Systema Naturae* [2]. The smaller parasites have been identified and described as the microscope's capability has advanced to recognize the role of microscopic agents in zoonotic diseases. Protozoa of zoonotic importance were not identified until the early 1900s, and smaller organisms are still being discovered today.

More refined microscopes and the use of stains allowed for the description of bacterial agents of disease in the 1870s. The ability to culture bacteria began in 1881, and most bacteria were quickly described in the next 20 years [3]. The ability to culture an organism allowed confirmation that the same agent present in a host animal could be the causative agent of a human disease. This is the basis of Koch's postulate: confirmation of the disease by isolating the proposed agent and then reproducing the disease by introducing the isolate into a host animal [4].

In 1934, the electron microscope allowed viruses to be visualized for the first time [5]. Most were known to exist from cellular changes seen with the light microscope, but once the viruses could be visually identified, they were quickly classified. If a carrier state exists or if only a small number of the host's population carry the disease, discovery of the etiology is more difficult. There may be an intermediate host or vector yet to be identified that is involved in the transmission.

It is interesting to note that various religions have historically had dietary restrictions that had the effect of curtailing the spread of foodborne zoonoses by limiting certain food products. For example, Jewish and Muslim religions banned the consumption of pork and other animals that rooted for food. Certain insect species that carry parasitic diseases can be accidentally ingested when the food animal roots in the ground. In some cases, the infected insect may be a part of the animal's regular diet.

Many processes and even whole industries have been developed as public health measures to deal with zoonoses. Pasteurization of milk, meat inspection, vaccinations, and insect control measures are examples of public health practices in the United States that are specifically aimed at preventing zoonotic diseases. Individual steps can be taken as well, such as boiling water that is of uncertain purity and cooking meat and fish properly. Improving the health of the public will require more education about food and safety issues if many of the dangerous zoonoses are to be avoided.

DEFINITIONS

HOST CHARACTERISTICS

A host is an animal (including humans) that can support an infective agent of a zoonotic disease. Many agents require more than one host to complete their lifecycle. The definitive host is an animal that supports an organism in the final reproduction phase of its lifecycle. Without the definitive host, normal reproduction of the organism will not occur. The secondary or intermediate host is needed in multiple lifecycle agents for some phase of their development. For example, the dog flea (*Ctenocephalides canis*) and the cat flea (*Ctenocephalides felis*) are the intermediate hosts for the dog tapeworm *Dipylidium caninum*. Ingestion of the flea, which carries the infective agent, leads to infection with the tapeworm.

A dead-end or aberrant host is one in which the organism can survive, perhaps only briefly, but from which it cannot reproduce or transmit disease. Such is the case with eastern equine encephalomyelitis (EEE) and the horse. The virus cannot continue to spread from an infected horse because it will kill the animal before it has a chance to reproduce. The horse in this situation is a sentinel for EEE, because the incubation period is shorter in horses than in humans. Deaths in horses from the infection will be seen prior to documented human cases in the same area. Many horses are vaccinated against the disease in endemic areas, so the number of sentinels may be very small. Eastern encephalomyelitis (EE) in humans carries a high case fatality rate (33% to 70%), and the sentinel serves as an early warning that human cases may soon be presenting at emergency rooms in the same vicinity [6]. Transmission does not occur between horse and human, as both are aberrant hosts. Another animal must serve as the reservoir. In many cases, the zoonosis is seen only sporadically because the vector that transmits the disease is not present. In addition, the reservoir can vary in its carrier status from year to year.

An animal may be the natural host for the disease, and humans or other animals may be aberrant hosts. The actual signs and symptoms of the disease in the aberrant host may be a result of the organism's inability to support itself in the wrong animal host. The aberrant host may be significantly different anatomically or physiologically, making the agent unable to find a suitable site in which to exist. Digestive tracts vary tremendously between different mammalian, avian, and reptilian species. This can lead to a disease agent searching for a part in the aberrant host's body that is similar to the natural host. The aberrant host may not even have the same organ system that the agent requires to grow. This is the case in diseases that are manifested by migration of parasites throughout organs while they search for a target organ or system that is reasonably similar to that of the regular host. In some cases, the agent is in an environment so unlike what it is searching for that it will not produce a zoonosis. Humans are constantly exposed to many agents that do not affect us, such as heartworm.

Parasites have evolved through natural selection in ways that, under normal circumstances, will not render a healthy definitive host incapacitated. Natural selection eliminates parasites that kill their hosts before reproduction and transmission can be successfully achieved. Most have a symbiotic relationship and affect the animal in subtle ways, such as slower weight gain or a decrease in egg production. For an animal to actually appear unhealthy usually requires a fairly heavy infestation with parasites. Obviously, seriously infected animals or those sick from other causes would be more vulnerable to the effects of a heavy parasite load.

Like parasitic diseases, most bacterial and fungal infections tend not to impact the definitive host in such a severe manner as to be immediately noticeable. Some zoonotic bacteria are normal flora or commensals in one animal and pathogenic in another species. *Pasteurella* spp. in a cat's mouth are considered normal flora but can be a difficult-to-treat zoonosis when transferred to a human via a bite wound. *Escherichia coli* contamination of meat is another example of normal flora from an animal making the consumer ill.

Viruses produce more variability in the degree of illness seen in the hosts. Reproduction of a virus occurs at the cellular level in the host, with either a cell's RNA or DNA. There are groups of RNA viruses that are transmitted through arthropod vectors, but most require some type of direct contact, such as a bite wound. Not being independent organisms, these viruses require direct transmission or a vector that can transmit effectively while maintaining the viability of the virus. Most are sensitive to temperature fluctuations and other environmental factors.

VECTORS

An insect that allows multiplication or growth of an agent while it is in the host is a biologic vector, as with the earlier example of the flea. Ticks and mosquitoes are biologic vectors for many zoonoses. Some of the more serious zoonoses transmitted by arthropods are Lyme disease, RMSF, Q fever, malaria, plague, and West Nile encephalitis. Insects can also transmit less serious diseases, such as tapeworms and some species of trematodes (parasitic flatworms).

Mechanical vectors can be something as simple as shoes carrying disease from work to home. Airborne sources or fomites can transmit diseases such as tuberculosis from animal to human or from human to animal. Meat or other animal-derived consumer products can carry zoonotic agents. For example, pork products are likely sources of trichinosis.

TRANSMISSION

Transmission of zoonoses can be either direct or indirect. A disease that is directly transmitted from an animal to humans usually requires close or intimate contact. As examples, direct transmission occurs when the act of touching a ringworm lesion on a cat directly results in infection, or when rabies is transmitted from the bite of a rabid animal. Indirect transmission occurs with the presence of a vector between animal and human. Insects, inanimate objects, or animal food products can all be sources of indirect transmission of a zoonosis. Some insects can transmit an infectious agent in their bite, as in the case of ticks and mosquitoes. Flies, such as the housefly, can carry many pathogenic organisms in their mouth parts and on their feet. They can spread a zoonosis by contaminating open wounds or other breaks in the skin of the host. Many arthropods, such as the horse fly (*Tabanus* spp.), bite and spread disease in the same manner.

There are associated risk factors that determine transmission rate. As noted, immunocompromised individuals, the elderly, and the very young may be at greater risk, depending on the zoonosis. Pregnant women are at risk for zoonoses that can cross placental barriers or potentially cause spontaneous abortion.

The time of year affects the shedding rates of some parasites. Many viruses and bacteria have temperature preferences that affect the time of year that they are most frequently seen. Some parasites reproduce at intervals that coincide with their definitive host's reproduction cycle. In this way, they increase their numbers when more hosts are potentially less able to combat the organism with natural immune capabilities. The environment will also affect the transmission rate of some organisms. Sunlight, pH, air quality, humidity, and temperature are classic variables used to determine the degree of transmission rate for a zoonosis and the agent's survivability in the environment.

State public health departments have surveillance plans for the more serious zoonotic diseases [7]. National public health concerns are also under the surveillance of the Centers for Disease Control and Prevention (CDC) and other organizations [7]. Global surveillance is monitored by several international concerns, including the World Health Organization (WHO) [7]. Depending on the degree of risk of a particular disease and how serious a threat it is, a report of a zoonosis will be considered an epidemic when a predetermined number has been exceeded. In animals, this is called an epizootic. If the disease occurs worldwide, it is referred to as a pandemic (panzootic). Even when a zoonosis is only an individual exposure without associated serious risks, the state public health department may be interested in being informed of the incidence, if only for monitoring purposes.

MORBIDITY, PREVALENCE, AND MORTALITY

Morbidity refers to individuals who become ill in the susceptible population in any outbreak. The susceptible population might be an isolated village or an entire country, depending on the disease and its transmission characteristics. The mortality rate is the number of individuals in the susceptible population who die of the illness over a specific period of time. The prevalence rate is the number of individuals out of the potential population who are ill at any one time or specified period of time. The case fatality rate is simply the fraction of known affected individuals who die, expressed as a percentage; for example, a zoonotic outbreak of 50 confirmed cases with 5 deaths would have a case fatality rate of 10%. This percentage gives a sense of the severity of the zoonosis, especially when the number of actual cases may be low. For example, Ebola carries a high case fatality rate, 80% to 90% in some regions, and rabies is nearly 100% fatal when untreated anywhere it occurs [8; 9].

CLASSIFICATION AND REPORTING

The scope and multitude of zoonotic diseases are too great for a single course to cover. There are a tremendous number of zoonoses that are not seen commonly in the United States but that are of major importance in other countries. These will not be addressed in detail, but healthcare professionals should have an idea of the basic concepts of the zoonoses and the agents that cause them. This knowledge can help serve the patient who has a recent travel history outside the United States and presents with a mysterious illness. If the illness is unexplained, a zoonotic disease may be considered when taking the history. Contacting an appropriate agency for assistance may be indicated. The CDC can provide information about specific diseases in different countries if a local resource, such as the Public Health Office, is not able to help. The United States Department of Agriculture (USDA) can also assist in identifying specific zoonoses prevalent in different countries and can caution travelers about what types of things to avoid in terms of food and animal products while traveling. In addition, the USDA carefully monitors agricultural products brought into the country.

There are many ways of categorizing common zoonoses. In this course, zoonoses will be categorized by causative agent initially, and some important specific zoonoses will be discussed in detail. Parasites are responsible for many zoonotic diseases, so the type of illness manifested can be similar for different species of parasite [10]. Bacterial agents are also a common etiology, as are viruses [10]. Although it is commonly overlooked, humans can transmit diseases to animals as well. For example, tuberculosis has been passed to elephants in zoos and primates in research facilities.

Some zoonoses are reportable by law for either animal or human cases. Typhus and tuberculosis are prime examples [11]. A classification system for zoonotic disease cases has been developed, with a rank of 1 to 5, with subclassifications that should be utilized when determining if a case report or notification is necessary (***Table 1***). This classification system has been agreed upon internationally and drafted by the American Public Health Association (APHA), which derived it from guidelines written by the WHO [12]. International animal zoonoses with serious risk are reportable to the Office International des Epizooties (OIE) [12]. Generally, if in doubt, there is no harm in reporting, because the case report could be helpful at some later date.

AGENTS

Parasites

Parasites that can cause disease directly in the host (not just transmission of a zoonosis) are represented in five different phyla: the pentastomida, nematodes, trematodes, cestodes, and protozoa (***Table 2***) [10].

The pentastomida are very primitive, worm-like parasites that primarily infect the lungs of reptiles. Human infection is by the larval stage. The spleen, liver, and/or lungs may be infected, but fortunately, the disease is self-limiting and usually not significant. While no fatalities have been reported, because any parasite is a foreign protein, a hypersensitivity reaction is a possible outcome with any of the parasitic zoonoses.

Nematodes are commonly referred to as roundworms, with hookworm being a common example. There are many zoonotic forms of nematode infections. One example is trichinosis, which will be discussed in detail later in this course. In general, most nematode zoonoses are transmitted through ingestion of the egg stage of the organism [10]. When in the feces, the eggs will hatch into the infective larval stage after 24 hours in most species. Occasionally, the larval phase of the parasite will penetrate the

CLASSIFICATION SYSTEM FOR REPORTING ZOONOTIC CASES			
Class	**Reporting Requirement**	**Subclass**	**Types of Diseases/Conditions**
1	Case report is universally required by International Health Regulations (IHR) or as a Disease Under Surveillance by the World Health Organization (WHO).	1A	Diseases subject to IHR or those that are internationally important and are quarantinable (e.g., plague, yellow fever)
		1B	Diseases under surveillance by the WHO (e.g., some forms of typhus)
2	Case report is regularly required whenever disease occurs.	2A	Notification to local health officials by expedient means (i.e., telephone report). Quick reporting could make a difference in preventing additional cases. Botulism or other clostridial infections fall into this category.
		2B	Notification by most practical means, as with trichinosis
3	Selectively reportable in recognized endemic areas. These are diseases that are not an issue in some locales and at the same time are significant problems in other areas.	3A	Where it is reportable, treat the disease as a 2A (e.g., Lyme disease in some areas)
		3B	Where it is reportable, treat as with 2B (e.g., Rocky Mountain spotted fever)
4	Obligatory report of epidemics. No case report is required, but make a prompt telephone report of unknown outbreaks or other diseases of public health importance.	NA	Food poisoning
5	Official report is not ordinarily justifiable. Those diseases are not as easily transmitted and/or are sporadic in occurrence. Outbreaks do not have control measures and are of low risk, but epidemiological interest exists.	NA	Common cold

Source: [12] *Table 1*

skin, usually through the sole of the foot because an individual has walked barefoot where larval forms of the nematode are present. This form of infection is referred to as cutaneous larval migrans. It is one of the better reasons not to walk barefoot in a city park, an unfamiliar backyard, or a veterinarian's office.

Trematodes, commonly called flukes or flatworms, are usually transmitted via ingestion [10]. As with the nematodes, some species can penetrate the skin and migrate to various organs. Most hatch in the gastrointestinal tract and migrate to other areas of the body to cause infection, unless they penetrate the skin. The liver and lungs are the most commonly affected tissues in a human host by the adult form of the agent.

Cestodes or tapeworms are primarily gastrointestinal parasites, but one type (*Taenia* spp.) can encyst in organs and cause severe disease, with occasional associated fatalities in humans [13]. These parasites reproduce by shedding segments (proglottids), so some species can autoinfect the host via the fecal-oral route. Some transmit by biologic vectors that are ingested by other hosts.

Protozoa are well documented as gastrointestinal parasites and can cause serious levels of disease [10]. Being the smallest of the parasites, they can inhabit a number of different locations in a host, including red blood cells (e.g., malaria) and the mucosal cells of the intestines. Another example is *Giardia*, which inhabit the brush border of intestinal epithelial cells.

PARASITIC ZOONOSES	
Agent	**Disease in Humans**
Nematodes	
Ancylostoma braziliense	Cutaneous larva migrans
Ancylostoma caninum	Cutaneous larva migrans
Anisakis marina	Anisakiasis
Baylisascaris procyonis	Visceral larva migrans
Bunostomum phlebotomum	Cutaneous larva migrans
Capillaria aerophila	Capillariasis
Capillaria hepatica	Capillariasis
Haemonchus contortus	Trichostrongyliasis
Ostertagia spp.	Trichostrongyliasis
Toxocara canis	Visceral larva migrans
Toxocara cati	Visceral larva migrans
Trichinella spiralis	Trichinosis
Uncinaria stenocephala	Cutaneous larva migrans
Trematodes	
Echinostoma ilocanum	Echinostomiasis
Fasciola gigantica	Fascioliasis
Fasciola hepatica	Fascioliasis
Fasciolopsis buski	Fasciolopsiasis
Paragonimus westermani	Paragonimiasis
Schistosoma japonicum	Schistosomiasis
Schistosoma mansoni	Schistosomiasis
Cestodes	
Diphyllobothrium latum	Fish tapeworm
Diphyllobothrium spp.	Sparganosis
Dipylidium caninum	Dog tapeworm
Echinococcus granulosus	Hydatidosis
Echinococcus multilocularis	Hydatidosis
Taenia saginata	Beef tapeworm
Taenia solium	Pork tapeworm
Protozoa	
Babesia bovis	Piroplasmosis/Babesiosis
Babesia microti	Piroplasmosis/Babesiosis
Balantidium coli	Balantidiasis
Cryptosporidium parvum	Cryptosporidiosis
Entamoeba histolytica	Amebiasis
Giardia lamblia (intestinalis)	Giardiasis
Leishmania mexicana	American leishmaniasis
Plasmodium spp.	Malaria
Sarcocystis hominis (bovihominis)	Sarcocystosis
Toxoplasma gondii	Toxoplasmosis
Source: Compiled by Author	*Table 2*

They produce diarrhea, which can be mild to severe depending on the agent causing the disease, the parasite burden present, and the underlying state of health of the host. Most protozoa spread via the fecal-oral route. Unlike the larger intestinal parasites, which are identified using routine direct stool sampling techniques where the eggs are "floated" up out of the fecal material for identification, protozoa can be difficult to detect because of their very small size.

Bacteria

The range of zoonotic diseases from bacteria is wider than that from parasites, although the total number of agents is less. Cholera, tularemia, shigellosis, salmonellosis, plague, and cat scratch fever are examples of gram-negative bacteria that can cause serious zoonotic diseases (***Table 3***). Gram-positive bacterial zoonoses include botulism, anthrax, Hansen disease (leprosy), and listeriosis. Diseases caused by spirochetes (specific types of gram-negative bacteria) include Lyme disease and leptospirosis. Some of the rickettsial diseases (gram-negative) are Rocky Mountain spotted fever, Q fever, and psittacosis.

Bacteria can be transmitted via all of the routes discussed, and more than one avenue of transmission may occur with the same agent. For example, tularemia can be transmitted by a bite wound from an infected cat or rabbit or from an arthropod source [14]. Tuberculosis is primarily transmitted by inhalation but can also be transmitted by the ingestion of raw milk [14].

Most bacterial zoonoses are treatable with appropriate antibiotics, antitoxin where applicable (e.g., tetanus), and supportive care [14]. However, recognition of the disease in a timely fashion is critical for a positive outcome in some bacterial zoonoses that can be fatal if not treated promptly.

Viruses

There are many viruses that may be transmitted from animals to humans (***Table 4***). Viral transmission can be through direct contact, bites, arthropods, airborne inhalants, and other vectors. Treatment and prevention are specific to each disease. Some, such as rabies, have vaccines available, but most must be managed by careful preventive measures and universal precautions rather than pre- or postexposure treatments.

Zoonotic DNA viruses of concern include herpes simian B and T virus. Simian B virus causes simian herpes in humans, which carries a 70% to 85% case fatality rate [15]. A bite wound from an infected monkey or contamination of broken skin with saliva is usually required for transmission; however, it is now known that infection can also occur though contamination of the mucous membranes or eyes [15]. Fortunately, people generally do not have direct contact with the species of monkeys that are carriers of herpes B unless they work in zoos or research facilities that house them.

Most zoonotic viruses are RNA viruses. Rabies, Ebola, yellow fever, and the hemorrhagic fevers are examples of RNA viruses with serious zoonotic potential. Other viral zoonoses are fairly common and include West Nile encephalopathy, avian influenza, and the hantavirus syndromes. These will be discussed in detail later in this course.

BACTERIAL ZOONOSES	
Agent	**Disease in Humans**
Gram-Negative Bacteria	
Aeromonas hydrophila	Vibriosis
Bartonella henselae	Cat scratch fever
Brucella abortus	Brucellosis
Brucella canis	Brucellosis
Brucella melitensis	Brucellosis
Brucella suis	Brucellosis
Campylobacter jejuni	Campylobacter enteritis
Escherichia coli	Colibacillosis
Francisella tularensis	Tularemia
Pasteurella haemolytica	Pasteurellosis
Pasteurella multocida	Pasteurellosis
Salmonella arizonae	Arizona infection
Salmonella spp.	Salmonellosis
Shigella spp.	Shigellosis
Vibrio spp.	Vibriosis/cholera
Yersinia enterocolitica	Yersiniosis
Yersinia pestis	Plague
Yersinia pseudotuberculosis	Yersiniosis
Gram-Positive Bacteria	
Bacillus anthracis	Anthrax
Clostridium spp.	Clostridial histotoxic infection
Clostridium botulinum	Botulism
Clostridium tetani	Tetanus
Erysipelothrix rhusiopathiae	Erysipeloid
Listeria monocytogenes	Listeriosis
Mycobacterium spp.	Tuberculosis
Mycobacterium leprae	Hansen disease (leprosy)
Staphylococcus aureus	Staphylococcosis/food poisoning
Streptococcus spp.	Streptococcosis
Spirochetes	
Borrelia spp.	Lyme disease
Borrelia spp.	Endemic relapsing fever
Leptospira spp.	Leptospirosis
Rickettsiales	
Chlamydia psittaci	Psittacosis
Coxiella burnetii	Q fever
Ehrlichia chaffeensis	Ehrlichiosis
Ehrlichia ewingii	Ehrlichiosis
Rickettsia rickettsii	Rocky Mountain spotted fever (RMSF)
Rickettsia typhi	Murine typhus
Source: Compiled by Author	*Table 3*

VIRAL ZOONOSES	
Agent	**Disease in Humans**
DNA Virus	
Herpes viruses B and T	Simian herpes
RNA Viruses	
Arthropod-borne (Arboviruses) Group A Group B	Encephalomyelitis (EE) St. Louis encephalitis Yellow fever
Coronaviruses (novel type)	SARS, MERS, COVID-19
Chikungunya virus	Chikungunya fever
Ebola virus	Ebola disease
Hepatitis A virus	Hepatitis infection
Influenza virus	Influenza infection Avian influenza
Lymphocytic choriomeningitis virus	Lymphocytic choriomeningitis
Marburg virus	Marburg disease
Rabies virus	Rabies

Source: Compiled by Author *Table 4*

TICKBORNE DISEASES

Tickborne zoonoses include Lyme disease, Rocky Mountain spotted fever (RMSF), tularemia, and babesiosis. These diseases are of significant medical interest.

LYME DISEASE

Lyme disease was first described as a zoonotic disease in 1975, although the rash common to this illness was originally documented in Sweden in 1909 [1]. After being reported as an arthritic process in a cluster of children in and around Lyme, Connecticut, it has become the most commonly reported vector-borne disease in the United States [16; 17]. In 2020, state health departments reported 18,000 confirmed or probable cases of Lyme disease to the CDC [18]. However, the true incidence of Lyme disease is estimated to be 8 to 10 times higher, with greater than five million diagnostic tests being performed every year [19]. The geographic distribution of high incidence areas has expanded over the past decade as the number of counties with an incidence of 10 or more confirmed cases per 100,000 persons increased from 324 in 2008 to 550 in 2020. The disease is concentrated heavily in the Northeast, middle Atlantic, and upper Midwest. However, case counts in most of these states have remained stable or decreased during the reporting period. In contrast, case counts have increased in states that neighbor those with high incidence [17]. Pennsylvania has had the greatest number of cases in recent years [18].

The primary agent of Lyme disease is the spirochetal organism *Borrelia burgdorferi*; however, in the United States, there are at least one other bacteria (*Borrelia mayonii*), two other known genospecies, and as many as 40 disease-causing subspecies of *Borrelia* [20; 21; 22]. The host reservoir, in most instances, appears to be the white-footed mouse (*Peromyscus leucopus*) [23]. White-footed mice are small and reddish brown in color with a tail that is usually shorter than their body length [24]. They do not commonly come into human habitation sites, preferring stone walls, fields, brush piles, and even old birds' nests as places in which to live. They are not likely to carry the agent or vector into a home as they tend to avoid such habitats.

The primary Lyme disease vectors are the ticks *Ixodes scapularis* or *Ixodes dammini* in the eastern United States and *Ixodes pacificus* in the West [18]. Other *Ixodes* spp. ticks, also known as deer ticks, can carry the organism in some of the less disease-prevalent areas [25; 26].

The vector has an interesting two-host lifecycle requiring both the white-footed mouse and the white tail deer (*Odocoileus virginianus*). The tick spends the first two years on the mouse host, and then it spends its third and final year on the deer, which is the definitive host. The spirochete *B. burgdorferi* does not reproduce well in the deer, only in the mouse. Disease rates are much higher in areas where both the white-footed mouse and high deer populations coexist. Research has shown it takes the nymph stage of the tick 72 hours and the adult 96 hours to transmit the disease to humans [16]. Finding a tick on a body can be difficult, considering a nymph, when fully engorged, is the size of a poppy seed, and more than 15 adults could fit on a dime. In addition, the saliva of the tick contains a local anesthetic agent, so the bite is not usually felt [16]. Fortunately, ticks in the smaller larval phase do not transmit disease. The larva has not yet fed on the reservoir and therefore cannot contain the spirochete.

As noted, Lyme disease is the leading arthropod zoonosis reported in the United States [18]. Although there is a year-round occurrence of Lyme disease, the ticks are most active in the spring and fall, when the ambient daytime temperature is in the 50s and the ticks have reached the maturation stage and must seek their final host. New cases cluster around the months after the spring and fall tick activity periods. Ticks climb up grasses and low shrubs and wait for deer to brush past or stop to browse. They will drop onto any animal that comes close enough to touch the vegetation where they are waiting. Ticks in the nymph stage tend to crawl on the lower grasses, as they are coming from ground dwelling mice. Adult ticks have more commonly dropped off a deer or an aberrant host. The adults are more adept at moving greater distances and can climb higher in the vegetation. Adult ticks will remain on the deer until engorged and will drop off when ready to lay their eggs. It is important to remove engorged adult ticks without rupturing or smashing the body, as this could release thousands of eggs.

Lyme disease has an extremely variable expression between species [27]. The hosts of *B. burgdorferi* can be asymptomatic or carriers. No outward signs of disease have been reported in mice or deer, but because they are wild animals, there may be unrecorded signs. Among domestic animals, the dog is the most commonly affected; however, no rash is seen in dogs, even with experimentally inoculated animals.

Diagnosis

Humans can have varied and severe reactions to Lyme disease; most organ systems have the potential to be affected. *B. burgdorferi* has an affinity for cartilage cells and the transitional cells of the urinary bladder.

The first signs of Lyme disease are usually flu-like symptoms and joint pain. In an elderly person, preexisting arthritis may complicate early diagnosis. Three distinct stages have been described in patients with untreated infections [27]. Stage 1 (early localized stage) occurs 3 to 30 days after the tick bite and is associated with the appearance of the characteristic "bull's-eye" skin lesion of erythema migrans. Various sources estimate that approximately 70% to 80% of the documented infections will have the characteristic expanding rash [18]. This initial stage may show the nonspecific clinical signs of malaise, headache, arthralgia, fever, myalgia, and regional lymphadenopathy. If they never see a rash, many patients will not consider Lyme disease as the source of their symptoms.

Stage 2 (early disseminated stage) develops through hematogenous spread and is evident after days to weeks post-tick bite [18; 28]. Possible manifestations include subtle encephalitis with headache and cognitive difficulty, stiff neck, cranial neuropathy (with facial palsy being a common finding), cerebellar ataxia, motor and sensory radiculoneuritis, myelitis, and visual disturbances. This stage is associated with

acute neuroborreliosis in a significant number of cases [18; 28]. Most patients with neuroborreliosis are affected by meningitis, facial nerve palsy, and/or radiculitis, with only a limited number having parenchymal spinal cord or brain involvement [29].

Stage 3 (late disseminated stage) is the chronic phase, which may appear months to years after the initial infection [18]. Various names for this stage have been proposed and are currently used, including post-Lyme syndrome, post-Lyme disease syndrome, post-treatment chronic Lyme disease, or chronic Lyme disease [29]. One of the most common findings in this stage is oligoarthritis, with the knee being the most frequently affected joint, although other joints can become inflamed [18; 28]. Pain is usually out of proportion to the swelling [18]. Musculoskeletal pain, spinal radiculopathy with paresthesias, encephalopathy, and the symptom complex of fibromyalgia or chronic fatigue syndrome may be present. This stage is associated with chronic borreliosis; consequently, cardiac arrhythmias, respiratory compromise, and spread to the entire nervous system are liable to occur. It is suspected that fibromyalgia may be a long-term sequela to chronic Lyme disease. If untreated, chronic expression results in potentially crippling arthritic changes as well as organ system involvement. The organism can establish itself in the bladder wall and reoccur with another exposure or stress from another illness [25].

Concurrent infection with other tickborne diseases occurs in approximately 4% of Lyme-positive patients [30]. The combination of Lyme disease and either *Ehrlichia chaffeensis*, or an as yet undefined *Ehrlichia* or babesiosis can cause overwhelming illness for some individuals. Those concurrently infected will have the additional discomfort of dealing with changes in their circulatory system, as erythrocytes or leukocytes are infected and cannot deal with the demands of mounting an immune response to Lyme disease. *Ehrlichia* infections usually produce a high fever in the initial infection period [31]. The rare patients who go on to develop acute respiratory distress syndrome have a high correlation of concurrent infection with *Ehrlichia* [32].

Many of the symptoms of Lyme disease are caused by the body's immune system. Because the spirochete infects the cartilage cells intracellularly, the neutrophils concentrate in the region, resulting in a pain similar to the pain of rheumatoid arthritis. Damage to the cartilage cell and subsequent pain is caused by neutrophils attacking both infected and healthy cells. The amount of discomfort and joint destruction varies among patients depending upon their individual immune response.

Clinical suspicion from history, signs, and symptoms is paramount in the diagnosis of Lyme disease [18]. Patients can present with a variety of clinical findings, and not all classic signs or symptoms are present in those with active Lyme disease. If patients have a rash and recognize it as visceral migrans, it may be too early for other symptoms to be noted or for testing to yield positive results. Additionally, early but inadequate antibiotic treatment may prevent full antibody development in patients who are still clinically ill [33]. Varying severity and expression can make Lyme disease difficult to diagnose in some patients. The criteria as set by the CDC do not always fit the signs, symptoms, and test results. This can be very frustrating for patients as well as medical professionals. A few good diagnostic procedures are available, although they require diligent interpretation.

Laboratory Tests

The CDC recommends using diagnostic tests for Lyme disease that have been cleared or approved by the U.S. Food and Drug Administration (FDA) [34]. The CDC recommends sampling blood with a two-step process. Both steps are required and can be done using the same blood sample [35]. The first test should include either an enzyme-linked immunosorbent assay (ELISA) or, rarely, an indirect immunofluorescence assay (IFA); however, false positives occur with cross reactions to other spirochetes, such as syphilis, mononucleosis, some autoimmune diseases, and oral cavity flora. If the first step is positive or indeterminate (sometimes called "equivocal"), the second step should be performed. The overall result is considered positive only when the first test is

positive (or equivocal) and the second test is positive (or, for some tests, equivocal) [35]. The second step, the Western blot test, identifies antibodies for the different spirochetes [18]. Western blot serology is both more sensitive and more specific than ELISA. Serologic assays for immunoglobulin G (IgG) and M (IgM) are frequently used blot tests but are not recommended without a previous ELISA [34]. In any serologic testing, a comparison test repeated after an interval of a few weeks should be performed. Antibody levels should be monitored over this period of time to determine if the disease is worsening or improving as determined by the immune system's reaction. The CDC recommends that ELISA or IFA should always be performed before immunoblot testing in order to decrease the likelihood of false positive results [18]. In 2019, the FDA cleared several Lyme disease serologic assays with new indications for use, allowing for an ELISA, rather than Western immunoblot assay, as the second test in the testing algorithm [36; 37]. With this new paradigm, two ELISAs can be run either concurrently or sequentially, rather than the traditional two-step process [36; 37]. According to the FDA, this new option is easier to interpret in a clinical laboratory due to the streamlined method of conducting the tests [37]. It is prudent to check the laboratory standards for what is deemed positive, as there is variability between individual testing laboratories. It is highly recommended that the laboratory report and specify the bands; many will just list the test as positive, equivocal, or negative. The CDC has published a list of laboratory tests and practices that are not recommended [34].

It is important to caution patients that exposure based on serology does not necessarily mean active disease. Many individuals have titers deemed positive without evidence of Lyme disease, and individuals may have evidence of disease without positive titers. The levels of IgG in the serum can remain high for many years [18].

The specific antibodies of importance appear as bands on the Western blot assay. The antibody bands are individual molecular weights of specific antibodies against *B. burgdorferi* antigens that give specific evidence of exposure to the agent. In reporting the bands, the designation kDa stands for kilo Daltons of molecular weight and Osp refers to the outer surface protein of the organism. The bands that are most specific to Lyme disease are 23-25 kDa (Osp C), 31kDa (Osp A), 34 kDa (Osp B), 39 kDa, 41 kDa and 83-93 kDa [38]. IgG and IgM Western blot assays have the same antibody band specificity. Ideally, both should be performed at the same time. IgM can be positive as early as one week after exposure, and the positive response can last for the first six to eight weeks. IgG takes longer to respond and has some varying levels of response.

The CDC requires that two of three bands (i.e., 23, 39, 41 kDa) on the IgM or five of ten bands (i.e., 18, 21, 28, 30, 39, 41, 45, 58, 66, 93 kDa) on the IgG be present to positively diagnose Lyme disease [18; 39; 40; 41]. This can be an insurance issue for some patients. If the national standard criteria are not met in the testing procedure, some insurance companies may deny payment. In some cases, the IgM test will be slightly more reactive, and this will meet the CDC criteria. In cases that seem to be Lyme disease but for which standard testing is not yielding a positive answer, the IgM Western blot can be a very helpful tool.

The Lyme Urine Antigen Test (LUAT) was once used widely as a diagnostic tool and is still used by some laboratories [28]. However, because of unreliability and inconsistencies, the FDA has advised against the use of this test for the diagnosis of Lyme disease. In addition, the agency recommends that polymerase chain reaction (PCR) analysis on inappropriate tissues, such as blood or urine, not be accepted as diagnostic, and that Western blot tests only be interpreted according to validated criteria [34; 40]. Like the CDC, the FDA advises initial testing be done by ELISA or IFA and specimens that are positive or equivocal be followed up with a standardized Western blot assay or a concurrent or sequential ELISA [37; 40].

As noted, PCR technology is also available for testing. Appropriate sources most likely to contain the agent are serum, cerebrospinal fluid (CSF), and synovial fluid. The result is positive in approximately 30% of patients with active Lyme disease [41]. Disadvantages of PCR testing include the likelihood of false-negative results due to a sparsity of spirochetes in infected tissues. Inexperience with PCR also can yield false-positive results when care is not taken to prevent contamination and when incorrect primers are used to prepare the specimen. PCR may be useful in confirming persistent or recurrent disease, because a positive result is highly specific for exposure to *B. burgdorferi*. However, the test has not been standardized and is not currently used in routine testing [41]. In general, all of these tests can be negative or inconclusive, and the patient can still have Lyme disease as documented with electron microscopy, but this is not a practical test due to cost and time issues. At this time, there are no good imaging procedures to help in the diagnosis of Lyme disease, and there are certainly no definitive test procedures that warrant withholding or denying treatment [28]. Treatment is usually indicated even if all, or almost all, routine diagnostic procedures are negative when there is a strong clinical suspicion of Lyme disease based on history and physical findings.

Treatment

Prompt and complete treatment of early Lyme disease with antibiotics is important to prevent the development of chronic Lyme disease and/or chronic neuroborreliosis and their troublesome sequelae. The International Lyme and Associated Diseases Society (ILADS) suggests that Lyme disease should be treated with doxycycline as the antibiotic of choice for prophylaxis following an *Ixodes* tick bite with known feeding, irrespective of the amount of tick engorgement or the local tick population infection rate [41; 42]. Where doxycycline is contraindicated, antibiotics known to be effective for treating Lyme disease, such as amoxicillin, azithromycin, or cefuroxime, may be substituted. The recommended adult dose and prophylactic regimen is 100–200 mg doxycycline twice daily for 20 days [42].

For high-risk *Ixodes* spp. bites in all age groups, the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN), and the American College of Rheumatology (ACR) recommend the administration of a single dose of oral doxycycline within 72 hours of tick removal over observation.

(https://www.idsociety.org/practice-guideline/lyme-disease. Last accessed April 28, 2023.)

Strength of Recommendation/Level of Evidence: Strong recommendation, moderate-quality evidence

According to ILADS guidelines, the treatment of erythema migrans rash in adults is a four- to six-week regimen with recommended first-line antibiotics, including amoxicillin 1,500–2,000 mg daily in divided doses, cefuroxime 500 mg twice daily, or doxycycline 100 mg twice daily [42]. Studies in Europe have shown that a minimum of 21 days of azithromycin 250–500 mg daily is equally or more effective than these three agents and may be considered, particularly for patients that place a high value on minimizing the number of days taking antibiotics. The recommended pediatric regimen is also four- to six-weeks of treatment of amoxicillin 50 mg/kg/day in three divided doses (maximum daily dose: 1,500 mg), cefuroxime 20–30 mg/kg/day in two divided doses (maximum daily dose: 1,000 mg), and azithromycin 10 mg/kg on day 1 then 5–10 mg/kg daily (maximum daily dose: 500 mg) [42]. Doxycycline is an additional option for children 8 years of age and older at 4 mg/kg/day in two divided doses (maximum daily dose: 200 mg). Higher daily doses of the individual agents may be appropriate in adolescents [42]. Patients should be instructed regarding the importance of completing the entire course of antibiotics; if a dose is missed, the course should be continued at the next regularly scheduled time and the missed dose taken at the end. Studies have found no evidence that treatment regimens of longer duration than those recommended result in better outcomes for patients whose rash is resolved, but they do increase the chance for antibiotic-related adverse events [42].

Patients who have not fully recovered (i.e., erythema migrans rash still visible) at the end of initial treatment but who show a strong-to-moderate response should be continued on the same agent; a dosage increase of the same antibiotic or switch to another first-line agent (or tetracycline) is recommended for a moderate response [42]. Patients with minimal or absent response should be prescribed two first-line agents. Injectable penicillin G benzathine or intravenous ceftriaxone may be considered for these patients and also for those with disease progression or recurrence [42]. This aggressive treatment is required if neurologic symptoms are present in either the acute or chronic stages or if quality of life impairments are significant or rapidly progressive.

Treatment of neuroborreliosis and chronic Lyme disease has been addressed by the American Academy of Neurology in a guideline reaffirmed in 2014. Three major recommendations are made [29]:

- Parenteral penicillin, ceftriaxone, and cefotaxime are probably safe and effective treatments for peripheral nervous system Lyme disease and for central nervous system Lyme disease with or without parenchymal involvement (Level B recommendation).
- Oral doxycycline is probably a safe and effective treatment for peripheral nervous system Lyme disease and for central nervous system Lyme disease without parenchymal involvement (Level B recommendation). Amoxicillin and cefuroxime axetil may provide alternatives, but supporting data are lacking.
- Prolonged courses of antibiotics do not improve the outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (Level A recommendation).

Doxycycline (suggested dosage: 200 mg daily for 14 days) is the only recommended oral regimen for neuroborreliosis, as it has shown a response rate of 98.6% compared with parenteral penicillin or ceftriaxone in an aggregation of data from eight studies (i.e., statistically equivalent) [29]. Symptomatic treatment is recommended if therapy fails to resolve arthritis and if PCR results from synovial fluid or tissue are negative [43]. Treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of corticosteroids, or disease modifying anti-rheumatic drugs, such as hydroxychloroquine; referral to a rheumatologist is also recommended.

Patients with Lyme disease can frequently be frustrated with the long-term nature of the treatment and will need support, especially to maintain the antibiotic regimens. The long-term effects can also be very discouraging for the unfortunate patients who eventually develop the syndrome, which mimics fibromyalgia or chronic fatigue syndrome. Fortunately, it appears that early treatment, and in most cases even late treatment, can prevent or eliminate these sequelae [18; 25].

Prevention

As with any disease, prevention is the best solution. Educating people about how the disease is transmitted and its early signs will help reduce the overall incidence and lessen the severity in those who receive early treatment. The following advice should be given to patients, family, and friends.

If walking where ticks might be present, wear clothing that provides protection from tick exposure. Bare legs should not be exposed, and socks should be pulled up over pant legs. Ticks are not able to get through clothing to exposed skin, but they can climb up socks and reach exposed skin if the pant legs are not inside the socks. Long-sleeve tops and having long hair under control will help as well. Clothing should be removed and washed on arrival home. A thorough tick check should be completed, especially in body creases such as the groin and the axilla (armpit) [18]. Many people have been fooled into thinking ticks were freckles and have not removed them before they became engorged. It is most important that embedded ticks be removed promptly. If the capitulum, or head, is broken off, it may cause a local reaction. *Borrelia* is actually in the body of the tick, so transmission likelihood will decrease the faster the body is removed. It takes at least 24 to 36 hours of contact by the tick for the disease to be transmitted.

Though the organism is shed in the urine of mammals, no transmission has been documented to have occurred from urine exposure. Pregnant women should be especially alert when in areas known to have ticks, as there appears to be placental transmission of Lyme disease [18]. Some question this, despite evidence that some infants have positive titers after maternal antibodies should have disappeared. For now, erring on the side of caution would seem prudent. Lyme disease, unlike its close relative syphilis, has not been shown to be a sexually transmitted infection.

Dogs and cats can bring ticks into the house. Usually, once on an animal, the tick will remain and not drop off unless the animal has been treated with repellents. Most products to repel ticks will prevent them from ever getting into the house, as they will not remain on the dog or cat long enough to get indoors. Some products are designed to kill the tick if it does succeed in embedding [18].

Public health strategies have included methods to curtail deer populations. This is one way to lower the incidence of Lyme disease in local human inhabitants, because without the definitive host for the tick, the tick population will decrease. It will take a few years after the reduction of the deer population to see a drop in the number of human cases. This is because the newer generation of ticks on the mice will remain at a higher level. In fact, ticks may seem more numerous for the first two to three years after lowering the deer population because of the lack of the correct definitive host.

Insecticides, such as permethrin, and insect repellents, especially n, n-diethyl-m toluamide (DEET) in a concentration of at least 20% to 30%, can be very useful if used properly. Permethrin kills ticks on contact and can be used in a backyard, around a house, or on clothing. DEET is a well-known repellent that can be applied to clothing or exposed skin [18; 44]. Some have suggested placing pesticide applicators at deer feeding stations to kill ticks on the deer that come to feed. Of course, controlling the mouse population will also help to reduce the number of cases.

Finally, it is important to know how to properly remove ticks. Petroleum jelly, mineral oil, heat, nail polish, or other materials should not be applied to the tick or immediate area. Embedded ticks are best removed with fine-tipped tweezers. The tick should be grasped as close to the body as possible and removed with a gentle steady pull. Even if all of the mouth parts are not removed, the threat of Lyme disease is very unlikely because *B. burgdorferi* is usually located in only the midgut and salivary glands of the tick. The area where the tick was located can be washed and cleansed with an antiseptic [18].

Vaccination

The FDA approved the first vaccine for human use, LYMErix, in 1998 [25]. However, in 2002 the manufacturer announced that they were discontinuing production of the vaccine, citing low demand; it is no longer commercially available [25; 45]. When available, the results of trials showed a 50% vaccine efficacy in the first year after vaccinations were given as two injections approximately two months apart. The effectiveness of the vaccine increased to 75% in the second year, after a single booster; however, those who were previously vaccinated are no longer protected [45]. Clinical trials of new vaccines are underway as of 2023 [45].

TULAREMIA

Tularemia is primarily a disease of rural populations, although occasional urban cases have occurred. The infective organism, *Francisella tularensis*, is a gram-negative intracellular coccobacillus with very marked pathogenic infectivity [46; 47]. Humans can become infected by ingestion of or contact with contaminated water, food (e.g., rabbit meat), or soil; handling infected animal tissues; the bites of infective mammals, such as cats; or the bite of infective ticks, biting flies, or mosquitoes. Person-to-person transmission does not occur [46; 47].

Tularemia occurs naturally in a wide variety of animals, including mice, rabbits, squirrels, water rats, and voles, which acquire the disease by bites from mosquitoes, flies, and ticks. Animals can also become infected by contact with contaminated soils.

Rabbits are the most commonly infected animals in the United States. The disease is endemic throughout much of North America and Europe, with the south central and western states being the most involved in the United States [48; 49]. In Europe, most tularemia cases are reported in the northern and central regions, especially Scandinavia and the former Soviet Union.

Classification

There are several classification systems for clinical tularemia. One such system categorizes tularemia as either ulceroglandular (occurring in the majority of patients) or typhoidal [49]. Ulceroglandular disease is characterized by lesions on the skin or mucous membranes (including conjunctiva), lymph nodes larger than 1 centimeter, or both. Typhoidal tularemia describes systemic manifestation of the disease without skin or mucous membrane lesions [46; 49]. In addition to these two types, pneumonic tularemia, caused by inhalation and primarily manifesting as pleuropneumonic disease, also occurs [46; 49]. Pneumonic tularemia is often considered a type of typhoidal tularemia.

Typhoidal Tularemia

As noted, typhoidal tularemia is an acute, nonspecific febrile illness and is not associated with prominent lymphadenopathy or skin lesions [46]. This type of tularemia is caused by inhalation or ingestion of bacilli and may involve significant gastrointestinal symptoms. It is believed that this type would be most prevalent during an act of bioterrorism [47; 50].

The incubation period is usually 3 to 5 days (range: 1 to 21 days), although aerosol exposures have been shown to result in incapacitation in the first day [46; 50]. Symptoms may include fever with chills, headache, myalgia, sore throat, anorexia, nausea, vomiting, diarrhea, abdominal pain, and cough [50]. Patients may develop tularemia sepsis and/or pneumonia, which can be fatal. This syndrome manifests with hypotension, respiratory distress syndrome, renal failure, disseminated intravascular coagulation, and shock [50].

Pneumonic tularemia results from inhalation of infected aerosols or spread of existing, untreated disease [50]. Hemorrhagic inflammation of the airways is an early sign [46]. Radiologic studies show pleuritis with adhesions and effusions and peribronchial infiltrates; hilar lymphadenopathy is also common [46; 49]. These signs, however, are not always present. Patients may develop acute respiratory distress syndrome and require mechanical ventilation [49].

Ulceroglandular Tularemia

Ulceroglandular tularemia occurs in 70% to 80% of cases [49]. It is generally caused by an arthropod bite or by handling the carcass of an infected small mammal, such as a wild rabbit; transmission has also been reported from ingestion of or contact with contaminated water, exposure to contaminated mud or animal bites, and exposure to aerosolized water droplets or dust from contaminated soil or grains [46; 49; 51; 52; 53]. A local papule develops at the inoculation site, with progression to a pustule and ulceration within a few days. The ulcer may be covered by an eschar [46; 49]. Lymphadenopathy may also occur [49]. The nodes are usually tender and may become fluctuant, rupture, or persist for months to years [49]. In most cases, there is a single ulcer with raised borders. Other symptoms include fever, chills, headache, and cough [49].

Ulceroglandular tularemia is characterized by the presence of a small, ulcerated papule at the site of a tick bite or other contaminated break in the skin, followed by tender regional adenopathy and fever. A variation of this syndrome is oropharyngeal tularemia, presenting with subacute to chronic exudative pharyngitis/tonsillitis, cervical adenopathy, low-grade fever, and malaise (easily confused with infectious mononucleosis). Oropharyngeal tularemia likely arises from direct transmission via the hands or by droplet nuclei or dust arising from handling the carcass or dressing out meat from an infected animal [49]. Finally, there is a well-described oculoglandular form of tularemia, whereby inadvertent direct inoculation of the eye, as from touching the face or eyebrow after handling a dead wild animal, results in a unilateral conjunctivitis and preauricular adenopathy [46; 49].

Diagnosis

Diagnosis of tularemia requires a high index of suspicion, as the disease often presents with nonspecific symptoms [49]. A history of tick bite or exposure to wild game (e.g., rabbit, deer) provides a clue. The diagnosis can be made by recovery of the organism from blood, ulcers, conjunctival exudates, sputum, pleural fluid, lymph nodes, gastric washings, or pharyngeal exudates. Because the organism is difficult to isolate and constitutes a potential danger to laboratory personnel, serologic evidence of infection in a patient with a compatible clinical syndrome is commonly used for diagnosis [49].

There are several biologic variants (biovars) or subspecies of *F. tularensis*. Type A is considered to be more virulent, while the European biovar, *F. tularensis* var. *palaearctic*, typically causes a milder form of the disease [46]. Both types can be identified with direct fluorescent antibody (dFA) analysis, which gives a presumptive diagnosis of tularemia. Direct examination with gram stain may not be helpful because *F. tularensis* is a weakly staining pleomorphic gram-negative coccobacillus that may be difficult to identify. *F. tularensis* can be grown in appropriate cultures but may not be identifiable for 48 hours. Antibody or other serologic tests and/or culture are necessary for confirmation of the diagnosis. The antibody detection assays include ELISA, tube, and microagglutination, but significant antibodies may not appear until 10 to 14 days after the onset of the illness [46]. A positive dFA test on a culture can confirm the diagnosis.

It should be reinforced that significant personal safety precautions be taken when handling tissues or other samples possibly containing *F. tularensis*, as it is among the top 10 most common causes of laboratory-associated infections in the United States [54].

Treatment and Prevention

All forms of tularemia may be treated with streptomycin or gentamicin [46; 49; 50]. Gentamicin may be more readily available and easier to administer [49]. Also, because streptomycin has been associated with ototoxicity in fetuses, gentamicin is the drug of choice for pregnant women [55]. Doxycycline or ciprofloxacin are also acceptable alternatives [46].

When using aminoglycosides parenterally, the dosage must be calibrated to the patient's renal function (as estimated by the creatinine clearance), taking into account the expected reduction in renal function associated with aging. For adults, the starting dosage of streptomycin is 1–2 g administered intramuscularly (IM) every 12 hours for 7 to 14 days [55]. In very sick patients, streptomycin may be given initially at 15 mg/kg IM every 12 hours, then adjusted downward once there is clinical improvement. This is also the common pediatric dose [55]. The usual adult starting dose for gentamicin is 3–5 mg/kg/day IV or IM once a day (or in three divided doses), to achieve a peak serum level of at least 5 mcg/ml and a trough level <2 mg/kg. This is continued for 7 to 14 days [55].

Doxycycline is a good alternative for patients who are not seriously ill; the dosage is 100 mg IV or orally twice daily at 12-hour intervals for 14 to 21 days; however, relapses are reported to occur more often than with aminoglycoside therapy. Unfortunately, fully virulent streptomycin-resistant organisms have been described. In these cases, ciprofloxacin may be used at a dose of 400 mg IV twice a day (may switch to 500 mg orally twice a day when indicated), although ciprofloxacin use for tularemia treatment is not FDA approved [55].

As with all tickborne diseases, prevention begins with wearing appropriate clothing while in areas where ticks may be present. Also, contact with animals that might harbor the disease should be avoided. If working with domestic animals, be aware of tick infestations and wear protective clothing if contact with possibly infected animals is necessary [49]. The use of tick repellents, such as DEET or the newer plant-derived agents, applied to the cloth-

ing or lightly on the skin can be helpful. Wearing light-colored clothing so that ticks can be spotted more easily and tucking pant legs into socks is also recommended. Ticks should be removed as soon as possible after being discovered on the body. Ulcers or wounds in patients with tularemia should be covered and contact isolation maintained as *F. tularensis* can be shed from such lesions for one month or longer. No licensed vaccine is available for protection against tularemia; however, a live vaccine strain (LVS) may be given to at-risk laboratory personnel as an investigational new drug (IND) [56]. This vaccine is not commonly available in the United States [57]. In lieu of vaccination, antibiotic prophylaxis with 14 days of oral doxycycline or ciprofloxacin is recommended after high-risk exposure (e.g., laboratory accident) [50]. An attenuated vaccine was used in the former Soviet Union to immunize tens of millions of people and was subsequently sold to the U.S. military in 1956. Testing of the vaccine in military personnel proved it to be safe and reasonably effective; however, the scarification technique (similar to smallpox inoculation) used to administer the vaccine is inconvenient and highly variable.

ROCKY MOUNTAIN SPOTTED FEVER

RMSF is the most common rickettsial disease in the United States. The incidence of RMSF and other rickettsial infections has increased over the past two decades, from 495 reported cases of spotted fever rickettsiosis in 2000, to more than 6,000 cases in 2017. Cases reported in 2018 and 2019 were slightly lower [58]. The case fatality rate for rickettsial infection has declined since the 1940s, when tetracycline antibiotics cane into use. Using surveillance data, the CDC estimates that the current case fatality rate for all spotted fever rickettsioses is roughly 0.5%, somewhat higher for RMSF [58].

RMSF is caused by the organism *Rickettsia rickettsii* and is found throughout the contiguous United States, although five states (Arkansas, Missouri, North Carolina, Tennessee, and Virginia) account for more than 50% of all cases. In Arizona, cases have recently been identified in an area where the disease had not been previously seen. From 2003 to 2019, nearly 470 cases were reported with a case fatality rate of approximately 5% [58]. This seasonality varies in different regions according to the climate and tick vectors involved. Most cases of illness are reported in May to August. This period coincides with the season when adult *Dermacentor* ticks are most active [58]. The incidence of RMSF is higher in men than in women. People older than 40 years of age account for the greatest number of reported cases; however, children younger than 10 years of age represent the greatest number (22%) of reported deaths. Surveillance data shows higher risk for hospitalization in people who are immunocompromised. In 2015–2019, the annual incidence was highest (26.99 cases per million) in adults 70 to 74 years of age; the incidence in children 5 to 9 years of age is 5 cases per million [58]. Human-to-human transmission is not documented and does not appear to occur [48; 58; 59].

Clinical Presentation and Diagnosis

The classical presentation of RMSF includes the sudden onset of headache, fever, chills, and an erythremic exanthem that appears within the first few days after the symptoms. The lesions are first present on the palms, soles, wrists, forearms, and ankles. The rash then appears on the buttocks, axilla, trunk, face, and neck. The lesions are initially pink and macular and blanch with pressure but later become maculopapular and petechial [58]. Occasionally, the lesions coalesce and become regions of ecchymosis and ulceration.

Symptoms usually appear within 2 to 14 days after the tick bite and can also include malaise, myalgia, nausea, and vomiting [58]. In rare cases, severe respiratory distress, circulatory failure, and neurologic complications may occur; this is especially true for patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The tick bite is remembered by 50% to 70% of patients who develop a tickborne disease [48]. As with the other tick-disseminated zoonoses, this is a helpful clue in establishing a diagnosis. Other information, such as exposure to high grass and tick-infested areas, contact with dogs, similar illnesses in family members or pets, or history of recent travel

to areas of high incidence also can help establish a diagnosis [58]. If a rash is present, a skin biopsy and PCR or immunohistochemical staining for *Rickettsia* can be used. These tests have good sensitivity (70%) when applied to tissue specimens collected during the acute phase of illness and before antibiotic treatment has been started [58].

IFA with *R. rickettsii* antigen is the gold-standard serologic test for diagnosis of RMSF. The test is performed on two paired serum samples [60]. The first sample should preferably be taken in the first week of symptoms; the second sample should be taken two to four weeks later. In most cases, the first IgG titer is low or negative, and the second typically shows a fourfold increase in IgG antibody levels. IgM antibodies usually rise at the same time as IgG (i.e., near the end of the first week of illness), but they are less specific than IgG antibodies and more likely to result in a false positive [60]. Both IgM and IgG levels can remain elevated for months or longer after RMSF has resolved, and they can be detected in up to 10% of currently healthy people who were previously exposed to *R. rickettsii* or a similar organism. For these reasons, clinicians requesting IgM serologic titers should also request a concurrent IgG titer [58].

Treatment and Prevention

The treatment of RMSF should begin immediately when the disease is suspected and not be delayed until a firm diagnosis is made during the convalescent period. The recommended first-line treatment is doxycycline. The recommended dosage for adults is 100 mg every 12 hours. The recommended dosage for children who weigh less than 45 kg is 2.2 mg/kg body weight, twice daily [58]. Treatment is most effective at preventing death if doxycycline is started in the first five days of symptoms. If the patient is treated within the first five days of infection, fever generally subsides within 24 to 72 hours. The minimum duration of therapy is five to seven days, though doxycycline should be continued until the patient has been afebrile for at least three days. Severely ill patients may require longer periods of treatment before fever resolves [58].

Doxycycline to treat suspected RMSF in children is standard practice recommended by both the CDC and the American Academy of Pediatrics Committee on Infectious Diseases. For patients with life-threatening allergies to doxycycline and in some pregnant patients for whom the clinical course of RMSF appears mild, chloramphenicol may be considered as an alternative antibiotic. Oral formulations of chloramphenicol are not available in the United States, and use of this drug carries the potential for other adverse risks (e.g., aplastic anemia, grey baby syndrome, increased fatality risk) [55; 58]. The standard treatment duration is 7 to 14 days [58]. The use of fluoroquinolones is not recommended at this time because their benefit has not been documented [48; 59; 60]. The preventive measures are the same as for the other tickborne diseases.

EHRLICHIOSIS

Ehrlichiosis is an emerging tickborne disease caused by *Ehrlichia* spp., gram-negative rickettsial organisms that infect human leukocytes. Ehrlichiosis was first recognized in the United States in the 1980s and became a reportable disease in 1999 [31]. The number of reported cases of ehrlichiosis has increased steadily, from 200 cases in 2000 to 2,093 cases in 2019 [31].

Most human disease is the result of infection with *E. chaffeensis*, but infection with *E. ewingii* was designated a separately reportable disease in 2008 [31]. In 2009, four cases of ehrlichiosis were attributed to a newly discovered *Ehrlichia* species closely related to *E. muris*, a species not found in the United States previously [61]. This section will focus mainly on *E. chaffeensis* infection, also referred to as human monocytotropic (or monocytic) ehrlichiosis.

Humans become infected through the bite of infected ticks; the lone star tick (*Amblyomma americanum*) is the primary vector for *E. chaffeensis*, and the white tail deer is the most common reservoir [31; 62]. Cases are predominantly reported in the summer (June and July) in the southeast and south-central United States, which generally corresponds with areas in which lone star ticks exist [31]. In 2019, four states (Missouri, Arkansas, North Carolina,

and New York) accounted for nearly one-half of all reported cases [31].

Clinical Presentation and Diagnosis

The clinical presentation of ehrlichiosis is very similar to that of RMSF, though the incidence of rash is less common. After an incubation period of one to two weeks, a patient with ehrlichiosis will typically present with acute onset of fever and one or more of the following symptoms or signs [31]:

- Headache
- Myalgia
- Malaise
- Anemia
- Leukopenia
- Thrombocytopenia
- Elevated hepatic transaminases

Nausea, vomiting, and diarrhea also occur in some patients. A non-pruritic skin rash may also develop (in 60% of children, but less than 30% of adults), with appearance ranging from maculopapular to petechial [31]. In some patients, the rash may resemble that often seen with RMSF, making careful differential diagnosis vital.

Diagnosis can be difficult, particularly in the early stages of illness; early recognition and treatment based on clinical suspicion are important to prevent severe illness. Diagnosis is generally made based on clinical presentation and clinical evidence and confirmed by IFA, PCR, or isolation of *E. chaffeensis* in cell culture [63]. IFA using *E. chaffeensis* antigen, performed on paired serum samples, is the gold-standard serologic diagnostic test [63]. Any tests completed in the first week should be repeated after two to four weeks, as antibodies may not be present in sufficient quantities to be detected in the first week.

The CDC recommends that healthcare providers consider Heartland virus testing in patients who develop fever, leukopenia, and thrombocytopenia who have tested negative for *Ehrlichia*. Heartland virus was first isolated in Northwestern Missouri in 2009; since then, more than 50 cases of Heartland virus disease have been reported from states in the Midwestern and Southern United States [64]. The virus likely is transmitted through the Lone Star tick or other arthropods [65].

Treatment and Prevention

Doxycycline is the first-line treatment for adults and children of all ages and should be initiated immediately if ehrlichiosis is suspected [60; 63]. The recommended regimen is 100 mg twice daily for adults or 2.2 mg/kg twice daily for children weighing less than 45.4 kg [60; 63]. For patients with severe diseases or who are hospitalized, intravenous administration is preferred. Treatment should continue for at least three days after the fever subsides and until evidence of clinical improvement, usually at least five to seven days [60; 63]. Prevention should focus on measures established for all tickborne diseases.

BABESIOSIS

Babesiosis is the only tickborne zoonosis in the United States caused by a protozoan, *Babesia microti*. Two other *Babesia* species, *B. bovis* and *B. divergens*, can be zoonotic as well but are less commonly identified [66]. Babesiosis is most prevalent in the United States in the Northeast and upper Midwest and usually peaks during the warm months [66]. *B. microti* is transmitted by the *Ixodes scapularis* (black-legged deer tick). Rodents are the primary reservoir for human cases [66].

Historically, the description of the early recognition of babesiosis parallels Lyme disease. The first case was documented on Nantucket Island, Massachusetts, in 1969 in an elderly woman whose case was described as a "malaria-like" illness. *B. microti* was identified, and the island's hospital began regularly treating cases shortly after identification and diagnosis of the first case [67].

Clinical Presentation and Diagnosis

Many cases of babesiosis remain subclinical. In fact, some young patients may be asymptomatic carriers for years. Those individuals who become ill may experience influenza-like symptoms, with fever, headache, malaise, myalgia, and hemolytic anemia and hemoglobinuria of varying severity. These symptoms usually occur within one week; jaundice

and renal failure may follow [48; 66]. Risk factors for severe disease include asplenia, advanced age, and immunodeficiency states. As noted, the clinical presentation may resemble malaria. The disease can be fatal in patients who have a prior history of splenectomy [66]. Animals other than humans with babesiosis have a very similar course.

Diagnosis of human babesiosis requires a high index of suspicion because the clinical manifestations are nonspecific. Examination of a blood smear from a suspected individual with infection will reveal the characteristic red blood cell parasite inclusions that resemble a Maltese cross. Fluorescent antibody serology and PCR amplification are available for diagnosis when the evaluation of the smear is not conclusive [66].

Treatment and Prevention

All cases of active babesiosis require treatment with a combination of either atovaquone plus azithromycin or clindamycin plus quinine (for severely ill patients) [66]. The suggested doses for adults include 750 mg of atovaquone two times per day for 7 to 10 days plus an initial oral dose of 500–1,000 mg azithromycin (decreasing to 250–1,000 mg/day as appropriate). An alternative is clindamycin 600 mg orally three times per day or 300–600 mg IV four times per day plus quinine 650 mg orally three times per day [44; 48; 68].

In severely ill patients with high titers of parasitemia (greater than 10%), significant hemolysis, or renal, hepatic, or pulmonary compromise, a partial or complete red blood cell exchange transfusion may be lifesaving. Patients in hemolytic crisis should be treated for shock, with particular consideration for maintaining renal function to counteract the potential damage from hemoglobinuria. The medical regimen is aimed at preventing anemia from becoming severe [48; 59].

Individuals who have previously undergone splenectomy should exercise extreme caution in *Ixodes* tick territory. A thorough tick check should be done after being in the woods. Insect repellent will provide deterrent but should not be relied upon for complete protection against any arthropod vector. Rodent control measures can help reduce the reservoir numbers around the home and yard [66].

VIRAL ZOONOTIC DISEASES

Several human viral diseases can be contracted from animals, some by means of an intermediate arthropod vector important to the life cycle of the virus, others by direct contact or inhalation of aerosols released by the animal or generated from the contaminated environment. Well-described mosquito-borne viral zoonoses include West Nile and similar forms of viral encephalitis, Zika virus (ZIKV) disease, and Dengue. Rabies is unique in its association with the bite of an infected wild or domestic mammal. Avian and swine influenza, hantavirus, and novel coronavirus infections have more complex modes of transmission involving direct (touch) contact and/or inhalation of infectious aerosols created by handling the host animal, processing a food product, or cleaning the immediate environment. Bovine spongiform encephalopathy ("mad cow disease") will be included in this section because the infective organism, a prion, is closer to a virus than the other zoonotic organisms.

WEST NILE VIRUS

The West Nile district of Uganda was the site of the first documented human case of West Nile virus in 1937. The virus was later identified in a serious outbreak of meningoencephalitis in Israel in the late 1950s. The first human cases in the United States occurred in the New York City area in 1999, where seven deaths were reported [69]. It has since been documented throughout the entire continental United States. A total of 47 states and the District of Columbia reported West Nile virus infections in people, birds, or mosquitoes in 2021 [70]. Overall, 2,911 human cases of West Nile virus disease have been reported to the CDC, of which 2,008 (69%) were classified as neuroinvasive disease (e.g., meningitis, encephalitis, flaccid paralysis) [70]. Hawaii, Maine, Puerto Rico, and West Virginia have been

free of the disease; however, the disease has spread throughout most of the contiguous United States and Canada. In Canada, the first human case of West Nile virus was reported in Ontario in 2002. A total of 35 cases were reported in Canada in 2021 [71]. The states with the greatest number of cases in the United States in 2021 were Arizona (1,715), Colorado (175), Texas (143), and California (130) [70]. Most cases occur between June and September, but as the disease has spread into the warmer southern and southwestern states, year-round exposures have become more frequent [70].

The West Nile virus is a single-stranded RNA flavivirus, similar in many respects to the virus that causes St. Louis encephalitis. Kunjin virus, present in Australia, is closely related to West Nile virus [72]. The virus is primarily transmitted by the *Culex* spp. mosquito, although it has been isolated from several other species. The *Culex* is an overwintering mosquito, meaning that adults can survive throughout the winter. The virus has also been documented to live throughout the winter while in the mosquito. Because a blood-feeding arthropod is the vector, the virus is called an arbovirus [73].

West Nile virus is transmitted from the primary reservoir, birds, to a vertebrate host after being maintained in a bird-mosquito-bird cycle. More than 160 species of birds have been documented to harbor the virus. Passerine birds have been noted to be the most commonly affected type of birds [69]. This group includes perching species such as songbirds and sparrows. The passerine group, crows, and many other common birds in the United States and around the world are evidently capable of being the amplifying host, in which the West Nile virus can replicate and markedly increase in number. It is also possible that other animals can harbor and amplify the organism. In a somewhat alarming finding, investigators confirmed that farmed alligators in Florida were capable of serving as an amplifying reservoir for West Nile virus. Humans and domestic animals that become infected with the organism are aberrant hosts, and the viremia is usually brief and low-grade [69; 74; 75; 76].

Clinical Presentation

Most (70% to 80%) human West Nile virus infections are subclinical and unapparent. Approximately 20% of those who contract the virus experience a mild febrile illness called West Nile fever [44; 77]. Only about 1 out of 150, or less than 1%, of those infected will develop severe neurologic effects [44]. Among patients with neuroinvasive disease, the case fatality rate is approximately 11% [70]. Although the full spectrum of West Nile fever cases in the United States has not been determined, there are degrees of clinical involvement that can be noted [77; 78].

The mild infection of West Nile fever appears after an incubation period of about 2 to 14 days and lasts for 2 to 6 days [44]. It is described as a febrile illness of sudden onset accompanied by malaise, anorexia, nausea, vomiting, headache, and myalgia. Some patients complain of eye pain and upper respiratory symptoms, and there may be a rash or lymphadenopathy [44]. Interestingly, the macular, papular, or morbilliform erythematous rash and lymphadenopathy seen in earlier outbreaks of the disease were not common in the more recent cases [69].

More severe infections have occurred in older patients and those with coexisting morbidities. The rate of severe neurologic disease was 10 times higher for patients 50 to 59 years of age and 43 times higher for those older than 80 years of age. This indicates that advanced age is the most significant factor involved in the development of severe disease [77]. In recent outbreaks, encephalitis was more common than meningitis. Hospitalized patients demonstrated significant fever, weakness, gastrointestinal symptoms, and cognitive changes. Several experienced muscle weakness and a flaccid paralysis with the more common neurologic findings being ataxia and extrapyramidal signs, myelitis, optic neuritis, seizures, polyradiculitis, and cranial nerve abnormalities. The constellation of findings is similar to other viral encephalitides and cannot be distinguished from them clinically [44].

The clinical signs of West Nile meningitis can include nuchal rigidity, Kernig or Brudzinski sign, and photophobia or phonophobia. A fever of 38 degrees C or more, or hypothermia of 35 degrees C or less, help to make the diagnosis. West Nile encephalitis can present with lethargy, an altered level of consciousness, or a personality change lasting more than 24 hours. There may also be focal neurologic deficits, seizures, and all of the usual findings seen with a viral encephalopathy [69; 78].

The acute flaccid paralysis seen with West Nile virus infections usually presents as a limb weakness that progresses markedly over a 48-hour period. There is an absence of pain, but paresthesia, areflexia or hyporeflexia, and asymmetry are commonly seen. About one-half of the patients hospitalized with severe disease in the United States experience a significant degree of weakness, and approximately 10% of the New York patients had acute flaccid paralysis, including several patients who developed a paralysis that resembled Guillain-Barré syndrome without the usual nerve conduction findings [79].

There is still no firm data regarding the long-term effects of West Nile virus infections. In the New York outbreak in 2000, over one-half of those hospitalized had not returned to their functional level by discharge, and only one-third were fully ambulatory. The most persistent long-term symptoms included fatigue, memory loss, difficulty walking, weakness, and depression [69; 77; 78; 79].

Diagnosis

A high index of suspicion based on symptoms, time of year, history, and the presence of other known cases is paramount in diagnosing West Nile fever. Other arboviral diseases, such as St. Louis encephalitis, Kunjin virus, or other diseases caused by flaviviruses can have a similar initial presentation [44; 80]. Fortunately, there is a specific neutralizing antibody to West Nile virus that can be used in serologic tests to help make the diagnosis. A fourfold rise in titer between acute and convalescent samples, determined by plaque-reduction neutralization assay, is confirmatory. A useful serologic test on serum or CSF is the assay for IgM using the antibody-capture ELISA procedure [44; 80]. The finding of IgM in the CSF is a very good indication of meningoencephalitis if found within eight days of the onset of symptoms [44; 69; 81]. Some IFA tests have also been suggested as being helpful in the diagnosis [80].

Because the IgM and IgG ELISA tests can cross-react between flaviviruses (e.g., dengue, yellow fever), they should be viewed as screening tests only. For a case to be considered confirmed, serum samples that are antibody-positive on initial screening should be evaluated by a more specific test. The plaque reduction neutralization test (PRNT) is currently recommended for differentiating between flavivirus infections [80; 81]. Additionally, in patients who report recent travel, specimens submitted for West Nile virus also should be tested by ELISA and PRNT against other arboviruses known to be active or present in the area or region where the patient traveled [80].

Peripheral blood samples are usually not helpful because the leukocyte count is often normal, although it can be elevated in some cases [81]. There can be a lymphocytopenia or even anemia. The CSF will frequently have an increase in cell count, with a predominance of lymphocytes and increased protein. CSF glucose is usually normal [81].

Imaging studies may be helpful after the development of meningoencephalitis to exclude other etiologies [81]. Computed tomography (CT) scans usually do not show evidence of acute disease, but about one-third of the magnetic resonance imaging (MRI) studies revealed changes in the leptomeninges or periventricular areas. MRI studies have also shown lesions in the basal ganglia and thalamus [69].

Culture of the organism is difficult, but an unambiguous diagnosis of West Nile fever can be made by virus isolation in cell culture, or in suckling mice by IFA analysis. In fatal encephalitis cases, the West Nile virus can be readily detected by immunohistochemistry or molecular amplification methods. Brain tissues at autopsy can be stained to show the viral antigens as well as the neuronal necrosis and microglial infiltrates caused by the disease.

Treatment and Prevention

The treatment of West Nile virus infections is supportive, with hospitalization of any patient who appears to have meningitis or encephalitis. Intravenous fluids and respiratory assistance are often required, and the prevention of secondary infections should be considered. Patients with severe neurologic findings will need a great deal of supportive care [82].

Interferon alpha-2b, IgG, and ribavirin in high doses have shown some activity against the virus in vitro, but there has been no confirming evidence of their usefulness in patients [82]. Other possible medications being tested are steroids, antiseizure drugs, and antiosmotic agents [77; 79; 81].

The most prudent means of protection against West Nile virus is to avoid mosquito bites by wearing long-sleeved shirts and pants and being aware of the usual biting times of early morning and evening. This is often not practical, so using the proper insect repellent is the next best means of protection [82]. The CDC recommends that consumers use repellent products that have been registered by the Environmental Protection Agency (EPA). These products include DEET, with a concentration of 20% to 30%, picaridin (KBR 3023), oil of lemon eucalyptus or para-menthane-3,8-diol (PMD), and IR3535 applied to the clothing and skin [18; 44]. Compounds containing permethrin may also be used and are highly effective in repelling and killing ticks, mosquitoes, and other arthropods but should only be applied to clothing, netting, and gear and not to the skin [18; 44]. Permethrin retains effectiveness on clothing even after laundering. Community-level mosquito control programs to reduce vector densities and screening of blood and organ donors also are useful preventive measures [82].

A vaccine for humans is not available at this time; however, the National Institutes of Health sponsored a trial of an inactivated vaccine developed by scientists at the Oregon National Primate Research Center in Portland [83]. The phase I trial including 50 adults was completed December 2016, and as of April 2023, no results have been published [84]. In mice, the vaccine protected against a lethal dose of West Nile virus, successfully eliciting neutralizing antibody responses and CD8+ T cells, which attack infected cells [83].

ZIKA VIRUS

ZIKV is the latest in a series of related human arboviral pathogens that has migrated out of Africa and Asia into the Americas over the past two decades [85; 86]. Like yellow fever, dengue, and chikungunya viruses, the vector for ZIKV is the *Aedes* mosquito, and epidemics within susceptible population groups are sustained by a mosquito-human-mosquito transmission cycle.

In the 2015–2017 outbreak within the United States, cases of ZIKV disease were primarily reported in returning travelers and in women having unprotected sex with men infected while traveling to regions with ongoing mosquito transmission. A total of 43,092 cases were reported between 2015 and 2018 in the United States and U.S. territories [87]. In 2017, the number of reported ZIKV disease cases started to decline. Since 2018, there have been no reports of ZIKV transmission by mosquitoes in the continental United States. Since 2019, there have been no confirmed ZIKV disease cases reported from U.S. territories [87]. However, the potential for a localized or regional outbreak of ZIKV disease in the United States is significant given the level of travel exposure, opportunities for ZIKV migration, and the prevalence of *A. aegypti* mosquitoes along the southern and southeastern rim of the country [88].

In epidemic settings and endemic areas, ZIKV infection is primarily vector-borne, transmitted by the bite of an infected *Aedes* mosquito. In addition, other modes of transmission are now known to be important in human ZIKV disease. These include sexual transmission from an infected male to female and male partners; transplacental transmission from mother to fetus during pregnancy, leading to congenital ZIKV disease; and perinatal transmission from a viremic mother to her newborn infant [89; 90]. There is theoretical concern that blood transfusion and tissue/organ transplantation could also serve as vehicles of transmission. Therefore,

the FDA has recommended universal screening of donated whole blood and components for ZIKV in the United States and its territories [91].

All reported cases of sexual transmission have involved vaginal or anal sex with men shortly before, during, or shortly after a symptomatic illness consistent with ZIKV disease [92]. It is not known whether infected men who never develop symptoms can transmit ZIKV to their sex partners. For now, the CDC recommends that men who have been diagnosed with ZIKV consider using condoms or abstaining from sex for six months following infection [92]. Sexual transmission of ZIKV from infected women to their sex partners has not been reported. The consistent and correct use of latex condoms is known to reduce substantially the risk of acquiring sexually transmitted infections, including those caused by viruses.

In the course of acute infection during pregnancy, ZIKV can be transmitted across the placenta to the developing fetus. Evidence for intrauterine fetal infection includes demonstration of ZIKV in the placenta and products of conception following spontaneous abortion, identification of ZIKV RNA in amniotic fluid by RT-PCR, and virologic and serologic studies of infants born with microcephaly. The true incidence and natural history of this phenomenon, including the importance of such factors as gestational age, level and duration of viremia, and immune enhancement by pre-existing heterologous anti-flavivirus antibodies, is currently unknown [93].

Two cases of intrapartum transmission of ZIKV from a newly infected, viremic mother to her newborn infant have been reported [94]. One infant was considered to be asymptomatic; the other child developed a rash and transient thrombocytopenia. Although ZIKV has been identified in breast milk, there have been no reports of transmission through breastfeeding.

Clinical Presentation and Diagnosis

In epidemic settings, the majority of primary ZIKV infections are asymptomatic, and those who do become ill usually experience a self-limited, mild febrile illness with rash, conjunctivitis, myalgia, and arthralgia lasting three to six days. The incubation period for ZIKV is not well defined; it is considered to be similar to that of other mosquito-borne flaviviruses—usually less than one week and in the range of 3 to 10 days.

During the period from September 2015 through February 2016, 72 of 88 women enrolled in a study tested positive for acute ZIKV infection by RT-PCR on blood, urine, or both. All women had rash, as this was an inclusion criterion; the prevailing pattern was a descending macular or maculopapular exanthem accompanied by pruritus in 94% of patients. Arthralgia was reported in 65% of ZIKV-positive women, conjunctival injection was seen in 58%, and lymphadenopathy (generalized or regional) was present in 41%. Fever was documented in only one-third of patients and, when present, was low-grade and of short duration. Nausea and vomiting were reported in 21%, and respiratory findings were evident in 7% [95].

From these observations there emerges a distinctive, though nonspecific, clinical ZIKV syndrome: an acute onset descending maculopapular rash (often with pruritus), conjunctival injection, arthralgia, myalgia, and transient low-grade fever. Lymphadenopathy may be present, but respiratory symptoms and signs are conspicuously uncommon. ZIKV disease should be considered in patients with any combination of these symptoms who have traveled to areas with ongoing transmission in the two weeks preceding onset of illness. Rare manifestations of acute ZIKV infection, based on isolated case reports, include meningoencephalitis, myelitis, thrombocytopenic purpura, and ocular complications [94; 96; 97].

Because dengue and chikungunya viruses have the same vector of transmission and share a similar geographic distribution and clinical profile with ZIKV, patients with suspected ZIKV disease should be evaluated and managed for these possibilities as well. Other considerations in the differential diagnosis include malaria, rubella, measles, parvovirus, adenovirus, enterovirus, leptospirosis, rickettsiosis, and group A streptococcal infections [98].

The possibility of ZIKV disease should be considered in the patient with a compatible clinical syndrome (e.g., febrile rash illness with arthralgia and conjunctivitis) and epidemiologic risk factors, such as residence in or travel to an area of active ZIKV transmission within the previous two weeks, or sexual contact with a person known or suspected of recent ZIKV infection. Laboratory confirmation relies on molecular detection of the viral genome (via RT-PCR) in blood or body fluids and serologic assay for acute-phase ZIKV-specific IgM antibody.

The FDA has issued an emergency use authorization for a number of diagnostic tools for ZIKV, including the Triplex Real-Time RT-PCR assay and the Zika MAC-ELISA for anti-ZIKV IgM [99; 100]. These have been distributed to qualified laboratories that are certified to perform high-complexity tests in the United States. Clinicians should contact local and state health departments to facilitate diagnostic testing. The CDC provides updated guidance for the selection and timing of ZIKV diagnostic testing at https://www.cdc.gov/zika/hc-providers/testing-for-zika-virus.html.

Treatment and Prevention

There is no effective antiviral therapy for ZIKV infection; treatment is supportive and directed toward relief of symptoms. When the diagnosis is uncertain and dengue, or co-infection with dengue, is a possibility, the patient should be managed expectantly for each. In consideration of dengue, aspirin and NSAIDs should be avoided and the patient should be monitored for signs of progression to hemorrhagic fever or shock [101]. In managing ZIKV disease, patient education and secondary prevention are important, especially in regard to sexual transmission and risk reduction in pregnancy. All pregnant women with molecular or serologic evidence of recent ZIKV infection should be evaluated and managed (monitored) for adverse pregnancy outcomes.

Pregnant women who report symptoms or signs consistent with acute ZIKV disease and who have traveled to or who live in areas with active ZIKV transmission or who have had potential sexual exposure (i.e., sexual contact without barrier/condom method with a person who lives in or has traveled to an area with ZIKV) should be tested for ZIKV infection. Updated recommendations include concurrent ZIKV nucleic acid test (NAT) serum and urine and ZIKV IgM serologic testing as soon as possible through 12 weeks after symptom onset. A positive ZIKV NAT result confirms the diagnosis of recent maternal ZIKV infection. If IgM result is negative, further testing may be warranted [102]. Patients with a negative ZIKV NAT and negative or nonnegative IgM test result should receive PRNT. A ZIKV PRNT result <10 means there is no evidence of ZIKV infection. Type and duration of ZIKV exposure before and during current pregnancy might limit interpretation of ZIKV IgM results. ZIKV testing is not routinely recommended for pregnant women with previous diagnosis of laboratory-confirmed ZIKV infection by either NAT or serology (positive/equivocal ZIKV or dengue virus IgM and ZIKV PRNT ≥10 and dengue virus PRNT <10 results). Preliminary data suggest that NAT might remain positive for several weeks after symptom onset. ZIKV IgM antibodies are most likely to be detected within 12 weeks after infection; however, IgM antibodies might be detected for months after infection, limiting the ability to determine whether infection occurred before or during the current pregnancy. Dengue virus IgM antibody testing is recommended for symptomatic pregnant women [102].

DENGUE FEVER

Dengue fever is caused by one of four similar flaviviruses (dengue viruses 1 through 4) that are transmitted via mosquito in tropical and subtropical regions [68; 103]. Because there are four viruses, people can be infected with dengue fever multiple times in their lives [104]. The WHO estimates that there may be 390 million dengue infections worldwide each year, of which 96 million have clinically significant symptoms [103]. The disease is endemic in more than 100 countries worldwide, including in Africa, the Eastern Mediterranean, Southeast Asia, the Americas, and the Western Pacific, with the Americas, Asia, and the Western Pacific being the most severely affected [103].

The incidence of dengue has been increasing rapidly in the last several decades, particularly since 1981 [103; 105]. The largest number of dengue cases ever reported globally was in 2019. The Americas reported 3.1 million cases, with more than 25,000 classified as severe [103]. In 2022, 1,188 cases of dengue were reported in the United States and an additional 828 cases were reported in U.S. territories [105]. The disease is both appearing in new areas and increasing in numbers of infections per year. In 2022, the majority (95%) of cases of dengue fever in the continental United States were acquired through travel to endemic regions, with the most cases reported in Florida (750), New York (73), and California (57) [105]. Although the geographic distribution of dengue is similar to that seen with malaria, it is more common in urban and more populated areas rather than more rural areas [68].

The principle vector for dengue is the mosquito *Aedes aegypti*, a species that originated in Africa but is now commonly found in most tropical and subtropical areas [106]. The *Aedes albopictus* mosquito, which is native to Asia, has also been implicated in the spread of dengue. World travel of the mosquitoes in cargo is a likely culprit [106]. Direct person-to-person transmission has not been documented, but there have been cases linked to dengue-infected blood, organs, or other tissues from blood transfusions; solid organ or bone marrow transplants; needlestick injuries; and mucous membrane contact with dengue-infected blood [106].

Clinical Presentation

The first signs and symptoms of dengue infection typically develop within 4 to 7 days of the infectious mosquito bite and last for 3 to 10 days [107]. The characteristic presentation of classic dengue fever includes a high fever (up to 105 degrees F), severe headache, retro-orbital pain, severe joint and muscle pain, nausea and vomiting, rash, hemorrhagic manifestation, and/or leukopenia [68; 107]. The characteristic rash is macular or maculopapular and generalized and usually develops as the fever subsides. About one in four people infected with dengue will become symptomatic. For those who develop dengue illness, symptoms can be mild or severe. Severe dengue can be life-threatening within a few hours and often requires hospital care. About 1 in 20 people with dengue illness will develop severe dengue [68]. Individuals who are infected for a second time are at greater risk of severe disease [103; 104].

Early clinical findings are nonspecific but require a high index of suspicion, because recognizing early signs of shock and promptly initiating intensive supportive therapy can reduce risk of death among patients with severe dengue to <0.5% [104]. The most clinically relevant sign of dengue hemorrhagic fever is vascular leakage, with all of the following criteria necessary for diagnosis: fever or recent history of fever, any hemorrhagic manifestation, thrombocytopenia (i.e., platelet count <100,000/mm^3), and evidence of increased vascular permeability [108]. In a few patients, most commonly children experiencing their second dengue infection, dengue shock syndrome will develop [107; 108]. Dengue shock syndrome is characterized by the presence of all of the criteria for dengue hemorrhagic fever with the addition of hypotension, narrow pulse pressure (≤20 mm Hg), or shock [108].

Diagnosis

Clinicians should obtain a complete personal and travel history for all patients suspected of having dengue fever or hemorrhagic fever and who live in or recently traveled to a disease-endemic area in the two weeks before symptom onset. All patients with clinically suspected dengue should receive appropriate management to monitor for shock and reduce the risk of complications resulting from increased vascular permeability and plasma leakage and organ damage without waiting for diagnostic test results to be received [104]. For patients with suspected dengue, nucleic acid amplification tests (NAATs) are the preferred method of laboratory diagnosis. NAATs should be performed on serum specimens collected seven days or less after symptom onset. Cases can be laboratory confirmed with the use of RT-PCR or dengue nonstructural protein-1 (NS1) antigen by immunoassay [104]. IgM antibody testing can

identify additional infections and is an important diagnostic tool. Interpreting results is complicated by cross-reactivity with other flaviviruses (e.g., ZIKV, West Nile), and determining the specific timing of infection can be difficult. PRNTs can resolve false-positive IgM antibody results caused by non-specific reactivity, and can help identify the infecting virus, in some cases. However, in areas with high prevalence of dengue and ZIKV neutralizing antibodies, PRNT may not confirm a significant proportion of IgM-positive results. PRNT testing is available through several state health departments and the CDC [104].

Treatment and Prevention

There are no approved treatments available for dengue, although a vaccine was approved for endemic areas (i.e., American Samoa, Guam, Puerto Rico, and the U.S. Virgin Islands) in 2019 [68; 103; 109; 110]. However, the vaccine manufacturer has announced that people who receive the vaccine and have not been previously infected with a dengue virus may be at risk of developing more severe manifestations of dengue. The Philippines suspended its dengue vaccine program, and other countries have specified that only people who have been infected with a dengue virus should receive the vaccine. Three other dengue vaccines are currently in phase 3 clinical trials [111]. Supportive care, in the form of bed rest and adequate fluids to maintain hydration, is recommended [103; 104]. In more severe cases, maintaining the patient's circulatory volume will be key. Antipyretics may be necessary to reduce fever, and the CDC recommends the use of acetaminophen [104]. Narcotics may be used to treat severe pain. Aspirin (and other salicylates) and NSAIDs should be avoided due to the risk of hemorrhage and, in children, Reye syndrome [104].

As with many zoonotic diseases, the best treatment for dengue fever is prevention. This includes vaccination (if indicated) and all measures necessary to prevent being bitten by an *Aedes* mosquito, such as bed nets, use of DEET-containing insect repellants, and wearing long-sleeved shirts and long pants [68; 103; 107]. Travelers should be advised to choose accommodations with air conditioning and window and door screens [68]. Because mosquitoes breed in standing water, eliminating these habitats (e.g., earthenware jars, metal drums, concrete cisterns used for domestic water storage, discarded plastic food containers, used automobile tires) in urban or residential areas has become a priority [68].

RABIES

Rabies is caused by the rabies virus, an RNA rhabdovirus belonging to the genus *Lyssavirus*, which under electron microscopy has a distinctive "bullet" shape [112]. Its genome and the various types of viral antigens particular to individual types of animals in given regions have been elucidated.

The disease, in animals and humans, has been known since ancient times. The name dates to about 3000 B.C.E. and means "to do violence" in Sanskrit. Detailed investigation of rabies began in the latter part of the 19th century, and Louis Pasteur discovered a vaccine for rabies in 1885. The development of a vaccine for animals, particularly the widespread vaccination of dogs and cats in the United States begun in the 1940s and the oral vaccination program for raccoons begun in the 2000s, has markedly decreased the number of human cases in the United States in the past century [113]. Additionally, effective human rabies immune globulin and human rabies vaccines have been developed. However, many thousands of human cases still occur worldwide each year, with 34 documented cases in the United States between 2003 and 2014 (10 of which were contracted outside of the United States and its territories); 5 cases occurred in 2021, all of which were fatal [114; 115; 116]. At the present time, approximately 5,000 animal rabies cases are reported to the CDC each year, of which more than 90% are in wildlife [113]. The most commonly identified rabies hosts in the United States are bats, raccoons, skunks, and foxes.

The number of human fatalities associated with rabies in the United States has decreased from 100 or more each year in the early 1900s to just one or two per year today. From 1960 to 2018, a total of 127 human rabies cases were reported in the United States, about 25% of which resulted from dog bites sustained during international travel [113]. Of infections acquired in this country, 70% were attributed to bats. Deaths are primarily due to failure to seek medical assistance, usually because the individual is unaware of exposure, as is common with bat bites. In addition to animal bites, cases have also been documented from corneal and organ transplants [113; 117]. It is estimated that about 59,000 people worldwide die from the disease every year, mostly in developing countries where preventive measures are not adequate [115].

Rabies is present in essentially every country in the world and in every state in the United States, except for Hawaii. During 2018, 54 jurisdictions reported 4,951 animal cases and 3 human cases. This represented an increase of 11.2% compared with 2017 [113]. Historically, human deaths have occurred in all regions where animal cases are present. In the United States, domestic animals accounted for 9% of all rabid animals reported in 2018 [113]. All mammals can contract rabies, but interestingly, birds do not get or carry the disease. Of the common wild animals in the United States, raccoons are the most infected in the East; skunks are the most infected animals in the Midwest and California; foxes and coyotes are most afflicted in Texas, the Southwest, and Alaska; and mongoose are most affected in Puerto Rico [114].

Rabies is the infectious disease with the highest known case-fatality rate in the world [118; 119]. It is an acute, progressive encephalitis that almost always leads to the death of the patient if they do not begin to receive the vaccine series soon after exposure. The disease occurs when the virus enters the body, most commonly by the bite from an infected animal. Infection can also occur from contact with contaminated animal body parts, saliva, or other body fluids, especially when it involves penetration through mucous membranes or broken skin [112]. Fortunately, case reports have shown this type of transmission is much less likely to happen. There does not appear to be human-to-human transmission of rabies, except via infected transplanted tissues or organs [117; 120]. After entering the body, the virus particles pass via the peripheral nervous system to lodge and replicate in the central nervous system. The rabies virus becomes distributed throughout the brain and is also disseminated to the salivary glands and other organs.

The incubation period is usually about two weeks but can be as long as several months [112]. Shorter incubation periods appear to be associated with inoculations closer to the head [119]. If untreated, rabies is almost 100% fatal [8; 112]. The only existing treatment for non-vaccinated humans is injection with rabies immune globulin and rabies vaccine within days after exposure; therefore, timely diagnosis of the disease is extremely important.

Clinical Presentation and Diagnosis

The clinical presentation often begins with a feeling of fatigue, malaise, and possible paresthesias near the site of inoculation. Most patients have a low-grade fever, but some remain afebrile in the early stages prior to developing a fever over the next few days. Nausea and vomiting can be present as well as lethargy and anorexia. The signs and symptoms of a central nervous system disease and encephalitis usually follow rapidly. Diplopia or other visual defects, unsteady gait, cranial nerve palsies, cognitive changes, photophobia, phonophobia, restlessness, and limb weakness are common findings. The neurologic condition of the patient rapidly declines, with increasing confusion, disorientation, tremors, twitching or myoclonic muscle movements, seizures, and increased pain sensations. Some patients develop laryngospasm when attempting to drink. Many patients eventually have pulmonary problems, leading to poor ventilation and respiratory failure. Autonomic system collapse and coma ensue, with death following regardless of supportive measures [112; 119].

There are descriptions of two possible forms of disease presentation. One is called the paralytic form, whereby an ascending paralysis similar to Guillain-Barré syndrome predominates. The other, which is more common, is the encephalitic or "furious" form described above [118; 119; 121].

It is imperative to make the diagnosis of a rabies-prone exposure during the period prior to the development of symptoms. A delay in diagnosis and treatment can mean almost certain death for the patient [119]. Therefore, a history of suspicious animal bite or contact with a victim of the disease, especially the saliva of a victim, must lead to the performance of diagnostic tests.

Several tests are necessary to diagnose rabies in humans; no single test is sufficient [122]. Fortunately, there are several very good diagnostic procedures that can be performed fairly quickly on serum, saliva, CSF, or skin biopsies taken from the nuchal region of the neck. Antibody analysis can be performed on serum or CSF, and skin biopsy samples can be examined for rabies antigen in the cutaneous nerves at the base of the hair follicles [122]. Other laboratory tests include electron microscopy, virus culture, and immunohistochemistry. Laboratory analysis also allows for the determination of the type of animal involved and, in many cases, the locality from which the infection originated. There are many public health and other designated facilities available to perform these procedures. Neuroimaging procedures, including CT scans and MRIs, are usually normal initially but show signs of cerebral edema and other features of encephalitis as the disease progresses.

If possible, the suspected animal should be tested for rabies antigen. Tests on animals may require samples of their brain tissue from at least two locations in the brain, preferably the brain stem and cerebellum [122]. Because of its high sensitivity and specificity, the direct fluorescent antibody (DFA) test is considered the gold-standard diagnostic method for rabies determination in animals in the United States [122]. The presence of Negri bodies, characteristic intracytoplasmic inclusion nodules within neurons, is confirmatory evidence of the disease. The rapid determination of whether an animal is rabid can save a potential victim from psychologic trauma and an expensive treatment regimen [122].

Treatment and Prevention

Any wound from an animal should be intensively cleaned with soap and water. Antiviral compounds (e.g., povidone iodine) should be used if available; thorough wound cleansing has been shown to markedly decrease the risk of bacterial infection [123]. As discussed, postexposure treatment can prevent the disease if given early and prior to the onset of symptoms.

In non-immunized individuals, treatment consists of the use of immune globulins and vaccine [123]. A human rabies immunoglobulin (HRIG) is available in the United States and most other developed countries. Historically, equine rabies immunoglobulin (ERIG) was used and regimens included a series of painful and sometimes dangerous injections. The currently available ERIG is highly purified and is considered safe by the WHO [124]. According to the WHO, there are no scientific grounds for performing a skin sensitivity test prior to administration of ERIG. However, the treating physician should be prepared to manage anaphylaxis, which, while rare, can occur at any stage of ERIG administration [124]. The safer HRIG is expensive, but requires only an intragluteal injection, usually with a dose of 20 IU/kg [124]. The WHO advises that HRIG, like ERIG, also be administered in the vicinity of the bite wound [124].

In addition, rabies vaccine must also be started. According to the CDC Advisory Committee on Immunization Practices (ACIP), the vaccine should be injected IM at a site distant from the HRIG injection site, possibly the deltoid. The ACIP recommends giving four doses of human diploid cell vaccine or purified chick embryo cell vaccine, 1.0 mL (at days 0, 3, 7, and 14) for immunocompetent individuals and the usual five-dose regimen for immunocompromised individuals [123; 125].

ACIP RISK CATEGORIES AND PrEP RECOMMENDATIONS		
Risk Category	**Affected Individuals**	**Recommendations**
Category 1 (highest risk)	People who work with live or concentrated rabies virus in laboratories	2 doses, days 0 and 7 Check titer every 6 months
Category 2	People who frequently do at least one of the following: handle or have contact with bats, enter high-density bat environments, perform animal necropsies	2 doses, days 0 and 7 Check titer every 2 years
Category 3	People who interact with or are at higher risk to interact with mammals other than bats that could be rabid, for a period longer than 3 years after they receive PrEP. This includes: most veterinarians, veterinary technicians, animal control officers, wildlife biologists, rehabilitators, trappers, and cave explorers.	2 doses, days 0 and 7, plus: Either a one-time titer check after 1 year and up to 3 years following the first 2-dose vaccination OR 1-dose booster between 3 weeks and 3 years following the first vaccine in the 2-dose vaccination
Category 4	Same population as risk category 3, but at a higher risk for up to three years after they receive PrPE	2 doses, days 0 and 7
Category 5 (lowest risk)	General U.S. population	None

Source: [129] *Table 5*

When symptoms appear, diligent supportive measures are required, including induced coma for patients with involuntary muscle movements and severe pain [119; 126]. Additional treatment regimens have included IV ribavirin and other antiviral agents under investigative drug protocols; however, there are very few reports of recovery [119; 127]. The experimental Milwaukee protocol is associated with significantly longer survival than conventional treatments for symptomatic rabies, but has been tested on an exceedingly small number of patients and "excellent and adaptive medical intensive care and careful avoidance of mistakes and complications of intensive care may prove to be essential to positive outcomes" with this treatment regimen [126]. The probability of treatment failure, even with this protocol, is extremely high [119].

Individuals who had been previously adequately vaccinated for rabies are treated differently. The ACIP suggests that these patients receive rabies vaccine IM immediately or as soon as practical with a second injection three days later [123; 125]. The recommended site is the deltoid muscle. They do not advise giving HRIG to previously immunized patients [123; 125].

In the United States, every state has some type of requirement that household dogs and cats be vaccinated for rabies. Although the vaccine is commercially available, almost all vaccinations of domestic animals are performed by veterinarians. Some states or municipalities also impose quarantines of varying periods to help reduce the possible spread of rabies [128].

The CDC and the WHO suggest that individuals who might have a higher risk of coming in contact with a rabid animal be vaccinated. This pre-exposure prophylaxis includes occupations such as veterinarians, laboratory workers, animal control officers, animal handlers, and those who travel to parts of the world where rabies is common and access to medical care is limited. In May 2022, the ACIP updated rabies vaccine recommendations for persons at high risk (***Table 5***) [129]:

- A two-dose pre-exposure prophylaxis (PrEP) schedule has replaced the three-dose PrEP schedule to protect for up to three years. Options for maintaining protection beyond three years also are described.
- Risk categories have been redefined into five risk groups.
- The minimum acceptable laboratory value (antibody titer) used to determine whether rabies vaccine booster doses are needed was revised and standardized.
- Many people for whom serial titers were recommended every two years now require only a one-time titer (and booster if below a certain level) OR a one-time booster.
- Clinical guidance for administering PrEP to people with weakened immune systems has been outlined and includes recommendations to confirm that the vaccine was effective.

The recommended vaccine is a cell culture vaccine (CCV) [130]. It is also recommended that the production and use of nerve-cell vaccines cease.

The WHO suggests that an intradermal administration of CCV 0.1 mL be used in three doses at day 0, 7, and then between 21 and 28 days or, alternately, intramuscular administration of 0.5 to 1 mL, depending on the type of vaccine, on the same three-day schedule [130]. However, rabies vaccine adsorbed is no longer available in the United States and therefore intradermal administration is no longer recommended [120]. Intramuscular vaccinations should be administered in the deltoid area of the arm for adults and the anterolateral area of the thigh for children younger than 2 years of age; the vaccine should not be administered in the gluteal area. Serologic analyses should be performed every six months for those at high risk and every two years for those at lower risk; a booster injection is not recommended unless rabies-virus neutralizing antibody titers fall below 0.5 IU/mL [130]. Booster injections are not recommended for individuals travelling to high-risk areas if they have previously completed pre-exposure or post-exposure prophylaxis.

AVIAN INFLUENZA

The influenza viruses that are carried by birds, both domesticated and wild, rarely have infected humans. This is partly due to the fact that avian influenza (AI) viruses attach to receptors found on bird cells but not found on human cells. Human viruses prefer the receptors found in the human respiratory tract. Pigs have receptors used by avian, swine, and human influenza viruses and have traditionally been the link between avian and human influenza viruses. Because pigs acquire all three types of viruses, reassortment/antigenic shift of the hemagglutinin and neuraminidase proteins occurs in the pig host, which then transmits the new strain to humans or other pigs [131; 132].

However, there now exists evidence that avian influenza can spread directly to humans [132]. In 2004, areas of Asia experienced large-scale outbreaks of avian influenza, specifically the H5N1 virus, in poultry. The virus went on to infect humans, with a high mortality rate. The number of countries, people, and animals affected by the virus reached unprecedented levels. In 2006, the CDC summarized the H5N1 outbreak. Wild birds and poultry had been infected in Asia, parts of Europe, the Middle East, and Africa. Human infections continued to be reported in China, Egypt, Indonesia, Azerbaijan, Cambodia, and Djibouti. There were some probable human-to-human transmissions of H5N1, but these were rare. As of January 2023, the WHO reported 868 human cases of H5N1, with a fatality rate of approximately 53% [133]. In January 2014, the first case of a human infection with H5N1 in the Americas was reported in Canada; the patient, who died, had recently travelled to Beijing, China [134]. Both the CDC and the WHO have reported that there is a strong threat of a future pandemic of avian influenza and that preparedness is vital [135; 136]. In August 2012, the Indonesian Ministry of Health announced another H5N1 death of a man infected either from birds he kept in his home or from exposure to H5N1 near his home, which is about 50 meters from a poultry slaughterhouse. This brings the total of confirmed cases of H5N1 in Indonesia to 191 with 159 deaths, a fatality rate of 83% [137].

Although influenza A viruses can infect all birds, domestic poultry flocks are more vulnerable to infections that can reach epidemic proportions. Generally, domesticated fowl transmit the virus in saliva, nasal secretions, and feces. However, it is thought that the fecal-oral route is the common way the virus is spread among flocks. Wild birds rarely become sick but are a source of infection through their droppings because they carry the virus in their intestines. Free-roaming domestic fowl are at more risk from wild bird droppings than housed flocks. Both food and water supplies can be contaminated by droppings or sharing with wild birds. At first it was thought that wild birds spread the virus from farm to farm, but further study indicated that people and equipment probably spread the virus to domesticated flocks [138; 139].

AI viruses are classified as low pathogenic and high pathogenic based on their genetic sequence and the resulting illness in birds. Low pathogenic AI has been detected in wild birds, mostly ducks, geese, and gulls, since 1975 [138; 140]. Low pathogenic AI virus causes only ruffled feathers and a reduction in egg production. Fortunately, most AI viruses are low pathogenic; however, in six to nine months, they can mutate to high pathogenic. High pathogenic AI viruses, first noted in 1878 in Italy, are highly contagious, spread rapidly, and are almost 100% fatal. Fowl can die the same day that they first exhibit symptoms [140; 141].

Whenever an AI virus infects a human directly, there is much concern. Humans rarely have any immunity to AI viruses. Medical resources around the world quickly mobilize when there is a case of AI that skips reassortment in swine and directly infects a human. Fowl within a 2-mile (3-kilometer) radius of the source bird/flock are killed in order to contain the virus. An AI virus in humans usually produces upper respiratory disease and conjunctivitis. The infected humans and their contacts are watched closely for secondary transmission. For a pandemic to follow, these factors are needed:

- Humans do not have immunity to the virus
- Direct transmission from bird to human
- Sustainable transmission from human to human
- Movement of infected/contagious individuals to other geographic locations

Once a new pandemic influenza virus emerges, it generally circulates for many years [138; 141]. Researchers at the University of Wisconsin, Madison, have been combining H5N1 with a seasonal flu strain (H3N2). As a result, they have found such reassortment flu viruses are highly pathogenic; 22 were more pathogenic for mice than the original H5N1, and 3 caused extremely severe disease [142].

Avian Influenza Viruses

The hemagglutinin antigens that historically have caused human influenza are H1, H2, and H3. Although all known hemagglutinin subtypes occur in birds, H5, H7, and H9 have been implicated more in recent outbreaks. Various combinations with the neuraminidase antigens occur. All of these AI viruses are type A, as B and C do not infect birds. Some of the cases focused on in the past two decades have included the following [143; 144]:

- H5N1 – Hong Kong, 1997, first documented human infection-18 hospitalized, 6 deaths, 1.5 million chickens culled
- H9N2 – Hong Kong, 1999, 2 mild cases in children, several in mainland China
- H7N2 – Virginia, 2002, 4.7 million chickens and turkeys culled
- H7N7 – Netherlands, 2003, 80 poultry workers, 3 family members infected (79 eye infections, 6 influenza-like), 1 veterinarian death due to acute respiratory distress syndrome and complications
- H5N1 – Hong Kong/China, 2003, 2 ill, 1 death
- H9N2 – Hong Kong, 2003, 1 case confirmed in a child
- H5N1 – Asia, 2004–2005 (H5N1 had been found in Asian chickens April, 2003), 112 confirmed cases, 57 deaths; too widespread to cull all fowl

- H7N3 – British Columbia, 2004
- H5N2 – Taiwan, 2004, low pathogenic, no human illness
- H7N2 – Delaware, 2004, no human illness
- H5N2 – Texas, 2004, no human illness
- H5N1 – Russia/Romania/Turkey/Azerbaijan, 2006, some human illness, unknown deaths
- H5 Outbreaks – 21 U.S. states and Canada, 2014–2015, highly pathogenic, found in backyard and commercial flocks and wild birds, no human illness
- H7N8 – Indiana, 2016, highly and low pathogenic virus detected in nine commercial turkey flocks, all culled, no human illness
- H7N9 – China, 2013–2017 (ongoing), contact with poultry at farms and live markets, 1,347 laboratory-confirmed human infections
- H5N1 – Chile, 2023, first case of human infection in Chile, source is subject of ongoing investigation; second human infection in South America was in Ecuador, associated with exposure to backyard poultry
- H5N1 – Peru, 2023, infections in sea lions and pelicans after die-offs in those animals
- H3N8 – China, Guangdong Province, 2023, human infection, patient hospitalized with severe pneumonia, later died

Fortunately, although in some of these outbreaks bird-to-human transmission did occur, human-to-human transmission has been extremely rare. Limited transmission possibly did occur between humans in the Netherlands, but no sustainable transmission occurred, so an epidemic or pandemic did not follow. There were 14 cases and 12 deaths (11 children) from H5N1 virus in Vietnam. The viruses isolated from those who expired in Vietnam were mostly resistant to amantadine and rimantadine. Studies are continuing as to the effectiveness of oseltamivir and zanamivir against H5N1 viruses. There is some evidence that H5N1 is sensitive to oseltamivir; however, some evidence of resistance to oseltamivir has been reported in highly pathogenic avian influenza H5N1 viruses isolated from human cases [141; 144]. Most of the H5N1 outbreaks were controlled by veterinarian officials or spontaneously died out. However, H1N1 continues to fulminate in poultry in Egypt [145].

Avian Influenza and Humans

Most cases of AI in humans have resulted from contact with infected poultry or contaminated surfaces. It is also possible for the virus to become aerosolized and then land on exposed surfaces of the mouth, nose, or eyes. Aerosolized virus could also be inhaled directly into the lungs. Eating poultry products has not been associated with the development of AI. Influenza viruses are destroyed by adequate heat.

Some patients might become concerned about contaminated poultry products from other countries entering our food supply. Some countries will not permit poultry to be imported from countries in which there were confirmed human cases of AI, such as China's ban of U.S. chicken in 2015. However, the risk of AI spreading through the global chicken industry is low because most chickens on the international market are killed and frozen or chilled. All documented transmission to date has been from live birds [144; 146].

Humans have no immunity to AI viruses, so illness tends to be severe and the fatality rate is high. Prevention is difficult because the viruses tend to be highly contagious. Because of the mobile nature of people and efficient, rapid transport, any virus can spread quickly around the world. The current manufacturing process of influenza vaccine requires several months. The elements are all in place for a pandemic.

In August 2007, a team of scientists at the National Institute of Allergy and Infectious Diseases reported that it had developed a way to generate vaccines and therapeutic antibodies that could target constantly mutating influenza viruses, such as H5N1. The team focused on mutations that enable H5N1 hemagglutinin protein to better recognize and enter human cells and those mutations that will elicit antibodies.

This information will enable researchers to consider how to design potential vaccines that will protect people from future emerging AI virus mutants, possibly helping to contain a pandemic in its early stages [147].

In order to understand how influenza viruses mutate, researchers have been working to synthesize the hemagglutinin responsible for the 1918 influenza ("Spanish flu") pandemic. The success of this endeavor was reported in 2004, and scientists have since discovered how subtle alterations enabled the virus to move from birds to people [148].

The H5N2 avian influenza virus continues to be monitored around the world by scientists. It is highly virulent but has not been transmitted person-to-person yet [136; 149]. In 2015, H5N2 avian influenza virus (along with H5N8 and H5N1) were found in more than 200 bird samples, indicating the likelihood that 40 million farm and backyard birds have been infected in 20 states [150].

Clinical Presentation and Diagnosis

As noted, humans have no immunity to avian influenza A viruses, so illness tends to be severe and the fatality rate is high. The symptom complex can range from the typical influenza findings of fever, headache, myalgia, sore throat, and cough to severe respiratory distress. Many humans develop conjunctivitis, which can be the initial complaint. This usually includes red, itching, and tearing eyes with associated photophobia and purulent discharge. The severe form progresses to pneumonia, which can be fulminant and followed by multiorgan failure and death. Although the very young and very old are most at risk for the viral pneumonia, fatalities have occurred among previously healthy adults [151].

Laboratory testing is required to diagnose avian viral disease; it cannot be determined by clinical signs and symptoms alone [151]. Diagnosis is initially based on the history from a patient with the symptoms of influenza who has had contact with birds, poultry, or an endemic area. A complaint of eye irritation, which on examination appears to be conjunctivitis, is another clue to the presence of the disease. The available laboratory tests include viral culture and reverse transcriptase PCR (RT-PCR). The CDC recommends testing by RT-PCR [151]. These can be performed on samples of eye exudate, tears, or throat swabs. Analyses are most useful if obtained within four days of the onset of symptoms, and eye swabs are more likely to be positive than throat culture [152].

Treatment and Prevention

As in other viral diseases, supportive treatment is a mainstay in avian viral infections. Over the past few years, several regimens have been attempted in the treatment of avian viral disease. The antiviral medications amantadine, rimantadine, oseltamivir, and zanamivir have been used in cases of human influenza in the United States. However, amantadine and rimantadine were shown to be ineffective against the H5N1 strain of avian influenza in humans during the outbreaks in Asia in 2004 and 2005 [153]. The CDC and the WHO recommend oseltamivir, peramivir, zanamivir, or baloxavir marboxil for treatment and prevention of human infection with avian influenza A viruses; however, as noted, some evidence of resistance to oseltamivir has been reported in viruses isolated from some human cases [68; 151]. The suggested adult dose for the treatment of influenza is 75 mg twice per day, starting within two days of symptoms and continuing for five days. Results are best if the drug is started within two days after contact with an infected individual or fowl. For prophylaxis, the dose is also 75 mg twice a day, but taken for 10 days [55].

A major step to limiting disease and transmission among domesticated fowl is to destroy all diseased birds and their flock mates. Because the virus appears to be carried by people and machines, possibly on shoes and tires to surrounding areas, the recommendation is that all fowl in a 2-mile (3-kilometer) radius of the diseased flock be culled. Obviously, no shipping of live poultry from the infected areas should occur.

During the outbreaks of avian influenza in poultry in Asia during 2003–2004, people were not restricted from traveling to outbreak areas because of the limited transmission to humans. However, the following recommendations were sent to embassies and Americans living abroad [68; 154]:

- Practice frequent and careful handwashing with soap and water or with a hand cleanser if soap and water are unavailable.
- Avoid bird markets and poultry yards where avian influenza is most likely to be transmitted.
- All poultry and eggs should be cooked well, as influenza virus is destroyed by heat.
- Protect pets by keeping them inside to avoid exposure to birds that may be sick, refraining from feeding them raw meat or poultry, and avoiding all contact with stray cats or dogs.
- Masks and other personal protective equipment in public areas are not recommended.
- Travelers should be immunized with the current influenza vaccine against human influenza strains before traveling and should be reminded that winter (flu season) occurs in the Southern Hemisphere when the Northern Hemisphere is experiencing summer.

The CDC has also developed guidelines for airline personnel dealing with a suspected case of avian influenza on board an international flight originating in an area in which avian influenza has been reported [155]:

- As much as possible, airline staffs are to keep the sick person separated from close contact with others.
- A surgical or procedural mask should be provided to limit the amount of droplets coughed into the air. If the passenger cannot wear the mask, anyone assisting him/her should be masked.
- The passenger should be taught cough etiquette if it is not being practiced.
- Disposable gloves are to be worn for any contact with body fluids, and hands are to be washed well when gloves are removed.
- The captain is to report the illness to the nearest U.S. Quarantine Station if the aircraft is coming to the United States. The Quarantine Station will coordinate appropriate medical assistance when the plane lands and will notify the appropriate CDC staff.

Influenza viruses are destroyed by adequate heat. Because the pathogen is found in poultry, all individuals should be reminded to cook poultry, including eggs, thoroughly. Chicken should be cooked until the internal temperature reaches 180 degrees F. All utensils and surfaces that have come in contact with raw poultry should be washed well with soap and water immediately following use. A separate cutting board should be used to cut raw poultry. In order to retard bacterial or viral replication, all poultry products should be defrosted in the refrigerator, not at room temperature.

Some patients might become concerned about contaminated poultry products from other countries entering our food supply. Some countries will not permit imported poultry from countries in which there were confirmed human cases of avian influenza. However, the risk of avian influenza spreading through the global chicken industry is low because most chickens on the international market are killed and frozen or well chilled. All documented transmission to date has been from live birds [146].

Vaccine Development

As with the development of all vaccines, the first step is to isolate the organism. In the case of AI, various research centers and companies around the world are working to make a vaccine. The first step is to isolate the virus (e.g., the H5N1 influenza A virus in 2004). Next, the virus is dismantled so the most virulent elements can be excluded. Then the virus is reassembled without those virulent elements, and attempts are made to produce it [146]. As noted, the virus has been isolated and the virulent elements

have been identified to allow vaccine development to proceed. In 2006, a new recombinant H5N1 virus became available for distribution to companies interested in pandemic vaccine development [156]. In 2007, GlaxoSmithKline received a contract from the U.S. Department of Health and Human Services to manufacture 22.5 million doses of AI vaccine in addition to the 5 million doses ordered in 2006 [157]. Research to find novel media or methods (rather than using eggs) is ongoing [158].

In April 2007, the FDA approved the first human vaccine for the AI virus H5N1 [159]. This vaccine is intended for individuals 18 to 64 years of age who could be at an increased risk of exposure to the H5N1 influenza virus. The vaccine is not available commercially, but rather has been purchased by the federal government to be distributed if necessary [160]. The vaccine consists of two 90-mcg IM doses given 28 days apart. There is thimerosal, a preservative, in this vaccine [55; 159]. Because this vaccine has been approved by the FDA and found to be safe and effective, it is no longer considered experimental. Therefore, it can be used during a pandemic without the time-consuming protocol and signed informed consent necessary for an experimental drug or vaccine [159]. Data from trials being conducted on ACAM-FLU-A show that the vaccine generates a robust antibody response against H5N1 avian influenza [161]. The WHO provides a summary of ongoing H5N1 vaccine development [162].

SWINE INFLUENZA

As discussed, pigs represent an important link in the interspecies transmission of influenza and in the creation of new virus types. In addition, swine influenza has the potential to cause significant disease in humans, although it is difficult to predict the potential impact of swine influenza in humans. Because most individuals, with the possible exception of those with regular contact with pigs, do not have immunity to these viruses, the potential for pandemic exists.

Swine influenza is usually caused by the H1N1 subtype, but other swine influenza A viruses do occur, including H1N2, H3N1, and H3N2 [163]. Although swine flu viruses do not typically infect humans, sporadic human infections have occurred. When this occurs, these viruses are called "variant viruses" and are denoted by adding the letter "v" to the virus subtype designation. Human infections with H1N1v, H3N2v, and H1N2v viruses have been detected in the United States [163; 164]. Pigs may become infected with more than one virus subtype simultaneously; in these cases, genes from the viruses may mix and create a new "reassortment" virus [165]. The main swine influenza viruses circulating in U.S. pigs in the past decade include triple reassortant (tr) H1N1, trH3N2, and trH1N2 [163; 164].

Among pigs, swine influenza is a highly contagious acute respiratory disease. In many countries, including the United States, swine populations are routinely vaccinated against the prevalent subtypes. Vaccination of pigs, while not sufficient to produce sterilizing immunity, can reduce the levels of virus shed by the animals and reduce the potential for human exposure and infection [165].

In 2009, an outbreak of H1N1 influenza A (hereafter referred to as 2009 H1N1), popularly referred to as the "swine flu," occurred. Tests showed this virus was similar to influenza viruses normally occurring in pigs in North America. However, with more extensive testing scientists learned that there were two genes present that typically occur in pigs in Europe and Asia. In addition, there were also avian and human genes. A quadruple reassortment virus was the result [166].

It should be noted that the so-called Spanish Influenza of 1918–1919 was also an H1N1 virus. The hemagglutinin gene in 2009 H1N1 influenza apparently descended from the avian-origin 1918 pandemic influenza virus. The 2009 H1N1 virus is not a new subtype, but many humans had no pre-existing antibody to it (especially those younger than 65 years of age) and widespread transmission resulted. This led to the first pandemic since 1968.

The virus quickly spread worldwide, and on June 11, 2009, the WHO declared it a worldwide pandemic. In the United States the virus was first detected in humans in April 2009. By September more than 99% of the circulating viruses were 2009 H1N1. It remained the predominant circulating virus for the entire 2009–2010 influenza season [166; 167]. On June 23, 2010, the public health emergency for 2009 H1N1 expired in the United States, and the WHO declared the pandemic over on August 10, 2010 [168].

Data from past pandemics show that influenza activity occurs in waves. A second wave of 2009 H1N1 occurred in August 2010 and peaked in the first three weeks of October [169]. Experts believe that 2009 H1N1 will continue to circulate for some time, perhaps as a typical winter flu. Components are included in the formulation of the 2022–2023 influenza vaccine [170].

Transmission

Like all flu viruses, 2009 H1N1 is mainly spread among people by coughing, sneezing, talking, and occasionally via fomites. It is not spread by food or by eating pork or pork products. There have been no cases acquired from influenza-contaminated drinking water. Chlorine treatment of drinking water has been shown to inactivate the highly pathogenic H5N1 virus, and H1N1 would be similarly affected. A documented case of influenza from any water exposure (drinking or recreational) has not occurred.

Pets, such as dogs, cats, and ferrets, can be infected with H1N1 from close contact with a sick human. All available information indicates that H1N1-infected dogs, cats, and ferrets do not transmit the illness to humans. So far, there is no H1N1 vaccine for animals. Most recover with supportive care [166].

When a swine influenza virus does become a source of widespread human illness, the transmission patterns change. Instead of being mainly limited to swine contact, the virus will spread by human-to-human contact. According to the CDC, available data indicate that the 2009 H1N1 virus is transmitted in ways similar to other influenza viruses, primarily large-particle respiratory droplet transmission [171]. Because humans have little to no immunity to influenza viruses of swine origin, transmission may be common.

H1N1 survives on surfaces, including kitchen counters, doorknobs, desktops, and other fomites, for two to eight hours. Individuals can pick up the virus when they touch contaminated objects and unconsciously then touch their eyes, mouth, or nose. Thus, it is vital for people to learn to keep their hands away from their mouths, eyes, and nose and to frequently wash their hands well with soap and water or use an alcohol-based hand sanitizer. An alcohol-based product, bleach solution, or hot, soapy water can be used to clean surfaces [172]. One positive result of the H1N1 pandemic, as indicated in a study conducted in Hong Kong, is that people are washing their hands more frequently and wearing face masks when having influenza-like illness or when in public areas [173].

A major transmission concern with 2009 H1N1 was regarding newborns whose mothers had the virus. The CDC and State Health Departments strongly recommended the 2009 H1N1 vaccine for this population because of demonstrated risks to both infants and pregnant women. However, many disregarded the recommendation. It was then decided that infant and mother should be separated until the mother had been on antivirals for at least 48 hours, was afebrile for 24 hours without antipyretics, and could control her cough and respiratory secretions. Before visiting the infant, the mother was instructed to clean her hands well with soap and water or an alcohol-based hand sanitizer, wear a face mask, and observe respiratory/cough etiquette. If her gown had been contaminated with byproducts of coughing or sneezing, she was instructed to change to a fresh gown. Following these guidelines, the mother was then permitted to hold, feed, and care for the infant [174].

Prevention

Like seasonal influenza, vaccination is the most important preventive measure. Other common-sense preventive steps (e.g., appropriate cough cover, correct disposal of used tissues, adequate rest, good fluid intake, staying home when ill) should be practiced. No vaccine specifically targeted against variant viruses is available at this time. Immunization with seasonal influenza vaccine does not provide protection against infection with variant viruses. Persons who are at high risk for influenza complications should avoid exposure to swine and to ill persons with swine exposure [175].

Vaccine

The CDC identified five groups who were given first priority 2009 H1N1 vaccination [176]:

- Pregnant women
- Persons who live with or provide care for infants younger than 6 months of age
- Healthcare and emergency medical services personnel
- Children and young adults 6 months to 24 years of age
- Persons 25 to 64 years of age at higher risk for influenza-related complications

These patients were vaccinated as soon as the vaccine was available. As with seasonal influenza vaccine, it is also important to note that two doses of the vaccine are necessary for previously unvaccinated children younger than 9 years of age, as they typically have had limited exposure to influenza viruses and are not immunologically primed [176; 177]. For the 2016–2017 flu season, the ACIP recommended that children 6 months through 8 years of age not previously immunized be given two doses at least four weeks apart [177]. At least one study has shown that a single injection is adequate when vaccinating pregnant women [177].

Symptoms and Diagnosis

Similar to seasonal flu, H1N1 symptoms include chills, fever, myalgia, fatigue, headache, cough, sore throat, and rhinitis. But unlike seasonal flu, there may be vomiting and diarrhea in some people. Others may have respiratory symptoms without fever [175].

Unless it becomes a pandemic, swine influenza infection in humans generally goes undistinguished from typical human influenza as a result of the overlapping flu seasons and the relatively mild clinical presentation. Clinicians should obtain a nasopharyngeal swab or aspirate (or a combined nasal swab and throat swab) collected in the first four to five days of illness, when an individual is most likely to be shedding the virus [175]. A new test for 2009 H1N1 was authorized by the FDA in June 2010 to be used on upper or lower respiratory secretions. The CDC Influenza 2009 A (H1N1) pdm Real-Time RT-PCR panel (IVD) replaced the test authorized in April 2009 [178].

The CDC currently recommends antigen detection tests, (e.g., rapid influenza diagnostic tests [RIDTs], immunofluorescence assays), which may detect variant viruses (e.g., H1N1v) in respiratory specimens [175]. Some RIDTs may not detect these viruses, producing a false-negative result. (A false-negative result also can occur with other influenza viruses.) While some variant virus infections have tested positive by RIDTs, other confirmed variant virus infections have tested negative by RIDTs. There also are a variety of commercially available molecular assays, including RT-PCR assays, that can detect influenza viruses. All of the available assays are likely to detect influenza A virus infection and, in general, are more sensitive and specific than RIDTs. However, commercially available molecular assays cannot differentiate variant viruses from seasonal influenza A viruses, and the sensitivity and specificity of molecular assays to detect variant viruses are not known. Some medical center laboratories may use non-commercially available molecular assays for influenza ("home brews"); the sensitivity and specificity of home-brew molecular assays to detect variant viruses are not known [175].

Because variant virus infection cannot be distinguished by clinical features from seasonal influenza virus infection, or from infection with other respiratory viruses that can cause influenza-like illness, the key to suspecting variant virus infection in an ill patient is to elicit an epidemiologic link to recent swine exposure in the week prior to illness onset. Exposure can be defined as follows [175]:

- Direct contact (e.g., showing, raising, feeding swine or cleaning swine waste)
- Indirect exposure (e.g., visiting a swine farm, walking through a swine barn), especially if swine were known to be ill
- Close contact (within 2 meters or approximately 6 feet) with an ill person who had recent swine exposure or is known to be infected with a variant virus

For any ill person with an exposure as defined above, respiratory samples should be taken for testing [175].

Treatment

While most swine influenza cases were sufficiently mild to resolve spontaneously, antiviral medications were used if treatment was indicated. The specifically recommended agents were determined based on clinical and epidemiologic assessment of the virus. For example, in the case of the 2009 H1N1 outbreak in North America, the virus's susceptibility profile indicated that the preferred antivirals would be oseltamivir or zanamivir (or peramivir in case of severe illness requiring hospitalization) [163; 165].

During the 2009 H1N1 pandemic, the CDC recommended antiviral treatment for all persons with suspected or confirmed influenza requiring hospitalization [167]. For the 2022–2023 influenza season, antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications, including [179]:

- Children younger than 2 years of age
- Persons 65 years of age or older
- Pregnant women and women up to two weeks postpartum (including following pregnancy loss)
- Persons of any age with certain chronic medical or immunosuppressive conditions
- Persons younger than 19 years of age who are receiving long-term aspirin therapy
- Persons living in nursing homes or other long-term care facilities

Four antiviral medications are FDA-approved for treatment of influenza: oral oseltamivir, inhaled zanamivir, intravenous peramivir, and oral baloxavir marboxil (endonuclease inhibitor) (***Table 6***) [179]. Use of these agents is not contraindicated during pregnancy [55].

For hospitalized patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically-administered oseltamivir is recommended as soon as possible. For outpatients with complications or progressive disease and suspected or confirmed influenza (e.g., pneumonia, exacerbation of underlying chronic medical conditions), initiation of antiviral treatment with oral oseltamivir is recommended as soon as possible. For outpatients with suspected or confirmed uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for treatment, depending upon approved age groups and contraindications [179].

Laboratory testing has found the H1N1 influenza A virus susceptible to both oseltamivir and zanamivir, with a few exceptions. Those resistant to oseltamivir have been sensitive to zanamivir. Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified, but the public health impact has been limited [181]. As of October 2012, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide [181].

RECOMMENDED DOSAGE AND DURATION OF ANTIVIRAL MEDICATIONS FOR INFLUENZA TREATMENT			
Antiviral Agent	**Use/Duration**	**Children**	**Adults**
Oral oseltamivir	5 days[a]	If <1 year[b]: 3 mg/kg/ dose twice daily[c d] If ≥1 year, twice daily dose, varies by weight: ≤15 kg, 30 mg >15–23 kg, 45 mg >23–40 kg, 60 mg >40 mg/ 75 mg	75 mg twice daily
Inhaled zanamivir[e]	5 days	10 mg in divided doses, twice daily (for children 7 years and older)	10 mg in divided doses, twice daily
IV peramivir[f]	1 day[a]	6 mos-12 years of age: One 12 mg/kg dose, up to 600 mg max; IV infusion for minimum of 15 minutes For children 6 months of age and older	13 years and older: One 600 mg dose, via IV infusion for minimum 15 minutes
Oral baloxavir[g]	1 day	5 years and older (dose varies by weight) <20 kg: single dose of 2 mg/kg by suspension 20–<80 kg: single dose of 40 mg tablet or suspension ≥80 kg: single dose of 80 mg tablet or suspension	Weight <80 kg: one 40 mg dose Weight ≥80 kg: one 80 mg dose[g]

[a]Longer treatment duration may be needed for severely ill patients.
[b]Approved by FDA for treatment within 2 days of onset with twice-daily dosing in people aged ≥14 days.
[c]FDA-approved dose for infants ≥14 and <1 year.
[d]Current weight-based dosing recommendations not appropriate for premature infants.
[e]Approved for treatment within 2 days of onset with twice-daily dosing in people aged ≥7 years.
[f]Approved for treatment within 2 days of onset with single dose in people aged ≥6 months.
[g]Approved for treatment within 2 days of onset in people aged ≥5 years who are otherwise healthy, or in people aged ≥12 years at high risk of developing influenza-related complications.

Source: [180] *Table 6*

Investigational Drugs

The use of antiviral treatments in combination for influenza is of interest. One potential benefit of this treatment strategy is that the combination of drugs with different mechanisms of action may lower the selection of resistance due to treatment. In addition, combination therapy may become an important treatment option to improve patient outcomes in those with severe illness due to influenza or those that are immunocompromised. Clinical trials increasingly evaluate drug combinations in a range of patient cohorts. Combination treatment regimens should be carefully evaluated to determine whether

they provide an added benefit relative to effectiveness of monotherapy and in a variety of patient cohorts, particularly, if there is a greater chance of an adverse outcome. Safe and effective treatment of influenza is important not only for seasonal influenza infection, but also in the event a pandemic strain was to emerge [182].

HANTAVIRUS SYNDROMES

In 1993, there was a series of mysterious deaths due to pulmonary failure in healthy young adults in the four corners region of the American Southwest [183; 184]. Considerable research into the problem resulted in the identification of a virus, harbored in local mice, as the cause of the illness. The virus identified was an RNA *Hantavirus*, a group related to the *Bunyaviridae* family that causes hemorrhagic fever with renal syndrome (HFRS) in Asia and hantavirus pulmonary syndrome (HPS) in the Americas. HPS became a nationally notifiable disease in 1995 [183].

Although many thought that HPS was a new entity, the local Navajo inhabitants described a similar disease that they had known about for many years. Between 1993 and the end of 2020, 833 cases were reported in the United States, with a 35% fatality rate [183; 184]. HPS has been documented in 40 states, with 96% occurring in states west of the Mississippi river and more than half of the confirmed cases reported outside the Four Corners area. In 2017, an outbreak of HPS was linked to home-based rat-breeding facilities in Wisconsin and Illinois; infected rats may have also been distributed or received in Colorado, Delaware, Georgia, Idaho, Iowa, Minnesota, Missouri, New Jersey, Pennsylvania, South Carolina, Tennessee, and Utah [185]. There have also been reported cases in Central and South America [184; 186].

The main host for HPS is the deer mouse (*Peromyscus maniculatus*), but other mice and rodents have been found to carry the organism. There have been other documented hantavirus infections in the United States, with some having specific rodent carriers. The Bayou virus caused disease in Louisiana, and the New York-1 virus was isolated after producing illness in a patient in the Northeast. The causative agent for the 1993 outbreak and subsequent HPS cases has become known as the Sin Nombre virus. In the United States and Canada, the Sin Nombre hantavirus is responsible for the majority of cases of HPS [184].

HPS virus particles are shed by the rodents in their saliva, urine, and feces. They do not seem to have any signs of illness while carrying the virus. Although the disease can be contracted by the bite from a rodent or by contamination of foodstuffs, the most common means of spread is from aerosols. The dried excrement of the animals is easily swept or blown into the air, where it is inhaled into the lungs [184; 187]. Most patients who contract the disease remember cleaning rodent excrement or dead mice from an enclosed area in or around their home. Human-to-human spread does not occur [184; 186; 187].

Clinical Presentation and Diagnosis

The incubation time from contact with the virus until the onset of symptoms is thought to be about one to eight weeks. Almost everyone who develops the disease will have fatigue, fever greater than 38.3 degrees C, and myalgia, usually in the large muscles of the back, thighs, and shoulders. There is usually hypotension, tachypnea, and tachycardia. About one-half of patients experience nausea and vomiting, headache, dizziness, and abdominal pain [184; 187]. After 4 to 10 days, the late symptoms of HPS appear with the onset of coughing, shortness of breath, increasing pulmonary distress, and pulmonary edema [184]. HPS appears to resemble acute respiratory distress syndrome in patients with advanced disease. In some patients, renal impairment may also develop, but this is more common in illness caused by hantaviruses other than the Sin Nombre virus.

Chest x-ray shows bilateral interstitial edema, which becomes progressively worse and develops into alveolar edema as the patient deteriorates. Differentiation from acute respiratory distress syndrome can usually be made based on clinical findings; however, good laboratory tests are also available. Laboratory diagnosis can be made by the detection of hantavirus-specific IgM or rising titers of hantavirus-specific

IgG. PCR analysis of clinical specimens is also useful. In addition, blood samples can be analyzed for hantavirus antigen by immunochemistry. Patients with HPS often have a left-shifted increase in neutrophils, which helps to differentiate the early symptoms from other viral infections [184; 186; 187].

Treatment and Prevention

No treatment has proven to be useful for HPS, with the exception of supportive care. Ribavirin, which has helped in some hantavirus infections in Europe, is not recommended for treatment of HPS [187; 188]. In most cases, admission to an intensive care unit is necessary, and oxygen is required as the patient becomes hypoxic. Broad-spectrum antibiotics are suggested to help combat secondary bacterial infections. Analgesics and antipyretics provide comfort, but fluids should be carefully monitored due to possible capillary leakage [187; 188]. Mechanical ventilation and cardiopulmonary support should be available in the event of a sudden onset of pulmonary failure.

As noted, even with treatment, about 33% of patients have died from the disease [184]. This makes prevention an important factor in decreasing the morbidity and mortality associated with HPS. Educating the public in the proper handling of rodents and their excrement is the primary method of prevention. Avoiding contact with rodents is an obvious rule, but this is not always possible. Using latex or other protective gloves is suggested if contact with a dead rodent or its excrement is necessary. Because aerosolizing of the excretory products is documented to cause the disease, it is advised to "wet down" dead rodents or any areas where rodents have been present before attempting to clean the region. An enclosed area should be left open to air out before entry, if possible [184].

Attempt to rodent-proof the home and outbuildings by sealing off the possible points of entry and removing foodstuffs from kitchen counters and tables, especially at night. Garbage cans and other refuse containers should have tight lids. Trapping rodents or using traps and baits to decrease their numbers has been shown to reduce the number of cases in a local area [184]. The virus is inactivated by alcohol and chlorine preparations, which can be used as disinfectants in indoor and outdoor areas. Complete drenching with a 10% bleach solution is recommended [184]. Sunlight can also kill the virus. The use of respirators is only suggested for workers in regions of high rodent population or where the disease is known to be present but is a sensible precaution when working in enclosed areas with limited ventilation [184].

LYMPHOCYTIC CHORIOMENINGITIS (LCM)

Lymphocytic choriomeningitis (LCM) has the house mouse (*Mus musculus* Linnaeus) as its reservoir species. The disease is primarily a mild one, though probably underdiagnosed in individuals with normal immune systems [189]. Transmission is through contaminated food ingestion, aerosols, and bites from infected rodents. The house mouse is a very common rodent throughout the world and is sold in many places as a pet. LCM virus can also be spread by hamsters and guinea pigs if they have contact with infected mice. The CDC has maintained contact with retail stores, and some have stopped selling these rodents during periods of outbreaks [190]. This is not an uncommon disease. The prevalence of LCMV antibodies in urban human populations is 2% to 5%, and its distribution is worldwide.

Clinical Presentation and Diagnosis

Rodents infected with LCM virus show little sign of illness. Serologic testing of the rodents has not been very reliable, and the animals can shed virus for the duration of their lives without appearing to be ill [190]. In humans, LCM is characterized by a flu-like illness lasting only a few days. A few cases will relapse afterward, and these rare cases may develop meningeal inflammation signs, beginning with nuchal rigidity, headache, fever, malaise, and muscular pain. A limited number of cases progress to meningoencephalitis with paralysis and coma. Most will recover, although severe cases may have a protracted recovery time [190; 191]. If a pregnant

woman contracts the disease in the first or second trimester, there can be serious consequences for the fetus. Case fatalities are rare, except in immunocompromised patients. LCM can be isolated from the blood of febrile patients or from CSF in patients with meningitis; however, laboratory diagnosis in a patient suspected of having LCM is usually made by CSF PCR or by serologic studies (IgM and IgG antibody titers) on acute and convalescent serum.

Treatment and Prevention

Treatment of LCM is based on symptom management. Prevention of the disease involves care in cleaning and disinfecting cages and regions of wild mouse activity. Pregnant women should avoid handling possibly infected rodents. Wholesale and retail merchants should be aware of outbreaks and keep groups of rodents isolated from each other to prevent cross contamination [190].

BOVINE SPONGIFORM ENCEPHALITIS (BSE)

Bovine spongiform encephalitis (BSE), commonly known as mad cow disease, has received a considerable amount of attention in the medical and lay press since the first reported outbreaks in 1986 [192]. The human disease is called variant Creutzfeldt-Jakob disease (vCJD) and is different from the naturally occurring Creutzfeldt-Jakob disease (CJD) seen mostly in older patients; both are degenerative, progressive, and fatal brain disorders with no known cure [192]. While CJD occurs spontaneously, vCJD has only been seen where there was a connection to ingestion of diseased animal tissue. As of April 2021, there were a total of 232 cases of vCJD reported throughout the world [193]. Most cases were in the United Kingdom (178) and France (28); however, cases have been reported by many countries, including the United States (4), Ireland (4), and 18 cases in eight other countries [193]. Several cases of the disease being diagnosed in the United States and other countries (excluding France) occurred in individuals who had contracted the disease in the United Kingdom [192]. Among the 178 cases in the United Kingdom, 18 were individuals who donated blood components that were traced to 67 transfusion recipients [193]. There have been four documented vCJD infections in this cohort that were likely transfusion transmitted. Of these cases, three deaths from vCJD were linked to blood transfusions between 1996–1999 of nonleukocyte reduced red blood cells collected from two blood donors who died from vCJD within one to three years of their donations. The fourth possible case was a latent transmission to a patient who died five years after the implicated transfusion without symptoms of vCJD [193]. To date, no cases of vCJD have been reported in persons treated with U.S.-licensed plasma derivative and, apart from the cases reported in the United Kingdom, no transfusion-transmitted cases of CJD have been reported worldwide [193].

In 1986, BSE was first identified in cattle in England, and in 1989, it was officially listed as a zoonosis. By 1996, the disease seemed to jump the species barrier to humans, presenting as a new variant of CJD [192; 194]. This new strain was linked to BSE, possibly through eating meat from BSE-infected cattle. BSE and vCJD are together called transmissible spongiform encephalopathies (TSEs) because they reduce the brain to the same spongy appearance, with gaps appearing within the tissue. TSEs present in sheep as scrapie, in cows as BSE, and in humans as vCJD.

By the end of 2004, millions of cattle throughout the world, but predominately in the United Kingdom, had been slaughtered as part of a plan to control the disease [194; 195]. Some researchers believe the disease has peaked already (during 2006–2008), while others point to the disease's long incubation period and suggest that thousands may be affected in the future. The number of new cases does appear to be decreasing annually [196].

Understanding the history of BSE and vCJD makes this complex zoonosis much easier to put into perspective. While sheep, cows, and humans were part of the outbreak in the 1990s and 2000s, heightened awareness as a result of this outbreak led to the knowledge that deer, elk, mink, and cats have related diseases as well [197]. Other species can be experimentally infected, but they do not appear to propagate the illness [197].

Part of the difficulty in making the connection between the species during the initial investigative stages was the lack of identification of a causative agent. Depending on the source, the agents are either prions, virions, or not named at all and merely referred to as TSEs. Most authorities now use the term prions, an acronym for proteinaceous infectious particles. Closely related to viruses, but not a virus, they have no DNA or RNA. Prions make their way into the brain and incorporate themselves into brain cells as proteinase-resistant fibrils. In cows, only the brain has measurable amounts of these fibrils. In sheep, the fibrils can be isolated from a number of different locations, including placental tissue.

In the final stage of the disease, brain tissue becomes sponge-like and the cows become "mad" or "maniacal" before dying. In sheep, advanced disease makes the animals scratch and bite at themselves until they scrape off their coats and excoriate their skin. The brain lesions found in scrapie are identical to that in BSE [197].

The initial recorded BSE outbreak in the 1980s coincided with changes in rendering sheep and an increase in the sheep population in the United Kingdom. The outbreak began after the winters of 1981 and 1982, when cattle were fed with meat and bone meal products contaminated by rendered brain parts from sheep infected with scrapie [197]. A ban on using ruminant rendered products in animal feeds was enacted in 1988 in the United Kingdom and was followed by most developed countries. The initial 1997 feed bans in the United States and Canada have since been replaced with enhanced feed bans in 2009 and 2007, respectively, to eliminate high-risk animal byproducts from all animal feeds, pet foods, and fertilizers, rather than from cattle feed alone [196]. These enhanced bans were implemented to mitigate the recognized limitations of the original bans [196].

The slaughter of possibly infected animals became mandated following the first death attributed to vCJD. It was determined that because of the possibility that the disease could be transmitted to humans in the same way as to animals, ruminant byproducts that might include the brain should be banned to prevent the possibility of transmission. A large number of products in the United Kingdom used ruminant byproducts, leading to public panic. Articles such as lipstick, which might have used rendered material, became objects of concern. This may have been warranted, but the slow release of information contributed to the public uneasiness. It was not until November 1998 that the European ban was lifted on beef from the United Kingdom. In cows, only brain tissue appears capable of transmitting disease [194; 198].

No direct transmission has been documented between cows; however, vertical (placental) transmission has been reported [199]. Sheep pass the disease vertically, and it has been theorized that transmission through ingestion of placental tissue from infected animals that give birth in the field is possible.

Kuru, another human disease characterized by a spongy appearance and gaps in the brain, is also contracted through ingestion of animal products infected with TSEs. The brain lesions in vCJD and kuru are identical to those seen in sheep with scrapie. As in vCJD, kuru causes the death of brain cells, with such symptoms as unsteadiness, insomnia, memory loss, and dementia. The Fore people of Papua New Guinea practiced ritualistic consumption of the brains of their deceased relatives as a sign of respect, thus propagating the disease [198]. Variant CJD is not transmitted like kuru. Proof that it is transmitted through ingestion of infected brains is quite difficult due to the long and somewhat unknown length of time from infection to first signs of disease. Injecting neuronal tissue from cows infected with BSE into mice will induce disease, as will brain tissue from infected sheep injected into monkeys. However, it is not possible to draw conclusions about human transmission from this research [200].

In 2007, a new neurologic disorder originating in pigs was reported in a group of slaughterhouse workers processing severed heads [201]. This new condition, referred to as progressive inflammatory neuropathy or immune polyradiculoneuropathy, is believed to be caused by inhalation of brain tissue that is aerosolized by the use of compressed air guns to harvest the organ. The condition is characterized by an enlarged spinal root, pain, weakness, fatigue, and numbness or tingling in the extremities [201; 202]. The condition is not believed to be infectious or foodborne, although investigations are ongoing. At this time, it is not believed to be directly related to spongiform encephalitis.

Clinical Presentation and Diagnosis

It is difficult to document the disease agent when it is non-antigenic, as the body does not mount any immune response, making tests such as standard antibody titers useless. Diagnosis of vCJD therefore tends to be based on signs and symptoms with confirmation by examining brain tissue.

This makes the differentiation of vCJD from other progressive, neurodegenerative processes difficult, especially in older patients. The diagnosis is also hampered by the very long incubation period of vCJD, which can be many years between contact with the organism and the development of symptoms [203]. Usual symptoms can include progressive dementia, myoclonus, visual changes, cerebellar dysfunction, pyramidal or extrapyramidal signs, and akinetic mutism. Pain is experienced by about one-half of the patients [204].

When the more common causes are eliminated and a spongiform encephalopathy is suspected, there are several ways to distinguish between "classic" CJD and vCJD. The most obvious is age; classic CJD causes death at a mean age of 68 years following a rapid course with a duration of illness of only four to five months [192]. Variant CJD is a disease of young people, with death at a mean age of 28 years following a more prolonged course, usually over a year. Classic CJD presents with early neurologic signs and dementia, but patients with vCJD often have early behavioral or psychiatric symptoms and painful dysesthesias, with delayed neurologic findings [192; 203].

MRI has been used successfully to diagnose vCJD. An unusual appearance of the thalamus or a specific increase in intensity in the posterior portion of the thalamus, the pulvinar region, has been found in neurologically confirmed cases of vCJD [203]. This finding, called "the pulvinar sign" has not been observed in classic CJD [203; 204].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Radiology notes diffusion-weighted imaging can help identify and characterize Creutzfeldt-Jakob disease.

(https://acsearch.acr.org/docs/69477/Narrative. Last accessed April 28, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

As noted, the firm diagnosis of vCJD is made with either a brain biopsy during life or examining pathology material at autopsy; however, Western blot analysis of lymph node specimens has shown the presence of prion material in patients with the disease. Florid plaques have been described in brain sections of patients with vCJD but not in those with classic CJD. The vacuolation (spongiform change) has been seen in many portions of examined brains, with most disease found in the occipital cortex and cerebellum [194; 205].

Prevention and Treatment

There is no treatment for this disease in any species mentioned. This makes prevention and radical public health measures essential to control BSE, vCJD, and scrapie. All are reportable diseases. Compulsory slaughter has been practiced to eradicate herds with BSE-positive cattle; this was obviously done at huge costs to the public, farmer, and government. The United States has a scrapie eradication program to eliminate scrapie from the sheep herds in the country. The United States and other countries had barred blood donations from people who have lived

in the United Kingdom or continental Europe for a cumulative three months or more between the years 1980 to 1996 as a precautionary measure against the spread of vCJD [206]. However, the FDA removed the recommendation for this deferral in a guidance document published in 2022 [193].

The best way to protect ourselves and educate patients is to have the correct information and to practice safe consumption. Due to the nature of the prion proteinase resistance and probably its small size, the agent is not destroyed with ultraviolet light, freezing or thawing, boiling for 30 minutes, or formaldehyde. In other words, there is no way to safely cook the agent out of a brain or render a tissue absolutely free of the agent. In 2006, the European Union ban on British beef was lifted due to enhanced BSE testing and control measures (e.g., the banning of feeding cow proteins, including brains, to other cows) [205]. Travelers to the United Kingdom, Ireland, or certain other European countries (France, Greece, and Poland) should be advised that if they are concerned about contracting vCJD, avoiding beef products altogether is the only certain option, but that eating whole muscle meat, rather than ground meat or foods made with brains, carries an "exceedingly low risk" of infection [205]. Aside from the European countries listed above, the risk posed by BSE in other European countries is similar to that from U.S. beef. The risk status of Canadian beef is an estimated 18 to 48 times higher than that of U.S. beef and is considered to have similar risk as United Kingdom beef. Cow milk and milk products from all countries are believed to be safe [205].

Because there is no cure or vaccine for the TSEs, treatment is generally confined to supportive measures and symptomatic therapies. It has been suggested that phenothiazines may inhibit prion production, but this has not been confirmed in a series of studies [207]. Anticonvulsants are used to manage seizures and violent outbursts [203]. Experimental therapies include the antimalarial quinacrine and the antipsychotic chlorpromazine to prevent abnormal prion protein conversion. One patient has been treated with pentosan polysulphate and had no evidence of disease progression for 23 months [203]. The agent inhibits prion protein production, replication, and cell toxicity associated with vCJD. Unfortunately, the treatment must be initiated soon after infection to prevent disease onset, which, outside of experiments, is likely impractical.

PROTOZOAL ZOONOTIC DISEASES

The common zoonotic diseases caused by protozoa include toxoplasmosis, giardiasis, babesiosis, cryptosporidiosis, malaria and balantidiasis. Toxoplasmosis and giardiasis are seen fairly often in North America.

TOXOPLASMOSIS

The agent of toxoplasmosis is *Toxoplasma gondii* (phylum Apicomplexa). *T. gondii* is one of the most widely disseminated parasites known in the world [208]. It has a two-host lifecycle, present in both predator and prey. The intermediate hosts are humans, swine, goats, sheep, dogs, rodents, cattle, and cats. Cats are the definitive host but can be intermediate hosts as well. All members of the cat family can carry the organism, but domestic cats are clearly the source of zoonosis in most people, resulting from fecal-oral transmission [14; 208; 209]. Studies of cat populations show 16% to 80% of cats in the United States have been infected; the estimated worldwide prevalence in domestic cats is 30% to 40% [210].

Cats become infected with toxoplasmosis when they ingest tissue infected with the bradyzoite phase of *T. gondii*, which is encysted in the muscle tissue of their prey. When shedding oocysts, a cat can excrete up to 20 million organisms per day. The cyst opens in the gastrointestinal tract, and the bradyzoites are released to enter the enteroepithelial cells in the cat's small intestine. They then shed eggs (oocysts) sporadically into the feces for 7 to 21 days after ingestion [208]. Antibody titers in the cat will not start to rise until after the first round of shedding has stopped. Immunity will last in the cat unless major re-exposure occurs or if high-dose steroid therapy is initiated. Some authorities believe that direct transmission from cats to humans is uncommon and that the organisms are more likely transmitted from contaminated soils or undercooked foods [211]. Kit-

tens, rather than adult cats, have been identified as a cause of direct transmission to humans [208]. It has been reported that 8% of beef, 20% of pork, and 20% of lamb is infected with toxoplasma [211]. In the United States, an estimated 40 million people may be infected with toxoplasma and are chronic, asymptomatic carriers of the parasite; some places in the world have shown infection rates as high as 95% [208].

When an intermediate host becomes infected or consumes meat with encysted toxoplasma, the bradyzoites enter the enteroepithelial cells of the host but do not remain there, as in the definitive host. In the intermediate host, they penetrate the lymphatics of the gastrointestinal tract and from there disseminate throughout other tissues, including the placenta and fetal tissue. Congenital toxoplasmosis is seen in children of mothers who may not realize that they are carrying the organism. In general, the infection must occur during the pregnancy for the disease to be transmitted to the fetus [208; 211; 212].

Immunocompromised individuals, especially acquired immunodeficiency syndrome (AIDS) patients, can suffer severe complications and should be advised to consult their healthcare providers to determine whether they have been infected with toxoplasma [208; 210; 211]. It is important to note that immunocompromised individuals have the same rate of infection regardless of whether they are cat owners or not [211]. Contaminated meat or contact with soil contaminated with cat feces is a more common transmission method than poor handling of a litter box. Nevertheless, the CDC advises pregnant women to avoid changing cat litter [208].

Clinical Presentation and Diagnosis

The clinical manifestations of infection in humans are similar to the flu or mononucleosis. As noted, the concern is greatest for pregnant women and HIV-positive individuals. In the first trimester of pregnancy, spontaneous abortions, retinochoroiditis, hydrocephalus, microencephaly, and psychomotor retardation of the fetus are the most common sequelae to exposure [208; 212]. In an immunocompromised host, toxoplasmosis can be life-threatening. These individuals are more prone to a disseminating version that can lead to hemorrhagic lesions in the brain. Myocarditis, hepatitis, meningoencephalitis, chorioretinitis, and internal organ involvement have also been reported [212].

Diagnosis of toxoplasmosis is usually made with serologic testing. Indirect IFAs of IgG and IgM are positive within a few days after infection [208]. Imaging studies and PCR analysis of CSF are useful in immunocompromised patients with signs of encephalitis or focal mass lesions within the brain. In such patients, a brain biopsy may be considered for definitive diagnosis and to exclude other diagnostic possibilities (e.g., brain abscess, lymphoma, metastatic carcinoma). In many cases, the history of the consumption of undercooked or raw meat aids in making the diagnosis [211].

Treatment and Prevention

Treatment is rarely necessary in people with normal immune systems as most recover without treatment. Suspected cases in persons who are ill may be treated with the combination of pyrimethamine and sulfadiazine, plus folinic acid (leucovorin) for a period of three to four weeks. Clindamycin may be substituted for sulfadiazine in patients sensitive to sulfa drugs [208]. For encephalitis, the treatment is continued for four to six weeks. Patients with HIV/AIDS who are toxoplasma-seropositive and who have CD4 counts <100 cells/mcL should receive prophylaxis against toxoplasmosis. This can be accomplished with trimethoprim/sulfamethoxazole (TMP-SMX) double-strength daily dose or alternately, TMP-SMX double-strength three times weekly [213]. The recommended therapy for acquired toxoplasmosis in HIV-infected children is sulfadiazine plus pyrimethamine and leucovorin [214].

It is very important to educate immunocompromised individuals and pregnant women in prevention techniques. All meat should be thoroughly cooked. Not coming in contact with cat feces or contaminated soil is very important, as is handwashing after gardening or yard work. If there is a sandbox in the backyard, it should be covered. If possible, limit a household cat's ability to consume rodents,

which would best be accomplished by keeping the cat indoors, and only feed commercial pet food [208]. Oocysts hatch about 24 hours after being shed in the feces and are not infective before hatching. If the litter box is changed daily, exposure risk will be reduced. Encourage others in the household to participate in the cat's care, and ask them to change the litter box to protect the family members who are at risk. If the at-risk person must change the box, gloves, dust mask (to prevent swallowing or inhaling oocysts), and diligent emptying of the box daily are recommended. If you are working with a woman in early prenatal screening who owns a cat or who comes in contact with them, recommend having a titer if exposure must be documented and explain the importance of handwashing after handling cats or raw meat. Because of the potential seriousness of this zoonosis for certain populations, research is being conducted on a vaccine. At this time, there is no approved vaccine available [208].

EVIDENCE-BASED PRACTICE RECOMMENDATION

In order to prevent *Toxoplasma gondii* infection, the American Academy of Pediatrics recommends that pregnant women avoid contact with material/soil potentially contaminated with cat feces, especially handling of cat litters or gardening.

(https://publications.aap.org/pediatrics/article/139/2/e20163860/59988/Diagnosis-Treatment-and-Prevention-of-Congenital. Last accessed April 28, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

GIARDIASIS

Giardiasis is one of the most common diarrheal diseases in the world, and nearly 33% of people in developing countries have had giardiasis [215]. The causative organism, *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis*), is found in food, soil, water, and surfaces that have been contaminated with feces. It is now the most commonly identified parasite in the United States [215]. The symptoms of giardiasis usually appear about a week or two after the *Giardia* cysts are ingested. Very few organisms are required for infection, with only about 10 cysts causing an infection rate of 100% [215].

The cysts produce trophozoites, which colonize the upper portion of the small bowel. They generally cause a significant non-bloody diarrhea in the human or animal victim, which can then be transmitted by the fecal-oral route. Contaminated water is the most common source of infection, but venereal transmission has also been reported [215].

Morbidity is moderate and primarily involves gastrointestinal symptoms. Mortality from giardiasis is unlikely, unless associated with extreme dehydration [14; 216].

Clinical Presentation and Diagnosis

The majority of patients present with an insidious onset of diarrhea. This usually consists of frequent loose stools that do not contain blood or mucus. Watery diarrhea and malodorous soft or greasy stools can be interspersed with episodes of constipation. The gastrointestinal symptoms are often exacerbated by eating and may be associated with mid abdominal pain and cramping. Nausea, gastroesophageal reflux, malaise, fatigue, lactose intolerance, and weight loss are common. Adult patients with long-term disease may develop malabsorption syndrome, while children can demonstrate the findings of failure to thrive [215; 217].

Physical examination is usually normal, with the exception of possible abdominal tenderness upon palpation. In extreme cases, there may be dehydration and wasting. Laboratory studies should include stool examination with at least three samples taken at two-day intervals [215; 218]. Because antibiotics, laxatives, or barium may mask the presence of the organism in the stool, the samples may need to be obtained after a 5- to 10-day hiatus. There are ELISA and IFA tests available for stool samples that have excellent sensitivity and specificity [218]. Microscopy with direct fluorescent antibody testing is considered the test of choice for diagnosis of giardiasis, because it provides increased sensitivity over nonfluorescent

microscopy techniques [215]. Cultures are useful primarily to detect other causes of diarrhea, because *Giardia* is not easily grown from stool samples. The most useful serum study is IgM analysis, but only for the determination of acute versus chronic infections [218]. Endoscopy, with duodenal aspiration or biopsy, may also be used to obtain a diagnosis.

Treatment and Prevention

Several drugs can be used to treat *Giardia* infection, including metronidazole, tinidazole, and nitazoxanide. Other medications include paromomycin, quinacrine, and furazolidone. Some of these drugs may not be readily available in the United States [215]. Metronidazole is the most commonly prescribed antibiotic for this condition. However, metronidazole use has been associated with significant failure rates in clearing parasites from the gut and with poor patient compliance. In addition, an increasing incidence of nitroimidazole-refractory giardiasis has been reported, particularly in travelers from India and other regions in Asia. An optimal treatment strategy for refractory giardiasis remains to be determined, and no standard treatment regimen for nitroimidazole-refractory giardiasis exists to date [218]. The usual adult dose of metronidazole is 500 mg orally twice daily for five to seven days [55]. Tinidazole can be administered in a single oral dose of 2 grams, taken with food. For children older than 3 years of age, the recommended dose is 50 mg/kg [55]. For women in the first trimester of pregnancy, for whom metronidazole and tinidazole are contraindicated, paromomycin 25–35 mg/kg/day in three divided doses should be used for 5 to 10 days [55]. Paromomycin has been recommended for use in pregnancy because systemic absorption is low, but the cure rate is lower than with other agents [218]. Quinacrine is commonly used outside the United States. It achieves a cure rate of 90% to 95% but is available in the United States only as an orphan drug [218]. Other antibiotics and antiparasitic agents, such as nitazoxanide, have also been used to effectively treat the disease [55; 215]. Some authorities feel that asymptomatic cases of diagnosed giardiasis infection, especially in children, should be left untreated. However, if untreated, an individual can shed the organisms for weeks to months. In rare cases, hospitalization is required for fluid and nutritional replacement, but most cases will resolve with minimal treatment.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The World Gastroenterology Organisation asserts that nitazoxanide is an effective antiprotozoal in the treatment of diarrhea caused by *Giardia intestinalis*.

(https://www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english. Last accessed April 28, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Prevention includes the avoidance of potentially contaminated water and foodstuffs. Drinking water from a stream, shallow well, or other unfiltered source can lead to ingestion of the cysts. The cysts can live for extended periods of time in an outdoor environment. However, they are inactivated by chlorine and can be eliminated from a water source by filters of less than 1 micron (e.g., National Safety Foundation [NSF] Standard 53 or NSF Standard 58 for cyst and oocyst reduction) [215].

Giardiasis cannot be transmitted by blood products, but any possible fecal contact can be a source of infection, which includes accidentally swallowing water in a recreational pool or pond. Peeling or washing fruits and vegetables in clean water is also recommended [14; 215]. When traveling to countries with an unsafe water supply, only drink water that has been boiled for more than one minute or bottled water labeled as reverse osmosis treated, distilled, filtered through an absolute 1 micron or smaller filter, or "1 micron absolute" [215]. Additionally, ice should not be used [215].

MALARIA

Malaria is a mosquito-borne parasite most common in sub-Saharan Africa. However, the disease is also apparent in Southeast Asia, the Middle East, Latin America, and areas of Europe [219]. It is mainly found in tropical and subtropical areas that allow for the growth and survival of the *Anopheles* mosquito and the malarial parasites. Because temperatures colder than 68 degrees F will halt the parasites' life cycles, transmission is seasonal in some areas [219]. In equatorial countries, malaria transmission is continual and more intense; these are considered malaria-endemic or malaria-stable countries [220].

Approximately 50% of the world's population is at risk for malaria [219; 220]. In 2020, malaria caused an estimated 241 million clinical episodes and 627,000 deaths, most of them (95%) young children in sub-Saharan Africa [220]. Preventive interventions reduced malaria mortality by 36% from 2010 to 2020 [220]. Although malaria has been considered eradicated in the United States since the 1950s, about 1,500 to 2,000 cases of the disease are diagnosed and treated each year [221]. The CDC has also reported a total of 63 local outbreaks in the United States since 1953, all of which originated from a person who contracted the disease in a malaria-endemic country. Because the vector for malaria transmission (*Anopheles* mosquito) is present in the United States, there is a risk that the disease will be reintroduced.

The four protozoan species known to cause malaria in humans, *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*, are transmitted from person to person via infected mosquitoes. The most common are the *P. falciparum* and *P. vivax* species; *P. falciparum* also results in the most significant morbidity and mortality [219]. Although, as noted, the female Anopheles mosquito is the natural vector for malaria, in rare cases, direct transmission from mother to child, blood transfusion, organ transplant, or shared needles has been documented. Transfusion-transmitted malaria is rare in the United States, but it is a potential severe complication in blood recipients. On average, only one case of transfusion-transmitted malaria occurs in the United States every two years. Because no approved tests are available in the United States to screen donated blood for malaria, prevention of transfusion-transmitted malaria requires careful questioning of prospective donors [222]. In areas of high transmission, it is children who are at risk of severe malaria and death, whereas in areas of low or unstable transmission, all age groups are at risk [220]. Pregnant women also have higher susceptibility to *P. falciparum* malaria, which increases infant mortality [220].

Clinical Presentation and Diagnosis

Prompt and accurate diagnosis of malaria is a cornerstone of the treatment process. Identification not only of the presence of the disease but also of the causative agent is necessary in order to implement appropriate and effective treatment. This can be difficult, as the initial signs and symptoms of malaria are nonspecific and may be confused for other systemic viral infections. After infection, there is typically a 7- to 30-day incubation period, or longer if antiviral medications have been taken prophylactically. The classically described malaria attack (cold, hot, and sweating stages) is rarely observed [223]. More often, the first symptoms are a combination of headache, weakness, fatigue, abdominal discomfort, and/or muscle and joint aches, followed by fever, chills, perspiration, anorexia, vomiting, and/or worsening malaise [223; 224]. Possible signs include elevated temperature, enlarged spleen, and perspiration. If the disease is limited to this stage, it is considered uncomplicated, and treatment is often successful. Relapse of malaria can occur after two to four symptom-free years in persons infected with *P. vivax* and *P. ovale* species [221].

If the disease is caused by the *P. falciparum* species, it can progress to severe malaria. Severe malaria is complicated by serious organ failures or abnormalities in the patient's blood or metabolism. Advanced severe malaria can result in [221; 223]:

- Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities
- Severe anemia
- Hemoglobinuria
- Pulmonary edema or acute respiratory distress syndrome, which may occur even after the parasite counts have decreased in response to treatment
- Abnormalities in blood coagulation and thrombocytopenia
- Cardiovascular collapse and shock

Other conditions that should raise concern in malarial patients are acute kidney failure, hyperparasitemia, metabolic acidosis, and hypoglycemia [223]. In patients for whom the malaria infection reaches the severe stage, the mortality rate is 15% to 20% [224].

In addition to the clinical diagnosis, there are three main tests used in the parasitologic confirmation of the diagnosis of malaria: light microscopy, rapid diagnostic tests, and PCR. Light microscopy remains the standard test for detection of malarial parasites [225]. The test is conducted by staining a blood smear, usually with the Giemsa stain, and examining the specimen by microscope. There are also several rapid tests available that utilize antigen detection. These tests provide results quickly (within 2 to 15 minutes), but their use is restricted by limited accuracy and higher costs [225]. When they are used, it is usually as an adjunct to microscopy or as the main test if microscopic analysis is not available, particularly because early treatment is so vital for positive clinical outcomes. The limitations of the rapid tests have shifted attention to PCR-based molecular diagnosis. Although the PCR tests available for malaria are more accurate than either the microscopy or antigen detection systems, the prohibitive costs and need for specialized equipment have made this option less useful [225; 226]. IFA and ELISA tests are available to test for past exposure to the disease [225].

Treatment and Prevention

Treatment for uncomplicated malaria varies based on the region in which the disease was acquired and the infective species (***Table 7***). Some areas have been particularly identified as sensitive to chloroquine, the traditional drug of choice for malaria. Because resistance to chloroquine has increased significantly, it is now generally used only for malaria known to originate from Central America (west of the Panama Canal), Haiti, the Dominican Republic, and most of the Middle East [227]. In all other areas, the organisms are considered to be resistant to the drug, and other agents are used. It is also recommended that, when possible, in vivo assessment of therapeutic efficacy, in vitro studies of parasite susceptibility to drugs in culture, or molecular genotyping be used to establish sensitivity of the parasite to the drug regimen [224].

Treatment of Severe Malaria

Patients with any manifestations of severe malaria (e.g., impaired consciousness/coma, acute kidney injury, circulatory collapse/shock) should be treated promptly and aggressively with IV artesunate, regardless of infecting species. When IV artesunate is not in stock, consider interim treatment with an effective oral antimalarial while obtaining IV artesunate emergently from a commercial source. If the patient is unable to tolerate oral medications, consider alternative ways to administer oral medications while awaiting IV artesunate. The preferred interim oral treatment is artemether-lumefantrine because of its fast onset of action. Other oral options include atovaquone-proguanil, quinine, and mefloquine. IV or oral clindamycin and tetracyclines (e.g., doxycycline) are not adequate for interim treatment. These drugs are slow-acting and would not take effect until well after 24 hours. They also are not effective for treatment of severe malaria when used alone. As for any malaria treatment, the interim regimen should not include the medication used for chemoprophylaxis, if possible. When IV artesunate arrives, immediately discontinue the oral medication and start parenteral treatment. Artesunate is dosed at 2.4 mg/kg at 0, 12,

TREATMENT RECOMMENDATIONS FOR UNCOMPLICATED MALARIA			
***Plasmodium* species**	**Drug**	**Dosing**	**Comments**
P. falciparum or "species not identified" in areas **without** chloroquine-resistant strains	Chloroquine	Initial oral dose: 600 mg base (1,000 mg salt), followed with 300 mg base (500 mg salt) at 6, 24, and 48 hours Maximum dose: 1,500 mg base (2,500 mg salt)	Use adult dosing in pregnancy. Adjust pediatric dosing by patient weight; do not exceed recommended adult dosing. Due to risk of progression to severe disease, hospitalize patient to monitor clinical response and parasite density every 12 to 24 hours. If infection initially "species not identified" subsequently diagnosed as *P. vivax* or *P. ovale*, additional treatment with primaquine or tafenoquine should be administered.
	Hydroxychloroquine (2nd-line alternative)	Initial oral dose: 620 mg base (800 mg salt), given immediately, followed with 310 mg base (400 mg salt) at 6, 24, and 48 hours Maximum dose: 1,550 mg base (2,000 mg salt)	
P. falciparum or "species not identified" in areas **with** chloroquine-resistant strains	Atovaquone/ proguanil	1 g/400 mg as a single dose, once daily for three days	These are fixed dose combination medicines that may be used for nonpregnant adult and pediatric patients ≥5 kg. Both have been found to be very effective.
	Artemether/ lumefantrine (preferred)	Patients 25 to <35 kg: Three tablets at hour 0 and hour 8 on the first day, then three tablets twice daily on days 2 and 3 Patients >35 kg: Four tablets at hour 0 and hour 8 on the first day, then four tablets twice daily on days 2 and 3	
	Quinine sulfate plus doxycycline, tetracycline, or clindamycin	648 mg every eight hours for three to seven days (seven days for infections acquired in SE Asia)	
	Mefloquine[a]	5 tablets (1,250 mg) as a single dose daily	
P. malariae	Chloroquine	Same as for *P. falciparum*	There is little evidence of chloroquine resistance in *P. malariae*. May be used during pregnancy.
	Hydroxychloroquine (2nd-line alternative)	Same as for *P. falciparum*	
P. vivax acquired in all areas except Papua New Guinea or Indonesia	Chloroquine	Same as for *P. falciparum*	If patient is nonresponsive, change treatment to one of the three options listed for treatment of *P. vivax* malaria acquired in Papua New Guinea and notify state health department and CDC.
	Hydroxychloroquine (2nd-line alternative)	Same as for *P. falciparum*	

Table 7 continues on the next page.

TREATMENT RECOMMENDATIONS FOR UNCOMPLICATED MALARIA *(Continued)*			
***Plasmodium* species**	**Drug**	**Dosing**	**Comments**
P. vivax acquired in Papua New Guinea or Indonesia	Quinine sulfate plus doxycycline or tetracycline	648 mg every eight hours for three to seven days	High possibility of chloroquine-resistant strains. Use mefloquine when no other options available due to risk of severe neuropsychiatric reactions. During pregnancy, treat with quinine for seven days, regardless of area of acquisition. Benefit of adding doxycycline or tetracycline is judged to outweigh risks. Weigh risk/benefit of using atovaquone-proguanil or mefloquine in pregnancy.
	Artemether/ lumefantrine	Patients 25 to <35 kg: Three tablets at hour 0 and hour 8 on the first day, then three tablets twice daily on days 2 and 3 Patients >35 kg: Four tablets at hour 0 and hour 8 on the first day, then four tablets twice daily on days 2 and 3	
	Atovaquone/ proguanil	1 g/400 mg as a single dose, once daily for three consecutive days	
	Mefloquine[a]	5 tablets (1,250 mg) as a single dose daily	
P. ovale	Chloroquine	Same as for *P. falciparum*	May be used during pregnancy
	Hydroxychloroquine (2nd-line alternative)	Same as for *P. falciparum*	
P. knowlesi	Chloroquine		There is little evidence comparing various medications for the treatment of this relatively new strain.
	Hydroxychloroquine (2nd-line alternative)		
[a]Mefloquine is associated with rare but potentially severe neuropsychiatric reactions at treatment doses; use is recommended only when other options not available.			
Source: [55; 227; 228]			*Table 7*

and 24 hours. The weight-based dosing applies to both adults and children [55; 227]. Assess parasite density at least four hours after last dose and proceed with therapy based on results [55].

Alternatives for Pregnant Women

Malaria in pregnant women is associated with high risk of both maternal and perinatal morbidity and mortality. Pregnant women of all gestational ages diagnosed with uncomplicated malaria acquired in areas with chloroquine-resistant *P. falciparum* can be treated with artemether-lumefantrine, mefloquine, or a combination of quinine sulfate and clindamycin. Quinine treatment should continue for seven days for *P. falciparum* infections acquired in Southeast Asia and for three days for infections acquired elsewhere; clindamycin treatment should continue for seven days regardless of where the infection was acquired [227]. Promptly treat uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, or chloroquine-sensitive *P. falciparum* infection, with chloroquine or hydroxychloroquine. Treat chloroquine-resistant *P. vivax* infections with artemether-lumefantrine, quinine plus clindamycin, or mefloquine [227].

Pregnant patients with *P. vivax* or *P. ovale* infections should be maintained on chloroquine chemoprophylaxis (300 mg base [500 mg salt] orally, once per week) for the duration of their pregnancy. After delivery, for pregnant patients with normal glucose-6-phosphate-dehydrogenase (G6PD) activity, subsequent treatment with primaquine phosphate or tafenoquine is needed but will depend on breast-

feeding. If not breastfeeding, either drug can be used depending on the regimen used to treat the acute malaria episode. For women who are breastfeeding, infants should be tested for G6PD deficiency and if found to have normal activity, oral primaquine phosphate can be given to the mother. Tafenoquine is not recommended during breastfeeding. Women who after delivery cannot take primaquine or tafenoquine should be maintained on weekly chloroquine chemoprophylaxis for a total of one year after the acute malaria episode [227].

Doxycycline and tetracycline are generally not indicated for use in pregnant patients. However, in rare instances, doxycycline or tetracycline can be used in combination with quinine if other treatment options are not available or are not being tolerated and the benefit of adding doxycycline or tetracycline is judged to outweigh the risks. Atovaquone-proguanil is not indicated for use in pregnant patients because of the lack of data on its safety in this population. However, for pregnant patients diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks [227].

CDC clinicians are on call at the Malaria Hotline 24 hours per day, seven days per week, to provide advice to healthcare providers on the diagnosis and treatment of malaria. They may reached during business hours 9 a.m. to 5 p.m. Monday through Friday) at (770) 488-7788 or (885) 856-4713. During off hours, weekends, and federal holidays, call (770) 488-7100 and ask to have the malaria clinician on call paged.

Individuals that are known to be traveling to malaria-endemic areas, and areas of resistance in particular, should be counseled regarding antimosquito measures and malarial symptoms prior to departure [229]. Chemoprophylaxis with the most appropriate antimalarial agents should be provided.

Vaccines

For years, research has focused on the development of an effective vaccine to prevent malaria in endemic areas. In 2021, the first vaccine to prevent malaria, RTS,S/AS01 (RTS,S), was approved and recommended by the WHO for children in sub-Saharan Africa and in other regions with moderate-to-high malaria transmission [278]. The vaccine is provided in a schedule of 4 doses in children from 5 months of age [279]. More than 2 million doses of the vaccine were administered prior to the WHO's recommendation, with good safety and efficacy [279].

In 2023, a second malaria vaccine, R21/Matrix-M, was approved by the WHO [280]. A phase 1/2b clinical trial demonstrated an 80% efficacy in the high-dose group, with efficacy up to 78% against multiple episodes of malaria disease at two-year follow-up [281]. The vaccine is given in a primary three-dose regimen, with a booster at one year and is the first vaccine to achieve the WHO goal of 75% efficacy. As a more effective and less expensive option, this vaccine is preferred over RTS,S/AS01 (RTS,S) as the vaccine of choice in areas with significant sustained malaria transmission [280].

BACTERIAL ZOONOTIC DISEASES

Animal products often contain several types of bacteria. The bacteria may be the animal's own flora that contaminates the meat in the process of being slaughtered and prepared for market. Bacterial contamination can also occur from an environmental source during poor handling, either before or after purchase for consumption. Only if the bacterial pathogen originated from the animal is it truly zoonotic. Factory workers who accidentally contaminate a product with a disease they are carrying, as has happened with *E. coli*, can create a public health problem. Because it does not originate from an animal, it is not considered a zoonotic infection in the true sense of the definition. In this section, anthrax, cholera, botulism, the diseases caused by *Salmonella* spp., and brucellosis will be discussed.

ANTHRAX

Anthrax can be transmitted by ingestion of meat from an infected animal, usually a ruminant. The agent of disease is *Bacillus anthracis*. Three forms of anthrax occur in humans, with manifestations depending upon how the organism is contacted; they are cutaneous, gastrointestinal, and inhalation anthrax. The diseases are distinct; however, infection with one form presents a risk for developing the others.

Most cases of anthrax are cutaneous in humans. The pulmonary and gastrointestinal forms are less common. If untreated, the pulmonary (inhalation) form has a 45% case fatality rate, intestinal 40%, and the cutaneous form less than 1% to 2% [230].

Cutaneous anthrax is the most common naturally occurring form, with an estimated 2,000 human cases reported annually [231]. The disease typically follows exposure to animals that are infected with anthrax. Cutaneous infections occur when the bacterium or spores enter a cut or abrasion on the skin, such as when handling contaminated wool, hides, or leather.

Gastrointestinal anthrax is not commonly seen; however, outbreaks have occurred in Africa and Asia [231]. GI anthrax follows the ingestion of insufficiently cooked contaminated meat.

Inhalation anthrax is the most lethal form of the disease, but it occurs less frequently as a naturally occurring disease than either the cutaneous or gastrointestinal forms. However, the dissemination of spores could cause widespread disease, and therefore, this is the most likely form of anthrax to be used as a biologic weapon [232]. Prior to the bioterror-related cases in 2001, inhalation anthrax had not been reported in the United States since 1976 [231; 232]. This makes even a single case a cause for alarm today.

The natural incidence of anthrax is rare in the United States, but infection is an occupational hazard among veterinarians, farmers, and individuals who handle animal wool, hair, hides, or bone meal products. It is endemic in Africa and Asia, despite vaccination programs, and is not uncommon in the Middle East, the Indian subcontinent, and Latin America [230]. Most cases are seen after heavy rains, which release the spores and bring them to the surface. Drought also can trigger anthrax spore germination, while flies and vultures spread the spores [230]. The spores produced by the bacteria are extremely resistant in the environment; they have been documented to survive 22 years in a dry culture [231]. They tolerate freezing and will not be killed by most disinfectants at regular strength concentrations. Methods for sterilizing or inactivating spores on contaminated materials include steam sterilization or ethylene oxide gas sterilization, boiling or using dry heat, or treating with formaldehyde, glutaraldehyde, or hypochlorite for specified periods of time and exposure concentrations; air drying does not destroy the spores [233]. Inhalation of spores is the most common way for the pulmonary form of the disease to be transmitted. When contaminated meat is cut, the spores can be released into the immediate area of the source. This could be in the field or in the kitchen of those who raise their own meat or consume wild ruminant meat, such as deer or elk. Anthrax is a mandatory reportable disease whenever a case is identified in an animal or human.

Clinical Presentation and Diagnosis

Cutaneous anthrax skin infection begins as a raised pruritic lesion or papule that resembles an insect bite. Within one to two days, the lesion develops into a fluid-filled vesicle, which ruptures to form a painless ulcer 1–3 cm in diameter with a necrotic area in the center. Pronounced edema is often associated with the lesions because of the release of an edema-producing toxin by the bacteria. The lymph nodes in the area may become involved and enlarged.

The incubation period in humans is usually 1 to 10 days but can be prolonged to almost two weeks [231; 234]. To describe the lesion in more detail, picture a painless macular eruption that appears within two to five days, most commonly on an exposed portion of the body. The lesion progresses from a red macule to a pruritic papule, then to a single or ring of vesicles.

This is followed by a depressed ulcer and finally a black necrotic eschar that falls off within 7 to 10 days. There is edema associated with the eschar but usually no permanent scarring of the affected area. The symptoms of purely cutaneous anthrax infection can include fever, headache, regional lymph node involvement, and myalgia. The cutaneous form of anthrax may progress to systemic disease, with a fatality rate of up to 20% if untreated [234].

Gastrointestinal anthrax is characterized by an acute inflammation of the intestinal tract. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and severe diarrhea [231; 232].

The first sign of inhalation anthrax is the acute onset of a flu-like illness. If inhalation anthrax progresses to the pneumonic form, the initial symptoms are often followed by a short period of improvement. Next, there is an abrupt development of severe respiratory distress with dyspnea, diaphoresis, stridor, and cyanosis. Shock and death usually occur within 24 to 36 hours after the onset of respiratory distress [230; 234]. In the later stages, mortality approaches 100% despite aggressive treatment. Physical findings can be nonspecific. The chest x-ray is usually disease-specific, revealing a widened mediastinum with pleural effusions, but typically without infiltrates [232]. Thoracic trauma can have similar signs, but often with infiltrates. A hemorrhagic mediastinitis often develops.

Laboratory tests of blood products are usually normal if the disease is not disseminated. The *B. anthracis* organism can be obtained for culture or gram stain; however, analysis beyond simple cultures should only be performed in a specialized laboratory environment [235]. On gram stain, the organism can be recognized as a large, rod-shaped, gram-positive, spore-forming bacillus [230]. More positive identification requires lysis by gamma phage and dFA, or most positively by immunohistochemical staining. There is an ELISA test available, but generally only at reference laboratories. A negative culture does not rule out cutaneous anthrax, especially if obtained after antibiotics are started [230].

Treatment and Prevention

Most *B. anthracis* strains are sensitive to a broad range of antibiotics. Either ciprofloxacin or doxycycline is usually recommended for the treatment of anthrax. In the past, penicillin was a first-line treatment, but due to concerns regarding resistance, it is no longer recommended by the CDC or the U.S. military [230]. To be truly effective, antibiotic treatment should be initiated as early as possible. If left untreated, the disease is highly fatal. Immediate prophylaxis with ciprofloxacin 500 mg (off-label) or doxycycline 100 mg orally twice daily is commonly recommended for cutaneous anthrax [55; 236; 237]. Treatment should continue for 60 days or longer; if the source in known to be from livestock or its products, a 7- to 10-day course is sufficient. If an individual has not been previously vaccinated, a three-dose series of vaccine should also be given subcutaneously at diagnosis and two and four weeks later [232; 237]. For inhalation anthrax treatment in adults, intravenous medications are suggested as the initial treatment and should be combined with one or two other effective agents [235; 237].

In some cases, other antibiotics may be considered, such as the other fluoroquinolones, including levofloxacin, clindamycin, and moxifloxacin. Clindamycin and moxifloxacin are not currently approved for this use by the FDA; however, the CDC indicates that these agents are effective, acceptable alternatives for postexposure prophylaxis or for treatment of systemic anthrax [55; 236; 238]. Rifampin and linezolid have been suggested as an adjunct treatment, and high-dose penicillins (e.g., amoxicillin, penicillin VK) may be tried if no other antibacterials are available and the strain is susceptible. In general, the cephalosporins are not useful in treating anthrax because the organism produces an enzyme that neutralizes them [236]. The monoclonal antibodies obiltoxaximab and raxibacumab (in combination with antimicrobial therapy) are indicated for postexposure prophylaxis of inhalation anthrax due to *B. anthracis* when alternative therapies are not available or are not appropriate [55; 232]. Supportive therapy for shock, fluid volume deficit, and adequacy of the airway may be needed.

In 2013, a new antibiotic with significant activity against *B. anthracis*, anthracimycin, was discovered [239]. Although it is not yet FDA-approved, it may have a place in the treatment of anthrax in the future.

Human-derived anthrax immune globulin (AIG) was used to successfully treat a naturally occurring inhalation anthrax case in Pennsylvania in 2006 [240]. In 2015, the FDA approved AIG for the treatment of inhalation anthrax [55; 241]. Immune globulin administration may be considered in combination with appropriate antibiotics when multiple organ systems are involved or following lack of response to standard therapy.

Vaccination for anthrax can prevent the disease if given prior to contact with the bacillus. However, it can also be used postexposure to help minimize the patient's reaction to the organism. Anthrax Vaccine Adsorbed (AVA) is the only licensed human anthrax vaccine in the United States [232]. For pre-exposure prophylaxis, the vaccination schedule consists of three injections of 0.5 mL of the vaccine administered subcutaneously in the deltoid region at 0, 1, and 6 months with boosters at 6 and 12 months after completion of the primary series and at 12-month intervals thereafter. For postexposure prophylaxis for adults 18 to 65 years of age, there are two options, both AVA agents: BioThrax and Cyfendus. The dosage of BioThrax is 0.5 mL administered subcutaneously at 0, 2, and 4 weeks [232]. Cyfendus is administered as an intramuscular injection as two doses (0.5 mL each) two weeks apart [277]. The vaccines are approved only for healthy, nonpregnant adults, although they will be made available under appropriate emergency use regulatory provisions [232]. The ACIP recommends that a booster dose of AVA for pre-exposure prophylaxis be given every three years to persons who are not at high risk for exposure to *B. anthracis* and who have previously completed the three-dose primary and the initial two-dose boosters AVA series and want to maintain protection. For persons at high risk for exposure to *B. anthracis*, booster doses at 12 and 18 months and annually thereafter are recommended [232]. There is an adverse reaction incidence of approximately 6% for local inflammation and 2% to 3% for systemic symptoms [55].

There is no data to suggest patient-to-patient transmission of anthrax; therefore, only standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax [237]. There is no need to immunize or provide prophylaxis to patient contacts unless a determination is made that they, like the patient, were exposed to the organism. Standard disinfectants used for hospital infection control are effective in cleaning surfaces contaminated with infected bodily fluids [231].

Proper burial or cremation of humans and animals that have died because of anthrax infection is essential to prevent further transmission of the disease. Serious consideration must be given to cremation. Embalming of bodies could be associated with special risks.

VIBRIO AND CHOLERA

Raw food has a potential for serious zoonotic diseases. Bacteria of the *Vibrio* genus exist in most fish and shellfish habitats. All members of this genus can produce gastrointestinal signs in varying degrees of severity. Raw oysters are one of the more prevalent shellfish to carry *Vibrio* spp. [242]. Ingesting the food items can produce the disease, but handling fish or shellfish contaminated with *Vibrio* can also lead to infection through chapped hands or finger cuts [242].

Cholera, the most well-known of the diseases caused by the *Vibrio* organisms, is caused by *V. cholerae*. Although *Vibrio* infections are much more common in developing countries, outbreaks and individual cases can occur in Europe and North America. Two serogroups of *V. cholerae* cause outbreaks: *V. cholerae* 0139 and *V. cholerae* 01 biotype El Tor. *V. cholerae* 0139 was first identified in Bangladesh in 1992 and is confined to Southeast Asia. *V. cholerae* 01 biotype El Tor has spread rapidly around the world and may be seen in patients returning from foreign countries [243].

Cholera is rarely spread from person to person without the contamination of food or water by animals or people. The organism can live in or on foodstuffs for up to five days at ambient temperatures and for 10 days at 5 to 10 degrees C. Most cases in endemic areas are in young children [243].

Clinical Presentation and Diagnosis

Some cases of cholera are asymptomatic or only produce a mild diarrhea. A major *Vibrio* infection is characterized by a sudden onset of severe enteritis with diarrhea, vomiting, and leg cramps. The usual incubation period is 0.5 to 5 days [243]. Marked dehydration can occur, especially in the instance where reinfection is occurring from a point source. There may be accompanying fever. If the bacteria infect a wound, the site can become necrotic and cellulitis can spread until the infection is no longer localized. Once septicemia occurs, the case fatality rate can be as high as 50%; it may be as high as 25% in wound infection cases [14]. Laboratory diagnosis can be made with gram stain or by culture of the organism.

Treatment and Prevention

The gastroenteritis form of *Vibrio* infection can usually be managed supportively in previously healthy individuals with intravenous followed by oral fluid and electrolyte replacement. It is the very young, the elderly, and patients with chronic disease, who may have a harder time dealing with vibriosis and require antibiotics. Antibiotic use for moderately and severely ill patients has been shown to reduce the volume of stool output, the duration of diarrhea, and the duration of positive stool cultures [244]. Doxycycline is recommended for adults, and azithromycin is recommended as first-line treatment for children and pregnant women [244].

Care must be taken with cooked shellfish to ensure that handling does not recontaminate the food product just before consumption. As noted, *Vibrio* spp. are relatively tolerant of wide temperature ranges and, consequently, can exist on a food preparation surface for a considerable time.

In 2016, the FDA approved the first cholera vaccine, Vaxchora. This one-dose oral vaccine is approved for adults 18 to 64 years of age traveling to cholera-affected areas. The vaccine should be administered at least 10 days prior to potential exposure [55; 245]. Other preventative measures recommended by the CDC include only drinking safe water, frequently washing hands with soap (or scrubbing hands with ash or sand) and safe water, cooking all foods and eating them hot, and only consuming raw fruits and vegetables that have been peeled recently by oneself.

BOTULISM

Botulinum toxins have gained widespread recognition as a result of the introduction of botulinum type A (Botox) into the field of cosmetology. The toxins have been important medically for many years due to the serious and often fatal consequences of ingesting improperly canned or bottled foods. However, the disease can also be caused by contact with, or ingestion of, contaminated fish and herbivores.

Botulinum toxins are proteins produced by the anaerobic bacterium *Clostridium botulinum* and consist of seven separate but related neurotoxins, denoted A through G. All of the strains produce similar effects when ingested or inhaled. They are among the most toxic compounds known, with an estimated toxic dose of only 0.001 mcg/kg of body weight [246]. These neurotoxins act by binding at the presynaptic nerve terminals and the cholinergic autonomic sites. They also block acetylcholine transmission, causing skeletal muscle weakness and paralysis as well as bulbar palsies [246].

Human disease is caused by strains A, B, E, and rarely, F [246; 247]. In the United States, toxin A is found predominantly west of the Mississippi River, while toxin B is found most commonly in the East. Toxin E is found in northern latitudes, such as the Pacific Northwest, the Great Lakes region, and Alaska. The frequency of botulism in native Alaskans is among the highest in the world, as toxin E outbreaks are frequently associated with fish products [246]. The disease can also be caused by wounds infected with *C. botulinum* and is known

as "wound botulism." An intestinal form has been reported in infants when the organism is ingested and germinates in the gastrointestinal tract. There is no person-to-person transmission of botulism, and airborne transmission of botulism does not occur naturally [246].

In 2015, potato salad prepared with home-canned potatoes sickened 29 people after it was eaten at a church potluck in Ohio. The coordinated effort by the area hospitals, county and state health departments, and the CDC, which sent 50 doses of botulinum antitoxin from the Strategic National Stockpile, is credited with saving the lives of 28 of the patients and vastly reducing their illness severity and length of hospital stay. The potatoes were bottled using a boiling water canner rather than a pressure canner, which is recommended and able to effectively deactivate spores. This was the largest outbreak of botulism in the United States in nearly 40 years [248].

Clinical Presentation and Diagnosis

Following an incubation period of 2 hours to 8 days, depending on the dose (typically 12 to 72 hours), the early signs and symptoms of diplopia, blurred vision, dry mouth, ptosis, and photophobia appear. This is followed by skeletal muscle weakness and paralysis, which is typified by a descending, symmetrical pattern, ending in respiratory difficulty and eventually respiratory failure. Interestingly, the patient usually remains alert and afebrile, although there may be dysarthria, dysphagia, and dysphonia. The pupils may be dilated and fixed, the gag reflex may be absent, and deep tendon reflexes are diminished or absent. The patient may develop hypotension, cyanosis, and evidence of carbon dioxide retention. In foodborne botulism, all of these findings may be evident in patients within 24 hours of the ingestion of the tainted items [246; 249].

Some cases of botulism may be confused with disorders such as Guillain-Barré syndrome or myasthenia gravis (MG). It has been suggested that the edrophonium (Tensilon) test may be used to differentiate it from MG, but because it may be transiently positive in botulism, its actual usefulness is in doubt [250]. The edrophonium test requires that the patient have a sign, such as ptosis, that can be reversed with an intravenous injection of a cholinesterase agent like edrophonium.

Very limited information can be obtained from laboratory tests. Survivors usually do not develop an antibody response to the toxin because of the subimmunogenic amount of material required to produce major symptoms. In cases of ingested botulinum toxin, culture of the serum or stool may be useful [246]. An ELISA test might possibly detect the toxin on nasal mucous membranes for 24 hours in cases of inhalation.

The recommended test for confirmation of botulism is the mouse neutralization bioassay [246; 249]. This assay can detect as little as 0.03 ng of botulinum toxin within one to four days after exposure.

Treatment and Prevention

There are good antitoxins available; however, they only halt the progression of future symptoms and do not reverse the existing clinical presentation. A licensed heptavalent antitoxin for all known types of botulinum (A, B, C, D, E, F, and G) has been approved by the FDA and is recommended for all cases of botulism in patients other than infants [180; 246]. The antitoxin is of equine origin, which means that skin testing must be performed to help prevent serum sickness or anaphylaxis in susceptible individuals [251]. Intravenous human botulism immune globulin (BIG-IV, BabyBIG) is available for the treatment of patients younger than 1 year of age with infant botulism caused by toxin type A or B. In cases of suspected infant botulism, for consultation, and to obtain BabyBIG, physicians should call (510) 231-7600 [252]. Antibiotics (i.e., penicillin G, chloramphenicol, clindamycin) are useful in wound botulism, but not in foodborne botulism [246].

For patients with symptoms of botulism, the prompt administration of botulinum antitoxin and supportive care can markedly reduce the mortality rate. Supportive care may include ventilatory assistance for several weeks or even months. Treatment is the same for children and adults [246].

Botulism poisoning is not an infection. It is not transmitted from person to person, and only standard precautions are required to control its spread. Because botulism poisoning is not transmittable, patients do not need to be isolated. The CDC recommends that contaminated objects or surfaces be cleaned with 0.1% hypochlorite bleach solution if they cannot be avoided for the hours to days required for natural degradation [253].

SALMONELLOSIS

The diseases caused by this group of organisms are well known in animals and in humans. Salmonellosis is caused by *Salmonella* spp., of which there are more than 2,500 serotypes. The species is divided into six subgroups or subspecies based on pathogenicity, DNA similarity, common host, and other factors. The classification system is complex, and the diseases that are expressed are quite diverse. Most pathogenic *Salmonella* spp. become localized in the body within the victim's cells [254; 255]. Consequently, after ingestion they are taken up by macrophages, which facilitate their spread through the lymphatic system.

It is from an animal host in the asymptomatic carrier state that many *Salmonella* diseases are transmitted to humans [256]. Domestic and wild animals can be reservoirs for these zoonoses, including domestic and wild reptiles, farm animals, chickens and other poultry (especially ducks), and small mammals. All transmissions to humans are from ingestion [255]. Most transmissions occur from meat, poultry, raw eggs, and milk products, but any food, including vegetables, may become contaminated. It can also be transmitted directly by the fecal-oral route [255]. Infected water sources can also transmit disease, and infected food handlers have been noted to cause sporadic outbreaks. Freezing does not destroy the agent.

Salmonellosis diseases fall into three categories in humans: gastroenteritis, septicemia, and enteric fever. Animal cases are more chronic, and an asymptomatic carrier state is seen in many species after the disease runs its course [256]. The carrier state is also common in humans, with typhoid fever being the most familiar. Inappropriate use of antibiotics can prolong the carrier state. Other examples of diseases seen in humans caused by *Salmonella* include paratyphoid fever and the many forms of gastroenteritis. The case fatality rate is less than 1% and is primarily seen in the young or elderly [257].

Clinical Presentation and Diagnosis

The common presentation of salmonellosis is gastroenteritis with fever, abdominal cramping, vomiting, diarrhea that is often bloody, chills, and weight loss [254; 255]. There is often a history of ingesting a possibly contaminated food product within the past few days, but in many cases a full epidemiologic investigation is necessary to find the source of infection. The symptoms usually appear within 12 to 72 hours after ingestion of the infective organism.

Serum is useful in testing for the enteric fever form *S. typhi* only. Culturing the feces is usually needed to verify the disease [257]. The samples can be serotyped, in most cases, to help identify the exact source of an infection.

Treatment and Prevention

Antimicrobial therapy is not recommended for the usual case of uncomplicated salmonella gastroenteritis, as this tends to be self-limited, lasting about four to seven days; antibiotic treatment does not shorten the duration and may prolong the carrier state, which could have adverse public health consequences if the patient is in close contact with others or is a food handler [255; 257]. Patients with enteric fever presentation or signs of disseminated foci of salmonella infection do require antibiotic treatment. Careful attention to antimicrobial sensitivity testing of the infecting strain is important, as some salmonella strains are multidrug-resistant [254; 257; 258]. Choices for antibiotic therapy for severe infections include fluoroquinolones, third-generation cephalosporins, and ampicillin (for susceptible infections) [257]. Third-generation cephalosporins, which must be given by injection, are widely used in children with serious infections because the quinolones are not generally recommended for this age group. The drugs commonly used in the past, chloramphenicol, ampicillin, amoxicillin, and trim-

ethoprim-sulfamethoxazole, are occasionally used as alternatives [255]. For cases in which a carrier state is identified, it is important to treat the individual who is the carrier. It is also especially important to identify sources of drug-resistant strains to avoid outbreaks similar to those in northern California during spring 1997 related to the home production of Mexican-style cheese [259].

In managing clusters of salmonellosis among livestock, fecal samples should be tested and the animal cleared of carrier status only after a series of samples are determined to be free of the bacteria. In the case of infection coming from a food handler, tracking the source will be hastened if the initial case is reported in a timely fashion to allow public health officials to investigate as quickly as possible.

Common sense (e.g., hand washing after handling raw foods or animals/animal feces) prevails in the prevention of these diseases. Avoiding raw eggs, unpasteurized dairy products, and other questionable food products will prevent most cases, as will proper cooking of poultry and meats [254; 256; 257].

According to the World Gastroenterology Organisation, two typhoid vaccines (with limited cost-efficiency) are approved for clinical use to prevent diarrhea associated with *Salmonella typhi* infection.

(https://www.worldgastroenterology.org/guidelines/global-guidelines/acute-diarrhea/acute-diarrhea-english. Last accessed April 28, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

BRUCELLOSIS

Brucellosis, also known as undulant fever, is a zoonotic disease caused by infection with a species of *Brucella*. The most common are *B. abortus* (cattle), *B. melitensis* (sheep), and *B. suis* (swine), with rare cases reported due to infection with *B. canis* (canine). *B. melitensis* is thought to be the most virulent, the most prevalent, and the cause of the most severe and acute cases of brucellosis worldwide; it is also the source of most human cases of brucellosis in the United States [260]. According to the USDA, the only known focus of *B. abortus* infection in the United States is among bison and elk in and around Yellowstone National Park [261]. Brucellosis is highly endemic in countries such as Peru, Mexico, Spain, Greece, Iraq, Iran, Jordan, and Kuwait. It is considered a rare disease in the United States, where an average of approximately 100 cases are reported per year, mostly from Florida, California, Virginia, and Texas [262]. Ingesting non-pasteurized milk or cheese is a likely cause for many of these cases [262; 263].

Clinical Presentation and Diagnosis

The brucellae are a group of gram-negative cocci bacillary organisms. The most common way to become infected is by drinking or eating unpasteurized milk or cheese products derived from sheep, goats, or cows. Meat packing and laboratory worker infections suggest that *Brucella* is highly infectious via direct contact with carcasses or by inhalation aerosol route [263]. It is estimated that inhalation of only 10–100 bacteria is sufficient to cause disease in humans. The incubation period is 5 to 60 days, and many infections are asymptomatic under natural conditions. Large aerosol doses may shorten the incubation period and increase the clinical attack rate. Brucellosis infection has a low mortality rate (2% to 5% of untreated cases), with most deaths caused by endocarditis or meningitis. It is an incapacitating disease in its natural form [237; 263].

Acute brucellosis presents as a flu-like illness, with fever, headache, joint pain, sweats, chills, and general weakness as common complaints. Cough and pleuritic chest pain may be present but may not correlate with radiographic results. Chest x-rays may show lung abscesses, single or miliary nodules, and pleural effusions. Gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhea, and constipation, colitis, or an infiltrative hepatitis occur in up to 70% of adult cases and less frequently in children. Hepatomegaly and splenomegaly can occur in as many as 20% to 30% of cases. Peripheral joint involvement may vary from pain on range of motion to joint immobility and effusion, usually involving the hips and sacroiliac joints [264]. Meningitis

occurs in less than 5% of brucellosis cases and may be an acute presenting illness of a chronic syndrome, occurring late in the course of a persistent infection [264]. Behavioral disturbances in children and psychoses may occur in the meningoencephalitic form of the disease.

Laboratory studies for *Brucella* spp. are most productive if accomplished early in the course of the disease. The organism is slow-growing and should be incubated for about three weeks before a negative result can be reported. Cultures can be obtained from blood, urine, CSF, or even bone marrow. Serologic testing is the most common diagnostic procedure, with rising titers or an agglutination titer of ≥1:160 is presumptive of brucellosis diagnosis [264].

Many other procedures have been utilized, including IFA, ELISA, and counter immunoelectrophoresis. The micro-agglutination test is still considered to be the gold standard test. This test allows for the differentiation of an acute (predominately IgM) infection versus a relapse (predominately IgG). Identification is made by culturing *Brucella* spp. from blood or bone marrow [237; 262]. Evidence of *Brucella* antibodies by nonagglutination-based tests does not meet the current CDC case definition for a presumptive diagnosis of brucellosis. However, any quantitative test can be used for confirmation if there is a four-fold or greater rise in *Brucella* antibody titer [264].

Treatment and Prevention

Brucellosis is treatable with antibiotics, but due to the intracellular nature of the infectious process, treatment usually requires combination therapy over a long duration. Optimal antibiotic therapy for brucellosis has been studied; however, recommendations differ [262]. Doxycycline (200 mg daily) plus rifampin (600–1,200 mg daily) for six weeks may be appropriate for uncomplicated disease in adults [264]. Fluoroquinolones (e.g., ciprofloxacin) have been used as monotherapy but carry a high relapse rate; adding these agents to doxycycline offers no specific advantages over other combination regimens but may be preferred in areas where resistance to rifampin is high [262]. The CDC guidelines for treatment of brucellosis recommend [264]:

- For adults and children >8 years of age: Doxycycline (100 mg) twice daily or oral tetracycline (30-40 mg) daily in four divided doses plus rifampin (600–900 mg/day) given orally for six weeks. This regimen is more convenient but may increase the risk of relapse. Combination therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) can be used if tetracyclines are contraindicated. Tetracyclines are contraindicated for pregnant patients.
- For children <8 years of age: Oral TMP-SMZ (trimethoprim, 10 mg/kg per day, maximum 480 mg/day; and sulfamethoxazole, 50 mg/kg per day, maximum 2.4 g/day) divided in two doses for four to six weeks. Combination therapy: consider adding rifampin. Tetracyclines should be avoided.
- For complicated cases: Streptomycin or gentamicin for first 14 days of therapy plus a tetracycline for six weeks (or TMP-SMZ if tetracyclines are contraindicated). Rifampin can be used in combination with this regiment to decrease the rate of relapse. For life-threatening complications (e.g., meningitis, endocarditis), duration of therapy can be extended for four to six months.

Arthritis may occur in recurrent cases.

A 2012 Cochrane review found that a regimen consisting of doxycycline for six weeks plus streptomycin for two to three weeks was more effective than one consisting of doxycycline plus rifampicin for six weeks [265]. The investigators also found that a regimen consisting of a fluoroquinolone plus rifampicin for six weeks was as effective overall as doxycycline plus rifampin (based on low-quality evidence) and was slightly better tolerated.

Prevention is largely limited to those occupations for which brucellosis is a risk, as naturally occurring forms of the disease have been drastically limited in the United States through the use of animal vaccines. However, food and animal products imported from other countries can pose a risk. Avoidance of high-risk food products, particularly unpasteurized dairy products, is an important step in avoiding the disease [263]. For those in direct contact with *Brucella* spp. cultures, prophylaxis is recommended [264].

PARASITIC ZOONOTIC DISEASES

Parasitic zoonoses may be the most widespread in the world [266]. Although they generally produce a much greater morbidity than mortality, these diseases have an enormous impact on economic and social well-being in many countries. Fortunately, most of the diseases are endemic in areas outside North America and only involve travelers or immigrants in the United States and Canada.

There are multitudes of parasitic organisms that affect animals, many of which can then be transmitted to humans. Trichinosis, tapeworm infestation, and anisakiasis will be discussed as examples due to their similar morphology.

TRICHINOSIS

Trichinosis, also known as trichinellosis, is caused by the nematode *Trichinella spiralis*. It is common in Europe and the United States and is a reportable disease [267]. Several other *Trichinella* spp. are found around the world in carnivorous mammals and birds. The typical hosts of the worm in North America are pigs, rats, and bears. Less commonly, humans, dogs, cats, wolves, and horses can also be hosts. In the host, the adult organism typically lives in the intestine. There, it produces larvae, which penetrate the intestinal wall and migrate into skeletal muscle, where they encyst.

Infection occurs when infected meat of a host is consumed. The common source in this country is undercooked pork, especially from small farm operations that feed uncooked meat scraps to the animals or from pig cannibalism [267]. People have been infected from consumption of horse and bear meat as well.

Clinical Presentation and Diagnosis

The symptoms of infection are initially diarrhea, vomiting, fever, and abdominal distress. This is followed by flu-like symptoms from the muscle infection. In this stage, patients may have headaches, chills, cough, arthralgia, and myalgia. In severe infections, there can be myocarditis, paresis, central nervous system involvement, and respiratory distress. There have been fatalities from the disease [267].

The initial symptoms usually appear one to two days after ingesting the contaminated food product, with the later signs and symptoms showing up after about two to eight weeks. A detailed patient history is very helpful in identifying this zoonosis, and cases frequently present in an isolated small group or family.

Some of the *Trichinella* larvae may be passed in the feces, which can assist in diagnosis. Laboratory analysis includes antibody detection, muscle biopsy, and microscopy. The patient may have a pronounced eosinophilia [267].

Treatment and Prevention

Treatment should begin as soon as possible once the diagnosis is suggested. The CDC suggests the anthelmintics mebendazole and albendazole as possible therapeutic medications, although they are not FDA approved for this purpose. Steroids may be required for severe symptoms [55; 267; 268].

Adequate cooking of meat products will kill the organisms. This usually means obtaining an internal temperature of 170 degrees F. Pork can also be frozen for 20 days at 5 degrees F (if less than 6 inches thick) to assure safety. Thorough cooking of wild game meats will provide protection, but the freezing

regimen is not always effective. In addition, curing by salting, smoking, or drying does not always kill the nematodes or cysts. Interestingly, microwaving does not consistently inactivate the organism, but ionizing irradiation has been used successfully to provide protection [267].

TAPEWORMS

The cestodes that produce the common human tapeworm infestation belong to the *Taeniidae* family. The most frequently seen in the United States are *Taenia saginata*, or beef tapeworm, and *Taenia solium*, the pork tapeworm. *Taenia asiatica* is limited to Asia and seen mostly in the Republic of Korea, China, Taiwan, Indonesia, and Thailand. *T. solium* can also cause cysticercosis [13]. *Dipylidium caninum* is found in dogs and cats and produces the disease dipylidiasis, most frequently seen in children younger than 8 years of age [269]. Humans are the only definitive hosts for *T. saginata* and *T. solium*, with pigs and cattle being common sources of the infestation.

All tapeworm organisms cause the disease process after being ingested by the victim in food or by direct contact, in the case of dipylidiasis. In addition, *D. caninum* can also be transmitted by ingesting infected fleas [269].

The lifecycle begins with egg packets within proglottids being released into the environment by a carrier. The eggs can survive for months on the ground or on most surfaces [13]. Once ingested, the organisms invade the intestinal wall of the victim and migrate to striated muscle, where they become cysticerci. The cysticerci can persist for years in an animal and cause significant morbidity. In humans, an adult tapeworm develops over a period of about two months. It attaches to the small intestine, where it can reside and excrete multitudes of proglottids for many years.

Clinical Presentation and Diagnosis

The symptoms of infestation with *T. saginata* are minimal, with mild abdominal pain being the most common finding. The clinical presentation of *T. solium* is even more minimal. It is usually the discovery of proglottids in the stool that signals the presence of the infestation [13]. Infrequently, the pork tapeworm progresses to cysticercosis, which can cause central nervous system symptoms if it invades the brain.

Dipylidiasis is typically asymptomatic; however, a severe worm burden can cause local pruritus, abdominal pain, allergic manifestations, and intestinal obstruction. The disease is often identified by the parent noting "rice stools" in a child's diaper [13; 270].

Microscopic identification of the eggs and proglottids in the feces is diagnostic. This may not be possible until three months after infection because the adult tapeworm must first be present. Repeated examinations may be necessary to find the organisms, especially in light infestations. Antibody detection methods can be useful in the early stages of the disease, before the presence of proglottids in the stool. The differentiation of the species of *Taenia* requires more detailed analysis, with examination of the gravid proglottids or the scolex of the organism [13; 270].

Treatment and Prevention

Treatment with antiparasitic medication is usually very effective. The CDC recommends praziquantel, although it is not yet approved for this use by the FDA [13; 55]. The usual anthelmintics (i.e., albendazole or praziquantel) have been used for the treatment of neurocysticercosis [271]. Treatment of dipylidiasis in adults and children can be with praziquantel or albendazole (off-label use) [55].

Prevention of dipylidiasis in pets and humans is aided by the control of fleas with pet medications or flea collars. Good hygiene and refraining from sleeping with or kissing the animal will also help prevent the infestation. Good sanitary practices are also the best way to prevent taeniasis [269].

ANISAKIASIS

There are many fish-borne zoonotic diseases, including ciguatera poisoning, tetrodotoxin poisoning from pufferfish, and infestations of *Diphyllobothrium* tapeworms. Because of the increasing consumption of uncooked fish in North America, there has been an increased awareness of anisakiasis. *Anisakis simplex* is a nematode (roundworm) found in several types of ocean fish and marine animals [272].

The adult nematodes reside in the intestines of marine mammals such as dolphins and sea lions. These mammals excrete the eggs, which are ingested by crustaceans. Fish then eat the crustaceans and become intermediate hosts, as the larvae imbed themselves in their flesh. Commonly affected fish include mackerel, salmon, squid, rockfish, anchovies, sardines, hake, and herring [273]. After ingestion by humans, the larvae attach themselves to the gastric mucosa or penetrate the stomach or intestinal wall. This can lead to abscess formation or eosinophilic granulomatosis. A severe allergic reaction often occurs, which causes more morbidity than the local effects of the adult nematodes [272; 273].

Clinical Presentation and Diagnosis

Patients may suffer a marked allergic response, including urticaria, angioedema, bronchospasm, and anaphylaxis, within 24 hours of eating raw or undercooked fish [272]. The latency of the reaction ranges from 15 minutes to 26 hours, with 5 hours after consumption being the mean [273]. Gastrointestinal symptoms of abdominal pain, diarrhea, fullness, nausea, and vomiting are often mild, although the vomiting may be violent enough to expel some of the larvae [272]. If the organisms lodge in the bowel, they can produce a granulomatous response, mimicking Crohn disease, after about one to two weeks [273]. They can also be found in organs or areas outside the gastrointestinal tract, such as the peritoneum and liver [274].

Diagnosis can be made by endoscopy, during which the 2-cm larvae can be seen and removed. The organisms can also be seen on biopsy specimens obtained during the endoscopic procedure or surgery [272].

Treatment and Prevention

The treatment of choice is removal of the organisms during fiberoptic endoscopy or surgery [272; 273]. Successful treatment of anisakiasis with albendazole 400 mg orally twice daily for 6 to 21 days has been reported in cases with a strong presumptive diagnosis based on history and/or serology [272]. Prevention is almost absolute if raw or uncooked fish is avoided. However, this is not practical in many parts of the world, including the United States. Fortunately, most chefs trained in handling and preparing raw fish can spot tainted fish. Freezing at negative 4 degrees F for at least seven days will kill the larvae, as will "blast-freezing" at negative 31 degrees F for 15 hours [272]. Irradiation of fish can also kill the organisms as will the cooking of thawed or fresh fish. Salting, in high concentration, and smoking may provide some prevention but not enough to assure a safe product [275]. When smoking, the flesh must reach 65 degrees C to kill the parasites.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Obtaining a detailed patient history is a vital aspect of diagnosing many zoonotic diseases, particularly those that are rare or that display similar signs and symptoms to other conditions. Furthermore, communication with patients regarding diagnostic procedures, treatment regimens, and prevention of zoonotic diseases depends on clear communication between the patient and clinician. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. The interpreter should be considered an active agent in the diagnosis and/or treatment processes, negotiating between two cultures and assisting in promoting culturally competent communication and practice [276]. This is particularly an issue for zoonotic diseases that commonly originate in countries outside the United States, for which English will be a second language for some or many of the patients.

In the increasingly multicultural landscape of the United States, interpreters are a valuable resource to help bridge the communication and cultural gap between patients or caregivers and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. When interacting with patients for whom English is a second language, the consideration of the use of an interpreter and/or patient education materials in their native language may improve understanding and outcomes.

CONCLUSION

The zoonotic diseases, in their many forms, have produced widespread morbidity and mortality. From the very old zoonoses, such as plague and rabies, to the relatively new diseases, like avian influenza and West Nile encephalitis, these diseases can be expected to cause disease in humans well into the future.

This course presented a spectrum of the more common zoonoses and briefly reviewed the background, clinical presentation, diagnostic procedures, treatment, and preventive measures associated with the individual diseases. It is vital for medical professionals to have a working knowledge of the zoonoses that they may encounter. Particularly considering the globalization of commerce and travel, early diagnosis and effective treatment can protect against potential outbreaks and pandemics.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.