HUMAN DISEASES

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Dengue Fever

Dengue fever is an infectious disease carried by mosquitoes and caused by any of four related dengue viruses. This disease used to be called break-bone fever because it sometimes causes severe joint and muscle pain that feels like bones are breaking, hence the name. Health experts have known about dengue fever for more than 200 years. Dengue fever is found mostly during and shortly after the rainy season in tropical and subtropical areas of Africa, Southeast Asia and China, India, Middle East, Caribbean and Central and South America, Australia and the South and Central Pacific.

The World Health Organization estimates 50 to 100 million cases of dengue infection occur each year. This includes 100 to 200 cases reported annually to the Centres for Disease Control and Prevention (CDC), mostly in people who have recently travelled abroad. Many more cases likely go unreported because some doctors do not recognize the disease. During the last part of the 20th century, cases of dengue began increasing in many tropical regions of the world. Epidemics also began occurring more frequently and with more severity. In addition to typical dengue, dengue hemorrhagic fever and dengue shock syndrome also have increased in many parts of the world.

Dengue fever is a benign acute febrile syndrome occurring in tropical regions. In some cases the virus causes increased vascular permeability that leads to a bleeding diathesis or disseminated intravascular coagulation (DIC) known as dengue hemorrhagic fever (DHF). Secondary infection by a different dengue virus serotype has been confirmed as an important risk factor for the development of DHF. In 20-30% of DHF cases, the patient develops shock, known as the dengue shock syndrome (DSS). Worldwide, children younger than 15 years comprise 90% of DHF subjects. Dengue is a homonym for the African word, *ki denga pepo,* which appeared in English literature during an 1827-28 Caribbean outbreak. The first definite clinical report of dengue is attributed to Benjamin Rush in 1789, but the viral aetiology and its mode of transmission via mosquitoes were not established until the early 20th century.

DENGUE VIRUS

Dengue fever can be caused by any one of four types of dengue virus: **DEN-1, DEN-2, DEN-3, and DEN-4.** A person can be infected by at least two, if not all four types at different times during a life span, but only once by the same type.

TRANSMISSION

Mosquitoes become infected when they bite infected humans, and later transmit infection to other people they bite. The two main species of mosquito, *Aedes aegypti* and *Aedes albopictus*, have been responsible for all cases of dengue transmitted in this country. Dengue is not contagious from person to person.

SYMPTOMS

Dengue fever usually starts suddenly with a high fever, rash, severe headache, pain behind the eyes, and muscle and joint pain. The severity of the joint pain has given dengue the name "break bone fever." Nausea, vomiting, and loss of appetite are common. A rash usually appears 3 to 4 days after the start of the fever. The illness can last up to 10 days, but complete recovery can take as long as a month. Most dengue infections result in relatively mild illness, but some can progress to dengue hemorrhagic fever. With dengue hemorrhagic fever, the blood vessels start to leak and cause bleeding from the nose, mouth, and gums. Bruising can be a sign of bleeding inside the body. Without prompt treatment, the blood vessels can collapse, causing shock which is called dengue shock syndrome. Dengue hemorrhagic fever is fatal in about 5 percent of cases, mostly among children.

Symptoms of typical uncomplicated **classic dengue** usually start with fever within 5 to 6 days after you have been bitten by an infected mosquito and include—

- High fever, up to 105 degrees Fahrenheit.
- Severe headache.
- Retro-orbital (behind the eye) pain.
- Severe joint and muscle pain.
- Nausea and vomiting.
- Rashes.

The rash may appear over most of your body 3 to 4 days after the fever begins. A second rash may appear later in the disease.

Symptoms of **dengue hemorrhagic fever** include all of the symptoms of classic dengue plus the following additional symptoms:

- Marked damage to blood and lymph vessels.
- Bleeding from the nose, gums, or under the skin, causing purplish bruises.

This form of dengue disease causes some deaths.

Symptoms of **dengue shock syndrome**—the most severe form of dengue disease—include all of the symptoms of classic dengue and dengue hemorrhagic fever, plus the following:

- Fluids leaking outside of blood vessels.
- Massive bleeding.
- Shock.

This form of the disease usually occurs in children (but sometimes adults too) experiencing their second dengue infection. The fatality rate is 5 to 15 percent.

DIAGNOSIS

The health care provider can diagnose dengue fever by doing two blood tests, 2 to 3 weeks apart. The tests can show whether a sample of your blood contains antibodies to the virus. In epidemics, a health care provider often can diagnose dengue by typical signs and symptoms.

TREATMENT

There is no specific treatment for classic dengue fever, and like most people you will recover completely within 2 weeks. To help with recovery, health care experts recommend the following:

- Getting plenty of bed rest.
- Drinking lots of fluids such as fruit juices, soups and water with electrolytes.
- Taking medicine to reduce fever.

It is advised that people with dengue fever do not to take aspirin as it dilutes blood which may complicate haemorrhage but Acetaminophen or other over-the-counter pain-reducing medicines are safe for most people. For severe dengue symptoms, including shock and coma, early emergency treatment with fluids and electrolytes can be lifesaving.

PREVENTION

The best way to prevent dengue fever is to take special precautions to avoid contact with mosquitoes. Several dengue vaccines are being developed but none is likely to be available in the next few years. When outdoors in an area where dengue fever has been found use a mosquito repellent and dress in protective clothing such as long-sleeved shirts, long pants, socks, and shoes. Because *Aedes* mosquitoes usually bite during the day, be sure to use precautions especially during early morning hours before day break and in the late afternoon before dark.

Other precautions include:

- Keeping unscreened windows and doors closed.
- Keeping window and door screens repaired.
- Getting rid of areas where mosquitoes breed, such as standing water in flower pots, containers, birdbaths, discarded tires, etc.

Japanese Encephalitis

Japanese encephalitis is a potentially severe viral disease that is spread by infected mosquitoes in the agricultural regions of Asia. It is one of several mosquito-borne virus diseases that can affect the central nervous system and cause severe complications and death. It can be a risk to travellers to rural areas where the disease is common. There is no specific treatment for Japanese encephalitis but a vaccine is recommended for travellers whose itineraries might put them at risk for Japanese encephalitis. All travellers should take precautions to avoid mosquito bites to prevent Japanese encephalitis and other mosquito-borne diseases.

Japanese encephalitis is a disease that is spread to humans by infected mosquitoes in Asia. It is one of a group of mosquito-borne virus diseases that can affect the central nervous system and cause severe complications and even death.

Infectious agent

Japanese encephalitis is caused by the Japanese encephalitis virus, an **arbovirus,** which is an arthropod-borne virus. Arboviruses are a large group of viruses that are spread by certain arthropods, most commonly blood-sucking insects. Japanese encephalitis is spread by infected mosquitoes.

Distribution

Japanese encephalitis is found throughout rural areas in Asia and can also occur near urban areas in some developing Asian countries. This is a seasonal disease that usually occurs in the summer and fall in the temperate regions of China, Japan, and Korea. Countries which have had major epidemics in the past, but which have controlled the disease primarily by vaccination, include China, Korea, Japan, Taiwan and Thailand. Other countries that still have periodic epidemics are Vietnam, Cambodia, Myanmar, India, Nepal, and Malaysia.

Mode of infection

Japanese encephalitis virus has a complex life cycle involving domestic pigs, birds and a specific type of mosquito, *Culex tritaeniorhynchus* that lives in rural rice-growing and pig-farming regions. The mosquito breeds in flooded rice fields, marshes, and standing water around planted fields. The virus can infect humans, most domestic animals, birds, bats, snakes, and frogs. After infection, the virus invades the central nervous system, including the brain and spinal cord. Mosquitoes become infected by sucking blood from domestic pigs and wild birds infected with the Japanese encephalitis virus. Infected mosquitoes then transmit the virus to humans and animals during the feeding process. The virus multiplies in the blood systems of domestic pigs and wild birds. Among persons who are infected by a mosquito bite, only 1 in 50 will develop an illness. Japanese encephalitis is the leading cause of viral encephalitis in Asia, where 30,000 to 50,000 cases are reported each year.

Symptoms

Most infected persons develop mild symptoms or no symptoms at all. In people who develop a more severe disease, it starts as a flu-like illness, with fever, chills, tiredness, headache, nausea, and vomiting. Confusion and agitation can also occur in the early stage. The illness can progress to a serious infection of the brain (encephalitis) and can be fatal in 30% of cases. Among the survivors, another 30% will have serious brain damage, including paralysis. Mild infections may occur without apparent symptoms other than fever with headache but in the case of more severe infections there is headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, occasional convulsions and spastic paralysis.

Symptoms usually appear 6-8 days after the bite of an infected mosquito, incubation period being 5-15 days.

Diagnosis

Diagnosis is based on tests of blood or spinal fluid.

Treatment

There is no specific treatment for Japanese encephalitis. Antibiotics are not effective against viruses, and no effective anti-viral drugs have been developed. Care of patients centres on treatment of symptoms and complications.

Prevention

Vaccination is recommended only for persons who plan to travel in the infection prone areas for 4 weeks or more and in special circumstances such as an ongoing outbreak of disease.

Because of the potential for other mosquito-borne diseases in Asia, all travellers should take steps to avoid mosquito bites. The mosquitoes that transmit Japanese encephalitis feed mainly outside during the cooler hours at dusk and dawn. Travellers should minimize outdoor activities at these times, use mosquito repellent on exposed skin and stay in well-screened rooms. Travellers to rural areas should use a bed-net and aerosol room with insecticides.

RABIES

Rabies is a serious viral disease that affects central nervous system. It is an infectious disease of animals caused by a bullet-shaped, enveloped RNA virus, 180 x 75 nm. Man is occasionally infected and once infection is established in the central nervous system, the outcome is almost invariably fatal. Typically rabies spreads by way of the saliva of infected animals, usually a rabid dog, that comes in contact with blood through a bite. Once

infected, the virus spreads from muscles to peripheral nerves to spinal cord and brain. From initial flu-like symptoms, the illness progresses to convulsions, hallucinations, paralysis or breathing failure and almost always to death. The severity of the bite determines the risk of infection. The disease does not usually spread from man to man.

Incubation

After inoculation, the virus enters small nerve endings at the site of the bite. The virus slowly travels up the nerve to reach the central nervous system, where it replicates and then travels down the nerves to salivary glands where there is further replication. The time it takes to do this depends upon the length of the nerves. A bite on the foot will have a much longer incubation period than a bite on the face. ***The incubation period may last from two weeks to six months***. Very often the primary wound is healed and forgotten by the time of clinical symptoms appear.

Clinical Symptoms

Furious Rabies

When the virus reaches the central nervous system, the patient suffers from *headache, fever, irritability, restlessness and anxiety.* This may progress to *muscle pains, salivation and vomiting.* After a few days to a week the patient may experience a **stage of excitement** and painful muscle spasms, triggered sometimes by swallowing of saliva or water. Hence they fear water **(Hydrophobia).** The patients are also excessively sensitive to air blown on the face. The stage of excitement lasts only a few days before the patient lapses into *coma and death*.

Once clinical disease manifests, there is a rapid, relentless progression to invariable death, despite all treatment. The symptoms may include: Fever, headache, malaise, insomnia, anxiety and confusion, slight or partial paralysis, excitation, hallucinations, agitation, salivation, difficulty swallowing, convulsions and fear of water (hydrophobia) because of the difficulty in swallowing

Dumb Rabies

Starts in the same way, but instead of progressing into excitement, the subject retreats steadily and quietly downhill, with some *paralysis*, to death. Rabies diagnosis may easily be missed.

ANIMAL RABIES

It is very similar to human rabies. In the stage of excitement the animal may bite vigorously and viciously at anything: sticks, stones, grass, other animals and humans, without provocation. Wild animals may be abnormally tame or appear sick – beware of approaching or picking up such animals.

An animal infected with rabies carries the virus in its saliva, so if it bites a person, the virus enters into the person's body. It's possible to get rabies from an animal scratch, too. People sometimes describe animals that have rabies as *"foaming at the mouth."* This happens because the animal's nerves no longer work properly and it can't swallow its own saliva.

Disease transmission

Most often rabies transmission occurs through the bite of a rabid animal. Rarely, people contract rabies when saliva from an infected animal comes in contact with their eyes, nose, mouth or a wound. This may occur if you're licked by an infected animal. Inhaling the rabies virus is another potential route of exposure, but one likely to affect only laboratory workers.

The disease is endemic in **wild animals** in most parts of the world although some countries (UK, Australia) have become rabies-free through vigorous control measures and campaign. The wild animal cycle constitutes the natural reservoir. Wild animals may bite and infect **domestic animals** (cattle, horses, pigs, dogs and cats) which in turn may infect man. Occasionally wild animals may infect man directly. In recent decades, a separate form of **dog rabies** spread from dog to dog has been recognized as spreading from West Africa eastwards and southwards in Africa and Asia.

You're at greatest risk of contracting rabies if your activities bring you into contact with the rabies virus or a potentially rabid mammals. People at risk can include veterinarians, animal caretakers, laboratory workers, hunters, forest rangers and people visiting bat-inhabited caves.

ANIMAL RESERVOIRS

Mongoose (main reservoir in RSA in the wild), jackals, bats(some evidence to suggest carrier status and droplet infection), foxes (in Europe), skunks, raccoons (in USA) and semi-wild dogs.

DIAGNOSIS

If you've been bitten or have had contact with an animal that may have rabies, certain information may help your doctor determine your risk of contracting rabies and how to treat you. Take note of the following:

Where the incident occurred, a description of the animal and the vaccination status of the domesticated animal should be found out. If the animal can be safely captured to be tested for rabies, then if it survives for 8 days it would not be rabid. Another option is for health professionals to conduct tests on the animal's brain tissue to determine whether it has rabies. Testing can be done quickly, but only after the animal is dead.

If you have the signs and symptoms of rabies, a number of tests using blood, saliva, spinal fluid, brain tissue or skin tissue taken from the nape of your neck may be required to identify or rule out rabies infection.

Prevention

Ways to help prevent exposure to rabies include: Keep your pets and other domesticated animals up-to-date with regular animal rabies shots. Avoid contact with wild or unfamiliar animals, whether they're alive or dead. Seal or close any openings where animals might find entry into your home. Report stray animals or any that act strangely or sick to your local animal control authorities. Teach your children to never handle unfamiliar animals. If your work or activities might bring you into contact with the rabies virus or a potentially rabid mammal, consider getting a preventive vaccination. This vaccination — called pre-exposure prophylaxis — involves three injections over three or four weeks. A booster shot can maintain the vaccination's effectiveness

TREATMENT

If bitten by an animal with rabies, thoroughly wash the wound or area of exposure with soap and water. Quick action is important. Once the earliest signs and symptoms appear, death almost always follows. Promptly contacting the doctor after a potential rabies exposure greatly increases chance of survival.

The treatment — called **post-exposure prophylaxis** — consists of one dose of rabies immunoglobulin and five doses of rabies vaccine over a 28-day period. Rabies immunoglobulin and the first dose of rabies vaccine are administered as soon as possible after the patient has been exposed. The immunoglobulin is given by injection around the site of bite and into the upper arm muscle.

Immunoglobulins are disease-fighting proteins that provide you with temporary antibodies. The rabies vaccine helps the body to start producing its own antibodies. Antibody production takes time, but the antibodies produced by the body provide longer lasting protection than do the ones contained in rabies immune globulin.

Although the vaccine isn't painful, there might be mild physical reactions. Watch for reactions such as swelling or redness where the injection was given. Headache, fever, nausea, muscle aches and dizziness are other possible side effects. Contact your doctor if side effects produce discomfort.

RABIES VACCINE

A good but expensive ***killed virus vaccine*** **(Human Diploid Cell Vaccine, HDCV)** grown in human fibroblasts is available for safe use in man. The unusually long incubation period of the virus permits the effective use of active immunization with vaccine post-exposure. When used, vaccine has dramatically cut the rabies death rate. *(Older killed virus vaccines, made from infected neural tissues, were poorly immunogenic and had allergic encephalitic side effects, but are still used in developing countries.)*

Prophylaxis

High-risk persons, e.g. veterinarians, may be immunized before exposure, and then merely require one or two booster doses if they should be exposed to rabies.

Animal Vaccines

A range of **live** and **killed virus vaccines** are available for domestic animals (farm animals, cats and dogs).

Epidemic Typhus

Several rickettsia species cause the disease known as epidemic typhus in humans. The disease is spread by ticks, mites, fleas, or lice, each agent having a distinct epidemiology, but all causing a disease with signs similar to a bad cold with fever lasting form one to several weeks, chills, headache, and muscle pains, as well as a body rash. There is often a large painful sore at the site of the bite and nearby lymph nodes are swollen and painful.

The four main types of typhus are:

- epidemic typhus
- Brill-Zinsser disease
- endemic or murine typhus
- scrub typhus

EPIDEMIC TYPHUS (European, Classic, Louse-borne)

Epidemic typhus is prevalent worldwide. It is an acute disease passed from human to human by the body louse. Endemic epidemic typhus exists in highland populations in Africa and South America but tourists are at minimal risk of acquiring lice and disease. Since World War II, large outbreaks of typhus have occurred mainly in Africa, with reported cases coming predominantly from three countries: Burundi, Ethiopia and Rwanda.

Epidemic typhus is caused by *Rickettsia prowazekii*, which is carried by the body louse, *Pediculus humanus corporis*. When the lice feed on a human, they may simultaneously defecate. When the person scratches the bite, the faeces, which carry the bacteria, are scratched into the wound. Body lice are common in areas in which people live in overcrowded, dirty conditions, with few opportunities to wash themselves or their clothing. Because of this fact, this form of typhus occurs simultaneously in large numbers of individuals living within the same community.

Epidemic typhus causes **fever**, **headache**, weakness, and muscle aches. It also causes a rash composed of both spots and bumps. The rash starts on the back, chest, and abdomen, then spreads to the arms and legs. The worst types of complications involve swelling in the heart muscle or brain (**encephalitis**). Without treatment, this type of typhus can be fatal. The disease is characterized by high fever, intractable headache, and rash. Temperature reaches 104° F in several days and remains high. Headache is generalized and intense. A macular eruption (dark spot on the skin) appears on the fifth to sixth day, initially on the upper trunk, which then spreads to the entire body excepting, usually, the face, palms and soles of the feet. The case-fatality rate is between 1% and 20%. Prostration is due to low blood pressure, may be followed by vascular collapse. Fatalities are rare in children; mortality increases with age.

Brill-Zinsser disease is a reactivation of an earlier infection with epidemic typhus. It affects people years after they have completely recovered from epidemic typhus due to weakening of their immune system. The bacteria can then gain hold again, causing illness, which tends to be extremely mild. Brill-Zinsser disease is quite mild, resulting in about a week-long fever, and a light rash similar to that of the original illness.

TICK TYPHUS (Spotted fever)

Tick typhus, actually a form of spotted fever, is not uncommon in travellers who spend time trekking or on safari in Africa or the Indian subcontinent. Trekkers in southern Africa may be at risk from cattle or wild-animal ticks.

Seek local advice on areas where ticks pose a danger and always check your skin carefully for ticks after walking in a danger area such as a tropical forest. A strong insect repellent can help, and serious walkers in tick areas should consider having their boots and trousers impregnated with benzyl benzoate and dibutylphthalate.

SCRUB TYPHUS (Mite-borne typhus)

Scrub typhus is spread by mites that feed on infected rodents and exists mainly on Pacific islands and in southeast and east Asia. Incidence is highest during the spring and summer when the activity of humans brings them in contact with mites seeking animal hosts.

Scrub typhus is caused by *Rickettsia tsutsugamushi*. This bacterium is carried by mites or chiggers. As the mites feed on humans, they deposit the bacteria. Scrub typhus occurs commonly in the southwest Pacific, Southeast Asia, and Japan. It is a very common cause of illness in people living in or visiting these areas. It occurs more commonly during the wet season.

Scrub typhus causes a wide variety of effects. The main symptoms include fever, headache, muscle aches and pains, **cough**, abdominal **pain**, **nausea and vomiting**, and **diarrhea**. Some patients experience only these symptoms. Some patients develop a rash, which can be flat or bumpy. The individual spots eventually develop crusty black scabs. Other patients go on to develop a more serious disease, in which encephalitis, **pneumonia**, and swelling of the liver and spleen (hepatosplenomegaly) occur. Onset is sudden with fever, chills, headache, and generalized swelling of lymph nodes. At onset of fever, a red lesion develops at the site of the bite. High fever to 104 °F develops during the first week as well as a severe headache. A cough is present during the first week of fever and pneumonia may develop. A rash also develops on the torso often extending to the arms and legs.

MURINE TYPHUS (Rat / flea typhus)

Murine typhus is relatively common throughout the world and is transmitted by fleas. It is clinically similar to epidemic typhus, but milder. Highest incidence of cases occurs during the summer months when rats and their fleas are most active and abundant.

Also called endemic typhus, it is carried by fleas. When a flea lands on a human, it may defecate as it feeds. When the person scratches the itchy spot where the flea was feeding, the bacteria-laden faeces are scratched into the skin, thus causing infection. The causative bacterium is called *Rickettsia typhi*. Endemic typhus occurs most commonly in warm, coastal regions. In the United States, southern Texas and southern California have the largest number of cases.

Symptoms of the disease include chills, headache and fever, lasting about 12 days. Rash and other manifestations are similar to epidemic typhus.

DIAGNOSIS

A number of tests exist that can determine the reactions of a patient's antibodies (immune cells in the blood) to the presence of certain viral and bacterial markers. When the antibodies react in a particular way, it suggests the presence of a rickettsial infection. Many tests require a fair amount of time for processing, so the practitioners will frequently begin treatment without completing tests, simply on the basis of a patient's symptoms.

PREVENTION,

Prompt removal of attached ticks and use of repellents to prevent tick attachment provide the best preventions against tick typhus. Laundering of louse-infested clothing is the most effective means to avoid person-to-person spread of lice and prevent epidemic typhus. Precautions taken when walking in rural areas and the use of insect repellents will help prevent tick and mite-borne typhus. Prevention for each of these forms of typhus includes avoidance of the insects that carry the causative bacteria. Other preventive measures include good hygiene and the use of insect repellents.

VACCINATION

Vaccination against typhus is not required by any country as a condition for entry. Treatment of all forms of typhus is similar. Production of typhus vaccine in the United States has been discontinued and there are no plans for commercial production of a new vaccine.

TREATMENT

The antibiotics tetracycline or chloramphenicol is used for treatment of each of the forms of typhus. Chloramphenicol, doxycycline or other forms of tetracycline result in rapid resolution of fever and relapses are infrequent. A single dose of 200 mg of doxycycline (two tablets), irrespective of the patient's age can be given.

Cleanliness is important in preventing body louse infestations. The easiest control method for occasional infestations is to expose infested clothing to a minimum temperature of 70^{o} C for at least one hour. In general, chemical control is required, which involves dusting technique to apply insecticides and treating clothing. Suitable insecticidal dusts for body louse control are permethrin (0.5%), temephos (2%), propoxur (1%) and carbaryl (5%). One thorough treatment of infested clothing with insecticide should be sufficient. Dusting is not recommended for people with dermatological problems or exposed wounds. Where infestation is known to be widespread, systematic application of insecticide to all persons in the community is recommended.

TUBERCULOSIS

Tuberculosis (TB) is an infectious disease caused by the bacterium, *Mycobacterium tuberculosi*. TB most commonly affects the lungs but can involve almost any organ of the body. There is also a group of organisms referred to as atypical tuberculosis. These involve other types of bacteria of *Mycobacterium* family. At times, these bacteria can cause an infection that sometimes appears as typical tuberculosis. These "atypical" mycobacteria are: *M. kansasii* that may produce similar clinical and pathologic symptoms of disease. *M. avium-intracellulare* (MAI) seen in persons with AIDS and is not primarily a pulmonary pathogen but occurs mostly in organs of the mononuclear phagocyte system.

Tuberculosis outside the lungs can appear in the following kinds:

Skeletal Tuberculosis: Tuberculous osteomyelitis, known as **Pott's disease,** involves mainly the thoracic and lumbar vertebrae followed by knee and hip. There is extensive necrosis and bony destruction with compressed fractures with kyphosis and extension to soft tissues.

Genital Tract Tuberculosis: *Tuberculous salpingitis* and *endometritis* result from infection of the fallopian tube that leads to *granulomatous salpingitis*, which can drain into the endometrial cavity and cause a *granulomatous endometritis* with irregular menstrual bleeding and infertility. In the male, tuberculosis involves prostate and epididymis leading to infertility.

Urinary Tract Tuberculosis: WBC's appear in urine but a negative routine bacterial culture may suggest the diagnosis of renal tuberculosis. Progressive destruction of renal parenchyma occurs if not treated. Drainage to the ureters can lead to inflammation and ureteral stricture.

CNS Tuberculosis: A meningeal spread can occur and the cerebrospinal fluid typically shows a high protein, low glucose, and lymphocytosis. The base of the brain is often involved, so that various cranial nerves may be affected. Rarely, a solitary granuloma, or "tuberculoma", may form and manifest with seizures.

Gastrointestinal Tuberculosis: This is uncommon today because routine pasteurization of milk has eliminated *Mycobacterium bovis* infections. However, *M. tuberculosi* coughed up in sputum may be swallowed through contamination. The classic lesions are circumferential ulcerations with stricture of the small intestine, with ileo-caecal involvement.

Adrenal Tuberculosis: Spread of tuberculosis to adrenals is usually bilateral, so that both adrenals are markedly enlarged. Destruction of cortex leads to Addison's disease.

Scrofula: *Tuberculous lymphadenitis* of the cervical nodes is caused by *Mycobacterium scrofulaceum* and may produce a mass of firm, matted nodes just under the mandible.

There can be chronic draining fistulous tracts to overlying skin. This complication may appear in children.

Cardiac Tuberculosis: The pericardium is the usual site for tubercular infection of heart. The result is a *granulomatous pericarditis* that can be hemorrhagic. There can be fibrosis with calcification, leading to a constrictive pericarditis.

HISTORY

Robert Koch isolated the tubercular bacillus in 1882 and established TB as an infectious disease. In the 19th century, due to the absence of antibiotics, patients were isolated in sanatoria and given treatment. Attempts were made to remove the infectious tissue by surgery called thoracoplasty. Till the first half of 20th century, no effective treatment was available. **Streptomycin**, the first antibiotic to fight TB, was introduced in 1946, and **isoniazid** (Laniazid, Nydrazid) became available in 1952.

M. tuberculosis is a rod-shaped, slow-growing bacterium. Its cell wall has high acidic content, which makes it hydrophobic, resistant to oral fluids. The cell wall absorbs a certain dye and maintains a red color, hence the name acid-fast bacilli.

MODE OF INFECTION

A person can become infected with tuberculosis bacteria through inhalation of droplets containing bacillus from the air. The bacteria get into the air when someone with tuberculosis lung infection coughs, sneezes or spits. TB is not transmitted by just touching the clothes or shaking the hands of someone who is infected. Tuberculosis is spread primarily from person to person by breathing infected air especially in closed rooms. TB caused by *Mycobacterium bovis*, however, is transmitted by drinking unpasteurized milk. Earlier this bacterium was a major cause of TB in children, but rarely causes TB now since most milk is pasteurized.

PATHOLOGY

When the inhaled tuberculosis bacteria enter the lungs, they can multiply and cause pneumonia. The local lymph nodes associated with the lungs may also become involved with the infection and usually become enlarged. The infection can also spread to other parts of the body. The body's immune system in healthy people can fight the infection and stop the bacteria from spreading. If the body is able to form scar tissue (fibrosis) around the TB bacteria, then the infection is contained in an inactive state. Such an individual typically has no symptoms and cannot spread TB to other people. The scar tissue and lymph nodes may eventually harden due to the process of calcification of the scars. However, if the body's immune system is weakened, the TB bacteria can break through the scar tissue. The breakthrough of bacteria can result in recurrence of the pneumonia and a spread of TB to other parts of the body. It may take many months from the time the infection initially gets into the lungs until symptoms develop. The usual symptoms that occur with an active TB infection are a generalized tiredness or weakness, weight loss, fever, and night sweats. If the infection in the lung worsens, then further symptoms can include coughing, chest pain, coughing up of sputum or blood, and shortness of breath. If the infection spreads beyond the lungs, the symptoms will depend upon the organs involved.

DIAGNOSIS

TB can be diagnosed in several different ways, including chest X-rays, analysis of sputum, and skin tests. The chest x-rays can reveal evidence of active tuberculosis pneumonia or scarring (fibrosis) or hardening (calcification) in the lungs. Examination of the sputum on a slide (smear) under the microscope can show the presence of the tuberculosis bacteria. A sample of the sputum can also be cultured in special incubators so that the tuberculosis bacteria can subsequently be identified.

Several types of skin tests are used to screen for TB, e.g. tuberculin skin tests that include the **Mantoux test**, the **Tine test,** and the **PPD** (Purified Protein Derivative) test. In each of these tests, a small amount of purified extract from dead tuberculosis bacteria is injected under the skin. If a person is not infected with TB, then no reaction will occur at the site of the injection. If a person is infected with tuberculosis, however, a raised and reddened area will appear around the site of the test injection within 48 to 72 hours after the injection.

If the infection with tuberculosis has occurred recently, the skin test may be negative, because usually it takes 2 to 10 weeks after infection for the skin to test positive. The skin test can also be falsely negative if a person's immune system is weakened due to another illness such as AIDS or cancer or he is on medication that can suppress the immune response such as cortisone or anti-cancer drugs.

TREATMENT

Treatment with antibiotics is recommended to treat as well as to prevent the TB from turning into an active infection in those where it is dormant. The antibiotic used for this purpose is called **isoniazid** (INH). If taken for 6 to 12 months, it will prevent the TB from becoming active in the future. In fact, if a person with a positive skin test does not take INH, there is a 5 to 10% lifelong risk that the TB will become active. Taking **isoniazid** is not advisable (contraindicated) during pregnancy or for those suffering from alcoholism or liver disease. Also, isoniazid can have side effects such as rashes, tiredness or irritableness. Liver damage from isoniazid is rare and typically reverses once the drug is stopped. Very rarely, however, in older people, the liver damage (INH hepatitis) can even be fatal. It is important therefore, for the doctor to monitor a patient's liver by periodically carrying out liver function tests during the course of INH therapy.

Active TB is treated with a combination of medications with **isoniazid**, **Rifampicin** (**Rifadin**), **ethambutol** (Myambutol) and **pyrazinamide**. Drugs are often taken for the first two months of therapy to help kill any potentially resistant strains of bacteria. Then the number is usually reduced to two drugs for the remainder of the treatment based on drug sensitivity testing. **Streptomycin**, a drug that is given by injection, may be used as well, particularly when the disease is extensive. Treatment usually lasts for many months and sometimes for years. Successful treatment of TB is dependent largely on the compliance of the patient.

Drug-resistant TB has become a very serious problem in recent years in certain populations. For example, INH-resistant TB is seen among patients in Southeast Asia. Even more serious problem is the multi-drug resistant TB that has been seen in prison populations. Poor compliance by the inmates is thought to be the main reason for the development of multi-drug resistance.

Surgery on the lungs may be indicated to help cure TB when medication has failed, but in most cases is not required. Treatment with appropriate antibiotics will usually cure the disease. Without treatment, however, tuberculosis can be lethal and hence early diagnosis is important.

SUMMARY

Tuberculosis (TB) is an infection primarily of lungs (a pneumonia), caused by bacteria called *Mycobacterium tuberculosis*. It is spread usually from person to person by breathing infected air during close contacts.

TB can remain in an inactive (dormant) state for years without causing symptoms or spreading to other people.

When the immune system of a patient with dormant TB is weakened, the TB can become active and cause infections in the lungs or other parts of the body.

The risk factors for acquiring TB include close-contact situations, alcohol and IV drug abuse, and certain diseases (e.g., diabetes, cancer, and HIV) and occupations (e.g., health care workers).

The most common symptoms of TB are fatigue, fever, weight loss, coughing, and night sweats.

The diagnosis of TB involves skin tests, chest x-rays, sputum analysis (smear and culture), and PCR tests to detect the genetic material of the causative bacteria.

Inactive tuberculosis may be treated with an antibiotic, isoniazid (INH), to prevent the TB infection from becoming active.

Active TB is treated, usually successfully, with INH in combination with one or more of several drugs, including **rifampicin, ethambutol, pyrazinamide**, and streptomycin.

Drug-resistant TB is a serious, as yet unsolved, public health problem, especially in Southeast Asia and in prison populations.

The occurrence of HIV has been responsible for an increased frequency of tuberculosis. Control of HIV in the future, however, should substantially decrease the frequency of TB.

AMOEBIASIS

Amoebiasis is an infection caused by the protozoan, *Entamoeba histolytica*, which is usually contracted by drinking water or eating food contaminated with amoebic cysts. Most of the infected people are asymptomatic but the disease has the potential to be chronic and it is estimated by WHO that about 70,000 people die annually worldwide.

Symptoms that appear within 2-4 weeks of infection, can sometimes last for years, which can range from mild diarrhoea to dysentery with blood and mucus. The blood comes from the damaged lining of the intestine. In about 10% of invasive cases the amoebae enter the bloodstream and may travel to other organs in the body, such as liver where blood from the intestine reaches first but they can end up almost anywhere.

In asymptomatic infections the amoeba lives by eating and digesting bacteria and food particles in the gut because it does not come in contact with the intestine due to the protective mucus layer lining the gut. Disease occurs when amoeba comes in contact with the intestinal lining, when it secretes enzymes that destroy cell membranes and proteins resulting in flask-shaped ulcers in the intestine. *Entamoeba histolytica* ingests the destroyed cells by phagocytosis and is often seen with red blood cells inside. A granulomatous mass known as an amoeboma may form in the wall of the colon due to persistant cellular response, which may be confused with cancer.

Symptom of Amoebiasis

Gastroenteritis, diarrhea or dysentery with abdominal pain and exhaustion is the main symptom of amoebiasis. Poor appetite or fear of food due to abdominal bloating and cramps and loose stools can occur. Later, with increased intensity of infection, fever, nausea and bloody stools with slimy mucous occurs and complicates the condition. In due course, the patient loses weight and stamina. Sometimes allergic reactions can occur throughout the body due to the release of toxic substances or dead parasites inside the intestines. Dehydration and gas formation and foul-smelling stools commonly occurs and diarrhea comes and goes. Mucus and blood appears in the stool.

Diagnosis

Asymptomatic human infections are usually diagnosed by finding cysts shed with the stool. Various flotation or sedimentation procedures have been developed to recover the cysts from fecal matter and stains help to visualize the isolated cysts for microscopic examination. Since cysts are not shed constantly, a minimum of 3 stools should be examined. In symptomatic infections, the motile form (the trophozoite) can often be seen in

fresh feces. Serological tests exist and most individuals (whether with symptoms or not) will test positive for the presence of antibodies. The levels of antibody are much higher in individuals with liver abscesses. Serology only becomes positive about two weeks after infection. More recent developments include a kit that detects the presence of ameba proteins in the feces and another that detects ameba DNA in feces. These tests are not in widespread use due to their expense.

Colon biopsy is still by far the most widespread method of diagnosis of amoebic dysenteri around the world. However it is not as sensitive or accurate in diagnosis as the other tests available. It is important to distinguish the *E. histolytica* cyst from the cysts of nonpathogenic intestinal protozoa such as *Entamoeba coli* by its appearance. *E. histolytica* cysts have a maximum of four nuclei, while the commensal *Entamoeba coli* has up to 8 nuclei. Additionally, in *E. histolytica*, the endosome is centrally located in the nucleus, while it is off-center in *Entamoeba coli*. Finally, chromatoidal bodies in *E. histolytica* are rounded, while they are jagged in *Entamoeba coli*. However, other species, *Entamoeba dispar* and *E. moshkovskii*, are also a commensal and cannot be distinguished from *E. histolytica* under the microscope. As *E. dispar* is much more common than *E. histolytica* in most parts of the world this means that there is a lot of incorrect diagnosis of *E. histolytica* infection taking place. The WHO recommends that infections diagnosed by microscopy alone should not be treated if they are asymptomatic and there is no other reason to suspect that the infection is actually *E. histolytica*.

Prevention

To help prevent the spread of amoebiasis around the home:

Wash hands thoroughly with soap and hot running water for at least 10 seconds after using the toilet or changing a baby's diaper, and before handling food

Clean bathrooms and toilets often. Pay particular attention to toilet seats and taps.

Avoid sharing towels or face washers.

Avoid raw vegetables when in endemic areas as they may have been fertilized using human feces.

Boil water or treat with iodine tablets.

Treatment

E. histolytica infections occur in both the intestine and (in people with symptoms) in tissue of the intestine and/or liver. As a result two different sorts of drugs are needed to rid the body of the infection, one for each location. **Metronidazole**, or related drugs such a **tinidazole** or **ornidazole** are used to destroy amebae that have invaded tissue. It is rapidly absorbed into the bloodstream and transported to the site of infection. Because it is rapidly absorbed there is almost none remaining in the intestine. Since most of the amoebae remain in the intestine when tissue invasion occurs, it is important to get rid of those also or the patient will be at risk of developing another case of invasive disease. Several drugs are available for treating intestinal infections, the most effective of which has been shown to be **Paromomycin** (also known as Humatin); **Diloxanide furoate** is used in the US. Both types of drug must be used to treat infections, with metronidazole usually being given first, followed by paromomycin or diloxanide. *E. dispar* does not require treatment, but many laboratories (even in the developed world) do not have the facilities to distinguish this from *E. histolytica*.

For amoebic dysentery a multi-prong approach must be used, starting with one of :

Metronidazole, 500-750 mg, three times a day for 5-10 days.

Tinidazole, 2g once a day for 3 days is an alternative to metronidazole.

Ornidazole, 500 mg, twice a day for 5 days.

In addition to the above, one of the following luminal amebicides should be prescribed as an adjunctive treatment, either concurrently or sequentially, to destroy *E. histolytica* in the colon:

Paromomycin, 500mg three times a day for 10 days.

Diloxanide Furoate, 500mg three times a day for 10 days.

Iodoquinol, 650mg three times a day for 20 days.

For amoebic liver abscesses the following drugs are prescribed:

Metronidazole, 400mg three times a day for 10 days.

Tinidazole, 2g once a day for 6 days is an alternative to metronidazole.

Diloxanide furoate, 500mg three times a day for 10 days must always be given afterwards.

Doses for children are calculated on the basis of body weight and a pharmacist should be consulted for help.

Yellow Fever

Yellow fever is a tropical disease that is spread to humans by infected mosquitoes and is caused by the yellow fever virus. The disease is found in urban and rural areas of tropical zone countries in Africa and South America. Yellow fever has not been reported in Asia.

Yellow fever is a viral disease of short duration and varying severity that is transmitted primarily by mosquitoes. The infection is so named because of the yellow skin colour (jaundice) observed in people with serious illness. Symptoms of infection can be mild but often increase in severity with the sudden onset of fever, muscle pain, nausea, vomiting, headache and prostration. The disease may progress to visible haemorrhage, jaundice, kidney and liver failure. The death rate in unvaccinated people may be as high as 50 per cent.

Yellow fever virus belongs to the Flaviviridae family, other members of which cause dengue fever. The virus is introduced into the bloodstream via the saliva of the mosquito as it bites. The virus can then be transported around the body and reproduce itself in a variety of the body's cells, usually the liver, kidneys and blood vessels. In serious cases, these cells may become damaged themselves. In addition, the cells of the immune system are affected and release large quantities of signalling substances. These substances are the cause of the normal disease symptoms, such as muscular pain and fever.

Jungle yellow fever is mainly a disease of monkeys. It is spread from infected mosquitoes to monkeys in the tropical rain forest. People get jungle yellow fever when they put themselves in the middle of this natural cycle and are bitten by mosquitoes that have been infected by monkeys. Jungle yellow fever is rare and occurs mainly in persons who work in tropical rain forests.

Urban yellow fever is a disease of humans. It is spread by mosquitoes that have been infected by other people. *Aedes aegypti* is the type of mosquito that usually carries yellow fever from human to human. These mosquitoes have adapted to living among humans in cities, towns, and villages. They breed in discarded tyres, flower pots, oil drums, and water storage containers close to human dwellings. Urban yellow fever is the cause of most yellow fever outbreaks and epidemics. People get yellow fever from the bite of an infected female mosquito. The mosquito injects the yellow fever virus into the bite.

Yellow fever is common in West and Central Africa and in parts of South America. Periodic epidemics in Africa lead to hundreds of thousands of cases. In total, yellow fever occurs in 33 countries and 468 million people are at risk of catching the disease.

SYMPTOMS

Many yellow fever infections are mild, but the disease can cause severe, life-threatening illness. Symptoms of severe infection are high fever, chills, headache, muscle aches, vomiting, and backache. After a brief recovery period, the infection can lead to shock, bleeding, and kidney and liver failure. Liver failure causes jaundice which is revealed by the yellowing of skin and the whites of the eyes, which gives yellow fever its name. Symptoms start 3 to 6 days after being bitten by an infected mosquito. Severe yellow fever infections can be fatal.

DIAGNOSIS

Yellow fever is diagnosed by a blood test in the laboratory, where specific yellow fever virus antibodies are detected in the blood.

PREVENTION

Yellow fever can be prevented by vaccination. Travellers should also take precautions against mosquito bites when in areas with yellow fever transmission. If necessary, get vaccinated for yellow fever before travel.

- Travellers should get vaccinated for yellow fever before visiting areas where yellow fever is found.
- International regulations require proof of yellow fever vaccination for travel to and from certain countries. People who get vaccinated should be given an International Certificate of Vaccination.
- Avoid mosquito bites when travelling in tropical areas. Mosquitoes that spread yellow fever usually bite during the day. Travellers should take steps to reduce contact with mosquitoes when outdoors and inside.

- Wear long-sleeved clothing and long pants. For extra protection, treat clothing with the insecticide permethrin or any other suitable insecticide.
- Use insect repellent on exposed skin. The most effective repellents contain 20% to 35% DEET (N, N-diethylmethyltoluamide).
- Spray living and sleeping areas with insecticide.
- Use a mosquito net when sleeping in a room that is not screened or air conditioned. For extra protection, treat the bed net with the insecticide permethrin.

TREATMENT

There is no specific treatment for yellow fever. Persons with yellow fever should rest and drink plenty of fluids. There are no medicines that are effective against this virus.

Serious cases of yellow fever always need hospital treatment. As there are no medicines that combat the virus itself and the doctor can only treat the symptoms. If there is lack of fluid in the body leading to disturbances in the electrolyte balance, this can be remedied by administration of fluids by intravenous drip. In mild cases, the pain may be relieved with simple painkillers. High temperatures can be treated by cooling the patient and giving appropriate medicines to lower the temperature.

VACCINATION REQUIREMENT

Many countries, particularly those in Asia, will refuse permission to enter to any person who has recently been in a yellow fever infected country and who does not possess a valid yellow fever vaccination certificate. Some countries will only allow unvaccinated persons to enter if they agree to be vaccinated at their border. In this situation, you may not be able to ensure the sterility of the items used to administer the vaccine.

To obtain a valid international yellow fever vaccination certificate you must be given a yellow fever vaccine that has been approved by the WHO from a vaccination provider who has been approved by a national health authority. The certificate must be in a form that has been approved by the WHO and be completed according to WHO requirements. The disease is covered by the International Quarantine Regulations, which are taken very seriously by authorities everywhere. Vaccination provides protection for 10 years.

If a traveller is unvaccinated and contracts yellow fever the consequences can be serious and may result in death.

KALA-AZAR

Leishmaniasis is a disease caused by the flagellate protozoan that belongs to the genus ***Leishmania*** and is transmitted by the bite of sand flies of the genus *Lutzomyia* in the New World and *Phlebotomus* in the Old World. The disease was named in 1901 after the Scottish pathologist William Boog Leishman. This disease is also known as Leishmaniasis, Orient Boils, Baghdad Boil, kala azar, black fever, sand fly disease, Dum-Dum fever or espundia. Human infection is caused by about 21 species of *Leishmania* that include *L. donovani*-complex with three species *(L. donovani, L. infantum, and L. chagasi);* the *L. mexicana*-complex with 3 main species *(L. mexicana, L. amazonensis,* and *L. venezuelensis); L. tropica; L. major; L. aethiopica* and the subgenus *Viannia* with four main species *(L. (V.) braziliensis, L. (V.) guyanensis, L. (V.) panamensis, and L. (V.) peruviana)*. The different species are morphologically indistinguishable, but they can be differentiated by isoenzyme analysis, DNA sequence analysis, or by monoclonal antibodies.

Leishmaniasis is commonly found in Mexico, Central America, and South America—from northern Argentina to southern Texas (not in Uruguay, Chile, or Canada), southern Europe, Asia (not Southeast Asia), the Middle East, and Africa (particularly East and North Africa). The disease is not found in Australia or Oceania.

There are four main forms of leishmaniasis:

Visceral leishmaniasis – the most serious form and potentially fatal if untreated.

Cutaneous leishmaniasis – the most common form which causes a sore at the bite site, which heal in a few months to a year, leaving an unpleasant looking scar. This form can progress to any of the other three forms.

Diffused cutaneous leishmaniasis – this form produces widespread skin lesions which resemble leprosy and is particularly difficult to treat.

Mucocutaneous leishmaniasis – commences with skin ulcers which spread causing tissue damage to nose and mouth

LIFE CYCLE

Leishmaniasis is transmitted by the bite of female phlebotomine sand flies. The sand flies inject into human blood the infective stage, metacyclic promastigotes, during blood meals. Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophages but are not digested and transform into amastigote form. Amastigotes multiply in infected cells and affect different tissues, depending upon the part on which *Leishmania* species is involved. These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sand flies become infected when blood meals are sucked from the infected host when they ingest macrophages infected with amastigote forms. In the sandfly's midgut, the parasites change into promastigote forms, which multiply, differentiate into metacyclic promastigotes and migrate to the proboscis from where they can be easily transferred into human blood while sand fly feeds.

SYMPTOMS

A nodule appears in the area of the sand fly bite or rash or ulceration may be formed. Four to six months after the bite, the following symptoms appear: Fevers twice a day with chills and sweats, cough, weakness, diarrhoea, weight loss, gums and nose may bleed and skin or eyes may turn yellow.

DIAGNOSIS

The spleen becomes extremely enlarged and hard. Liver becomes enlarged. The skin turns darker in colour and warty eruptions appear on skin or ulcers may occur. Rashes of small, red colour appear or raised lesions are found.

LABORATORY TESTS

Leishmania donovani infection is identified on the following tests:

- Buffy coat preparation of the blood is a special technique of preparing blood film on slides, bone marrow, liver, lymph nodes, or the spleen for identification of the causative organism. The organism may also be cultured and then identified.
- **IgM** (an antibody reaction to the organism) agglutination testing is positive in infected persons.
- White blood cell count is usually low in patients.
- The total protein in the blood becomes elevated (10g/dL or more), while albumin level is low (3g/dL).

TREATMENT

The most common treatment for visceral leishmaniasis was developed in1930s, using derivatives of antimony. **Sodium stibogluconate** (SSG) is taken as an intramuscular injection over 30 or more days. It is available under the brand name **Pentostam**. Another antimonial drug is **Meglumine antimoniate** available under the brand name **Glucantime**. It is not completely understood how these drugs act against the parasite. They may be disrupting its energy production or trypanothione metabolism. Unfortunately, in many parts of the world, the parasite for visceral or muco-cutaneous leishmaniasis has become resistant to antimony drugs but the level of resistance varies according to species.

Amphotericin is now the treatment of choice. **AmBisome** is an amphotericin B liposome formulation that is given as an intravenous infusion. AmBisome was registered for VL in the USA and Europe in the 1990s and has shown remarkable efficacy even after a single dose in India.

Miltefosine (Impavido) is a new drug for visceral and cutaneous leishmaniasis. Oral **miltefosine** was registered in India in 2002 and is now in Phase IV trials.

Currently, two drugs are under development, a drug to treat Chagas disease in Latin America and a drug, **Paromomycin** to cure visceral leishmaniasis in India. **Paromomycin** (aminosidine) is a low-cost intramuscular formulation that was registered in late 2006 in India and is currently in Phase III trials in East Africa.

FILARIASIS

Filariasis is an infectious tropical disease caused by three thread-like parasitic filarial worms, *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori,* all transmitted by mosquitoes. Lymphatic Filariasis, known as **Elephantiasis** puts at risk more than a billion people in more than 80 countries. Over 120 million are already affected by and over 40 million of them are seriously incapacitated and disfigured by the disease. One-third of the infected people live in India, one third in Africa and the rest are in South Asia, the Pacific and the Americas.

PATHOGENS

Pathogenic filarial parasites affect the lives of millions of people, especially those living in tropical countries. The filarial parasites that pose the most serious public health threats are *Wuchereria bancrofti, Brugia malayi, Brugia timori, Onchocerca volvulus*, and *Loa loa.* All of these cause cutaneous manifestations. One filarial nematode, *Mansonella streptocerca,* also causes cutaneous changes but is not a significant public health threat.

Human Filarial Parasites and Their Vectors

Disease	Parasite	Vector
Onchocerciasis	*O. volvulus*	Blackflies: *Simulium* species
Bancroftian filariasis	*W. bancrofti*	Mosquitoes: *Anopheles, Aedes, Culex,* and *Mansonia* species
Malayan filariasis	*B. malayi* and *B. timori*	Mosquitoes: *Anopheles, Aedes, Culex,* and *Mansonia* species
Loiasis	*Loa loa*	Red flies: *Chrysops* species
Mansonelliasis	*M. streptocerca*	Midges: *Culicoides* species
Dirofilariasis	*Dirofilaria* species	Mosquitoes: *Culex* species

LIFE CYCLE

The thread-like, parasitic filarial worms *Wuchereria bancrofti* and *Brugia malayi* that cause lymphatic filariasis live almost exclusively in humans. These worms are lodged in the lymphatic system, the network of nodes and vessels that maintain the delicate fluid balance between the tissues and blood and are an essential component for the body's immune system. They live for 4-6 years, producing millions of immature microfilariae (minute larvae) that circulate in the blood. The disease is transmitted by mosquitoes that bite infected humans and pick up the microfilariae that develop, inside the mosquito, into the infective stage in a process that usually takes 7-21 days. The larvae then migrate to the mosquitoes' mouth-parts, ready to enter the punctured skin following the mosquito bite and completing the cycle.

SYMPTOMS

Patients suffer from hydrocoel (fluid-filled balloon-like enlargement of scrotal sacs) and elephantiasis of the legs and penis. Elephantiasis of the entire leg, the entire arm, the vulva or the breast (swelling up to several times normal size) can take place.

Elephantiasis affects mainly the lower extremities and is caused when the parasites are lodged in the lymphatic systemand block lymph flow. *W. bancrofti* can affect the legs, arms, vulva, breasts, while *Brugia timori* rarely affects the genitals. Infection by *Onchocerca volvulus* and the migration of its microfilariae through the cornea of eye is a major cause of blindness.

DIAGNOSIS

Until very recently, diagnosing lymphatic filariasis had been extremely difficult, since parasites had to be detected microscopically in the blood, and in most parts of the world, the parasites have a "nocturnal periodicity" that restricts their appearance in the blood to only the hours around midnight. The diagnosis is made by identifying microfilariae on a stained blood film. Blood must be drawn at night, since the microfilariae circulate at night when their vector, the mosquito, is most likely to bite.

The new development of a very sensitive, very specific simple "card test" to detect circulating parasite antigens without the need for laboratory facilities and using only finger-prick blood droplets taken anytime of the day has completely transformed the approach to diagnosis.

TREATMENT

Vector control, use of mosquito nets, and improved living conditions are still vital for the control of these infections.

The drugs of choice for killing adult worms are **Albendazole** and **Ivermectin**.

Ivermectin (dihydroavermectin) is the drug of choice for the treatment of onchocerciasis. It is a macrocyclic lactone derived from the actinomycete, *Streptomyces avermitilis* found in soil. It functions as a single dose and is effective microfilaricide for *O. volvulus*. Unlike **diethylcarbamazine** (DEC), ivermectin does not produce reaction in onchocerciasis because it acts by paralyzing the microfilariae in the skin tissue spaces and lymphatics. They are then swept away into the local lymph nodes, which may swell up and only cause some local limb edema. On the other hand, DEC "unmasks" the microfilariae in the tissue spaces where they are attacked by the various protective cells which cause reaction in the skin.

The addition of oral **doxycycline** (100 mg/d) given for 6 weeks from the start of ivermectin to kill off *Wolbachia* organisms enhanced the effects of ivermectin.

Diethylcarbamazine or **DEC** (Hetrazan) is a microfilaricide with no effect on the adult worm. It produces Mazzotti reactions that become severe in heavily infected persons. A low dose of dexamethasone (3 mg/d) after onset of Mazzotti reaction controls the progression of reaction without interfering with the macrofilaricidal efficacy of DEC.

Suramin is a microfilaricide given intravenously, starting with a test dose of 100 mg of fresh 10% solution over 2 minutes. If no hypersensitivity develops, weekly dosages of 0.2 g, 0.4 g, 0.6 g, 0.8 g, and 1 g are given to adult patients. Rarely, patients experience eye lesions, dermatitis, kidney damage, a Mazzotti-like reaction and/or death. Thus, the use of suramin requires great caution and hence is generally not recommended.

Amocarzine is a new oral macrofilaricidal compound that has promising effects on onchocerciasis in Latin America.

Doramectin (Dectomax, Pfizer) is a new drug related to ivermectin. Its efficacy and safety in onchocerciasis are untested.

NODULECTOMY

A useful adjunct to chemotherapy popular in South America is removal of the palpable nodules. In Africa, nodulectomy has never been practiced widely because the nodules tend to be deeper and located near delicate joint spaces. Alternatively, **chloroquine** can be injected into young nodules that kill the worms.

Wolbachia organisms appear to play a critical role in the biology and metabolism of filarial worms. The use of tetracycline to kill *Wolbachia* appears to be lethal to the adult *O. ochengi* and recent evidences suggest that it is also effective against *O. volvulus* and perhaps other filarial worms.

SMALLPOX

Smallpox, which is believed to have originated over 3,000 years ago in India or Egypt, is one of the most devastating diseases known to mankind. Smallpox killed Queen Mary II of England, Emperor Joseph I of Austria, King Luis I of Spain, Tsar Peter II of Russia, Queen Ulrika Elenora of Sweden and King Louis XV of France.

The causative agent, ***Variola*** virus is a member of the genus ***Orthopoxvirus***, subfamily **Chordopoxvirinae** of family **Poxviridae**. Other members of the genus include cowpox, camelpox, and monkeypox, the last one has caused the most serious recent human poxvirus infections.

The *Variola* virus measures 260 by 150 nanometers and contains a molecule of double-stranded DNA, coding for some 200 different proteins. It is one of the largest viral genomes known and this large size of the genome makes it especially difficult to create a synthetic copy of the virus.

There are two forms of smallpox virus out of which ***Variola major*** causes the severe and most common form of smallpox, with a more extensive rash and higher fever. There are four strains of *Variola major*, namely, **ordinary type** that accounts for 90% or more of cases; **modified type** which is mild and occurs in previously vaccinated persons; **flat type** and **haemorrhagic type,** the last two of which are rare but very severe and fatal. Historically, *Variola major* has an overall fatality rate of about 30%. *Variola minor* causes a less common form of smallpox that is much less severe disease, with death rates of less than 1%.

The smallpox disease has now been eradicated after a successful worldwide vaccination program. The last case of smallpox in the United States was in 1949. The last naturally occurring case in the world was in Somalia in 1977.

TRANSMISSION

Smallpox can be spread through direct contact with infected body fluids or contaminated objects such as bedding or clothing. Exposure to the virus is followed by an incubation period during which people do not have any symptoms and may feel fine. This averages about 12 to 14 days but can range from 7 to 17 days. During this time, people are not contagious.

SYMPTOMS

The **first symptoms** of smallpox include fever, malaise, head and body aches and sometimes vomiting. The fever is usually high, in the range of 101 to 104 degrees Fahrenheit. At this time, people are usually too sick to carry on their normal activities. This is called the ***prodrome*** phase and may last for 2 to 4 days. **Rashes** emerge first as small **red spots** on the tongue and mouth. Later, red spots change into **sores** that break open and spread large amounts of virus into the mouth and throat. At this time, the person becomes most contagious. Then rashes appear on the skin, starting on the face and then spreading to the arms and legs and then to the hands and feet. Usually the rashes spread to all parts of the body within 24 hours. As the rashes appear, fever usually falls and the person may start to feel better. By the third day, the rashes become raised into **bumps**. By the fourth day, the bumps fill with a thick, opaque fluid and often have a button-like depression in the center. Fever often will rise again at this time and remain high until scabs form over the bumps. The bumps become **pustules** which are sharply raised, usually round and firm to the touch. The pustules begin to form a crust and then turn into **scabs**. By the end of the second week after the rashes appear, most of the sores are scabbed over. Then the scabs begin to fall off, leaving marks on the skin that eventually turns into pitted **scars**. Most scabs fall off by the fourth week after the rashes appear. The disease is contagious to others until all of the scabs have fallen off.

There is no animal reservoir of the disease and insects do not play any role in transmission.

In the past, smallpox was sometimes confused with chickenpox, a worldwide infection of children that is seldom lethal. Chickenpox can be distinguished from smallpox by its much more superficial lesions, their appearance more on the trunk than on face and extremities, and by the development of successive crops of lesions in the same area.

TREATMENT

The disease, for which no effective treatment is known, killed as many as 30% of infected persons. Between 65–80% of the survivors were left with deep pitted scars or pockmarks, most of which are prominent on the face.

Edward Jenner (1798) demonstrated that inoculation with cowpox could protect against smallpox, which brought the first hope that the disease could be controlled.

Through the success of global eradication campaign smallpox was finally restricted back to Africa and then to a single last natural case that occurred in Somalia in 1977. A fatal laboratory-acquired case occurred in the United Kingdom in 1978. The global eradication of smallpox was certified, based on intense verification activities in several countries by a commission of eminent scientists in December 1979 and subsequently endorsed by the World Health Assembly in 1980. The vaccination administered up to 4 days after exposure to the virus and before the rashes appear, provides protective immunity and prevents severity of the disease.

No effective treatment, other than the management of symptoms, is currently available. A number of compounds are under investigation as chemotherapic agents. One of these, **Cidofovir**, has produced promising results in laboratory studies.

Due to the success of an intense worldwide public health campaign, no naturally occurring case of this deadly disease has occurred since October 26, 1977, when an unvaccinated hospital cook in Somalia became the last person to have naturally contracted the smallpox virus.

The World Health Organization (WHO) officially declared smallpox eradicated in 1980.

VACCINES

In 1796, Edward Jenner tested his theory of disease protection by inoculating a young boy with material obtained from a milkmaid who was infected with the milder cowpox virus. The success of that experiment led to the development of a **vaccine** (name from *vacca*, the Latin word for cow) against smallpox.

Smallpox vaccine contains live ***Vaccinia*** virus of the orthopoxvirus family and closely related to *Variola* virus, the agent that causes smallpox. Immunity resulting from immunization with *Vaccinia* virus protects against smallpox. Vaccination usually prevents smallpox infection for at least ten years. Most existing vaccine stocks and the vaccine used in the WHO eradication campaign consist of pulp scraped from *Vaccinia*-infected animal skin, mainly calf or sheep, with phenol added to a concentration sufficient to kill bacteria but not so high as to inactivate the *Vaccinia* virus. The vaccine is then freeze dried and sealed in ampules for later re-suspension in sterile buffer and subsequent intradermal inoculation by multiple puncture with a bifurcated needle.

CURRENT LOCATIONS OF SMALLPOX VIRUS

Only two laboratories in the world are known to house smallpox virus, namely, the **Centers for Disease Control and Prevention (CDC)** in Atlanta, Georgia, and the **State Research Center of Virology and Biotechnology** in Koltsovo, Russia. The seed virus (*Vaccinia* virus strain Lister Elstree) used for producing vaccine is being held for WHO by the **WHO Collaborating Centre for Smallpox Vaccine** in Bilthoven, the Netherlands.

PLAGUE

Bubonic plague is mainly a disease of rats and rat fleas *(Xenopsylla cheopis)*. Infection in a human occurs when a person is bitten by an infected flea. The bacteria multiply inside the stomach of flea by forming a mucilaginous plug at the entry to gizzard that blocks its passage and causes the flea to starve. The ever-hungry flea then bites again and again to feed as it cannot satisfy its hunger. In 1894, two bacteriologists, **Alexandre Yersin** of France and **Shibasaburo Kitasato** of Japan working in Hong Kong isolated the bacterium responsible for plague. Though both investigators reported their findings, a series of confusing and contradictory statements by Kitasato eventually led to the acceptance of Yersin as the primary discoverer of the organism. Yersin named it *Pasteurella pestis* in honor of the Pasteur Institute, Paris, where he worked. In 1967 it was renamed as *Yersinia pestis* in honor of AlexandreYersin.

In 1898, the French scientist, **Paul-Louis Simond**, who was working in China to battle the epidemic, established that rat-flea was vector of the disease.

PATHOLOGY

An infected flea bites man and contaminates the wound with regurgitated blood that contains the plague bacteria. *Yersinia pestis* can reproduce inside cells, so even if phagocytised, they can still survive inside macrophage. Once inside body, bacteria enter lymphatic system. Plague bacteria secrete several toxins, one of which is known to cause dangerous beta-adrenergic blockade. *Y. pestis* spreads through the lymphatics of the infected person until it reaches a lymph node, where it stimulates severe hemorrhagic inflammation causing the lymph nodes to swell, the condition is called the characteristic **"bubo"** that is associated with the disease.

Lymphatics ultimately drain into the bloodstream, so the plague bacteria enter blood and travel to any part of body. In **septicemic plague**, there is rupture of blood capillaries of the skin and other organs which creates black patches on the skin. There are red bite-like bumps on the skin. Untreated, septicemic plague is universally fatal, but early treatment with antibiotics reduces the mortality rate to between 4 and 15 percent. People who die from this form of plague often die on the same day symptoms first appear.

The **pneumonic plague** infects the lungs and infection spreads from person-to-person transmitted through respiratory droplets released by coughing. The incubation period for pneumonic plague is usually between two and four days, but sometimes can be as little as a few hours. The initial symptoms, of headache, weakness, and coughing with hemoptysis are indistinguishable from other respiratory illnesses. Without diagnosis and treatment, the infection can be fatal in one to six days and mortality in untreated cases is 50–90%.

SYMPTOMS

Infected persons usually start with flu-like symptoms after an incubation period of 3-7 days. Patients typically experience the sudden onset of fever, chills, head and body-aches and weakness, vomiting and nausea. Clinical plague infection manifests itself in three forms depending on the route of infection: bubonic, septicaemic and pneumonic.

Bubonic plague is the most common form of plague resulting from the bite of an infective flea. Plague bacillus enters the skin from the site of the bite and travels through the lymphatic system to the nearest lymph

node. The lymph node then becomes inflamed because the plague bacteria replicate there in large numbers. The swollen lymph node is called a "**bubo**" which is very painful and can become suppurated as an open sore in advanced stage of infection. Symptoms of bubonic plague generally appear within two to eight days after the flea-bite. The bubo is usually 1 to 10 centimeters in diameter, in groin, armpit or neck, swollen, painful and warm to touch. It can cause so much pain that you can't move the affected part of body. More than one bubo can develop, but typically buboes affect only one area of your body.

Septicaemic plague occurs when infection spreads directly through the bloodstream without evidence of a "bubo". Septicaemic plague may result from flea bites and from direct contact with infective materials through cracks in the skin.

Pneumonic plague is the most severe and least common form of plague that occurs due to a secondary spread from the advanced infection of an initial bubonic form. Primary pneumonic plague results from inhalation of infective droplets released into the air by coughing patients and can be transmitted from human to human without involvement of fleas. Untreated pneumonic plague has a very high fatality ratio.

PREVENTION

People who live and work in areas with active plague infection should take these precautions:

- Eliminate food and shelter for rodents around homes, work places, and certain recreation areas, such as picnic sites or camp-grounds where people congregate. Remove brush, rock piles, junk, and food sources, including pet food.
- Health authorities should use appropriate and licensed insecticides to kill fleas during the plague outbreaks in wild animals.
- Treat pets such as cats and dogs for flea control regularly.
- Avoid sick or dead animals and report such animals to the health department. Hunters and trappers should wear rubber gloves when skinning animals.
- Use insect repellents when outdoors in areas where there is a risk of flea exposure.

Preventive treatment with **antibiotics** is recommended for:

- People who are bitten by fleas or who are exposed to tissues or fluids from a plague-infected animal.
- People living in a household with a bubonic plague patient, since they may also be exposed to infected fleas.
- People in close contact with a person or pet with suspected plague pneumonia.

People who travel to countries where plague occurs should take these additional precautions:

- Avoid exposure to fleas from diseased rats. The risk of being bitten by infected fleas is especially high after large numbers of plague-infected rats have died. Therefore, avoid places that are infested with rats.
- If travel to such areas is essential, apply insect repellents to legs and ankles. Also apply repellents and insecticides to clothes and outer bedding.
- Take preventive antibiotics if the risk of exposure is high.

TREATMENT

Vladimir Havkin, a doctor of Russian-Jewish origin who worked in India, was the first to invent and test a plague antibiotic. The traditional treatments are:

Streptomycin 30 mg/kg of body weight, twice daily for 7 days
Chloramphenicol 25–30 mg/kg of body weight, single dose, followed by 12.5–15 mg/kg of body weight, 4 times daily
Tetracycline 2 g single dose, followed by 500 mg, 4 times daily for 7–10 days. The drug is not suitable for children).
Gentamicin 2.5 mg/kg of body weight, twice daily for 7 days.
Doxycycline 100 mg (adults) or 2.2 mg/kg of body weight for children, orally twice daily have also been shown to be effective.

VACCINATION

Plague vaccines at one time were widely used but have not proven to be successful in preventing plague effectively. Vaccines are not recommended for protection in outbreak situations. Vaccination is only recommended as a prophylactic measure for high-risk groups such as laboratory personnel who are constantly exposed to the risk of contamination.

A formalin-inactivated vaccine is available for adults of high risk group but severe inflammatory reactions frequently appear. Primary intramuscular injection is given, followed by boosters at 3-5 months and another booster at 5-6 months. Then 3 more booster shots are given at 6 months interval, followed by doses at 1-2 year interval.

MALARIA

Malaria is one of the most common infectious diseases and an enormous public health problem. The disease is caused by a protozoan parasites of the genus *Plasmodium,* which is usually referred to as malaria parasites.

The term malaria originated from the medieval Italian term, *mala aria* meaning "bad air" and the disease was formerly called marsh fever due to its association with swamps.

In 1880, a French army doctor working at the military hospital in Algeria named **Charles Louis Alphonse Laveran** observed malarial parasites for the first time inside the red blood cells of people suffering from malaria. For this and later discoveries, he was awarded the 1907 Nobel Prize for Physiology or Medicine. The protozoan was named *Plasmodium* by the Italian scientists **Ettore Marchiafava** and **Angelo Celli**. A year later, **Carlos Finlay**, a Cuban doctor treating patients with yellow fever in Havana, first suggested that mosquitoes were transmitting disease to humans. However, it was **Sir Ronald Ross** working in India who finally proved in **1898** that malaria was transmitted by mosquitoes to birds. He isolated malarial parasites from the salivary glands of mosquitoes that had fed on infected birds. For this work Ross received the **1902** Nobel Prize in Medicine. The findings of Finlay and Ross were confirmed by a medical board headed by Walter Reed in 1900.

MALARIA PARASITES

Malaria is caused by protozoan parasites of the genus *Plasmodium* (Phylum Apicomplexa). In humans malaria is caused by ***P. falciparum, P. malariae, P. ovale,*** and ***P. vivax,*** the last one is the most common one responsible for about 80 % of all malaria cases. However, *P. falciparum* is the most deadly one, responsible for about 15% of infections but 90% of deaths. Parasitic *Plasmodium* species also infect birds, reptiles, monkeys, chimpanzees and rodents. There have been documented human infections with several **simian species** of malaria, namely ***P. knowlesi, P. inui, P. cynomolgi, P. simiovale, P. brazilianum, P. schwetzi* and *P. simium.***

LIFE CYCLE

The parasite's primary (definitive) hosts and vectors are female mosquitoes of the *Anopheles* genus. A mosquito becomes infected when it takes a blood meal from an infected human. Once ingested, the parasite's **gametocytes,** taken up along with the blood differentiate into male or female **gametes**, which fuse to form **zygote** in the mosquito gut. The zygote is also called **ookinete** that penetrates the gut lining and produces an **oocyst** outside the stomach wall. The diploid zygote first undergoes reduction division and then divides by multiple fission to produce haploid sporozoites inside the oocyst. When the oocyst ruptures, **sporozoites** are released that migrate through the mosquito's body to reach salivary glands, where they are ready to infect a new human host when the mosquito bites a healthy man. This type of transmission is occasionally referred to as anterior station transfer. Only female mosquitoes feed on blood, thus males do not transmit the disease..

Malaria in humans develops via two phases: an **exoerythrocytic** (hepatic) and an **erythrocytic** phase. When an infected mosquito pierces a person's skin to take a blood meal, sporozoites in the mosquito's saliva enter the bloodstream and migrate to the liver. Within 30 minutes of being introduced into the human host, they infect hepatocytes, multiplying asexually to form **schizont** for a period of 6–15 days. Once in the liver they produce thousands of **cryptozoites** and secondary **metacryptozoites,** which, following rupture of their host cells escape into the blood and infect red blood cells, thus beginning the erythrocytic stage of the life cycle. The parasites escape from the liver undetected by wrapping themselves in the cell membrane of the host liver cell. Within red blood cells the parasites multiply further asexually producing **schizont** that burst to release about

two dozens of **merozoites** that invade fresh red blood cells. Such cycles continue to occur every 48 hours causing chill and fever at the release of merozoites from RBCs.

Some *P. vivax* and *P. ovale* sporozoites do not immediately develop into exoerythrocytic merozoites but instead produce **hypnozoites** that remain dormant for periods ranging 6–12 months to as long as three years. After a period of dormancy, they reactivate and produce merozoites. **Hypnozoites** are responsible for long incubation and late relapses in these two species of malaria.

The parasite is protected from attack by the body's immune system because for most of its life it resides within the liver and blood cells and is hidden from immune surveillance. However, circulating infected blood cells are destroyed in the spleen. To avoid this, *P. falciparum* produces adhesive proteins on the surface of the infected blood cells, causing the blood cells to stick to the walls of smaller blood vessels, thereby sequestering the parasite from the passage through the general circulation and spleen. This stickiness of RBCs is the main factor that gives rise to hemorrhagic complications associated with *falciparum* malaria. The smallest branches of the circulatory system can be blocked by the attachment of masses of these infected red blood cells. In cerebral malaria the sequestrated red blood cells can breach the blood brain barrier, leading to coma.

Although the red blood cell surface adhesive proteins (called **PfEMP1** for *Plasmodium falciparum* erythrocyte membrane protein 1) are exposed to the immune system, they do not serve as good immune targets because of their extreme diversity. There are at least 60 types of these proteins within a single parasite and perhaps limitless types in general parasite populations. Also, the parasite switches between a broad repertoire of **PfEMP1** surface proteins thus staying one step ahead of the pursuing immune system.

TREATMENT

The first effective treatment for malaria was the bark of **cinchona tree**, which contains **quinine**. This tree grows on the slopes of the Andes, mainly in Peru.

Treatment with Chloroquine

Day 1	4 tablets (600mg base) or 10 mg/kg first dose. 2 tablets (300mg base) or 5 mg/kg 6-8 hours later.
Day 2	2 tablets (300mg base) or 5 mg/kg.
Day 3	2 tablets (300mg base) or 5 mg/kg
Next 14 days	**Primaquine,** 2 tablets (each tablet contains 7.5 mg base daily with food).

Most drugs used in treatment of malaria are active against the parasite stages in blood and include the following:

Chloroquine
Sulfadoxine-pyrimethamine combination
Mefloquine
Atovaquone-proguanil combination
Quinine
Doxycycline
Artemisinin derivatives

In addition, **primaquine** is active against the dormant parasite in liver called **hypnozoites** and hence prevents relapses. **Primaquine** should not be taken by pregnant women or by people who are deficient in G6PD (glucose-6-phosphate dehydrogenase).

Mefloquine is an antimalarial agent that acts as a blood schizonticide. It is effective against all species of malaria *(P. falciparum, P. vivax, P. malariae and P. ovale).* Its exact mechanism of action is not known. Mefloquine is active against the erythrocytic stages of *Plasmodium* species. However, the drug has no effect against the exoerythrocytic (hepatic) stages of the parasite and mature gametocytes. **Mefloquine** is effective against malaria parasites resistant to chloroquine and other 4-aminoquinoline derivatives, proguanil, pyrimethamine and pyrimethamine-sulphonamide combinations.

Malarone (**Atovaquone** 250 mg plus **Proguanil** 100 mg), 4 tablets daily for three consecutive days. This combination therapy is relatively new and appears to be very effective but it is also very expensive.

For over 1,500 years Chinese have used leaves from *Artemisia annua* shrub (sweet wormwood) to treat malaria. However, it is only in the late 1960s that its anti-malarial ingredient, **artemisinin** was identified and extracted. Today, **artemisinin** is considered the treatment of choice for uncomplicated *falciparum* malaria, as prescribed by the World Health Organization in 2001.

BENEFICIAL EFFECTS OF MALARIA

Sickle-cell disease

Distribution of malaria.The best-studied influence of the malaria parasite upon the human genome is the blood disease, sickle-cell disease. In sickle-cell disease, there is a mutation in the HBB gene, which encodes the beta globin subunit of haemoglobin. The normal allele encodes a glutamate at position six of the beta globin protein, while the sickle-cell allele encodes a valine. This change from a hydrophilic to a hydrophobic amino acid encourages binding between haemoglobin molecules, with polymerization of haemoglobin deforming red blood cells into a "sickle" shape. Such deformed cells are cleared rapidly from the blood, mainly in the spleen, for destruction and recycling.

In the merozoite stage of its life cycle the malaria parasite lives inside red blood cells, and its metabolism changes the internal chemistry of the red blood cell. Infected cells normally survive until the parasite reproduces, but if the red cell contains a mixture of sickle and normal haemoglobin, it is likely to become deformed and be destroyed before the daughter parasites emerge. Thus, individuals heterozygous for the mutated allele, known as sickle-cell trait, may have a low and usually unimportant level of anaemia, but also have a greatly reduced chance of serious malaria infection. This is a classic example of heterozygote advantage.

Individuals homozygous for the mutation have full sickle-cell disease and in traditional societies rarely live beyond adolescence. However, in populations where malaria is endemic, the frequency of sickle-cell genes is around 10%. The existence of four haplotypes of sickle-type hemoglobin suggests that this mutation has emerged independently at least four times in malaria-endemic areas, further demonstrating its evolutionary advantage in such affected regions. There are also other mutations of the HBB gene that produce haemoglobin molecules capable of conferring similar resistance to malaria infection. These mutations produce haemoglobin types HbE and HbC which are common in Southeast Asia and Western Africa, respectively.

Thalassaemias

Another set of mutations found in the human genome associated with malaria are those causing blood disorders known as thalassaemias. Studies in Sardinia and Papua New Guinea have revealed that the gene frequency of **β-thalassaemias** is related to the level of malarial endemicity in a populations. A study on more than 500 children in Liberia revealed that those suffering with β-thalassaemia had a 50% decreased chance of getting clinical malaria. Similar studies have found links between gene frequency and malaria endemicity in the **α+** form of **α-thalassaemia.** Presumably these genes have also been selected in the course of human evolution with malaria epidemic.

Duffy antigens

The **Duffy antigens** are antigens expressed on red blood cells and other cells in the body acting as a chemokine receptors. The expression of Duffy antigens on blood cells is encoded by **Fy genes** (Fya, Fyb, Fyc etc.). *Plasmodium vivax* malaria uses the Duffy antigen to enter blood cells. However, it is possible to express no Duffy antigen on red blood cells owing to the absence of Fy genes (Fy-/Fy-). This genotype confers complete resistance to *P. vivax* infection. The genotype is very rare in European, Asian and American populations, but is found in almost all indigenous population of West and Central Africa. This is thought to be due to high exposure of populations to *P. vivax* in Africa in the last few thousand years.

G6PD

Glucose-6-phosphate dehydrogenase **(G6PD)** is an enzyme which normally protects from the effects of oxidative stress in red blood cells. However, a genetic deficiency in this enzyme results in increased protection against severe malaria.

HLA and interleukin-4

HLA-B53 is associated with low risk of severe malaria. This MHC class I molecule presents liver stage and sporozoite antigens to **T-Cells**. **Interleukin-4** is produced by activated **T-cells** and promotes proliferation

and differentiation of antibody-producing **B-cells**. A study of the Fulani of Burkina Faso found that the **IL4-524 T** allele was associated with elevated antibody levels against malaria antigens, which raises the possibility that this might be a factor in increased resistance to malaria.

CHOLERA

Cholera is an acute intestinal infection caused by ingestion of food or water contaminated with the bacterium *Vibrio cholerae*. It has a short incubation period of one to five days and produces a toxin that causes painless, watery diarrhoea and vomiting that can quickly lead to severe dehydration and death. The genus **Vibrio** consists of Gram-negative straight or curved rod-like bacteria, with a single polar flagellum. Vibrios are capable of both respiratory and fermentative metabolism. Most species are oxidase-positive. *V. cholerae* and *V. parahaemolyticus* are pathogens of humans. *V. parahaemolyticus* is an invasive organism affecting primarily the colon, while *V.* Another species, *Vibrio vulnificus* is another emerging pathogen of humans that causes *cholerae* is noninvasive affecting the small intestine by producing an enterotoxin. wound infections, gastroenteritis or a syndrome known as "primary septicaemia."

HISTORY

During the 19th century cholera spread repeatedly from the Ganges delta in India to the rest of the world before receding to South Asia. Six epidemics were recorded that killed millions of people across Europe, Africa and the Americas. Cholera is mainly transmitted through contaminated water and food and is closely related to unhygienic conditions of surrounding environment. The absence or shortage of safe drinking water and insufficient sanitation, combined with an unhygienic environmental status are the main causes of spread of the disease. Cholera still remains a global threat to public health and one of the key indicators of social development. While the disease is no longer an issue in countries where minimum hygiene standards are met, it remains a threat in almost every developing country where populations are large. The number of cholera cases reported to WHO during 2006 rose dramatically, reaching the level of the late 1990s. A total of 236 896 cases were notified from 52 countries, including 6311 deaths, an overall increase of 79% compared with the number of cases reported in 2005.

CHOLERA TOXIN

Cholera toxin activates the adenylate cyclase enzyme in cells of the intestinal mucosa leading to increased levels of intracellular cAMP, and the secretion of H_20, Na^+, K^+, Cl^-, and HCO_3^- into the lumen of the small intestine. The effect is dependent on a specific receptor, monosialosyl ganglioside (GM1 ganglioside) present on the surface of intestinal mucosal cells. The bacterium produces invasin, neuraminidase, during the colonization stage which has the interesting property of degrading gangliosides to the monosialosyl form, which is the specific receptor for the toxin. Once it has entered the cell, the A1 subunit enzymatically transfers ADP ribose from NAD to a protein (called Gs or Ns), that regulates the adenylate cyclase system which is located on the inside of the plasma membrane of mammalian cells. Enzymatically, fragment A1 catalyzes the transfer of the ADP-ribosyl moiety of NAD to a component of the adenylate cyclase system. Adenylate cyclase (AC) is activated normally by a regulatory protein (GS) and GTP.

TRANSMISSION

The highly liquid diarrhea during cholera infection is loaded with bacteria that can spread under unsanitary conditions to infect water used by other people. Cholera is transmitted from person to person through ingestion of faeces-contaminated water.The sources of contamination are typically other cholera patients whose diarrhoeal discharge is allowed to get into waterways or into groundwater or drinking water supply. Any infected water or food washed in such water and fish and shellfish living in the affected waterways can cause infection. Cholera is rarely spread directly from person to person. *V. cholerae* occurs naturally in the planktons of fresh, brackish, and salt water, attached primarily to copepods. Both toxic and non-toxic strains exist. Coastal cholera outbreaks typically follow zooplankton blooms.

COLONIZATION OF INTESTINE

There are several characteristics of pathogenic *V. cholerae* that help it in the colonization process, namely, **adhesins**, **neuraminidase**, intestinal motility, chemotaxis and toxin production. *V. cholerae* is resistant to bile salts and can penetrate the mucus layer of small intestine, possibly aided by secretion of

neuraminidase and proteases (mucinases). They also withstand the propulsive gut motility by their own swimming ability and chemotaxis directed against the gut mucosa. Two other possible adhesins in *V. cholerae* are a surface protein that agglutinates red blood cells **(hemagglutinin)** and a group of outer membrane proteins which are products of the **acf** (accessory colonization factor) genes. **acf** mutants have been shown to have reduced ability to colonize the intestinal tract. It has been suggested that *V. cholerae* might use these nonfimbrial adhesins to mediate a tighter binding to host cells than is attainable with fimbriae alone

VACCINES

The oral vaccines are made from a live attenuated strain of *V. cholerae*. The ideal properties of such a vaccine of the bacterium would be to possess all the pathogenicity factors required for colonization of the small intestine but not to produce toxin molecules. Ideally it should produce only the **B** subunit of the toxin which would stimulate formation of antibodies that could neutralize the binding of the native toxin molecule to epithelial cells.

A new vaccine has been developed to combat the Bengal strain of *Vibrio cholerae* that has started spreading in epidemic fashion in the Indian subcontinent and Southeast Asia. The Bengal strain differs from previously isolated epidemic strains in that it is sero group is 0139 rather than 01, and it expresses a distinct polysaccharide capsule. Since previous exposure to 01 *Vibrio cholerae* does not provide immunity against 0139, populations suffer from the Bengal form of cholera.

The noncellular vaccine is relatively nontoxic and contains little or no LPS and other impurities. The vaccine will be used for active immunization against *Vibrio cholerae* O139 and other bacterial species expressing similar surface polysaccharides. In addition, human or other antibodies induced by this vaccine could be used to identify *Vibrio cholerae* Bengal for the diagnosis of the infection and for environmental monitoring of the bacterium.

TREATMENT

Cholera can be simply and successfully treated by immediate replacement of body fluids and salts lost through diarrhoea and vomiting. Patients can be treated with **Oral Rehydration Solution,** a mixture of sugar and salts to be mixed with water and taken in large amounts but patients who become severely dehydrated must be given intravenous fluids. With prompt rehydration, less than 1% of cholera patients die.

In severe cases, an effective antibiotic can reduce the volume and duration of diarrhoea and the period of *Vibrio* excretion. **Tetracycline** is the usual antibiotic of choice, but resistance to it is increasing. Other antibiotics that are effective include, **cotrimoxazole, erythromycin, doxycycline, chloramphenicol and furazolidone.**

Antibiotics used to treat cholera

Doxycycline, a single dose of 300 mg tablet
Tetracycline, 12.5 mg/kg or 500 mg tablet, 4 times per day for 3 days.
Trimethoprim/sulfamethoxazole (TMP/SMX), TMP 5 mg/kg and SMX 25 mg/kgc TMP 160 mg and SMX 800 mg twice a day for 3 days.
Furazolidone, 1.25 mg/kg or 100 mg tablet, 4 times per day for 3 days.
Erythromycin or **chloramphenicol** may be used when the antibiotics recommended above are not available, or where *Vibrio cholerae* O1 is resistant to them.
Doxycycline is the antibiotic of choice for adults but not for pregnant women.
TMP-SMX is the antibiotic of choice for children.
Tetracycline is equally effective in all age groups.
Furazolidone is the antibiotic of choice for pregnant women.

AIDS

AIDS stands for Acquired Immunodeficiency Syndrome. It is the most advanced stage of infection with the Human Immunodeficiency Virus (HIV) which kills or damages cells of the body's immune system. HIV most often spreads through unprotected sex with an infected person, by sharing drug needles or through contact with the blood of an infected person. Women can give it to their babies during pregnancy or childbirth.

The first signs of HIV infection may appear as swollen glands and flu-like symptoms which may come and go a month or two after infection. Severe symptoms may not appear until months or years later. The CD4 count indicates how far the HIV disease has advanced. CD4 counts in adults range from 500 to 1,500 cells per cubic millimeter of blood. In general, the CD4 count goes down as HIV disease progresses, to below 200, regardless of whether the persons are sick or not.

MODE OF INFECTION

Once HIV enters the human body, it attaches itself to a White Blood Cell (WBC) called CD4, also called T4 cell, which are the main disease fighters of the body. Whenever there is an infection, CD4 cells lead the infection-fighting army of the body to protect it from falling sick. Hence damage of these cells can affect a person's disease-fighting capability and general health. After making a foothold on the CD4 cell, the virus injects its RNA into the cell. The RNA then produces its DNA by using enzyme reverse transcriptase. The viral DNA then gets attached to the DNA of the host cell and thus becomes part of the cell's genetic material. It is a virtual takeover of the cell. Using the cell's division mechanism, the virus now replicates and churns out hundreds of thousands of its own copies. These cells then enter the blood stream, get attached to other CD4 cells and continue to replicate. As a result the number of virus in the blood rises and CD4 cell count declines.

There are several common ways that HIV can be passed from person to person that include:
Having unprotected sex with someone who is infected

- Using needles or syringes that have been used by people who are infected
- Receiving infected blood products or transplanted organs.
- Transmission from mother to child – An infected mother may pass the virus to her developing fetus during pregnancy, birth or through breastfeeding.

SYMPTOMS

Many people do not develop any symptoms when they first become infected with HIV. Some people, however, get flu-like illness within three to six weeks after exposure to the virus. This illness, called Acute HIV Syndrome may include fever, headache, tiredness, nausea, diarrhea and enlarged lymph nodes. These symptoms usually disappear within a week to a month and are often mistaken for another viral infection. During this period, virus in the body abounds and spreads to different parts, particularly to lymphoid tissue. At this stage, the infected person is more likely to pass the infection to others.

More severe symptoms may not surface for several years, even a decade or more after the first entry of the virus or within two years in children born with the virus. Some people may begin to have symptoms as soon as a few months while others may be symptom-free for more than 10 years. During the "asymptomatic" period, the virus will be actively multiplying, infecting, and killing cells of the immune system. The following symptoms may appear in the infected person:
Lack of energy.

- Weight loss.
- Frequent fevers and sweats.
- A thick, whitish coating on the tongue or mouth that is caused by a yeast infection and sometimes accompanied by a sore throat.
- Severe or recurring vaginal yeast infections.
- Chronic pelvic inflammatory disease or severe and frequent infections like *Herpes zoster*.
- Periods of extreme and unexplained fatigue that may be combined with headaches, lightheadedness or dizziness.

- Rapid loss of weight that is not due to increased physical exercise or dieting.
- Bruising more easily than normal.
- Long-lasting bouts of diarrhea.
- Swelling or hardening of glands located in the throat, armpit or groin.
- Periods of continued, deep and dry coughing.
- Increasing shortness of breath.
- The appearance of discolored or purplish growths on the skin or inside the mouth.
- Unexplained bleeding from skin mucous membranes or from any opening in the body.
- Recurring and unusual skin rashes.
- Severe numbness or pain in the hands or feet, loss of muscle control and reflex and paralysis or loss of muscular strength.
- An altered state of consciousness, personality change or mental deterioration.
- Children's growth may be slow or they may fall sick frequently. HIV positive persons are also found to be more vulnerable to cancers.

SYMPTOMS IN FEMALES

Although most of the symptoms of HIV infection are similar in men and women, some are more typical of females. For example: Vaginal yeast infections may be chronic, more severe and difficult to treat in women with HIV infection than in healthy women.

Pelvic inflammatory disease, an infection of the female reproductive organs, may also be more frequent and severe in women with HIV infection. Human papillomavirus (HPV) infection, which causes genital warts may occur more frequently in HIV-infected women and can lead to pre-cancerous lesions of the cervix or cancer of the cervix.

OPPORTUNISTIC INFECTIONS

The number of CD4 cells per ml of blood which ranges from 500 to 1,500 in a healthy individual falls below 200 in AIDS infected people. The Viral Load will be very high at this stage. Opportunistic infections are caused by bacteria, virus, fungi and parasites. Some of the common opportunistic infections that affect HIV positive persons are: *Mycobacterium avium*, Tuberculosis, Salmonellosis, Bacillary Angiomatosis, Cytomegalovirus, Viral hepatitis, Herpes, Human papillomavirus, Progressive multifocal leukoencephalopathy; Candidiasis, Cryptococcal meningitis and Pneumocystis Carinii pneumonia, Toxoplasmosis, Cryptosporidiosis. HIV positive persons are also prone to cancers like Kaposi's sarcoma and lymphoma.

DIAGNOSIS

In the early stages of infection, HIV often produces no symptoms and the infection can be diagnosed only by testing a person's blood. Two tests are available to diagnose HIV infection — one that looks for the presence of antibodies produced by the body in response to HIV and the other that looks for the virus itself. If antibodies are present, the test gives a positive result. A positive test has to be confirmed by another test called **Western Blot** or **Immunoflouroscent Assay** (IFA). All positive tests by **ELISA** need not be accurate and hence Western Blot and other tests are necessary to confirm a person's HIV status. ELISA requires specialized equipment and blood samples need to be sent to a laboratory. To cut short this waiting period, **Rapid Tests** that give results in 5 to 30 minutes are increasingly being used the world over.

The HIV antibodies generally do not reach detectable levels in the blood till about three months after infection. This period, from the time of infection till the blood is tested positive for antibodies is called the **Window Period.** Sometimes, the antibodies might take even six months to show up. Even if the tests are negative during the Window Period, the amount of virus may be very high in an infected person.

PREVENTION

Because there is no effective vaccine and no cure for HIV, the only way to protect one is by taking preventive measures.

People should either abstain from having sex or use latex condoms during sex. People who are allergic to latex can use polyurethane condoms.

Although some laboratory evidence shows that spermicidal creams can kill HIV, there is no conclusive evidence if it can prevent transmission.

The risk of HIV transmission from a pregnant woman to her baby is significantly reduced if she takes **AZT** during pregnancy, labour and delivery and her baby takes it for the first six weeks of life. **Nevirapine** is also found to be useful.

Having a sexually transmitted disease (STD) can increase a person's chances of getting HIV through sexual contact. Hence it is necessary to treat STD as soon as possible.

All donated blood must be screened for HIV as well as for Hepatitis B and Syphilis.

TREATMENT

Three classes of drugs are available for treatment of AIDS.

1. Nucleoside analogue Reverse Transcriptase Inhibitors (NRTIs). These were first antiretroviral drugs that were developed for inhibiting the replication of HIV in the early stage by inhibiting an enzyme called Reverse Transcriptase. The drugs include **Zidovudine** (Retrovir, AZT), **Lamivudine** (Epivir, 3TC), **Didanosine** (Videx, ddI), **Zalcitabine** (Hivid, ddC), **Stavudine** (Zerit, d4T) and **Abacavir** (Ziagen).

The major reported side effect of **Zidovudine** is bone marrow suppression, which causes a decrease in the number of red and white blood cells. The drugs **ddI, ddC** and **d4T** can damage peripheral nerves, leading to tingling and burning sensation in hands and feet. Treatment with **ddI** can also cause pancreatitis, and **ddC** may cause mouth ulcers. Approximately 5 percent of people treated with **Abacavir** experience hypersensitivity with rash along with fever, fatigue, nausea, vomiting, diarrhea and abdominal pain. Symptoms usually appear within the first 6 weeks of treatment and generally disappear when the drug is discontinued.

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). These drugs bind directly to the enzyme, Reverse Transcriptase. There are three NNRTIs currently approved for clinical use: **Nevirapine** (Viramune), **Delavirdine** (Rescriptor) and **Efavirenz** (Sustiva). A major side effect of all NNRTIS is appearance of rash. In addition, people taking Efavirenz may also have side effects such as abnormal dreams, sleeplessness, dizziness and difficulty concentrating.

3. Protease Inhibitors (PIs). They interrupt HIV replication at a later stage in its life cycle by interfering with an enzyme known as HIV protease. This causes HIV particles in the body to become structurally disorganized and noninfectious. Among these drugs are **Saquinavir** (Fortovase), **Ritonavir** (Norvir), **Indinavir** (Crixivan), **Nelfinavir** (Viracept), **Amprenavir** (Agenerase) and **Lopinavir** (Kaletra).

The triple cocktail treatment, also known as **Highly Active Antiretroviral Therapy (HAART),** is the closest thing that medical science has to an effective therapy, which has the ability to disrupt HIV at different stages of replication. Reverse transcriptase inhibitors, which usually make up two drugs in the HAART regimen, restrain an enzyme crucial in the early stage of HIV replication. Protease inhibitors hold back another enzyme that functions near the end of the HIV replication process.

As of now, there is no vaccine to prevent HIV infection.