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Epidemiology and Tropical Diseases

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GENERAL INTRODUCTION

Researchers like Dr. Robert Koch, Louis Pasteur, Carlos Chagas, Neisser, Dr. Ronald Ross, David Bruce, Paul Ehrlich, G.H.A Hansen and other different researchers in the science of medicine gave a good contribution in the science of medicine to improve the future of the world in the science of medicine. We may strive ourselves by imitating their good examples, to help the people of our generation in the science of medicine and other different disciplines relating to health.

Our world, especially Africa of ours needs good researchers in the science of medicine to provide the best healthcare of people. I am reminding Africans to be good researchers for changing Africans' life. If we get lucks of education, we have to be active using our knowledge and skills, to develop our Africa, possibly all over the world. For this I want to be among good researchers in the science of medicine that is why I am striving to do everything so that I share knowledge and skills with others. My friends come and share what we have for future success in medicine.

This book covers basic knowledge of epidemiology which can help the readers to know what epidemiology is, it describes also some epidemics, and some measures of disease frequency. It comes also on tropical diseases which are diseases found in tropical and subtropical parts of the world; here the readers will require many different things concerning some tropical diseases. You know prevention is better than treatment; this book will help in some procedures used in preventing some tropical diseases and different epidemics. If defeat for prevention it will support you to identify different kinds of disease by clinical features of each disease found from here.

As public health academician, I am asking medical doctors, medical officers and other health strivers to work together for the aim of increasing the capacity of each one, providing the good health care of people, providing new ways of treatment if possible, and other different important things which can improve the science of medicine. Thus I am welcoming you with heavy skillful ideas which will help us to change and improve our mind for future success in medicine, also giving good examples for our generation as our first fathers talked above did for us.

PART: I

EPIDEMIOLOGY

Definition: - This is the branch of medicine which deals with the incidence, Distribution and possible control of diseases and other Factors relating to health.

Is the study of how often diseases occur in different groups of people and why. Epidemiology of a disease is an integral part of its basic description like data collection, interpretation and necessary jargon for technical terms.

- Is the branch of medical sciences that investigates all the factors that determine the presence or absence of diseases and disorders. epidemiological research helps us to understand how many people have a disease or disorders if those numbers are changing , and how the disorders affects our society and our economy .
- Is a basic science of public health. Epidemiology is also a quantitative discipline built on a working knowledge of probability, statistics and sound research methods, a method of causal reasoning based on developing and testing hypotheses pertaining to occurrence and prevention of morbidity and mortalit , atool for public health actions to promote and protect the public's health based on science, cause reasoning , and a dose of practice common sense .
- The word epidemiology comes from the Greek word "epi" meaning or Upon "demos" meaning people and "logos" meaning the study of . Then epidemiology is the study of the distribution and determinantshealth related states or events in specified population and the application of this study to the control of health problem. Etc

What are epidemics?

EPIDEMIC: Is a disease that spreads rapidly and affects an inordinately large number of People within a very short time.

Characteristics of an epidemic

The characteristics of an epidemic are:

- They spread rapidly and efficiently from person to person. This means that everyone in a given Area gets a disease all at once.
- they are acute illness where you only have them for a short time. You either die quickly or Recover. This means that a lot of people who could get the disease die. Then the disease has Fewer people to infect. The rest become immune.
- The diseases have to have human host they can't live in the soil.

How can you control an epidemic here you may only precise control measures.

- Trade barrier to prevent the international spread of infection or importation of a disease
- Immunization of susceptible individuals.

Mention some epidemics.

- Cholera
- Plague of justinian
- Bubonic plague (Black Death in Europe).
- Viral hemorrhagic fever.
- Measles: 1592 - 1596
- Plague
- Yellow fever
- Smallpox
- Typhus
- Hepatitis B and D
- Italian plague of 1629 - 1631
- Influenza

1cholera

Cholera is an infection of the small intestine caused by the bacterium VIBRIO CHOLERA the main symptoms are watery diarrhea and vomiting. This may result in dehydration and severe cases grayish - bluish skin. Transmission occurs primarily by drinking water or eating food that has been contaminated by the faeces of an infected person. Including one with no apparent symptoms the severity of diarrhea and vomiting can lead to rapid dehydration and electrolyte imbalance and death i some cases. The primary treatment is ORAL REHYDRATION THERAPY. Typically with oral rehydration solution to replace water and electrolytes. If this is not tolerated or does not provide improvement fast enough, IV fluids can also be used. Antibacterial drugs are beneficial in that severe disease to shorten its duration and severity.

Epidemiology of cholera

⇒ **Signs and symptoms**

- Diarrhea and vomiting
- Rice watery diarrhea
- Dehydration
- Sunken eyes
- The patients can be lethergic
- Dry mouth
- Cold clammy skin
- Urine output decreases
- Muscles cramping
- Weakness
- Coma due to electrolytes loses
- Blood pressure , turgor .

⇒ **Causes and susceptibility**

Vibrio cholerae is the bacterium that causes cholera. Children are more susceptible with two to four years old having the highest rate of infection, for adult millions of bacteria are needed to cause infection. Individuals also may be affected by their blood group "O" group being the most susceptible. Person with lower immunity and malnourished children.

⇒ **Transmission**

Cholera is typically transmitted by either contaminated food and water in developed world sea food is the usual cause, while in the developing world it is more often water. Most cholera cases in developed countries are a result transmission by food. This occurs when people harvest oysters in waters infected with sewage as vibrio cholera accumulate in zooplankton and the oysters eat the zooplankton. Cholera is found in two animals' population: shellfish and plankton, people infected with cholera often have diarrhea, and this highly liquid stool, colloquially referred to as "**rice-water".** Contaminated water used by others, disease transmission may occur. The source of contamination is typically other cholera suffers when their untreated diarrheal discharge is allowed to into waterways supplies. Drinking any infected water and eating any foods washed in the water, as well as shellfish living in the affected waterways can cause a person to contact an infection. Cholera is rarely spread directly from person to person.

Diagnosis

A rapid dipstick test is available to determine the presence of V. cholera, in those samples that test positive further testing should be done to determine antibiotic resistance. In epidemic situations, a clinical diagnosis may be made by taking a patient history and doing a brief examination. Treatment is usually started without or before confirmation by laboratory analysis. Stools and swab samples collected in the acute stage of disease, before antibiotics have been administered, are most useful specimens for laboratory diagnosis.

Prevention

- Water treatment and sanitation practices, cholera are no longer a mayor health threat. The last mayor outbreak of cholera in the united stated occurred in 1910-1911.

- Medical citation needed: Sterilization, proper disposal and treatment of infected faecal Waste water produced by cholera victims and all contaminated materials (e.g: clothing, Bedding, etc) are essential. All materials that come in contact with cholera patient should be sanitized by washing in hot water , using chlorine bleach if possible . Hands that touch Cholera patients or their clothing, bedding, etc should be thoroughly cleaned and disinfected with chlorined water or other effective antimicrobial agent .
- Decontaminate, the water (boiling, chlorination, etc) for possible use.
- Water purification: all water used for drinking, washing or cooking should be sterilized by Either boiling, chlorination, ozone water treatment, ultraviolet light sterilization. (E.g by solar water disinfection) or antimicrobial filtration in any area where cholera may be present . Chlorination and boiling are often the least expensive and most effective means of halting Transmission.
- Cloth filters , though very basic , have significantly reduced the occurrence of cholera when used in poor villages in bangladesh that rely on untreated surface water . Better antimicrobial filters , like those present in advanced individual water treatment hiking kits , are most effective .

Public health education and adherence to appropriate sanitation practices are of primary importance to help prevent and control transmission of cholera and other disease.

Surveillance

Surveillance and prompt reporting allow for containing cholera epidemics rapidly. Cholera exists as seasonal disease in many endemic countries , occurring annually mostly during rainy season .

Surveillance systems can provide early alerts to outbreaks, therefore leading to coordinated response and assist in preparation of preparedness plans. Efficient surveillance systems can alsoimprove the risk assessment for potential cholera outbreak. Understanding the seasonality And location of outbreaks provides guidance for improving cholera control activities for the most vulnerable.

Treatment

- Oral Rehydration Therapy (ORT) which is highly effective, safe, and simple to administer.
- Rice-based solution is preferred to glucose-based ones due to greater efficiency. In severe cases with significant dehydration , IV rehydration may be necessary .
- Ringer's lactate is the preferred solution, often with added potassium. Large volumes and continued replacement until diarrhea has subsided may be needed . Ten percent of person's body weight in fluid may need to be given in the first two to four hours .
- ORT can be made: one litter of boiled water, 1/2 teaspoon of salt, 6 teaspoon of sugar, and added mashed banana for banana for pota

2 Plagues

Plague: Plague is serious bacterial infection that's transmitted by fleas. Known as the black death during medieval times , today plague occurs in fewer than 5000 people a year worldwide It can be deadly if not treated promptly with antibiotics. The organism that causes plague is yersinia pestis , lives in small rodents on every continent except Australia . The organism is transmitted to humans who are bitten by fleas that have fed on infected rodents or by human handling infected animals . The most common of plague result in sudden and tender lymph nodes - called buboes in the groin , armpits or neck . The rarest and deadliest form of plague affects the lungs and it can be spread from person to person .

Symptoms

Plague is divided into three main types - Bubonic, Septicemic and Pneumonic depending on which part of your body is involved. Signs and symptoms vary depending on the type of plague.

Bubonic Plague

Bubonic plague is the most common variety of the disease it is named after the buboes swollen lymph nodes - which typically develop within a week after an infected flea bites you. Buboes may be : situated in the groin, armpit, or neck, sudden onset of fever and chills, headache, fatigue or malaise, muscles ache, about the size of chicken egg tender and warm to touch.

Septicemic Plague

Septicemic plague occurs when plague bacteria multiply in your bloodstream.

Signs and symptoms: Abdominal pain, diarrhea and vomiting, bleeding from yer mouth, nose, or rectum or under your skin.

Shock

Blackening and death of tissue (gangrene) in your extremities, most commonly yer fingers, toes and nose.

Pneumonic Plague

Pneumonic plague affects the lungs. It is the least common variety of plague but the most dangerous, because it can be spread from person to person via cough droplets. Signs and symptoms can begin within a few hours after infection, and may include:

- cough, with bloody sputum
- Difficulty breathing
- High fever
- Nausea and Vomiting
- Weakness
- Pneumonia plagues progresses rapidly and may cause respiratory failure and shock within two days of infection. if antibiotics treatment is not initiated within a day after signs and symptoms first appear , the infection is likely to be fatal . You may seek immediate medical help if you find signs and symptoms. This disease is very common in USA, MEXICO, ARIZONA and

COLORADO.

Risk factors

- Living and traveling
- Your occupation
- By some hobbies
- Overcrowding
- Poor sanitation
- High rate population

The greatest number of human plague infections occurs in Africa.

Occupation

Veterinarians and their assistants have a higher risk of coming into contact with domestic cats that may have become infected with plague. Also at higher risk are people who work outdoor in areas where plague - infested animals are common.

Hobbies

Camping, hunting or hiking in areas where plague infected animals reside can increase your risk of being bitten by an infected flea.

Complication

Complication of plague may include:

- Death. Most people who receive prompt antibiotic treatment survive bubonic plague. untreated plague has high fatality rate.
- Gangrene. Blood clots in the tiny blood vessels of your finger and toes can disrupt. The flow of blood and cause that tissue to die. The portion of your fingers and toes that have died may need to be amputated .
- Meningitis: rarely, plague may cause an an inflammation of the membranes surrounding yer brain and spinal cord (meningitis) .

Test and diagnosis

If your doctor suspects plague, he/she may look for the yersinia pestis bacteria in sample taken from your:

Buboes: If you have the swollen lymph nodes (buboes) characteristics of bubonic plague, a Fluid sample can be taken from then with a needle.

Blood: Yersinia pestis bacteria generally are present in yer bloodstream only if you have Septicemia plague.

Lungs: To check for pneumonic plague, your doctor will take sputum or fluid from airways using - ENDOSCOPY- a thin flexible tube inserted through your nose or mouth and down your throat

Treatment

Medications as soon as your doctor suspects that you have plague, you will need to be admitted to an isolation room in a hospital, there you will receive powerful antibiotics such as:

- Gentamicin,Doxycycline (Vibramycin),Ciprofloxacin

In addition , the food and drug administration has approved another antibiotics Levofloxacin (Levaquin), for treatment of plague.

Prevention

Although no effective vaccine available, scientists are working to develop one, antibiotics can help to prevent infection if you are at risk of or have been exposed to plague, take the following precautions if you live or spend a time in regions where plague outbreaks occur:

- Rodents - proof your home. Remove potential nesting areas, such as piles of brush, rock, firewood and junk. Don't leave pet food in areas that rodents can easily access. Keep your pets free of fleas. Ask your veterinarian which flea - control products will work best.
- Use insecticide, repellent. Closely supervise your children and pests when spending a time outside in areas with large rodent population. Use insect repellent. (Mayo Clinic)

3. Measles

Measles is a child hood infection caused by virus. Once quite common, measles can now almost always be prevented with a vaccine.

Signs and symptoms

The signs and symptoms of measles include: Dry cough, runny nose, inflamed eyes, sore throat, fever and red blotchy skin rash .Also called rubella, measles can be serious and even fatal for small children. While death rates have been falling worldwide as more children receive the measles vaccine, the disease still kills more than 100 000 people a year , most under the age of 5.

Risk factors

Risk factors of measles include:

- Being unvaccinated. If you have not received the vaccine for measles you are much more likely to develop the disease.
- Traveling internationally. If you travel to developing countries where measles is more common you are at higher risk of catching the disease .
- Having a vitamin A deficiency. If you do not have enough vitamin A in yer diet you are more likely to contract measles and to have more - severe symptoms .

Complications

Complications of measles may include:

- Ear infection. One of the most complications of measles is the bacterial ear infection.
- Bronchitis, Laryngitis or croup. Measles may lead to inflammation of your voice box (larynx) or inflammation of the inner walls that line the main air passageways of your lungs . (Bronchial tubes).
- Pneumonia. Pneumonia is a common complication of measles. People with compromised Immune systems can develop an especially dangerous variety of pneumonia that is sometimes fatal.
- Encephalitis. About 1 in 100 people with measles develops encephalitis, an inflammation of the brain that may cause vomiting , in convulsion , and rarely coma , or even death . Encephalitis can closely follow measles or it can occur months later.
- Pregnancy problems. If you are pregnant, you need to take special care to avoid measles because the disease can cause pregnancy loss , preterm labor or low birth weight .
- Low platelet count (thrombocytopenia). Measles may lead to a decrease in platelet - the type Of blood cells that are essential for blood clothing.

Test and diagnosis

Your doctor can usually diagnose measles based on the disease 's characteristics , rash as well as small bluish - white spot on a bright red back ground - koplik’s spot - on the inside lining of the cheek. If necessary, a blood test can confirm whether the rash is truly measles.

Treatment and drugs

- No treatment can get rid of an established measles infection. However, some measures can be taken to protect vulnerable individuals who have been exposed to the virus .
- Post-exposure vaccination. Nonimmunized people including infants, may be given the Measles vaccination within 72 hours to the measles virus to provide protection against the disease. If measles still develop, the illness usually has milder symptoms and lasts for a shorter time.
- Immune serum globulin. Pregnant women in infants, and people with weakened immune systems who are exposed to the virus may receive an injection of protein (antibodies) called immune serum globulin , when given within six days of exposure to the virus , these antibodies can prevent measles or make symptoms less severe .
- Medications. Fever reducers. You or your child may also take over - the - counter medications such as ACETAMINOPHEN (tylenol , others) , Ibuprofen (advil , Motrin others) or Naproxen (aleve) to help relieve fever that accompanies measles .
- Use caution when giving aspirin to children or teenagers. Though aspirin is approved for use in children older than age 3 , children and teenagers recovering from chickenpox or flu - like symptoms should never take aspirin . This is because aspirin has been linked to reye’s syndrome, a rare but potentially life - threatening condition in such children .
- Antibiotics. If a bacterial infection, such as pneumonia, such as pneumonia or an ear infection develop while you or your child has measles, your doctor may prescribe an antibiotic.
- Vitamin A. People with low level of vitamin A are more likely to have a more severe case of measles. Giving Vitamin A may lessen the severity of the measles. It’s generally given a large dose of 200,000 internationally units (IU) for 2 days .

Prevention

If someone in your household has measles take these precautions to protect vulnerable family and friends :
Isolation. Because measles is highly contagious from about four days before to four days after the rash breaks out, people with measles should not return to activities which they interact with other people during this period. It may also be necessary to keep non-immunized people. siblings, for example - away from the infected person.
Vaccinate. Be sure that any one who is at risk of getting the measles who has not been fully vaccinated receives the measles vaccine as well as possible. This includes anyone born after 1957 who has been vaccinated, as well as infants older than 6 months.

Preventing New Infections

If you have already has measles, your body has built up its immune system to fight the infection, and you cannot get measles again. Most people born or living in the United States before 1957 are immune to measles, simply because they have already had it. For everyone else there is the measles vaccine, which is important for:

Promoting and preserving herd immunity. Since the introduction of the measles vaccine has virtually been eliminated in the United States, even tough not everyone has vaccinated. This effect is called "HERD IMMUNITY".But herd immunity may now be weakening a bit. The rate of measles in the USA recently tripled. Preventing a resurgence of measles. Sooner after vaccination rates declines, measles begins to come back. In 1998, a now - discredited study was published erroneously linking autism to the measles, mumps and rubella (MMR) vaccine.

In the United Kingdom, where the study originated, the rate of vaccination to an all-time low of just fewer than 80% of all children in 2002. Between 2012-2013, more than 1200 children in the UK contracted measles, up from 380 children in 2010

4 Yellow fever

Yellow fever is a viral infection spread by a particular species of mosquito. It is most common in areas of Africa and South America, affecting travelers to and resident of those areas.

Signs and symptoms

During the first three days to six days after you have contracted yellow fever-the incubation period-you won't experience any signs or symptoms. After this, the virus enters an acute phase and then, in some cases a toxic phase that can be life-threatening.

Acute phase

Once the yellow fever virus enters the acute phase, you may experience signs and symptoms including:
- Fever
- Headache
- Muscles aches, particulary in your back and knees.
- Nausea, Vomiting or both
- Loss of appetite
- Dizziness
- Red eyes, face or tongue

These signs and symptoms usually improve and are gone within several days.

Toxic phase

Although signs and symptoms may disappear for a day or 2 following the acute phase, some people with acute yellow fever then enter a toxic phase. During toxic phase, acute signs and symptoms return and more-severe and life-threatening ones also appear. These can include:

- Yellowing of your skin and the whites of your eyes (Jaundice)
- Abdominal pain and vomiting, sometimes of blood
- Decreased urination
- Bleeding from your nose, mouth and eyes
- Heart dysfunction (arrhythmia)
- Liver and kidney failure
- Brain dysfunction, including delirium, seizures and coma
- The toxic phase of yellow fever can be fatal

Causes

Yellow fever is caused by a virus that is spread the aedes aegypti mosquitoes thrive in and near human habitations where they breed in even the cleanest water. Most cases of yellow fever occur in sub-Saharan Africa and tropical South America.
Human and Monkey are most commonly infected with the yellow fever virus. Mosquitoes transmit the virus back to forth between monkeys, humans or both. When a mosquito bites a human or monkey infected with yellow fever, the virus

enters the mosquitoes bloodstream and circulates before settling in the salivary glands. When the infected mosquito bites another monkey or human, the virus then enters the host's bloodstream, where it may cause illness.

Risks factors

- You may be at risk of disease if you travel to an area where mosquitoes continue to carry the yellow fever virus these areas include sub-Saharan Africa and tropical south America
- Even if there are not current reports of infected humans in these areas, it does not mean you are risk- free. It is possible that local populations have been vaccinated and are protected from the disease or that case of yellow fever just have not been detected and officially reported.
- If you are planning on traveling to these areas, you can protect yourself by getting a yellow fever vaccine at least 10 to 14 days before traveling
- Anyone can be infected with the yellow fever virus, but older adults are at greater risk of getting seriously ill

Complications

Yellow fever results in death for 20 or 50 percent of those who develop severe. Death usually occurs within 2 weeks from the short of infection. Complications during the toxic phase of yellow fever infection include kidney and liver failure, jaundice, delirium and coma. People who survive the infection recover gradually over a period of several weeks to months, usually without significant organ damage. During this time a person may experience fatigue and jaundice. Other complications include secondary bacterial infections, such as pneumonia or blood infection.

Test and diagnosis

Diagnosing yellow fever based on signs and symptoms can be difficult because early in its course, the infection can be easily confused with malaria, typhoid, dengue fever, and viral hemorrhagic fevers. To diagnose your condition, the doctor will likely ask questions about your medical and traveling history.

Collect blood for testing:

If you have yellow fever, your blood may reveal the virus itself. If not blood test known as Enzyme-Linked Immunosorbent Essay (ELISA) and polymerase chain reaction (PCR) also can detect antigens and antibodies specific to the virus. Result of these tests may not be available for several days.

Treatment and drugs

No antiviral medications have proved helpful in treatment of yellow fever. As a result, treatment consists primarily of supportive care in hospital. This including providing fluids and oxygen, maintaining adequate blood pressure replacing blood loss, providing dialysis for kidney failure, and treating any other infections that develop some people receive transfusion of plasma to replace blood proteins that improve clotting, if you have yellow fever, you may also be kept away from mosquitoes, to avoid transmitting the disease to others.

Prevention

Vaccine: A safe and highly effective vaccine prevents yellow fever. Yellow fever is known to be prevented in sub-Saharan Africa and parts of South America. Talk to your doctor about whether you need a yellow fever vaccine at least 10 to 14 days before traveling to these areas or if you are a resident of one of them. Some of these countries require a valid certificate of immunization in order to enter the country. a single dose of the vaccine provides protection for at least 10years. Side effects of yellow fever vaccine are usually mild, lasting five to ten days, and may include headaches, low grade fevers, muscles pain, fatigue and soreness at the site of injection. more-significant reaction-such as developing a syndrome similar to actual yellow fever, inflammation of the brain (encephalitis) or death-can occur, most often in infants or older adults. The vaccine is considered safest for those between the ages of 9months and 60years.Talk to your doctor about whether the yellow fever vaccine is appropriate if your child is younger than 9months, if you have a weakened immune system (immunocompromised), or if you are older than 60years.

Mosquito protection: In addition to getting the vaccine, you can help protect yourself against yellow fever by protecting yourself against mosquitoes. To reduce your exposures to mosquitoes:

- Avoid unnecessary outdoor activity when mosquitoes are most active
- Wear long-sleeved shirts and long pants when you go into mosquito-infested areas
- Stay in air-conditioned or well-screened housing

To ward off mosquitoes with repellent, use both of the following:

- Non skin repellent. Apply permethrim - containing mosquitoes repellent to your clothing, shoes camping, gear and bed netting. You can buy some articles of clothing and gear pre-treated with permethrim. Permethrim is not intended for use on your skin.
- Skin repellent. Product with the active ingredients DEET or picaridin provide the longest lasting skin protection.
- Choose the concentration based on the hours of protection you need. In general, higher concentration last longer. Keep in mind that chemical repellents can be toxic, and use only the amount needed for the time you will be outdoors. Do not use DEET on the hands of of young children or on infants under 2months of age. Instead, cover your infant's stroller or playpen

with mosquito netting when outside. According to the centers for disease control and prevention, oil of lemon eucalyptus, a more natural product, offers the same protection as DEET when used in similar concentrations. However, these products should not be used on children younger than age 3

5 Influenza

Influenza is a viral infection that attacks your respiratory system-your nose, throat and lungs. Influenza commonly called flu is not the same as stomach "flu" viruses that cause diarrhea and vomiting.

Symptoms

Initially, the flu may seem like a common cold with a runny nose, sneezing and sore throat, but colds usually develop slowly, whereas the flu tends to come on suddenly. And although a cold can nuisance, you usually feel much worse with the flu.

Common signs and symptoms of the flu include:

- Fever over 100F (38C)
- Aching muscles, especially in your back, arms and legs
- Chills ad sweat
- Dry cough
- Fatigue and weakness
- Nasal congestion

Causes

Flu viruses travel through the air in droplets when someone with the infection coughs, sneezes or talks. You can inhale the droplets directly, or you can pick up the germs from an object-such as a telephone or computer keyboard - and transfer to your eyes, nose or mouth.

Risk factors

Factors that may increase your risk of developing influenza or its complications include:

Age. Seasonal influenza tends to target young children and people over 65

Occupation. Health care workers and child care personnel are more likely to have close contact with people infected with influenza.

Living conditions: People who live in facilities along with many other residents, such as nursing homes, military barracks, are more likely to develop influenza.

Weakened immune system: Cancer treatment, anti-rejection drugs, corticosteroids and HIV/AIDS can weaken your immune system. This can make it easier you to catch influenza and may also increase yer risk of developing complication.

Chronic illness: Chronic conditions, such as asthma, diabetes or heart problems may increase yer risk of influenza complications.

Pregnancy: Pregnant women are more likely to develop influenza complications particularly in the second and third trimester.

Complication

If you are young and healthy, seasonal influenza usually is not serious. Although, you may feel miserable while you have it, the flu usually goes away with no lasting effects. But high risk children and adults may develop complications such as: pneumonia, bronchitis, sinus infections, and ear infections. Pneumonia is the most common and most serious. for older adults and people with a chronic illness , pneumonia can be deadly. The best protection is vaccination against both pneumococcal pneumonia and influenza.

Treatments and drugs

Usually, you will need nothing more than bed rest and plenty of fluids to treat the flu.but in some cases, your doctor may prescribe an antiviral medications such as oseltamivir (tamiflu) or zanamivir (relenza) if taken soon after you notice symptoms , these drugs may shorten your illness by a day or so and help prevent serious complications. Oseltamivir is an oral medication. Zanamivir is included through a device similar to an asthma inhaler and should not be used by anyone with respiratory problems, such as asthma and lungs disease. Antiviral side effects may include nausea, and vomiting. Oseltamivir has also been associated with derilium and self harm behavior recommend further study on both of these drugs, however, due to uncertainty about their effects beyond the initial reduction symptoms. Some strains of influenza have become resistant to oseltamivir and to amantadine which is an older antiviral drug.

Prevention

The centers for disease control and prevention (CDC) now recommends annual flu vaccination for all Americans over age of six months. Each year's seasonal flu vaccine contains protection from the three influenza viruses that are expected to be the most common during that year's flu season. The vaccine is typically available as an injection or as a nasal spray.

Controlling the spread of infection
The influenza vaccine is not 100 percent effective, so it is also important to take measures to reduce the spread of infection:

- -wash your hands. Through and frequent hand washing is the best way to prevent many common Infection. Scrub your hands vigorously for at least 15 seconds.
- -Alcohol-based hand sanitizers if soap and water are not readily available.
- -Contain your coughs and sneezes, cover your mouth and nose when you sneezes or cough. To avoid contaminating your hands, cough or sneeze into a tissue or the inner crook of your Elbow.
- -Avoid crowds. Flu spread easily wherever people congregate – in child care centers, schools, Office buildings, auditorium and public transportation. By avoiding crowds during peak flu Season, you reduce your chance of infection.

6 Smallpox

Smallpox is a contagious, disfiguring and often deadly to disease that has affected humans thousands of years.

Symptoms
The first symptoms of smallpox usually appear 12 to 14 days after you are infected. During the incubation period of seven to 17 days, you look and feel healthy and cannot infect others. Following the incubation period, a sudden onset of flu-like signs and symptoms occurs. These include:
-fever
-overall discomfort -headache
-severe fatigue -severe back pain
-sometimes vomiting or diarrhea or both
-a few days later flat red spots appear first on your face, hands and later on your trunk.

Within a day or two, many of these lesions turn into small blisters filled with clear fluids, which then turns into pus. Scabs begin to form eight to nine days and eventually fall off; leaving deep, pitted scars. The rash is usually most noticeable on the palms of your hands and the soles of your feet. Lesions also develop in the mucous membranes of your nose and mouth quickly turns into sores that break open, spreading the virus into your saliva.

Causes
Smallpox usually requires fairly prolonged face to face contact to spread. It is most transmitted through the air by droplets that escape when an infected person coughs sneezes or talks. In rare instances, airborne virus may spread further, possibly through the ventilation system in buildings, infecting people in other rooms or on other floors. Smallpox can also spread through contact with contaminated clothing and bedding, although the risk of infection from these sources is slight.

Complications
Most people who get smallpox survive. However, there are a few rare varieties of smallpox that are almost always fatal. These mere severe forms of smallpox most commonly affect pregnant women and people with impaired immune system. People who recover from smallpox usually have severe scars, especially on the face, arms and legs. In some cases, smallpox may cause blindness.

Test and diagnosis
Even a single confirmed case of smallpox would be considered an international health emergency. The centers for disease control and prevention can do definitive testing using a tissue sample taken from one of the lesions on the skin of the other infected person.

Treatment and drugs
No cure smallpox exists. Treatment would focus on relieving symptoms and keeping the person from becoming dehydrated. Antibiotics may be prescribed if a person develops a bacterial infection in the lungs or on the skin

Prevention
-To control the spread of the virus, people who have smallpox would be kept in isolation at hospital. All the people they have had contact with, would receive the smallpox vaccine, which can prevent or lessen the severity of the disease if given within three days of exposure to the smallpox virus.
-The vaccine uses a live virus that is related to smallpox, and it can occasionally cause serious complications, such as infections infecting the heart or brain. That is why a general vaccination program for everyone is not recommended at this time. The potential risk of vaccine outweighs the benefit, in the absence of an actual smallpox outbreak.

If you were vaccinated as a child:

It is known how long immunity lasts after a smallpox vaccine. Studies to answer that question have had conflicting results. The duration of protection can be affected by the type of vaccine used and how it was administered. It is likely vaccination is the most effective for about three to five years, with the immunity decreasing after that. Partial immunity may last much longer.

7 Viral hemorrhagic fevers

Viral hemorrhagic fevers are infectious diseases that interfere with the blood's ability to clot.
These diseases can also damage the wall of tiny blood vessels, making them leaky. The internal bleeding that results can range from relatively minor to life-threatening. Some viral hemorrhagic fevers includes: Dengue, Ebola, Lassa, Marburg, and Yellow fever. These diseases most commonly occur in tropical areas of the world. When viral hemorrhagic fevers occur in the United States, they were usually found in people who have recently traveled internationally. Viral hemorrhagic fevers are spread by contact with infected animals, no current treatment can cure viral hemorrhagic fevers, and immunizations exist for only few types. Until additional vaccines are developed, the best approach is prevention.

Symptoms

Signs and symptoms of viral hemorrhagic fevers vary by disease. In general initial symptoms may include:
-High fever -Fatigue
Dizziness
-Muscles, bone or joint aches -Weakness
-Symptoms can become life-threatening
Severe cases of some types of viral hemorrhagic fevers may cause bleeding, but people rarely die of blood loss. Bleeding may occur:
-Under the skin -Internal
organs
-From the mouth, eyes or ears

Other signs and symptoms of severe infections can include: -Shock
-Nervous system malfunction -Coma
-Delirium -Kidney failure -
Liver failure

Causes

The viruses that cause viral hemorrhagic fevers live naturally in a variety of animals and insects host-most commonly mosquitoes, ticks, rodents, or bats. Each of these hosts typically lives in a specific geographic area, so each particular disease usually occurs only where that viruses host normally lives. Some viral hemorrhagic fevers also can be transmitted from to person

How is it transmitted?

The route of transmission varies by specific virus. Some viral hemorrhagic fevers are spread by mosquitoes or tick bites. Others are transmitted by contact with infected blood or semen. A few varieties can be inhaled from infected rat faeces or urine. If you travel to an area where a particular hemorrhagic fever is common will increase your risk, you may infected there and then develop symptoms after you return home. It can take up 21 days for symptoms to develop.

Risk factors

Simply living in or traveling to an area where a particular viral hemorrhagic fever is common will increase your risk of becoming infected with that particular virus. Several other factors can increase your risk even more, including:
-Working with the sick -Slaughtering infected
animals -Sharing needles to use IV drugs -Having
unprotected sex

-Working outdoors or in rat-infested building

Complications
Viral hemorrhagic fevers can damage your: brain, eyes, heart, kidneys, liver, lungs and spleen. In some cases, the damage is severe enough to cause death.

Test and diagnosis
Diagnosing specific viral hemorrhagic fevers in the first few days of illness can be difficult because the initial signs and symptoms –high fever, muscles aches, headache and extreme fatigue are common to many other diseases. To help with diagnosis your doctor is likely to ask about your medical and travel history and any exposure to rodent or mosquitoes. Be sure to describe international trips in details, including the countries you visited and the dates, as well as any contact you may have had with possible source of infection.
Laboratory tests, usually using a sample of your blood are needed to confirm a diagnosis because viral hemorrhagic fevers are particularly virulent and contagious; these tests are usually performed in special designated laboratory using strict precautions.

Treatment and drugs
While no specific treatment exists for most viral hemorrhagic fevers, the antiviral drug RIBAVIRIN (Rebetol, virazole, others) may help shorten the course of some infections and prevent complication in some cases.

Therapy
Supportive care is essential. To prevent dehydration you may need fluids to help maintain your balance of electrolytes-minerals that critical to nerves and muscles function.

Surgical and other procedures
Some people may benefit from kidney dialysis, an artificial way of removing wastes from your blood when your kidney fails

Prevention
Preventing viral hemorrhagic fevers, especially in developing nations, presents enormous challenges. Many of the social, economic and ecological factors that contribute to the sudden
-War, displacement, destruction and habitat, lack of sanitation and proper medical care – are problems that have no easy solutions. If live in or travel to areas where viral hemorrhagic fevers are common, take precautions to protect yourself from infection

Get vaccinated:
The yellow fever vaccine is generally considered safe and effective, although in rare cases, serious effect can occur. Check with the centers for disease control and prevention about the status of the countries you are visiting – some require certificates of vaccination for entry. The yellow fever vaccine is not recommended for children under nine months of age or for pregnant women, especially during the first trimester. Vaccines for several less common types of viral hemorrhagic fevers are currently in developments.

Avoid mosquitoes and ticks
Do your best to avoid mosquitoes and ticks especially when traveling in areas where there are outbreaks of viral hemorrhagic fevers. Wear light-colored long pants and long-sleeved shirts or better yet, permethrin-coated clothing. Do not apply permethrin directly to the skin.
Avoid unnecessary activities at dust and down when mosquitoes are most active and apply mosquito repellent with a 20 to 25 percent concentrations DEET to your skin and clothing. If you are staying intended camps or local hotels, use bed nets and mosquito coils.

Guard against rodents
If you live in an area where there are outbreaks of viral hemorrhagic fevers, take these steps to prevent rodents' infestations in your home:
*Keep pet food covered and stored in rodent-proof containers
*Store trash in rodent-proof containers, and clean the containers often. *Dispose of garbage on a regular basis
*Make sure doors and windows have tight-fitting
*Place woodpiles and stacks of bricks and other materials at least 100 feet from your house *Mow your grass closely and keep brush trimmed to within 100 feet from your house

8 Thyphus
Signs and symptoms
-Back pain –Delirium
-High fever (40°c to 104°c) -Joint pain

-Low blood pressure -Photophobia (sensitivity to light) –Rashes
-Severe headache -Severe muscle pain

Marine typhus:
-Abdominal pain –Backache
-Dull red rash that begins on the middle of the body and spreads. -Extremely high fever (41°c or 105-106°c)
-Severe headaches -Joint pain -Muscles pain -Vomiting

Epidemic typhus

Epidemic typhus (also called "camp fever", "jail fever", hospital fever, ship fever, putrid fever, famine fever, petechial fever, epidemic louse-borne typhus and louse – borne typhus) is a form of typhus so named because the disease often cause epidemics following wars and natural disasters. The causative organism is **rickettsia prowazekii** transmitted by the human body louse.

Signs and symptoms
Symptoms include:
-Severe headache -High fever
-Cough, rash, severe muscles pain, chills, falling blood pressure -Stupor, sensitivity to light, delirium and death.
A rash begins on the chest about five days after the fever appears, and spreads to the trunk and extremities. A symptom to all forms of typhus is a fever which may reach 39°c or 102°f

Transmission
Epidemic typhus is thus found most frequently during times of war and deprivation. For example, typhus killed hundreds of thousands of prisoners in Nazi concentration camps during World War II.
The deteriorating quality of hygiene in camps such as theresienstadt and Bergen – Belsen created conditions where diseases flourished. Situations in the twenty-first century with potential for a typhus epidemic would include refugee camps during a major famine or natural disasters. In periods between outbreaks, when human to human transmission occurs less often, the flying squirrel serves as a zoonotic reservoir for the Rickettsia Prowazekii bacterium.

Treatment
The infection is treated with antibiotics. IV fluids and oxygen may be needed to stabilize the patient.
The antibiotics used are:
Tetracycline: are used before eight days
Chloramphenicol: is also used. Infection may be prevented by vaccination

Marine typhus

Signs and symptoms
Abdominal pain, backache, dull red rash that begins on the middle of the body and spreads. High fever, hacking, dry cough, severe headache, joint pain and vomiting.

Causes
Marine typhus is caused by RICKETTSIA TYPHI FLEAS

Prevention
The most effective way to prevent typhus is inoculation with the vaccine series before travelling to endemic areas, and avoids contact with lice

Treatment
Marine typhus may be treated by sulphonamides, penicillin…

9. Hepatitis b

Hepatitis B is a virus that infects the liver

Signs and symptoms
-Loss of appetite -Nausea -Vomiting -Body aches -Mild fever -Dark urine –Jaundice

Transmission
Transmission of hepatitis B virus result from exposure to infections blood or body fluids containing blood. Possible forms of transmission include:
-Sexual contact
-Blood transfusion and transfusion with other human blood products -Re-use of contaminated needles and syringes.
-Vertical transmission from mother to child during childbirth

Diagnosis

Hepatitis B viral antigens and antibodies detectable in the blood following acute infection. Hepatitis B viral antigens and antibodies detectable in the blood of chronically infected person, the test called assays for detection of hepatitis B virus infection involves serum or blood test.

Prevention

Vaccines for the prevention of hepatitis B have been routinely recommended for infants since 1991 in the United States. Most vaccines are given in three doses over a course of months. A protective response to the vaccine is defined as anti-HBs antibody-concentration of at least
10mlv/ml in the recipient's serum. The vaccine is more effective in children and 95% of those vaccinated have protective level of antibody.
This drops to around 90% at 40 years of age and to around 75% in those over 60 years. The protection afforded by vaccination is long-lasting even after antibody levels fall below 10mlv/ml. Vaccination at birth is recommended for all infants of HBV infected mothers.

Treatment

In treatment, antiviral drugs may be used, those are: Lamivudine (Epivir), Adefovir (Hepsera), Tenofovir (Viread), Telbivudine (tyzeke) and Entecavir and the two immune system modulators interferon alpha-2a and pegylated interferon alpha-2a (pegasys). The use of interferon, which requires injection daily or thrice weekly, has been supplanted by long-long acting. Pegylated interferons, which is injected only once weekly.

Measures of disease frequency and disease burden

Introduction

Learning objectives: you will about commonly used epidemiological measurements to describe the occurrence of disease. This section covers:
Measures of disease frequency including:

a) Prevalence
b) Incidence
c) Calculation of person - time at risk
d) Issues in defining population at risk
e) The relation between incidence and prevalence
f) Commonly used measures of disease frequency

Measures of effects include:

g) Main measures of effects
h) Interpreting measures of effects

The essence of epidemiology is to measures disease occurrence and make comparison between population groups. The current section introduces the commonly used measures that help our understanding of distribution of diseases in a given population
Please now read the the source text below
Resources text: a principal role of epidemiology is to describe and explain differences in the distribution of disease or other health outcomes of interest between populations.

Examples of health outcomes measured in epidemiological studies include:

1) Morbidity
2) Mortality
3) Infectious disease incidence
4) Birth defects
5) Disability
6) Injuries
7) Vaccine efficacy
8) Utilization of hospital services

Measures of disease frequency are used to describe how common an illness (other health events) is with reference to the size of the population (the population at risk) and measure of time.
There are two main measures of disease frequency:

1. Prevalence

Prevalence measures the proportion of individuals in a defined population that have a disease or other health outcomes of interest at a specified point in a time (point prevalence) or during a specified period of time (period prevalence).

Example

Of 10,000 female residents in town A on first January 2006, 1,000 has hypertension, the prevalence of hypertension among women in town A on this date is calculated as:
1,000/10,000 = 0.1 or 10%
Prevalence is useful measures for quantifying the burden of disease in a population at a given point in time. Calculating prevalence of various conditions across different geographical areas or amongst different sub-groups of the population and examining prevalence of other potential risk factors can be of particular use when planning health services. Prevalence is not a useful measure for establishing the determinants of disease in a population.

Incidence
In contrast to prevalence, incidence is a measure of the number of new cases of disease (or other health outcomes of interest) that develops in a population at risk during a specified time – period.

There two main measures of incidence:
Risk (or cumulative incidence) is related to the population at risk at the beginning of the study.
Period
Rate
Is related to a more precise
*Measure of the population at risk
During the study period and is measured in person time-time unit.

Risk
Risk is the proportion of individuals in a population (initially fully of disease) who develop the disease within a specified time intervals. Incidence is expressed as a percentage (or if small as per 1,000 persons.)
The incidence risk assumes that the entire population at risk at the beginning of the study period has been followed for the specified time period for the development of the outcome under investigation. However, in a cohort study participants may be lost during follow – up.
For example, some participants may:

- Develop the outcome under investigation
- Refuse to continue to participate in the study
- Migrate
- Die
- Enter the study sometime after it starts

To account for these variations during follow-up, a more precise measure can be calculated, the incidence rate.
Incidence rate
Incidence rate also measure the frequency of new cases of disease in a population. However incidence rates take into account the sum of the time that each person remained under observation and at risk of developing the outcome under investigation.

Calculation of person-time at risk
The denominator in an incidence rate is the sum of each individual's time at risk and is commonly expressed in person years at risk.The incidence rate is the rate of contracting the disease among these still at risk. When a study subject develops the disease, dies or leaves the study, they are no longer at risk and will no longer contribute person-time units at risk.

Issues in defining population at risk
For many measures of disease frequency, precise definition of the denominator is essential for accuracy and clarity. The population at risk (denominator) should include all persons at risk of developing the outcome under investigation. Therefore, individuals who currently have the disease understudy or who are immune (e.g due to immunization) should be excluded from the denominator. However this is not always possible in practice.
Note that individuals not at risk of the disease are included in the denominator (population at risk) the resultant measure of disease in the population under investigation.

The relation between prevalence and incidence
The proportion of the population that has a disease at a point in time (prevalence) and the rate of occurrence of new disease during a period of time incidence are closely related.
Prevalence depends on:
1) Incidence rate
2) The duration of the disease
For example, if the incidence of a disease is low but the duration of disease (i.e. until recovery or death) is long, the prevalence will be high relative to the incidence. For example, disease like leprosy or tuberculosis tends to persist for a longer duration, from months to years. Hence the prevalence (old and new cases) would be longer than the incidence.
Conversely, if the incidence of disease is high and the duration of the disease is short, the prevalence will be low relative to the incidence.
For example, acute conditions like diarrhea have a relatively short duration (a few days).

A change in duration a disease for example the development of new treatment which prevent death but does not result in a cure will lead to an increase in prevalence. Fatal diseases or disease from which a rapid recovery is common have a low prevalence, whereas diseases with a low incidence may have a higher prevalence.
If there are incurable but rarely fatal and have a long duration.
The relationship between incidence and prevalence can be expressed as
P=ID: where P= Prevalence
I= Incidence
D=Average duration of the disease
A population in which the number of people with and without the disease remain stable as known as a "steady-state population". In such circumstances, the point prevalence of the disease is approximately equal to the product of the incidence rate and the mean duration of disease (e.g length of time from diagnosis to recovery or death), providing that prevalence is less than about 0.11
That is prevalence =incidence x duration
As a result, when two of the measures are known, the third can be calculated by substitution.

Other commonly used measures of disease frequency in epidemiology
*Measure of effects
Measures of effects are used in epidemiological studies to assess the strength of an association between a putative risk factor and the subsequent occurrence of disease. This requires that the incidence of disease in a group of person exposed to a potential risk factors.
The comparison can be summarized by calculating either the ratio of measures of disease frequency for the two groups or the difference between the two, and reflects the increase in frequency of disease in one population compared with another, treated as baseline.
These measures are often collectively referred to as measures of relative risk.
The relative risk is a measure of the strength of an association between an exposure and disease and can be used to assess whether a valid observed association is likely to be causal. The most commonly used measures of effect is the ratio of incidence rates that is:

- Rate (or risk) in exposed group
- Rate (or risk) in unexposed group

Three main measures of effect
Example: there are ten times more lungs cancers in smokers than in nonsmokers (Rate ratio is 10)

Interpreting measures of relative risk RR
A relative risk of 1.0-indicates that the incidence of disease in the exposed and unexposed group is identical and that there is no association observed between the disease and risk.

Factor / Exposure
A relative risk >1.0 when risk of disease is greater among those exposed and indicates a positive association or an increased risk among those exposed to the risk factor compared with those unexposed. A relative risk of 1.3means 30% rises in risk for those exposed to the risk factor compared to those who were unexposed.

A relative risk
Note: rate ratios and risk ratios tend to be numerically similar for rare diseases
The choice of a ratio measure or a difference measure should be based on our understanding of the mechanism by which a risk factor increases the incidence of disease.

PART: II
TROPICAL DISEASES
TROPICAL DISEASES: are diseases that are prevalent in or unique to tropical and subtropical regions. The diseases are less prevalent in temperate climates, due in part to the occurrence of cold season, which control the insect population by forcing hibernation. Insects such as mosquitoes and flies are by far the most common disease carrier or vector.

BACKGROUND OF SOME TROPICAL DISEASES
1.Chagas disease or American trypanosomiasis
Is a tropical parasitic disease caused by the protozoan trypanosoma cruzi and spread mostly by insect known as triatominae or kissing bags. The symptoms change over the course of the infection. In the early stage symptoms are typically either not present or mild and may include:

- Fever
- Swollen lymph nodes
- Headaches
- Local swelling at the site if the bite

After 8-12weeks individuals enter the chronic phase of disease and in 60-70% it never produces further symptoms. 30 to 40% of people develops further symptoms 10 to 30 years after the initial infection, these symptoms includes:

- Enlargement of the ventricles of the heart in 20 to 30% leading to heart failure
- Enlargement of oesophagus

T. Cruzi is commonly spread to human and other animals by the blood-sucking "kissing bag" of the subfamily Triatominae. These insects are known by a number of local names, including **vinchuca** in Argentina, **bolivia** in Chile and Paraguay, **barbeiro** in Brazil, **pito** in Colombia, **chinche** in central America and **chipo** in Venezuela. They may also be spread through blood transfusion, Organ transplantation (the removing of an organ from one body to another or from a donor site to another location on the patient's own body for the purpose of replacing the recipient's damaged or absent organ), eating food contaminated with the parasites and from mother to foetus. Diagnosis of early disease is by finding the parasite in the blood using a microscope. Chronic disease is diagnosed by finding antibodies for T.Cruzi in the blood.

Prevention involves eliminating kissing bugs and avoiding their bites. Other preventive efforts include screening blood used for transfusion. A vaccine has not been developed. Early infections are treatable with the medications: benznidazole, or nifurtimox. They nearly always result in a cure if given early however become less effective the longer a person has had chagas disease. When used in chronic disease they may delay or prevent the development of end stage symptoms. Benznidazole and nifurtimox cause temporary side effects in up to 40% of people including skin disorders, brain toxicity, and digestive system irritation. It is estimated that 7 to 8 millions people mostly in Mexico, Central America and South America have chagas disease. The disease was first described in 1909 by **Carlos Chagas** after whom it is named.

Signs and symptoms

The human disease occur in two stages: An acute stage which occurs shortly after an initial infection and a chronic stage that develops over many years. The acute phase lasts for the first few weeks or months of infection. It usually occurs unnoticed because it is symptoms – free or exhibit only mild symptoms that are not unique to chagas disease.

This can include: fever, fatigue, body aches, headache, rash, loss appetite, diarrhea and vomiting. The signs on physical examination can include mild enlargement of the liver or spleen, swollen glands, and local swelling (a choma) where the parasite entered the body. The most recognized marker of acute chagas disease is called Roma~~n~~a's signs which including swelling of the eyelids on the sides of the face near the bite wound or where the bug feces were deposited or accidentally rubbed into the eye. Rarely, young children, or adults may die from the acute disease due to severe inflammation, infection of the heart muscles (myocarditis) or brain (meningoencephalitis).the acute phase also can be severe in people with weakened immune systems. If systems develop during the acute phase, they usually resolve spotantaneously within three to eight weeks in approximately 90% of individuals.

Although, the symptoms resolve, even with treatment the infections persists and enters a chronic phase. Individuals with chronic chagas disease, 60-80% will never develop symptoms (called indeterminate chronic chagas disease), while the remaing 20-40% will develop life-threathening heart and/or digestive disorders during their lifetime (called determinate chronic chagas disease), in 10% of individuals, the disease progresses directly from the acute form to a symptomatic clinical form of chronic chagas disease. The symptomatic (determinate) chronic stage affects the nervous system, digestive system and the heart. About two-thirds of people with chronic symptoms have cardiac damage including dilated cardiomyopaty, (DCM), a condition in which the heart becomes weakened and enlarged and cannot pump blood efficiently. This may cause heart rhythm abnormalities and may result in death. About one-third of the patients go on to develop digestive system damage, resulting in dilation of digestive tract (megacolon and megaesophagus), accompanied by severe weight loss. Swallowing difficulties (secondary achalasia) may be the first symptoms of digestive disturbance and may lead to:

- Malnutrition, Neuritis, Dementia, Confusion, Chronic encephalopathy
- Sensory and motor deficits

The clinical manifestation of chagas disease are due to cell death in the target tissues that occurs during the infecting cycle, by sequentially inducing an inflammatory response, cellular lesions and fibrosis. For example, intracellular amastigotes , destroy the intramural neurons of the autonomic nervous system in the intestine and heart leading to megaintestine and heart aneurysms respectively. If left untreated, chagas disease can be fatal, in most cases due to heart muscle damage.

Management

There two approaches to treating chagas disease, antiparasitic treatment, to kill the parasites and symptomatic treatment, to manage the symptoms and signs of infection. Management uniquely involves addressing selective incremental failure of the parasympathetic nervous system. Autonomic disease imparted by chagas may eventually result in megaesophagus, megacolon and accelerated cardiomyopaty. The mechanisms that explain why chagas targets the parasympathetic autonomic nervous system remain poorly understood.

Medication

Antiparasitic treatment is most effective early in the course of infection but is not limited to cases in the acute phase. Drug of choice include: Azol or Nitro derivatives, such as benznidazol or Nifurtimox. Both agents are limited in their capacity to affect parasitological cure. (complete elimination of T.Cruzi from the body), especially in chronically infected patients, and resistance to these drugs has been reported. Studies suggest antiparasitic leads to parasitological cure in about 60-85% of adults and more than 90% of infants treated in the first year of acute phase chagas disease.

Children (aged six to twelve years) with chronic disease have cure rates of about 60%with benznidazole. While rate of cure declines the longer an adult has been infected with chagas, treatment with benznidazole has been shown to show the onset of heart disease in adults with chronic chagas infections.
Treatment of chronic infection in women prior to or during pregnancy does not appear to reduce probability the disease will be passed on the infants. Likewise it is unclear whether. **PROPHYLACTIC** treatment of chronic infection is beneficial in person who will undergo immunosuppression (for example, organ transplant recipients) or in persons who are already immunosupressed (for example, those with HIV infection).

Complications
In chronic stage, treatment involves managing the clinical manifestation of the disease. For example pacemakers and medications for irregular heartbeats, such as the ant-arrhythmia drug. Amiadarone, may be life saving for some patients with chronic cardiac disease, while surgery may be required for megaintestine. The disease cannot be cured in this phase, however. Chronic heart disease caused by chagas disease is now common reason for heart transplantation surgery. Until recently, however chagas disease was considered a contraindication for the procedure, since the heart damage could recur as the parasite was expected to seize the opportunity provided by immunosuppression that follows surgery. It was noted that survival rates in chagas patients could be significantly improved by using lower dosage of the immunosupression drug. Cyclosporine. Recently, direct stem all the therapy of the heart muscles using the bone marrow all transplantation has been shown to dramatically reduce risk of the heart failure in chagas patients.

Epidemiology
Chagas disease in Latin America (endemic zone)
Chagas disease affects 8 to 10 millions people living in endemic Latin American countries, with an additional 300,000-400,000 living in nonendemic countries, including Spain and the United States. An estimated 41,200 new cases occur annually in endemic countries, and 14,400 infants are born with congenital chagas disease annually. In 2010 it resulted in approximately 10,300 deaths up from in 1990. The disease is present in 18 countries on the American continents, ranging from the southern United States to northern Argentina. Chagas exists in two in different ecological zones. In the southern cone region, the main vector lives in and around human homes. In Central America and Mexico, the main vector species lives both inside dwellings and in uninhabited areas. In both zones, chagas occurs almost inclusively in rural areas, where triatomines breed an feed on the over 150 species from 24 families of domestic and wild animals, as well as humans that are the natural reservoir of T-Cruzi.
Although triatominae bugs feed on them, birds appear to be immune to infection and therefore are not considered to be a T.cruzi reservoir. Even when colonies of insects are eradicated from a house and surrounding domestic animal shelters, they can re-emerge from plants or animals that are part of the ancients sylivatic (referring to wild animals) infection cycle. This is especially likely in zones with mixed open savannah, with clumps of trees interspersed by human habitation. The primary wildlife reservoir for trypanosoma cruzi in the United States includes opossums, caccooms, armadillos, squirrels, woodrats, and mice. Opossums are particularly important as reservoirs, because the parasite can complete its life
Cycle in the anal glands of the animal without having to re-enter the insect vector. Recorded prevalence of the disease in the opossums in the US, ranges from 8.3% studies on raccoons in the southeast have yielded infection rates ranging from 47% to as low as 15.5%. armadillo prevalence studies has been described in Louisiana, and range from a low of 1.1% to 28% additionally, small rodents, including squirrels, mice, and rates, are important in the sylvatic transmission cycle because of their importance as blood meal sources for the insect vector. A Texas study revealed 17.3% T.cruzi prevalence in 75 specimens representing four separate small rodent species. Chronic chagas disease remains a major health problem in many Latin American countries, despite the effectiveness of hygienic and preventive measures, such eliminating the transmitting insects. However, several landmarks have been achieved in the fight against it in the latin America, including a reduction by 72% of the incidence of human infection in children and young adults in the countries of the southern cone initiative, and at least three countries (Uruguay, in 1997, chile, in 1999, and Brazil, in 2006) have been certified free of vectorial and transfusional transmission. In Argentina vectorial transmission has been interrupted in 13 of 19 endemic provinces, and major progress toward this goal has also been made in both Paraguay and Bolivia. Screening of donated blood, blood components, and solid organ donors, as well as donors of cells, tissues, and cell and tissue products for T.cruzi is mandated in cell chagas-endemic countries and has been implemented. Approximately 300,000 infected people live in the United States, which is likely the result of immigration from Latin American countries. With increased population movements, the possibility of transmission by blood transfusion became more substantial in the United States. Transfusion blood and tissue products are now actively screened in the US, thus addressing and minimizing this risk.

History
Carlos chagas in his laboratory at the Instituto oswaldo cruzi.
The disease was named after the Brazilian physician and epidemiologist **CARLOS CHAGAS** who first described it in 1909 but the disease was not seen as major public health problem in humans until the 1960 (the outbreak of chagas disease in brazil in the 1920 went widely ignored.
He discovered that the intestines of triatomidae (now reduviidae: triatominae) harbored a flagellate protozoan, a new species of trypanosome genus, and was to prove experimentally that it could be transmitted to marmoset monkeys that were bitten by the infected bug. Later studies showed out squirrel monkeys were also vulnerable to infection. Chagas named the pathogenic parasite as trypanosoma cruzi and that year as schizotrypanum cruzi, both honoring oswaldo cruzi, the noted Brazilian

physician and epidemiologist who successfully fought epidemics of yellow fever, smallpox and bubonic plague in Rio de Janeiro and cities in the beginning of 20th century. Chagas was also the first to unknowingly discover and illustrate the parasitic fungal genus. Pneumocytis, later infamously linked to PCP (pneumocytis pneumonia in AIDS victims)

2 Dengue Fever

Dengue fever or also known as breakbone fever, is a mosquito-borne tropical disease caused by dengue virus.

Signs and symptoms

Schematic depiction of the symptoms of dengue fever, typically, people infected with dengue virus are asymptomatic (80%) or only have mild symptoms such as an uncomplicated fever. Others have more severe illness (5%) and in a small proportion it is life-threatening. The incubation period (the time-between exposure and onset of symptoms) range from 3-14 days, but most often it is 4-7days. Therefore travelers returning from endemic areas are unlikely to have dengue fever or other symptoms starts more than 14 days after arriving home. Children often experience symptoms similar to those of the common-cold and gastroenteritis(vomiting and diarrhea) and have greater risk of severe complications, though initial symptoms are generally mild but include high fever.

Clinical Course

Clinical course of dengue fever the characteristic symptoms of dengue are: onset fever, headache (typically located behind the eyes), muscles and joint pain, and a rash. The alternative name for dengue "breakbone fever" comes from the associated muscle and joint pain. The course of infection is divided into three phases: Febrile, Critical, and Recovery. The febrile phase involves: high fever, potentially over 40°c (104°f) and associated with generalized pain and headache, this usually lasts 2 to 7 days. Nausea and vomiting may also occur. A rash occur in 50-80% of those with symptoms in the first or second day of symptoms as flushed skin, or later in the course of illness (days 4-7), as a rash described as islands of white in the sea of red has also been described. Some petechial (small red spots that do not disappear when the skin is pressed , which are caused by broken capillaries) can appear at this point, as may some mild bleed from the mucous membranes of mouth and nose. The fever itself is classically biphasic or saddleback in nature, breaking and then returning for one or two days. In some people the disease proceeds to critical phase as fever resolves. During this stage there is leakage of plasma from the blood vessels which typically lasts one to two days. This may result in fluid accumulation in the chest and abdominal cavity as well as depletion of fluid from the circulation and decreased supply to vital organs. There may also be organ dysfunction and severe bleeding, typically from the gastrointestinal tract. Shock (dengue shock syndrome) is less than 50% of all cases of dengue. However those who have previously been infected with other serotype of dengue virus (secondary infection) are at an increased risk. This critical phase, while rare, occurs in children and young adult. The recovery phase occurs next with resorption of the leaked fluid into the bloodstream. This lasts two to three days. Improvement is often striking and can be accompanied with severe itching and a slow heart rate. Another rash may occur with either maculopapular or vasculitic appearance, which is followed by peeling of the skin. During this stage, a fluid over load state may occur, if it affects the brain, it may cause a reduced level of consciousness or seizures. A feeling of fatigue may lasts for weeks in adults.

Associated problems

Dengue can occasionally affects several other body systems, either in isolation or along with the classic dengue systems. A decreased level of consciousness occur in 0.5-6% of severe cases, which is attributable either to inflammation of the brain by the virus or indirectly as a result of impairment of vital organs, for example, the liver other neurological disorders have been reported in context of dengue such as transversemyelitis and guillain- barre syndrome infection of the heart and acute liver failure are among the rarer complications.

Causes

Dengue fever is caused by dengue virus. Dengue fever virus (DENV) is an RNA virus of the family flaviviridae, genus flaviviridae. Other members of the same genus include yellow fever virus, west Nile virus, Japanese encephalitis virus, tick borne encephalitis virus etc. the dengue virus genome (genetic materials) contains about 11000 nucleotide base, which code for the three different types of protein molecules that form virus particle and seven other type of protein molecule (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are only found in infected host cells and are required for replication of the virus. There five strains of the virus called serotypes of which the first four, are referred to as DENV-1, DENV-2, DENV-3 and DENV-4 the distinction between the serotype is based on their antigenicity.

Transmission

Dengue virus is primarily transmitted by Aedes Mosquitoes particularly AEDES AEGYPTI these mosquitoes usually live between the latitude of 35° north and 35° south below an elevation of 1000 meters. They typically bite during the day, particularly in the early morning and evening but they able to bite and thus spread infection at any time of the day all during the year. Other Aedes species that transmit the disease include: A.albopictus, A.polynesiensis and A.seutellaris. humans are the primary host of the virus, but it also circulates in nonhuman primates. An infection can be acquired via a single bite. Female mosquitoes that take a blood meal from a person infected with dengue fever, during the initial 2-10 days febrile period become itself infected with the virus in the cell lining its gut. About 8-10 days later the virus spreads to other tissues including the mosquito's salivary glands and is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remain infected for life. Aedes aegypti prefers to lay its eggs in artificial water containers, to

live in close proximity to humans, and transmitted via infected blood products and through organ donation in countries such as Singapore, where dengue is endemic, the risk is estimated to be between 1.6 and 6 per 10,000 transfusions. Vertical transmission (from mother to child) during pregnancy or at birth has been reported. Other person to person modes of transmission have also been reported, but are very unusual.

Predisposition (risk factors)

Severe disease is more common in babies and young children, and in contrast to many other infections it is more common in children that are relatively well nourished. Other risk factors for severe disease include female sex, high body mass index, and viral load. While each serotype can cause the full spectrum of disease, virus strain is a risk factor; infection with the serotype is thought to produce lifelong immunity to that type, but only short protection against the other three. The risk of severe disease from secondary infection if someone previously exposed to serotype DENV-1 contrasts serotype DENV-2 or DENV-3 or if someone previously exposed to DENV-3 acquires DENV-2. Dengue can be life-threatening in people with chronic disease such as diabetes and asthma.

Diagnosis

The diagnosis of dengue is typically made clinically, on the basis of reported symptoms and physical examination; this applies especially in endemic areas. Eary disease can be difficult to differentiate from other viral infection. Probable diagnosis is based on thefindings of fever plus two of the following: nausea and vomiting, rash, generalized pain, low white blood cell count, positive tourniquet test or warning signs in someone who lives in an endemic area. Warning signs typically occur before the onset of severe dengue. The tourniquet test which is particularly useful in settings where no laboratory investigations are readily available, involves the applications of a bloodpressure cuff at between the dialstolic and systolic pressure for five minutes, followed by the counting of any petechial hemorrhages, a higher number makes diagnosis of dengue more likely with the cut off being more than 10 to 20 per 1 inch.and The diagnosis should be considered in anyone, who develops a few within two weeks of being ithe tropics or subtropics. It can be difficult to distinguish dengue fever and chikungunya, a similar viral infection that shares many symptoms and occurs in similar parts of the world. To dengue often, investigations are performed to exclude other conditions that cause similar symptoms such as malaria, leptospirosis, viral hemorrhagic fever, typhoid fever, meningococcal disease, measles and influenza. The earliest change detectable on laboratory investigations is a low white blood cell count, which may then be followed by low platelets and metabolic acidiosis. A moderately elevated level of aminotranferase (AST and ALT) from the liver is commonly associated with low platelets and white blood cell.

Prevention

There is no approved vaccine, for the dengue virus. Prevention thus depends on control of and protection from the bites of the mosquito that transmits it. The World Health Organization recommends an integrated vector control program consisting five elements:

1 Eliminating habitats of Aedes Aegypti

This is done by getting rid of open sources of water, or if this possible,

2 Using insecticides or biological control of agents

3 Reducing open collections of water through environmental modification is the preffered method of control, given the concerns of negative health effects from insecticides and greater logistical difficulties with control agents.

4 Using mosquito netting

5 Using insect repellent

Management

There no specific antiviral drugs for dengue, however maintainingproper fluids balance is important. Treatment depends on symptoms, those who are able to drink, are passing urine have no “warning signs” and are other wise healthy can be managed at home with daily follow up and ORT. Those who have other health problems have “warning signs”or who cannot manage regular follow up should be cared for in hospital. In those with severe dengue care should be provided in an area where there is access to to an intensive care unit. IV hydration, if recquired is typically only needed for one or two days. The rate of administration is titrated to a urinary output of 0.5-1ml/kg/h, stable vital signs and normalization of hematocrit. The smallest amount of fluid recquired to achieve this is recommended. Invasive medical procedures such as nasogastric intubation, intramascular injections and arterial punctures are avoided, in view of the bleeding risk. Paracetamol (acetaminophen) is used fever and discomfort while NSAIDS such as ibuprofen and aspirin are avoided as they might aggravate the risk of bleeding. Blood transfusion is initiated early in people presenting with unstable vital signs in the face of a decreasing hematocrit, rather than waiting for the hemoglobin concentration to decrease to some predeterminate “transfusion trigger” level. Packed red blood cell or whole blood is recommended while platelets and fresh frozen plasma are usually not. Corticosteroid do not do not appear to affect outcomes and may cause harm, thus are not recommended. During the recovery phase intravenous fluids are discontinued to prevent a state of fluid overload. If fluid overload occurs, and vital signs are stable, stopping further fluids may be all that is needed. If a person is outside of the critical phase, a loop diuretic such as furosemide may be used to eliminate excess fluid from the circulation.

Epidemiology

Epidemic dengue and A.aegypti A.aegypti, epidemic dengue Most people with dengue recover without any ongoing problems. The mortality is 1-5%. Without treatment, and less than 1% with adequate treatment, however severe disease carries a mortality of 26%. Dengue is endemic in more than 110 countries. It infect 50 to 528 million people worldwide a year, leading to half a million hospitalization, and approximately 25,000 deaths. For the decade of 2000, 12countries in Southeast Asia were estimated to have about 3millions infections and 6,000 deaths annually. It is reported in at least 22 countries in Africa, but is likely present in all of most commonly acquired urban environment. In recent decades, the expansion of villages, towns and cities in endemic areas, and the decreased morbidity of people have increased the number of epidemics circulating viruses. Dengue fever, which was once confined to Southeast Asia, has now spread to southern chine, countries in the Pacific Ocean and America, and might pose a threat to Europe. Rates dengue increased 30 folds between 1960 and 2010. This increase is believed to be due to a combination of urbanization growth, increased international, travel, and global warming. The geographical distribution is around the equator, with 70% of the total 2.5 billion people living in endemic areas from Asia to the pacific. Infection with dengue is second only to malaria as a diagnosed cause of fever among returning travelers. It is the most common viral disease burn estimated at 1600 disability adjusted life years per million populations. The world health organization counts dengue as one of seventeen neglected tropical disease. Like most arbovirus, dengue virus is maintained in nature in cycles that involves preferred blood-sucking vectors and vertebrate hosts. The viruses are maintained in the forests of Southeast Asia and Africa by transmission from female aedes mosquitoes of species other than A. aegypti-to other offspring and to lower primates. In towns and cities the virus is primarily transmitted by the highly domesticated A.aegypti. in rural settings the virus is transmitted to human by A.aegypti and other species of aedes such as A. albopictus.

History

The first record of the case of probable dengue fever is a Chinese medical encyclopedia from the Jin dynasty (256-420AD) which preferred to a "water poison" associated with flying insects. The primary vector, A.aegypti, spread out of Africa in the 15^{th} to 19^{th} centuries due in parts to increased globalization secondary to the slave trade. There have been descriptions of epidemics in the 17^{th} century but the most plausible early reports of dengue epidemics are from 1779 and 1780, when an epidemic swept across Asia, Africa and North America. From that time until 1940 epidemics were infrequent. In 1906 transmission by A. mosquitoes was confirmed, and 1907 dengue was the second disease (after yellow fever) that was shown to be caused by the virus. Further investigations by **John Burton Clendand** and **Joseph Flanklin Siler** completed the basic understanding of dengue transmission. The marked spread of during and after Second World War has been attributed to ecologic description. The same trends also led to the spread of different serotypes of the disease to new areas, and to the emergence of dengue hemorrhagic fever. This severe form of the disease was first reported in the Philippines in 1953 by the 1970, it had become a major cause of child mortality and had emerged in the pacific and Americas. Dengue hemorrhagic fever and dengue shock syndrome were first noted in central and South America in 1981 as DENV-2 was contracted by people who had previously been infected with DENV-1 several years earlier.

3. Helminths

Helminths are large, multicellular organisms, generally can be seen with naked eyes in their mature stages. They are worm-like organisms living in and feeding on living hosts, receiving nourishment and protection while disrupting their hosts' nutrient absorption, causing weakness and disease. Those that live inside the digestive tract are called intestinal parasites. They can live inside humans and other animals.

Helminthology is the study of parasitic worms and their effects on their hosts. The word helminth comes from Greek hélmins, a kind of worm.

Categorization

Helminths is a polyphyletic group of morphologically similar organisms, consisting of members of the following taxa: monogeneans, cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes). The following table shows the principal morphological distinctions for each of these helminth families:

	Cestodes (tapeworms)	**Trematodes (flukes)**	**Nematodes (roundworms)**
Shape	Segmented plane	Unsegmented plane	Cylindrical
Body cavity	No	No	Present
Body covering	Tegument	Tegument	Cuticle
Digestive tube	No	Ends in cecum	Ends in anus

Sex	Hermaphroditic	Hermaphroditic, except schistosomes which are dioecious	Dioecious
Attachment organs	Sucker or bothridia, and rostellum with hooks	Oral sucker and ventral sucker or acetabulum	Lips, teeth, filariform extremities, and dentary plates
Example diseases in humans	Tapeworm infection	Schistosomiasis, swimmer's itch	Ascariasis, dracunculiasis, elephantiasis, enterobiasis (pinworm), filariasis, hookworm, onchocerciasis, trichinosis, trichuriasis (whipworm)

Note: ringworm (dermatophytosis) is actually caused by various fungi and not by a parasitic worm.

Acquisition

Helminths often find their way into a host through contaminated food or water, soil, mosquito bites, and even sexual acts. Poorly washed vegetables eaten raw may contain eggs of nematodes such as Ascaris, Enterobius, Trichuris, and/or cestodes such as Taenia, Hymenolepis, and Echinococcus. Plants may also be contaminated with fluke metacercaria (e.g. Fasciola). Undercooked meats may transmit Taenia (pork, beef and venison), Trichinella (pork and bear), Diphyllobothrium (fish), Clonorchis (fish), and Paragonimus (crustaceans). Schistosomes and nematodes such as hookworms (Ancylostoma and Necator) and Strongyloides can penetrate the skin. Finally, Wuchereria, Onchocerca, and Dracunculus are transmitted by mosquitoes and flies.

Populations in the developing world are at particular risk for infestation with parasitic worms. Risk factors include inadequate water treatment, use of contaminated water for drinking, cooking, irrigation and to wash food, undercooked food of animal origin, and walking barefoot. Simple measures can have strong impacts on prevention. These include use of shoes, soaking vegetables with 1.5% bleach, adequate cooking of foods, and sleeping under mosquito-proof nets.

Immune response

Response to worm infection in humans is a Th2 response in the majority of cases. Inflammation of the gut may also occur, resulting in cyst-like structures forming around the egg deposits throughout the body. The host's lymphatic system is also increasingly taxed the longer helminths propagate, as they excrete toxins after feeding. These toxins are released into the intestines to be absorbed by the host's bloodstream. This phenomenon makes the host susceptible to more common diseases, such as viral and bacterial infections.

Intestinal helminthes

Intestinal helminths, a type of intestinal parasites, reside in the human gastrointestinal tract. They represent one of the most prevalent forms of parasitic disease. Scholars estimate over a quarter of the world’s population is infected with an intestinal worm of some sort, with roundworms, hookworms, and whipworms infecting 1.47 billion people, 1.05 billion people, and 1.30 billion people, respectively. Furthermore, the World Bank estimates 100 million people may experience stunting or wasting as a result of infection. Because of their high mobility and lower standards of hygiene, school-age children are particularly vulnerable to these parasites. Overall, an estimated 400 million, 170 million, and 300 million children are infected with roundworm, hookworm, and whipworm, respectively. Children may also be particularly susceptible to the adverse effects of helminth infections due to their incomplete physical development and their greater immunological vulnerability.

Symptoms

In people with a heavy worm load, infection is frequently symptomatic. Conditions associated with intestinal helminth infection include: intestinal obstruction, insomnia, vomiting, weakness, and stomach pains,and the natural movement of worms and their attachment to the intestine may be generally uncomfortable for their hosts. The migration of Ascaris larvae through the respiratory passageways can also lead to temporary asthma and other respiratory symptoms. In addition to the low-level costs of chronic infection, helminth infection may be punctuated by the need for more serious, urgent care; for example, the World Health Organization found worm infection is common reason for seeking medical help in a variety of countries, with up to 4.9% of hospital admissions in some areas resulting from the complications of intestinal worm infections and as many as 3% of hospitalizations attributable to ascariasis alone. Also, the immune response triggered by helminth infection may drain the body’s ability to fight other diseases, making affected individuals more prone to coinfection. Reasonable evidence indicates helminthiasis is responsible for the unrelenting prevalence of AIDS and tuberculosis in developing, particularly African, countries. A review of several data clearly revealed the effective treatment

of helminth infection reduces HIV progression and viral load, most likely by improving helminth-induced immune suppression.

Nutrition

One way in which intestinal helminths may impair the development of their human hosts is through their impact on nutrition. Intestinal helminth infection has been associated with problems such as vitamin deficiencies, stunting, anemia, and protein-energy malnutrition, which in turn affect cognitive ability and intellectual development. This relationship is particularly alarming because it is gradual and often relatively asymptomatic.

Parasite infection may affect nutrition in several ways. Some scholars argue worms may compete directly with their hosts for access to nutrients; both whipworms and roundworms are believed to impact their hosts in this way. Nonetheless, the magnitude of this effect is likely to be minimal; after all, the nutritional requirements of these intestinal worms are small when compared with that of their host organism.

A more probable source of infection-induced malnutrition is the nutrient malabsorption associated with parasite presence in the body. For example, in both pigs and humans, Ascaris has been tied to temporarily induced lactose intolerance and vitamin A, amino acid, and fat malabsorption. Impaired nutrient uptake may result from direct damage to the intestines' mucosal walls as a result of the worms' presence, but it may also be a consequence of more nuanced changes, such as chemical imbalances caused by the body's reaction to the helminths. Alternatively, the worms' release of protease inhibitors to defend against the body's digestive process may impair the breakdown of other nutritious substances, as well. Finally, worm infections may also cause diarrhea and speed "transit time" through the intestinal system, further reducing the body's opportunity to capture and retain the nutrients in food.

Worms may also contribute to malnutrition by creating anorexia. A decline in appetite and food consumption due to helminthic infection is widely recognized by the literature, with a recent study of 459 children in Zanzibar reporting even mothers noticed spontaneous increases in appetite after their children underwent a deworming regimen. Although the exact cause of such anorexia is not known, researchers believe it may be a side effect of body's immune response to the worm and the stress of combating infection. Specifically, some of the cytokines released in the immune response have been tied to anorexic reactions in animals.

Helminths may also affect nutrition by inducing iron-deficiency anemia. This is most severe in heavy hookworm infections, as N. americanus and A. duodenale feed directly on the blood of their hosts. Although the impact of individual worms is limited (each consumes about .02-.07 ml and .14-.26 ml of blood daily, respectively), this may nonetheless add up in individuals with heavy infections, since they may carry hundreds of worms at a given time. One scholar went so far as to predict, "the blood loss caused by hookworm was equivalent to the daily exsanguination of 1.5 million people" while a study in Zanzibar showed a 15¢ triannual application of mebendazole could avert 0.25 l of blood loss per child per year. Although whipworm is milder in its effects, it may also induce anemia as a result of the bleeding caused by its damage to the small intestine. The connection between worm burden and malnutrition is further supported by studies indicating deworming programs lead to sharp increases in growth; the presence of this result even in older children has led some scholars to conclude, "it may be easier to reverse stunting in older children than was previously believed."

Delayed intellectual development

Once the links between helminth infection and various forms of malnutrition are established, a number of pathways of parasite burden may affect cognition. For example, poor performance on normal growth indicators appears to be correlated with lower school achievement and enrollment, worse results on some forms of testing, and a decreased ability to focus; iron deficiency may result in "mild growth retardation", difficulty with abstract cognitive tasks, and "lower scores...on tests of mental and motor development...[as well as] increased fearfulness, inattentiveness, and decreased social responsiveness" among very young children. Anemia has also been associated with reduced stamina for physical labor, a decline in the ability to learn new information, and "apathy, irritability, and fatigue". These connections are supported by a number of deworming studies. For example, using 47 students from the Democratic Republic of the Congo, iron supplements acted as a complement to deworming medication, producing better effects on mental cognition when they were applied in conjunction than when they were individually administered. This result may be because iron supplements may "improve [students'] physical well-being to the point of enhancing attentional or arousal mechanisms influential in learning and cognitive performance", with deworming medication only acting to extend these benefits by further reducing the tendency to anemia.

A number of papers take the study of intestinal helminth beyond the malnutrition-cognition link to focus on the connections between worm infections and memory formation. For example, interventions to reduce whipworm infection in 159 Jamaican schoolchildren led to better "auditory short-term memory" and "scanning and retrieval of long-term memory;" particularly fascinating was his discovery that a nine-week period was all that was necessary for dewormed students to "catch up" to their worm-free peers in test performance. Nokes' optimistic conclusion that "whipworm infection['s]...adverse effect on certain cognitive functions...is reversible by therapy" is particularly significant because it suggests the effects of worms on intellectual performance may not be restricted to the mechanism of long-term malnutrition, since the physical and developmental effects of such malnutrition would theoretically be irreversible. The studies of Ezeamama et al. (2005) and Sakti et al. (1999) studied worm burden in the Philippines and Indonesia, respectively. Both authors found significant negative impacts of helminthic infection on memory and fluency, findings that are particularly meaningful because they included controls for socioeconomic status, hemoglobin levels, and proxies of nutrition (nutritional status and stunting, respectively). As Ezeamama observes, these studies suggest "undernutrition is not the primary mediator of the observed relationships" between worm infection and intellectual performance, particularly because their findings were significant in

aspects of intellect that went beyond mere cognition and reaction time. Finally, much as physical activity is "nutritionally mediated" as patients with heavy worm burden struggle to preserve energy and fight malnutrition, so too could "the poorly nourished mind similarly adapt...by reducing mental effort in the form of arousal and sustained attention." While they find little evidence this adaptation would provide benefits in the form of energy conservation, the active course of ongoing parasitic disease clearly could impose other, more direct limitations on an individual's attention span.

School attendance and outcomes

The day-to-day costs of illness provide a strong explanation for yet another negative consequence of helminth infection, or the observation that it acts as "a very real barrier tochildren's progress in school" as quantified by "outcome measures such as absenteeism, under-enrollment, and attrition." Parasite-heavy students may be too weak to attend classes, or their families may be too indebted by medical bills and low worker productivity to pay for school enrollment fees. This effect may be conceptually distinct from previous findings about the impact of parasitism on cognition and learning; for example, deworming programs improve school attendance by 25% without affecting test outcomes at all. Nonetheless, these effects may also be related; school attendance and enrollment grew significantly in the school-age populations that benefited most from the Rockefeller Foundation's deworming programs, leading to a long-term increase in income, as well as a rise in literacy rates.

Prevention

One popular approach to intestinal helminth control is school deworming programs. These programs have a number of advantages. They allow health policymakers to take advantage of existing infrastructure and institutions for the dispensation of medical treatment. Furthermore, students already plan to attend school on a somewhat regular basis, and can be educated about the importance of deworming.School deworming programs have also been shown to have strong positive externalities. A difference-in-difference model proved the deworming programs in some schools reduced the burden of disease in neighboring, untreated schools; deworming children also has strong benefits for adult infection rates, since children are a significant source of transmission. The nature of the intestinal helminths and the medications available to treat them also favor universal deworming programs. Infection is generally diffuse, so it is worth treating a wide sample of the population; furthermore, a drug such as albendazole is a cheap, safe intervention that is not particularly specific, so can be used fairly effectively against all three of the main intestinal helminths (or any coinfection of them). Finally, because these worms cannot replicate inside their hosts, reducing transmission may be the best way to reduce prevalence, and mass interventions on an annual or biannual basis may in fact be a reasonable means of achieving this goal.

Use in medicine

Parasitic worms have been used as a medical treatment for various diseases, particularly those involving an overactive immune response. As humans have evolved with parasitic worms, proponents argue they are needed for a healthy immune system. Scientists are looking for a connection between the prevention and control of parasitic worms and the increase in allergies such as hay-fever in developed countries Parasitic worms may be able to damp down the immune system of their host, making it easier for them to live in the intestine without coming under attack. This may be one mechanism for their proposed medicinal effect.One study suggests a link between the rising rates of metabolic syndrome in the developed worlds and the largely successful efforts of Westerners to eliminate intestinal parasites. The work suggests eosinophils (a type of white blood cell) in fat tissue play an important role in preventing insulin resistance by secreting interleukin 4, which in turn switches macrophages into "alternative activation". Alternatively-activated macrophages are important to maintaining glucose homeostasis (i.e., blood sugar regulation). Helminth infection causes an increase in eosinophils. In the study, the authors fed rodents a high-fat diet to induce metabolic syndrome, and then injected them with helminths. Helminth infestation improved the rodents' metabolism. The authors concluded: Although sparse in blood of persons in developed countries, eosinophils are often elevated in individuals in rural developing countries where intestinal parasitism is prevalent and metabolic syndrome rare. We speculate that eosinophils may have evolved to optimize metabolic homeostasis during chronic infections by ubiquitous intestinal parasites….

History

Public health campaigns to reduce helminth infections in the US may be traced as far back as 1910, when the Rockefeller Foundation began the fight against hookworm – the so-called "germ of laziness" – in the American South. This campaign was enthusiastically received by educators throughout the region; as one Virginian school observed: "children who were listless and dull are now active and alert; children who could not study a year ago are not only studying now, but are finding joy in learning...for the first time in their lives their cheeks show the glow of health."

From Louisiana, a grateful school board added: "As a result of your treatment...their lessons are not so hard for them, they pay better attention in class and they have more energy...In short, we have here in our school-rooms today about 120 bright, rosy-faced children, whereas had you not been sent here to treat them we would have had that many pale-faced, stupid children." Similar (albeit somewhat more imperialist) reports emerged from various other regions of the developing world at the time; for example, two scholars in Puerto Rico found that: "Over all the varied symptoms with which the unfortunate jibaro [peasant], infected by uncinaria [hookworm], is plagued, hangs the pall of a drowsy intellect, of a mind that has received a stunning blow...There is a hypochondriacal, melancholy, hopeless expression, which in severe cases deepens to apparent dense stupidity, with indifference to surroundings and lack of all ambition.' Such observations made an intuitive

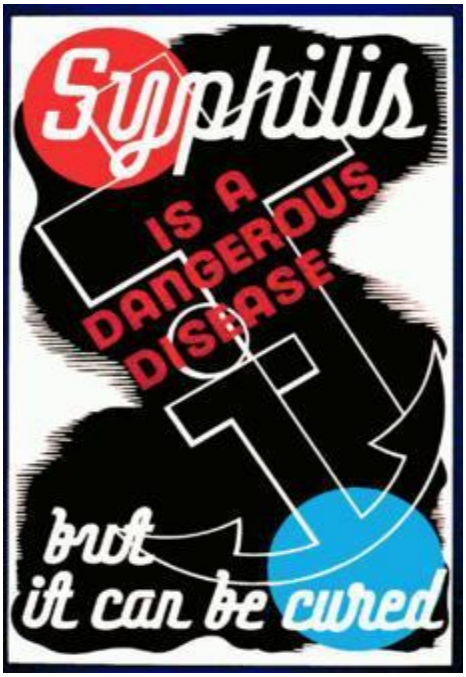
connection between worm burden and intellectual performance, but even today this link is anything but well-established. While it seems that worms may impair cognition in some way, the mechanisms driving this relationship are still hotly debated.

4 Sexually transmitted disease

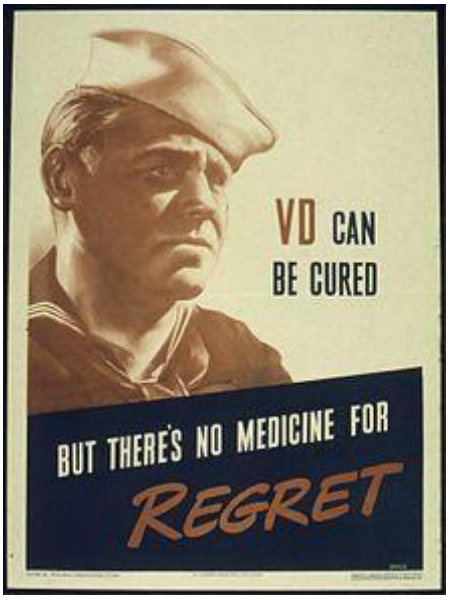
"Syphilis is a dangerous disease, but it can be cured." Poster for treatment of syphilis, showing text a design of an anchor and a cross. Published: Rochester, N.Y.: WPA Federal Art Project, between 1936 and 1938, by Hans Erik Krause.

Sexually transmitted diseases (**STD**), also referred to as **sexually transmitted infections** (**STI**) and **venereal diseases** (**VD**), are illnesses that have a significant probability of transmission between humans by means of sexual behavior, including vaginal intercourse, anal sex and oral sex. Some STIs can also be contracted by using IV drug needles after their use by an infected person, as well as through any incident involving the contact of a wound with contaminated blood or through childbirth or breastfeeding.

Sexually transmitted infections have been well known for hundreds of years, and venereology is the branch of medicine that studies these diseases. While in the past, these illnesses have mostly been referred to as STDs or VD, the term sexually transmitted infections (STIs) has been preferred by many up-to-date medical sources, as it has a broader range of meaning; a person may be infected, and may potentially infect others, without having a disease.There are 19 million new cases of sexually transmitted infections every year in the United States, and, in 2005, the World Health Organization estimated that 448 million people aged 15–49 were being infected a year with curable STIs (such as syphilis, gonorrhea and chlamydia).



Classification



A poster from the Office for Emergency Management. Office of War Information, 1941-1945

Until the 1990s, STIs were commonly known as venereal diseases, the word venereal being derived from the Latin word venereus, and meaning relating to sexual intercourse or desire, ultimately derived from Venus, the Roman goddess of love. Social disease was a phrase used as a euphemism.Sexually transmitted infection is a broader term than sexually transmitted disease. An infection is colonization by a parasitic species, which may not cause any adverse effects. In a disease, the infection leads to impaired or abnormal function. In either case, the condition may not exhibit signs or symptoms. Increased understanding of infections like HPV, which infects a significant portion of sexually active individuals but cause disease in only a few has led to increased use of the term STI. Public health officials originally introduced the term sexually transmitted infection, which clinicians are increasingly using alongside the term sexually transmitted disease in order to distinguish it from the former. STD may refer only to infections that are causing diseases, or it may be used more loosely as a synonym for STI. Most of the time, people do not know that they are infected with an STI until they are tested or start showing symptoms of disease. Moreover, the term sexually transmissible disease is sometimes used since it is less restrictive in consideration of other factors or means of transmission. For instance, meningitis is transmissible by means of sexual contact but is not labeled an STI because sexual contact is not the primary vector for the pathogens that cause meningitis. This discrepancy is addressed by the probability of infection by means other than sexual contact. In general, an STI is an infection that has a negligible probability of transmission by means other than sexual contact, but has a realistic means of transmission by sexual contact (more sophisticated means— blood transfusion, sharing of hypodermic needles—are not taken into account). Thus, one may presume that, if a person is infected with an STI, e.g., chlamydia, gonorrhea, genital herpes, HPV it was transmitted to him/her by means of sexual contact.The diseases on this list are most commonly transmitted solely by sexual activity. Many infectious diseases, including the common cold, influenza, pneumonia, and most others that are transmitted person-to-person can Also be transmitted during sexual contact, if one person is infected, due to the close contact involved. However, even though these diseases may be transmitted during sex, they are not considered STIs.

Signs and symptoms

Not all STIs are symptomatic, and symptoms may not appear immediately after infection. In some instances a disease can be carried with no symptoms, which leaves a greater risk of passing the disease on to others. Depending on the disease, some untreated STIs can lead to infertility, chronic pain or even death.

Cause

Transmission

The risks and transmission probabilities of sexually transmitted diseases are summarized by act in the table:

Risk per unprotected sexual act with an infected person		
	Known risks	**Possible**
Performing oral sex on a man	Throat chlamydia Throat gonorrhea (25–30%) Herpes (rare) HPV Syphilis (1%)	Hepatitis B (low risk) HIV (0.01%) Hepatitis C (unknown)
Performing oral sex on a woman	Herpes HPV	Throat gonorrhea Throat chlamydia
Receiving oral sex—man	Chlamydia Gonorrhea Herpes Syphilis (1%)	HPV

Receiving oral sex— woman	Herpes	HPV
		Bacterial Vaginosis Gonorrhea
	Chlamydia (30–50%) Crabs	
	Scabies	
Vaginal sex—man		
	Gonorrhea (22%) Hepatitis B	Hepatitis C
	Herpes (0.07% for HSV-2) HIV (0.05%)	
	HPV (high: around 40-50%) Syphilis	
	Trichomoniasis	
	Chlamydia (30–50%) Crabs Scabies	
Vaginal sex—woman		
	Gonorrhea (47%)	Hepatitis C
	Hepatitis B (50–70%) Herpes	
	HIV (0.1%)	
	HPV (high; around 40-50%) Syphilis	
	Trichomoniasis	
Anal sex—insertive	Chlamydia Crabs	Hepatitis C
	Scabies (40%) Gonorrhea	
	Hepatitis B Herpes	
	HIV (0.62%) HPV	
	Syphilis (14%)	
Anal sex—receptive	Chlamydia Crabs	
	Scabies	Hepatitis C
	Gonorrhea Hepatitis B Herpes	
	HIV (1.7%) HPV	
	Syphilis (1.4%)	

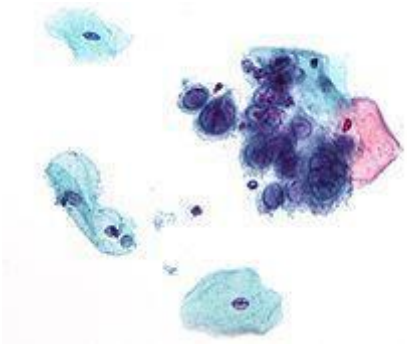
50

	Amebiasis	
	Cryptosporidiosis (1%)	
	Giardiasis	HPV (1%)
Anilingus		
	Hepatitis A (1%)	
	Shigellosis (1%)	

Bacterial
Chancroid (Haemophilus ducreyi)
Chlamydia (Chlamydia trachomatis)
Gonorrhea (Neisseria gonorrhoeae), colloquially known as "the clap" Granuloma inguinale or (Klebsiella granulomatis)
Syphilis (Treponema pallidum)

Fungal
Candidiasis (yeast infection)

Viral



Micrograph showing the viral cytopathic effect of herpes (ground glass nuclear inclusions, multi-nucleation). Pap test. Pap stain.
Viral hepatitis (Hepatitis B virus)—saliva, venereal fluids.
(Note: Hepatitis A and Hepatitis E are transmitted via the fecal-oral route; Hepatitis C is rarely sexually transmittable, and the route of transmission of Hepatitis D (only if infected with B) is uncertain, but may include sexual transmission.)
Herpes simplex (Herpes simplex virus 1, 2) skin and mucosal, transmissible with or without visible blisters
HIV (Human Immunodeficiency Virus)—venereal fluids, semen, breast milk, blood HPV (Human Papillomavirus)—skin and mucosal contact. 'High risk' types of HPV cause almost all cervical cancers, as well as some anal, penile, and vulvar cancer. Some other types of HPV cause genital warts.
Molluscum contagiosum (molluscum contagiosum virus MCV)—close contact

Parasites
Crab louse, colloquially known as "crabs" or "pubic lice" (Pthirus pubis) Scabies (Sarcoptes scabiei)

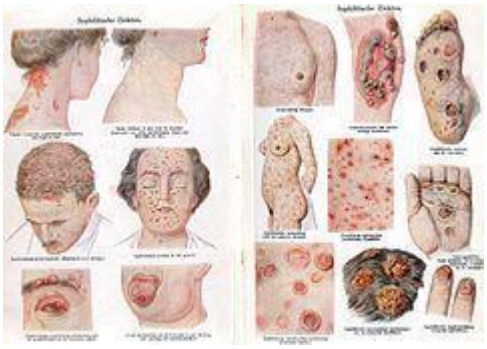
Protozoal
Trichomoniasis (Trichomonas vaginalis), colloquially known as "trich"

Main types
Sexually transmitted infections include:
Chlamydia is a sexually transmitted infection caused by the bacterium Chlamydia trachomatis. In women, symptoms may include abnormal vaginal discharge, burning during urination, and bleeding in between periods, although most women do not experience any symptoms. Symptoms in men include pain when urinating, and abnormal discharge from their penis. If left untreated in both men and women, Chlamydia can infect the urinary tract and potentially lead to pelvic inflammatory disease (PID). PID can cause serious problems during pregnancy and even has the potential to cause infertility. It can cause a woman to have a potentially deadly ectopic pregnancy, in which the child is born outside of the uterus. However, Chlamydia can be cured with antibiotics.
The two most common forms of herpes are caused by infection with herpes simplex virus (HSV). HSV-1 is acquired orally and causes cold sores. HSV-2 is acquired during sexual contact and affects the genitals. Some people are asymptomatic or have very mild symptoms. Those that do experience symptoms usually notice them 2 to 20 days after exposure which last 2 to 4 weeks. Symptoms can include small fluid-filled blisters, headaches, backaches, itching or tingling sensations in the genital or anal area, pain during urination, Flu like symptoms, swollen glands, or fever. Herpes is spread through skin contact with a person infected with the virus. The virus affects the areas where it entered the body. This can occur through kissing, vaginal intercourse, oral sex or anal sex. The virus is most infectious during times when there are visible symptoms, however those who are asymptomatic can still spread the virus through skin contact. The primary attack is the most severe because the

body does not have any antibodies built up. After the primary attack, one might have recurring attacks that are milder or might not even have future attacks. There is no cure for the disease but there are antiviral medications that treat its symptoms and lower the risk of transmission (Valtrex). Although HSV-1 is typically the "oral" version of the virus, and HSV-2 is typically the "genital" version of the virus, a person with HSV-1 orally CAN transmit that virus to their partner genitally. The virus, either type, will settle into a nerve bundle either at the top of the spine, producing the "oral" outbreak, or a second nerve bundle at the base of the spine, producing the genital outbreak.

The human papillomavirus (HPV) is the most common STI in the United States. There are more than 40 different strands of HPV and many do not cause any health problems. In 90% of cases the body's immune system clears the infection naturally within 2 years. Some cases may not be cleared and can lead to genital warts (bumps around the genitals that can be small or large, raised or flat, or shaped like cauliflower) or cervical cancer and other HPV related cancers. Symptoms might not show up until advanced stages. It is important for women to get pap smears in order to check for and treat cancers. There are also two vaccines available for women (Cervarix and Gardasil) that protect against the types of HPV that cause cervical cancer. HPV can be passed through genital-to-genital contact as well as during oral sex. It is important to remember that the infected partner might not have any symptoms.

Gonorrhea is caused by bacterium that lives on moist mucous membranes in the urethra, vagina, rectum, mouth, throat, and eyes. The infection can spread through contact with the penis, vagina, mouth or anus. Symptoms of Gonorrhea usually appear 2 to 5 days after contact with an infected partner however, some men might not notice symptoms for up to a month. Symptoms in men include burning and pain while urinating, increased urinary frequency, discharge from the penis (white, green, or yellow in color), red or swollen urethra, swollen or tender testicles, or sore throat. Symptoms in women may include vaginal discharge, burning or itching while urinating, painful sexual intercourse, severe pain in lower abdomen (if infection spreads to fallopian tubes), or fever (if infection spreads to fallopian tubes), however many women do not show any symptoms. There are some antibiotic resistant strains for Gonorrhea but most cases can be cured with antibiotics.



Secondary syphilis

Syphilis is an STI caused by a bacterium. If acquired, syphilis needs to be treated adequately; otherwise it can cause long-term complications and death. Clinical manifestations of syphilis include the ulceration of the uro-genital tract, mouth or rectum; if left untreated the symptoms worsen. In recent years, the prevalence of syphilis has declined in Western Europe, but it has increased in Eastern Europe (former Soviet states). A high incidence of syphilis can be found in places such as Cameroon, Cambodia, and Papua New Guinea.Trichomoniasis is a common STI that is caused by infection with a protozoan parasite called Trichomonas vaginalis. Trichomoniasis affects both women and men, but symptoms are more common in women. Most patients are treated with an antibiotic called metronidazole, which is very effective.

HIV (human immunodeficiency virus) damages the body's immune system which interferes with fighting off disease-causing agents. The virus kills CD4 cells, which are white blood cells that help fight off various infections. HIV is carried in body fluids, and is spread by sexual activity. It can also be spread by contact with infected blood, breast feeding, childbirth, and from mother to child during pregnancy. When HIV is at its most advanced stage, an individual is said to have AIDS (acquired immunodeficiency syndrome). There are different stages of the progression of and HIV infection. The stages include primary infection, asymptomatic infection, symptomatic infection, and AIDS. In the primary infection stage, an individual will have flu like symptoms (headache, fatigue, fever, muscle aches) for about 2 weeks. In the asymptomatic stage, symptoms usually disappear, and the patient can remain asymptomatic for years. When HIV progresses to the symptomatic stage, the immune system is weakened, and has a low cell count of CD4+ T Cells. When the HIV infection becomes life-threatening, it is called AIDS. People with AIDS fall prey to opportunistic infections and die as a result. When the disease was first discovered in the 1980s, those who had AIDS were not likely to live longer than a few years. There are now antiretroviral drugs (ARVs) available to treat HIV infections. There is no known cure for HIV or AIDS but the drugs help suppress the virus. By suppressing the amount of virus in the body, people can lead longer and healthier lives. Even though their virus levels may be low they can still spread the virus to others.

Unscreened

There are many species of bacteria, protozoa, fungi, and viruses, many which remain undocumented or poorly studied with regards to sexual transmission. Despite that the above include what are generally known as STIs, sexually transmission of microbes is far from limited to the above list. Since the sexual route of transmission is not considered common, and/or the microbe itself is not implicated in a major research study on disease, the following pathogens are simply not screened for in sexual health clinics. Some of these microbes are known to be sexually transmittable.

Microbes known to be sexually transmissible (but not generally considered STDs/STIs) include:
Ebola- transmissible 2 months after recovery.
Marburg virus - Virus in semen for 7 weeks after clinical recovery.
HTLV (both types 1 and 2) - Sexually transmissible, consumption of breast milk breastfeeding, and once mistaken as a HIV, risk of leukemia.

Pathophysiology

Many STIs are (more easily) transmitted through the mucous membranes of the penis, vulva, rectum, urinary tract and (less often—depending on type of infection) the mouth, throat, respiratory tract and eyes. The visible membrane covering the head of the penis is a mucous membrane, though it produces no mucus (similar to the lips of the mouth). Mucous membranes differ from skin in that they allow certain pathogens into the body. The amount of contact with infective sources which causes infection varies with each pathogen but in all cases a disease may
result from even light contact from fluid carriers like venereal fluids onto a mucous membrane.This is one reason that the probability of transmitting many infections is far higher from sex than by more casual means of transmission, such as non-sexual contact—touching, hugging, shaking hands—but it is not the only reason. Although mucous membranes exist in the mouth as in the genitals, many STIs seem to be easier to transmit through oral sex than through deep kissing. According to a safe sex chart, many infections that are easily transmitted from the mouth to the genitals or from the genitals to the mouth are much harder to transmit from one mouth to another. With HIV, genital fluids happen to contain much more of the pathogen than saliva. Some infections labeled as STIs can be transmitted by direct skin contact. Herpes simplex and HPV are both examples. KSHV, on the other hand, may be transmitted by deep-kissing but also when saliva is used as a sexual lubricant.Depending on the STI, a person may still be able to spread the infection if no signs of disease are present. For example, a person is much more likely to spread herpes infection when blisters are present than when they are absent. However, a person can spread HIV infection at any time, even if he/she has not developed symptoms of AIDS.All sexual behaviors that involve contact with the bodily fluids of another person should be considered to contain some risk of transmission of sexually transmitted diseases. Most attention has focused on controlling HIV, which causes AIDS, but each STI presents a different situation.As may be noted from the name, sexually transmitted diseases are transmitted from one person to another by certain sexual activities rather than being actually caused by those sexual activities. Bacteria, fungi, protozoa or viruses are still the causative agents. It is not possible to catch any sexually transmitted disease from a sexual activity with a person who is not carrying a disease; conversely, a person who has an STI got it from contact (sexual or otherwise) with someone who had it, or his/her bodily fluids. Some STIs such as HIV can be transmitted from mother to child either during pregnancy or breastfeeding.Although the likelihood of transmitting various diseases by various sexual activities varies a great deal, in general, all sexual activities between two (or more) people should be considered as being a two-way route for the transmission of STIs, i.e., "giving" or "receiving" are both risky although receiving carries a higher risk.Healthcare professionals suggest safer sex, such as the use of condoms, as the most reliable way of decreasing the risk of contracting sexually transmitted diseases during sexual activity, but safer sex should by no means be considered an absolute safeguard. The transfer of and exposure to bodily fluids, such as blood transfusions and other blood products, sharing injection needles, needle-stick injuries (when medical staff are inadvertently jabbed or pricked with needles during medical procedures), sharing tattoo needles, and childbirth are other avenues of transmission. These different means put certain groups, such as medical workers, and haemophiliacs and drug users, particularly at risk.Recent epidemiological studies have investigated the networks that are defined by sexual relationships between individuals, and discovered that the properties of sexual networks are crucial to the spread of sexually transmitted diseases. In particular, assortative mixing between people with large numbers of sexual partners seems to be an important factor.It is possible to be an asymptomatic carrier of sexually transmitted diseases. In particular, sexually transmitted diseases in women often cause the serious condition of pelvic inflammatory disease.

Prevention

San Francisco City Clinic a municipal STI testing center in San Francisco. Main article: Safe sex
Prevention is key in addressing incurable STIs, such as HIV and herpes. Sexual health clinics promote the use of condoms and provide outreach for at-risk communities.The most effective way to prevent sexual transmission of STIs is to avoid contact of body parts or fluids which can lead to transfer with an infected partner. Not all sexual activities involve contact: cybersex, phonesex or masturbation from a distance is methods of avoiding contact. Proper use of condoms reduces contact and risk. Although a condom is effective in limiting exposure, some disease transmission may occur even with a condom. Both partners should get tested for STIs before initiating sexual contact, or before resuming contact if a partner engaged in contact with someone else. Many infections are not detectable immediately after exposure, so enough time must be allowed

between possible exposures and testing for the tests to be accurate. Certain STIs, particularly certain persistent viruses like HPV, may be impossible to detect with current medical procedures.Many diseases that establish permanent infections can so occupy the immune system that other diseases become more easily transmitted. The innate immune system led by defensins against HIV can prevent transmission of HIV when viral counts are very low, but if busy with other viruses or overwhelmed, HIV can establish itself. Certain viral STI's also greatly increase the risk of death for HIV infected patients.

Vaccines

Vaccines are available that protect against some viral STIs, such as Hepatitis A, Hepatitis B, and some types of HPV. Vaccination before initiation of sexual contact is advised to assure maximal protection.

Condoms

Condoms and female condoms only provide protection when used properly as a barrier, and only to and from the area that it covers. Uncovered areas are still susceptible to many STDs. In the case of HIV, sexual transmission routes almost always involve the penis, as HIV cannot spread through unbroken skin, thus properly shielding the insertive penis with a properly worn condom from the vagina or anus effectively stops HIV transmission. An infected fluid to broken skin borne direct transmission of HIV would not be considered "sexually transmitted", but can still theoretically occur during sexual contact, this can be avoided simply by not engaging in sexual contact when having open bleeding wounds. Other STIs, even viral infections, can be prevented with the use of latex, polyurethane or polyisoprene condoms as a barrier. Some microorganisms and viruses are small enough to pass through the pores in natural skin condoms, but are still too large to pass through latex or synthetic condoms.

Proper usage entails:

Not putting the condom on too tight at the end, and leaving 1.5 cm (3/4 inch) room at the tip for ejaculation. Putting the condom on snug can and often does lead to failure.

Wearing a condom too loose can defeat the barrier.

Avoiding inverting, spilling a condom once worn, whether it has ejaculate in it or not. Avoiding the use of oil based lubricants (or anything with oil in it) with latex condoms, as oil can eat holes into them.

Using flavored condoms for oral sex only, as the sugar in the flavoring can lead to yeast infections if used to penetrate.

Not following the first five guidelines above perpetuates the common misconception that condoms are not tested or designed properly.In order to best protect oneself and the partner from STIs, the old condom and its contents should be assumed to be infectious. Therefore the old condom must be properly disposed of. A new condom should be used for each act of intercourse, as multiple usage increases the chance of breakage, defeating the effectiveness as a barrier.

Nonoxynol-9

Researchers had hoped that nonoxynol-9, a vaginal microbicide would help decrease STI risk. Trials, however, have found it ineffective and it may put women at a higher risk of HIV infection.

Screening

Sexually active women under the age of 25 and those over 25 with risk should be screened for chlamydia and gonorrhea yearly. After being treated for gonorrhea all people should be re tested for the disease after three months. Nucleic acid amplification tests are the recommended method of diagnosis for gonorrhea and chlamydia. This can be done on either urine in both men and women, vaginal or cervical swabs in women, or urethral swabs in men.

Diagnosis

Testing may be for a single infection, or consist of a number of tests for a range of STIs, including tests for syphilis, trichomonas, gonorrhea, chlamydia, herpes, hepatitis and HIV tests. No procedure tests for all infectious agents.

STI tests may be used for a number of reasons:

as a diagnostic test to determine the cause of symptoms or illness

as a screening test to detect asymptomatic or presymptomatic infections

as a check that prospective sexual partners are free of disease before they engage in sex without safer sex precautions (for example, when starting a long term mutually monogamous sexual relationship, in fluid bonding, or for procreation).

as a check prior to or during pregnancy, to prevent harm to the baby

as a check after birth, to check that the baby has not caught an STI from the mother to prevent the use of infected donated blood or organs as part of the process of contact tracing from a known infected individual as part of mass epidemiological surveillance

Early identification and treatment results in less chance to spread disease, and for some conditions may improve the outcomes of treatment. There is often a window period after initial infection during which an STI test will be negative. During this period the infection may be transmissible. The duration of this period varies depending on the infection and the test. Diagnosis may also be delayed by reluctance of the infected person to seek a medical professional. One report indicated that people turn to the Internet rather than to a medical professional for information on STIs to a higher degree than for other sexual problems.

Management

High-risk exposure such as that which occurs in rape cases may be treated preventatively using antibiotic combinations such as azithromycin, cefixime, and metronidazole.An option for treating partners of patients (index cases) diagnosed with chlamydia or gonorrhea is patient-delivered partner therapy, which is the clinical practice of treating the sex partners of index cases by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner.

Epidemiology

Age-standardized, disability-adjusted life years for STDs (excluding HIV) per 100,000 inhabitants in 2004

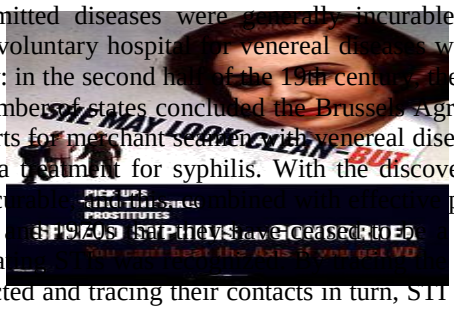
no da	360–420
< 60	420–480
60–120	480–540
120–180	540–600
180–240	600–1000
240–300	> 1000
300–360	

STD incidence rates remain high in most of the world, despite diagnostic and therapeutic advances that can rapidly render patients with many STDs noninfectious and cure most. In many cultures, changing sexual morals and oral contraceptive use have eliminated traditional sexual restraints, especially for women, and both physicians and patients have difficulty dealing openly and candidly with sexual issues. Additionally, development and spread of drug-resistant bacteria (e.g., penicillin-resistant gonococci) makes some STDs harder to cure. The effect of travel is most dramatically illustrated by the rapid spread of the AIDS virus (HIV-1) from Africa to Europe and the Americas in the late 1970s. Commonly reported prevalences of STIs among sexually active adolescent girls both with and without lower genital tract symptoms include chlamydia (10–25%), gonorrhea (3–18%), syphilis (0–3%), Trichomonas vaginalis (8–16%), and herpes simplex virus (2–12%).Among adolescent boys with no symptoms of urethritis, isolation rates include chlamydia (9–11%) and gonorrhea (2–3%).A 2008 CDC study found that 25–40% of U.S. teenage girls has a sexually transmitted disease. AIDS is among the leading causes of death in present-day Sub-Saharan Africa. HIV/AIDS is transmitted primarily via unprotected sexual intercourse. More than 1.1 million persons are living with HIV/AIDS in the United States, and it disproportionately impacts African Americans.[57] Hepatitis B is also considered a sexually transmitted disease because it can be spread through sexual contact. The highest rates are found in Asia and Africa and lower rates are in the Americas and Europe. Approximately two billion people worldwide have been infected with the hepatitis B virus.

History

1930s Works Progress Administration poster

The first well-recorded European outbreak of what is now known as syphilis occurred in 1494 when it broke out among French troops besieging Naples. The disease may have originated from the Columbian Exchange. From Naples, the disease swept across Europe, killing more than five million people. As Jared Diamond describes it, "[W]hen syphilis was first definitely recorded in Europe in 1495, its pustules often covered the body from the head to the knees, caused flesh to fall from people's faces, and led to death within a few months," rendering it far more fatal than it is today. Diamond concludes,"[B]y 1546, the disease had evolved into the disease with the symptoms so well known to us today.



U.S. propaganda poster targeted at World War II servicemen appealed to their patriotism in urging them to protect themselves. The text at the bottom of the poster reads, "You can't beat the Axis if you get VD."Prior to the invention of modern medicines, sexually transmitted diseases were generally incurable, and treatment was limited to treating the symptoms of the disease. The first voluntary hospital for venereal diseases was founded in 1746 at London Lock Hospital. Treatment was not always voluntary: in the second half of the 19th century, the Contagious Diseases Acts were used to arrest suspected prostitutes. In 1924, a number of states concluded the Brussels Agreement, whereby states agreed to provide free or low-cost medical treatment at ports for merchant seamen with venereal diseases the first effective treatment for a sexually transmitted disease was salvarsan, a treatment for syphilis. With the discovery of antibiotics, a large number of sexually transmitted diseases became easily cu[illegible] combined with effective public health campaigns against STDs, led to a public perception during the 1960s [illegible] serious medical threat.During this period, the importance of contact tracing in trea[illegible] sexual partners of infected individuals, testing them for infection, treating the infected and tracing their contacts in turn, STI clinics could effectively suppress infections in the general population.In the 1980s, first genital herpes and then AIDS emerged into the public consciousness as sexually transmitted diseases that could not be cured by modern medicine. AIDS in particular has a long asymptomatic period—

during which time HIV (the human immunodeficiency virus, which causes AIDS) can replicate and the disease can be transmitted to others—followed by a symptomatic period, which leads rapidly to death unless treated. HIV/AIDS entered the United States from Haiti in about 1969. Recognition that AIDS threatened a global pandemic led to public information campaigns and the development of treatments that allow AIDS to be managed by suppressing the replication of HIV for as long as possible. Contact tracing continues to be an important measure, even when diseases are incurable, as it helps to contain infection.

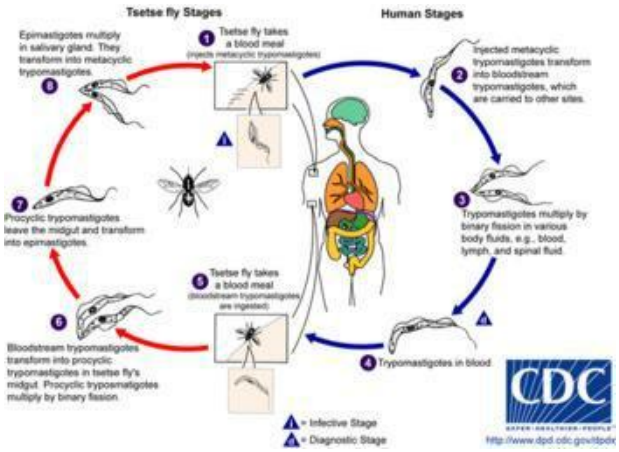
5. African trypanosomiasis

African trypanosomiasis or **sleeping sickness is** parasitic disease of humans and other animals. It is caused by protozoa of the species Trypanosoma brucei. There are two types that infect humans, Trypanosoma brucei gambiense (T.b.g) and Trypanosoma brucei rhodesiense (T.b.r) T.b.g causes over 98% of reported cases. Both are usually transmitted by the bite of an infected tsetse fly and are most common in rural areas. Initially, in the first stage of the disease, there are fevers, headaches, itchiness, and joint pains. This begins one to three weeks after the bite. Weeks to months later the second stage begins with confusion, poor coordination, numbness and trouble sleeping. Diagnosis is via finding the parasite in a blood smear or in the fluid of a lymph node. A lumbar puncture is often needed to tell the difference between first and second stage disease.Prevention of severe disease involves screening the population at risk with blood tests for T.b.g. Treatment is easier when the disease is detected early and before neurological symptoms occur. Treatment of the first stage is with the medications pentamidine or suramin. Treatment of the second stage involves: eflornithine or a combination of nifurtimox and eflornithine for T.b.g. While melarsoprol works for both it is typically only used for T.b.r. due to serious side effects. The disease occurs regularly in some regions of sub-Saharan Africa with the population at risk being about 70 million in 36 countries. As of 2010 it caused around 9,000 deaths per year, down from 34,000 in 1990. An estimated 30,000 people are currently infected with 7000 new infections in 2012. More than 80% of these cases are in the Democratic Republic of the Congo. Three major outbreaks have occurred in recent history: one from 1896 to 1906 primarily in Uganda and the Congo Basin and two in 1920 and 1970 in several African countries. Other animals, such as cows, may carry the disease and become infected.

Signs and symptoms

African trypanosomiasis symptoms occur in two stages. The first stage, known as the haemolymphatic phase, is characterized by fever, headaches, joint pains, and itching. Fever is intermittent, with attacks lasting from a day to a week, separated by intervals of a few days to a month or longer. Invasion of the circulatory and lymphatic systems by the parasites is associated with severe swelling of lymph nodes, often to tremendous sizes. Winterbottom's sign, the tell-tale swollen lymph nodes along the back of the neck, may appear. Occasionally, a red sore called a chancre will develop at the location of the tsetse fly bite. If left untreated, the disease overcomes the host's defenses and can cause more extensive damage, broadening symptoms to include anemia, endocrine, cardiac, and kidney dysfunctions. The second, neurological phase, begins when the parasite invades the central nervous system by passing through the blood–brain barrier. Disruption of the sleep cycle is a leading symptom of this stage and is the one that gave the disease the name 'sleeping sickness.' Infected individuals experience a disorganized and fragmented 24-hour rhythm of the sleep-wake cycle, resulting in daytime sleep episodes and nighttime periods of wakefulness. Other neurological symptoms include confusion, tremor, general muscle weakness, hemiparesis and paralysis of a limb. Parkinson-like movements might arise due to non-specific movement disorders and speech disorders. Individuals may also exhibit psychiatric symptoms such as irritability, psychotic reactions, aggressive behaviour, or apathy which can sometimes dominate the clinical diagnosis. Without treatment, the disease is invariably fatal, with progressive mental deterioration leading to coma, systemic organ failure, and death. An untreated infection with T. b. rhodesiense will cause death within months whereas an untreated infection with T. b. gambiense will cause death after several years. Damage caused in the neurological phase is irreversible.

Cause



Life cycle of the Trypanosoma bruceiparasites, source: CDC

Trypanosoma brucei

There are two subspecies of the parasite that are responsible for initiating the disease in humans. Trypanosoma brucei gambiense causes the diseases in west and central Africa whereas, Trypanosoma brucei rhodesiense has a limited geographical range and is responsible for causing the disease in east and southern Africa. In addition, a third subspecies of the parasite known as Trypanosoma brucei brucei is responsible for affecting animals but not humans. Humans are the main reservoir for T. b. gambiense but this species can also be found in pigs and other animals. Wild game animals and cattle are the main reservoir of T. b. rhodesiense. These parasites primarily infect individuals in sub-Saharan Africa because that is where the vector (tsetse fly) is located. The two human forms of the disease also vary greatly in intensity. T. b. gambiense causes a chronic condition that can remain in a passive phase for months or years before symptoms emerge and the infection can last about 3 years before death occurs. T. b. rhodesiense is the acute form of the disease and death can occur within months since the symptoms emerge within weeks and it is more virulent and faster developing than T. b. gambiense. Furthermore, trypanosomes are surrounded by a coat that is composed of variant surface glycoproteins (VSG). These proteins act to protect the parasite from any lytic factors that are present in human plasma.

The host's immune system recognizes the glycoproteins present on the coat of the parasite leading to the production of different antibodies (IgM and IgG). These antibodies will then act to destroy the parasites that circulate around the blood. However, from the several parasites present in the plasma, a small number of them will experience changes in their surface coats resulting in the formation of new VSGs. Thus, the antibodies produced by the immune system will no longer recognize the parasite leading to proliferation until new antibodies are created to combat the novel VSGs. Eventually the immune system will no longer be able to fight off the parasite due to the constant changes in VSGs and infection will arise.

Vector

The tsetse fly (genus Glossina) is a large, brown, biting fly that serves as both a host and vector for the trypanosome parasites. While taking blood from a mammalian host, an infected tsetse fly injects metacyclic trypomastigotes into skin tissue. From the bite, parasites first enter the lymphatic system and then pass into the bloodstream. Inside the mammalian host, they transform into bloodstream trypomastigotes, and are carried to other sites throughout the body, reach other body fluids (e.g., lymph, spinal fluid), and continue to replicate by binary fission.The entire life cycle of African trypanosomes is represented by extracellular stages. A tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host. In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission, leave the midgut, and transform into epimastigotes. The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission.

The entire life cycle of the fly takes about three weeks. In addition to the bite of the tsetse fly, the disease can be transmitted by:

Mother-to-child infection: the trypanosome can sometimes cross the placenta and infect the fetus

Laboratories: accidental infections, for example, through the handling of blood of an infected person and organ transplantation, although this is uncommon.

Blood transfusion

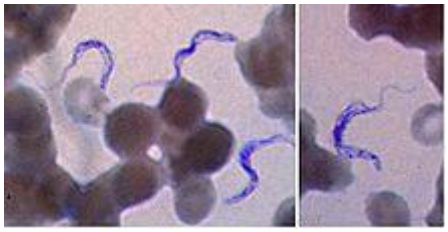
Sexual contact (This may be possible).

Horse-flies (Tabanidae) and stable flies (Muscidae) possibly play a role in transmission of nagana (the animal form of sleeping sickness) and the human disease form.

Mechanism

Tryptophol is a chemical compound that induces sleep in humans. It is produced by the trypanosomal parasite in sleeping sickness.

Diagnosis



Two areas from a blood smear from a patient with African trypanosomiasis, thin blood smear stained with Giemsa: Typical trypomastigote stages (the only stages found in patients), with a posterior kinetoplast, a centrally located nucleus, an undulating membrane, and an anterior flagellum. The two Trypanosoma brucei subspecies that cause human trypanosomiasis, T. b. gambiense and T. b. rhodesiense, are indistinguishable morphologically. The trypanosomes' length range is 14 to 33 µm, Source: CDCThe gold standard for diagnosis is identification of trypanosomes in a patient sample by microscopic

examination. Patient samples that can be used for diagnosis include chancre fluid, lymph node aspirates, blood, bone marrow, and, during the neurological stage, cerebrospinal fluid. Detection of trypanosome-specific antibodies can be used for diagnosis, but the sensitivity and specificity of these methods are too variable to be used alone for clinical diagnosis. Further, seroconversion occurs after the onset of clinical symptoms during a T. b. rhodesiense infection, so is of limited diagnostic use.Trypanosomes can be detected from patient samples using two different preparations. A wet preparation can be used to look for the motile trypanosomes. Alternatively, a fixed (dried) smear can be stained using Giemsa's or Field's technique and examined under a microscope. Often, the parasite is in relatively low abundance in the sample, so techniques to concentrate the parasites can be used prior to microscopic examination. For blood samples, these include centrifugation followed by examination of the buffy coat; mini anion-exchange/centrifugation; and the quantitative buffy coat (QBC) technique. For other samples, such as spinal fluid, concentration techniques include centrifugation followed by examination of the sediment·Three serological tests are also available for detection of the parasite: the micro-CATT, wb-CATT, and wb-LATEX. The first uses dried blood, while the other two use whole blood samples. A 2002 study found the wb-CATT to be the most efficient for diagnosis, while the wb-LATEX is a better exam for situations where greater sensitivity is required.

Prevention

See also: Tsetse fly § Control techniques

Currently there are few medically related prevention options for African Trypanosomiasis (i.e. no vaccine exists for immunity). Although the risk of infection from a tsetse fly bite is minor (estimated at less than 0.1%), the use of insect repellants, wearing long-sleeved clothing, avoiding tsetse-dense areas, implementing bush clearance methods and wild game culling are the best options to avoid infection available for local residents of affected areas. At the 25th ISCTRC (International Scientific Council for Trypanosomiasis Research and Control) in Mombasa, Kenya, in October 1999, the idea of an African-wide initiative to control tsetse and trypanosomiasis populations was discussed. During the 36th summit of the African Union in Lome, Togo, in July 2000, a resolution was passed to form the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC). The campaign works to eradicate the tsetse vector population levels and subsequently the protozoan disease, by use of insecticide-impregnated targets, fly traps, insecticide-treated cattle, ultra-low dose aerial/ground spraying (SAT) of tsetse resting sites and the sterile insect technique (SIT. The use of SIT in Zanzibar proved effective in eliminating the entire population of tsetse flies but was expensive and is relatively impractical to use in many of the endemic countries afflicted with African trypanosomiasis. Regular active surveillance, involving detection and prompt treatment of new infections, and tsetse fly control is the backbone of the strategy used to control sleeping sickness. Systematic screening of at-risk communities is the best approach, because case-by-case screening is not practical in endemic regions. Systematic screening may be in the form of mobile clinics or fixed screening centres where teams travel daily to areas of high infection rates. Such screening efforts are important because early symptoms are not evident or serious enough to warrant patients with gambiense disease to seek medical attention, particularly in very remote areas. Also, diagnosis of the disease is difficult and health workers may not associate such general symptoms with trypanosomiasis. Systematic screening allows early-stage disease to be detected and treated before the disease progresses, and removes the potential human reservoir. A single case of sexual transmission of West African sleeping sickness has been reported.

Treatment

First stage

The current treatment for first-stage disease is intravenous or intramuscular pentamidine for T. b. gambiense or intravenous suramin for T. b. rhodesiense.

Second stage

For T. b. gambiense intravenous eflornithine or the combination of nifurtimox and eflornithine appear to be more effective and easier to give. These treatments may replace melarsoprol when available with the combination being first line. Intravenous melarsoprol was previously the standard treatment for second-stage (neurological phase) disease and is effective for both types. It is the only treatment for second stage T. b. rhodesiense however causes death in 5% of people who take it. Resistance to melarsoprol can occur.

Epidemiology

Deaths per 100,000 population due to African trypanosomiasis by country in 2002As of 2010 it caused around 9,000 deaths, down from 34,000 in 1990. As of 2000, the disability-adjusted life-years (9 to 10 years) lost due to sleeping sickness are 2.0 million. Over 60 million people living in some 250 locations are at risk of contracting the disease, and under 10,000 new cases were reported in 2009. The disease has been recorded as occurring in 37 countries, all in sub-Saharan Africa. It occurs regularly in southeast Uganda and western Kenya, and killed more than 48,000 Africans in 2008. The population at risk being about 69 million with one third of this number being at a 'very high' to 'moderate' risk and the remaining two thirds at a 'low' to 'very low' risk.

Prognosis

If untreated, T. b. gambiense almost always results in death, with only a few individuals shown in a long-term 15 year follow-up to have survived after refusing treatment. T. b. rhodesiense, being a more acute and severe form of the disease, is consistently fatal if not treated. Disease progression greatly varies depending on disease form. For individuals which are infected by T. b. gambiense, which accounts for 98% of all of the reported cases, a person can be infected for months or even years without signs or symptoms until the advanced disease stage, where it is too late to be treated successfully. For individuals affected by T. b. rhodesiense, which accounts for 2% of all reported cases, symptoms appear within weeks or

months of the infection. Disease progression is rapid and invades the central nervous system and causes death within a short amount of time.

History

The condition has been present in Africa for thousands of years. Because of a lack of travel between indigenous people, sleeping sickness in humans had been limited to isolated pockets. This changed once Arab slave traders entered central Africa from the east, following the Congo River, bringing parasites along. Gambian sleeping sickness travelled up the Congo River, then further eastwards. In 1901, a devastating epidemic erupted in Uganda, killing more than 250,000 people, including about two-thirds of the population in the affected lakeshore areas. According to The Cambridge History of Africa, "It has been estimated that up to half the people died of sleeping-sickness and smallpox in the lands on either bank of the lower river Congo."

In 1903, David Bruce recognized the tsetse fly as the arthropod vector.

The causative agent and vector were identified in 1903 by David Bruce, and the differentiation between the subspecies of the protozoa made in 1910. The first effective treatment, atoxyl, an arsenic-based drug developed by Paul Ehrlich and Kiyoshi Shiga, was introduced in 1910, but blindness was a serious side effect.Suramin was introduced in 1920 to treat the first stage of the disease. By 1922, Suramin was generally combined with tryparsamide (another pentavalent organoarsenic drug) in the treatment of the second stage of the gambiense form. It was used during the grand epidemic in West and Central Africa in millions of people and was the mainstay of therapy until 1969.The American medical missionary Arthur Lewis Piper was the first person to use and bring back tryparsamide to the Belgian Congo in 1925. Pentamidine, a highly effective drug for the first stage of the disease, has been used since 1939. During the 1950s, it was widely used as a prophylactic agent in western Africa, leading to a sharp decline in infection rates. At the time, eradication of the disease was thought to be at hand.The organoarsenical melarsoprol (Arsobal) developed in the 1940s is effective for patients with second-stage sleeping sickness. However, 3–10% of those injected have reactive encephalopathy (convulsions, progressive coma, or psychotic reactions), and 10–70% of such cases result in death; it can cause brain damage in those who survive the encephalopathy. However, due to its effectiveness, melarsoprol is still used today. Resistance to melarsoprol is increasing, and combination therapy with nifurtimox is currently under research.

Eflornithine (difluoromethylornithine or DFMO), the most modern treatment, was developed in the 1970s by Albert Sjoerdsma and underwent clinical trials in the 1980s. The drug was approved by the United States Food and Drug Administration in 1990, but Aventis, the company responsible for its manufacture, halted production in 1999. In 2001, however, Aventis, in association with Médecins Sans Frontières and the World Health Organization, signed a long-term agreement to manufacture and donate the drug. It has previously been known as African lethargy, and Congo trypanosomiasis. The genome of the parasite has been sequenced and several proteins have been identified as potential targets for drug treatment. Analysis of the genome also revealed the reason why generating a vaccine for this disease has been so difficult. T. brucei has over 800 genes that make proteins the parasite "mixes and matches" to evade immune system detection. Using a genetically modified form of a bacteria that occurs naturally in the gut of the vectors is being studied as a method of controlling the disease. Recent findings indicate the parasite is unable to survive in the bloodstream without its flagellum. This insight gives researchers a new angle with which to attack the parasite. A trial in 2005 is testing the efficacy of the first potential oral treatment for sleeping sickness, pafuramidine. Trypanosomiasis vaccines are undergoing research.Additionally, the Drugs for Neglected Disease Initiative has contributed to the African sleeping sickness research effort by developing a compound called fexinidazole. This project was originally started in April 2007 and is currently in a pivotal study in clinical phase II/III.36 The goal is to have the drug succeed and be proven effective again stage one and stage two HAT caused by T. b. gambiense, as well HAT caused by T. b. rhodesiense.

6. Leprosy

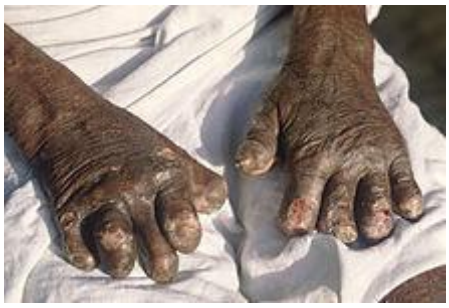
Leprosy

Classification and external resources

A 24-year-old man from Norway, infected with leprosy, 1886.

Leprosy, also known as **Hansen's disease** (**HD**), is a chronic infection caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis. Initially infections are without symptoms and typically remain this way for 5 to as long as 20 years. Symptoms that develop include granulomas of the nerves, respiratory tract, skin, and eyes. This may result in a lack of ability to feel pain and thus loss of parts of extremities due to repeated injuries. Weakness and poor eyesight may also be present. There are two main types of disease based on the number of bacteria present: paucibacillary and multibacillary. The two types are differentiated by the number of poorly pigmented numb skin patches present, with paucibacillary having five or fewer and multibacillary having more than five. The diagnosis is confirmed by finding acid-fast bacilli in a biopsy of the skin or via detecting the DNA by polymerase chain reaction. It occurs more commonly among those living in poverty and is believed to be transmitted by respiratory droplets. It is not very contagious. Leprosy is curable with treatment. Treatment for paucibacillary leprosy is with the medications dapsone and rifampicin for 6 months. Treatment for multibacillary leprosy consists of rifampicin, dapsone, and clofazimine for 12 months. These treatments are provided for free by the World Health Organization. A number of other antibiotics may also be used. Globally in 2012 the number of cases of leprosy was 180,000, having decreased a great deal since the 1960s. Most new cases occur in 16 countries, with India accounting for more than half. In the past 20 years, 16 million people worldwide have been cured of leprosy. Leprosy has affected humanity for thousands of years. The disease takes its name from the Latin word Lepra, which means "scaly", while the term "Hansen's disease" is named after the physician Gerhard Armauer Hansen. Separating people in leper colonies still occurs in countries like India, where there are more than a thousand; China, where there are hundreds; and in the continent of Africa. However, most colonies have closed. Leprosy has been associated with social stigma for much of history which remains a barrier to self-reporting and early treatment. World Leprosy Day was started in 1954 to draw awareness to those affected by leprosy.

Signs and symptoms

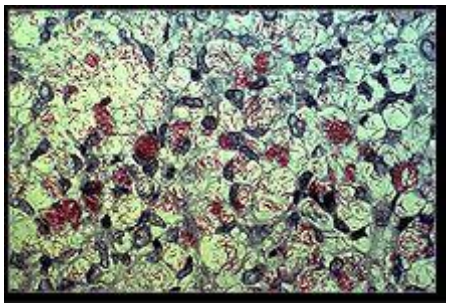


Hands deformed by leprosy, 1990, India

Lepers in Tahiti, c. 1895

Leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs and eyes. Contrary to folklore, leprosy does not cause body parts to fall off, although they can become numb or diseased as a result of secondary infections; these occur as a result of the body's defenses being compromised by the primary disease.Secondary infections, in turn, can result in tissue loss causing fingers and toes to become shortened and deformed, as cartilage is absorbed into the body.

Cause
Mycobacterium leprae



Mycobacterium leprae, one of the causative agents of leprosy. As acid-fast bacteria, M. leprae appear red when a Ziehl-Neelsen stain is used.Main article: Mycobacterium leprae Mycobacterium leprae and Mycobacterium lepromatosis are the causative agents of leprosy. M. lepromatosis is a relatively newly identified mycobacterium isolated from a fatal case of diffuse lepromatous leprosy in 2008. An intracellular, acid-fast bacterium, M. leprae is aerobic and rod-shaped, and is surrounded by the waxy cell membrane coating characteristic of the Mycobacterium genus. Due to extensive loss of genes necessary for independent growth, M. leprae and M. lepromatosis are obligate pathogens, and unculturable in the laboratory, a factor that leads to difficulty in definitively identifying the organism under a strict interpretation of Koch's postulates. The use of non-culture-based techniques such as molecular genetics has allowed for alternative establishment of causation.While the causative organisms have to date been impossible to culture in vitro, it has been possible to grow them in animals.Naturally occurring infection also has been reported in non-human primates including the African chimpanzee, sooty mangabey, and cynomolgus macaque, as well as in armadillos.

Risk factors
At highest risk are those living in areas with polluted water and poor diet or people suffering from diseases that compromise immune function.There appears to be little interaction between HIV and the risk of leprosy.

Transmission
Although the mode of transmission of leprosy remains uncertain, many think that M. leprae is usually spread from person to person in nasal droplets. Studies have shown that leprosy can be transmitted to humans by armadillos. Leprosy is not known to be either sexually transmitted or highly infectious after treatment. Approximately 95% of people are naturally immune and sufferers are no longer infectious after as little as two weeks of treatment.

Pathophysiology
The precise mechanism of transmission of leprosy is unknown; however, both prolonged close contact and transmission by nasal droplet are thought to be implicated. In addition to humans, leprosy has been observed in the nine-banded armadillo, (which, it has recently been confirmed, is among the primary sources of new cases of leprosy in the population of North America), and three species of non-human primates. The bacterium can also be grown in the laboratory by injection into the footpads of mice. There is evidence that not all people who are infected with M. leprae develop leprosy, and genetic factors have long been thought to play a role, due to the observation of clustering of leprosy around certain families, and the failure to understand why certain individuals develop lepromatous leprosy while others develop other types of leprosy. It is estimated that due to genetic factors, only 5% of the population is susceptible to leprosy. This is mostly because the body is naturally immune to the bacteria, and those persons that do become infected experience severe allergic reactions to the disease. However, the role of genetic factors is not entirely clear in determining this clinical expression. In addition, malnutrition and prolonged exposure to infected persons may play a role in development of the overt disease.
The most widely held belief is that the disease is transmitted by contact between infected persons and healthy persons. In general, closeness of contact is related to the dose of infection, which in turn is related to the occurrence of disease. Of the various situations that promote close contact, contact within the household is the only one that is easily identified, although the incidence among contacts and the relative risk for them appear to vary considerably in different studies. In incidence

studies, infection rates for contacts of lepromatous leprosy have varied from 6.2 per 1000 per year in Cebu, Philippines to 53 per 1000 per year in part of Western India to 55.8 per 1000 per year in a part of Southern India

Two exit routes of M. leprae from the human body often described are the skin and the nasal mucosa, although their relative importance is not clear. Lepromatous cases show large numbers of organisms deep in the dermis, but whether they reach the skin surface in sufficient numbers is doubtful. Although there are reports of acid-fast bacilli being found in the desquamating epithelium (sloughing of superficial layer of skin) of the skin, Weddell et al. had reported in 1963 that they could not find any acid-fast bacilli in the epidermis, even after examining a very large number of specimens from patients and contacts. In a recent study, Job et al. found fairly large numbers of M. leprae in the superficial keratin layer of the skin of lepromatous leprosy patients, suggesting that the organism could exit along with the sebaceous secretions.

The importance of the nasal mucosa was recognized as early as 1898 by Schäffer, in particular that of the ulcerated mucosa. The quantity of bacilli from nasal mucosal lesions in lepromatous leprosy was demonstrated by Shepard as large, with counts ranging from 10,000 to 10,000,000. Pedley reported that the majority of lepromatous patients showed leprosy bacilli in their nasal secretions as collected through blowing the nose. Davey and Rees indicated that nasal secretions from lepromatous patients could yield as much as 10 million viable organisms per day.

The entry route of M. leprae into the human body is also not definitively known: The skin and the upper respiratory tract are most likely. While older research dealt with the skin route, recent research has increasingly favored the respiratory route. Rees and McDougall succeeded in the experimental transmission of leprosy through aerosols containing M. leprae in immune-suppressed mice, suggesting a similar possibility in humans. Successful results have also been reported on experiments with nude mice when M. leprae were introduced into the nasal cavity by topical application. In summary, entry through the respiratory route appears the most probable route, although other routes, particularly broken skin, cannot be ruled out.

In leprosy, both the reference points for measuring the incubation period and the times of infection and onset of disease are difficult to define, the former because of the lack of adequate immunological tools and the latter because of the disease's slow onset. Even so, several investigators have attempted to measure the incubation period for leprosy. The minimum incubation period reported is as short as a few weeks and this is based on the very occasional occurrence of leprosy among young infants. The maximum incubation period reported is as long as 30 years, or over, as observed among war veterans known to have been exposed for short periods in endemic areas but otherwise living in non-endemic areas. It is generally agreed that the average incubation period is between three and five years.

Diagnosis

Endemic areas

Per the World Health Organization, diagnosis in an endemic area is based on one of the following cardinal signs:

Skin lesion consistent with leprosy and with definite sensory loss Positive skin smears

Skin lesions can be single or multiple, usually hypopigmented although occasionally reddish or copper colored. The lesions may be macules (flat), papules (raised), or nodular. Sensory loss at the skin lesion is important because this feature can help differentiate from other causes of skin lesions such as tinea versicolor.Thickened nerves are associated with leprosy and can be accompanied by loss of sensation, muscle weakness. However, without the characteristic skin lesion and without the sensory loss and/or muscle weakness is not considered a reliable sign of leprosy.Positive skin smears: In some case, acid fast leprosy bacilli, are considered diagnostic; however, it should be emphasized that the diagnosis is clinical

United States

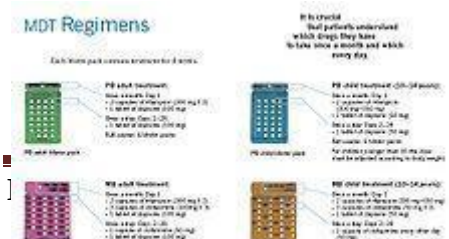
Diagnosis in the U.S. is often delayed because healthcare providers are unaware of leprosy and its symptoms. Early diagnosis and treatment prevents nerve involvement, the hallmark of leprosy, and the disability it causes. There are many kinds of leprosy but there are common symptoms, including: runny nose; dry scalp; eye problems; skin lesions; muscle weakness; reddish skin; smooth shiny diffuse thickening of facial skin, ear, and hand; loss of sensation in fingers and toes; thickening of peripheral nerves; and flat nose due to destruction of nasal cartilage. There is also phonation and resonation of sound during speech. Often there is atrophy of the testes and impotency.

Prevention

Medications can decrease the risk of those living with people with leprosy from acquiring the disease and likely those with whom people with leprosy come into contact outside the home. There are however concerns of resistance, cost, and disclosure of a person's infection status when doing follow up of contacts, thus the WHO however recommends that people who live in the same household be examined for leprosy and only be treated if symptoms are present.

The Bacillus Calmette–Guérin (BCG) vaccine offers a variable amount of protection against leprosy in addition to tuberculosis. It appears to be 26 to 41% effective (based on controlled trials) and about 60% effective based on observational studies with two doses possibly working better than one. Development of a more effective vaccine is ongoing as of 2011.

Treatment



MDT anti-leprosy drugs: standard regimens

A number of leprostatic agents are available for treatment. For paucibacillary (PB or tuberculoid) cases treatment with daily dapsone and monthly rifampicin for six months is recommended. While for multibacillary (MB or lepromatous) cases treatment with daily dapsone and clofazimine along with monthly rifampicin for twelve months is recommended.
Multi-drug therapy (MDT) remains highly effective, and people are no longer infectious after the first monthly dose. It is safe and easy to use under field conditions due to its presentation in calendar blister packs. Relapse rates remain low, and there is no known resistance to the combined drugs.

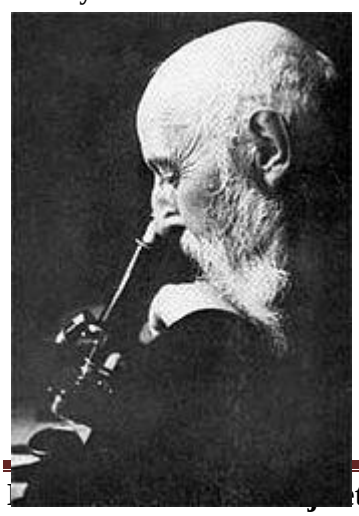
Epidemiology
World distribution of leprosy, 2003.
Disability-adjusted life year for leprosy per 100,000 inhabitants in 2004

no data	9–10.5
<1.5	10.5–12
1.5–3	12–13.5
3–4.5	13.5–15
4.5–6	15–20
6–7.5	>20
7.5–9	

Globally in 2012 the number of cases of leprosy was 180,000. In 2011 the approximate number of new cases diagnosed was 220,000. The number of cases has decreased significantly from the 1960s to the 2010s. In 1995 two to three million people were estimated to be permanently disabled because of leprosy. India has the greatest number of cases, with Brazil second and Myanmar third. In 2000, the World Health Organization (WHO) listed 91 countries in which leprosy is endemic. India, Burma, and Nepal contained 70% of cases. India reports over 50% of the world's leprosy cases. In 2002, 763,917 new cases were detected worldwide, and in that year the WHO listed Brazil, Madagascar, Mozambique, Tanzania, and Nepal as having 90% of leprosy cases. Although the number of cases worldwide continues to fall, pockets of high prevalence continue in certain areas such as Brazil, South Asia (India, Nepal), some parts of Africa (Tanzania, Madagascar, Mozambique), and the western Pacific.

Disease burden
Although the number of new leprosy cases occurring each year is important as a measure of transmission, it is difficult to measure due to leprosy's long incubation period, delays in diagnosis after onset of the disease, and the lack of laboratory tools to detect it in the very early stages. Instead, the registered prevalence is used. Registered prevalence is a useful proxy indicator of the disease burden, as it reflects the number of active leprosy cases diagnosed with the disease and receiving treatment with MDT at a given point in time. The prevalence rate is defined as the number of cases registered for MDT treatment among the population in which the cases have occurred, again at a given point in time. New case detection is another indicator of the disease that is usually reported by countries on an annual basis. It includes cases diagnosed with onset of disease in the year in question (true incidence) and a large proportion of cases with onset in previous years (termed a backlog prevalence of undetected cases).Endemic countries also report the number of new cases with established disabilities at the time of detection, as an indicator of the backlog prevalence. Determination of the time of onset of the disease is, in general, unreliable, is very labor-intensive, and is seldom done in recording these statistics.

History



G. H. A. Hansen, discoverer of M. leprae

Evidence of leprosy dates back to ancient Egypt in 4000 BC and was discussed by Hippocrates in 460 BC. It was recognized in the civilizations of ancient China, Egypt, Israel, and India. The earliest proven human case was verified by DNA taken from the shrouded remains of a man discovered in a tomb next to the Old City of Jerusalem dated by radiocarbon methods to 1–50 AD. A reference to an individual receiving treatment for leprosy is found in the Bible book of 2 Kings Chapter 5. Naaman was a Syrian army chief of the tenth century B.C.E., during the reigns of Jehoram of Israel and Ben-hadad II of Syria. He was instructed by the prophet Elisha to bathe in the Jordan River seven times to be relieved of his malady. Naaman eventually complied and was cured, according to the Bible passage. Early writings showing individuals cured from leprosy are documented in the Synoptic Gospels (Gospel of Mark, Gospel of Matthew,and Gospel of Luke) where Jesus is described as cleansing multiple people of their infirmity. The term leprosy is derived from either the Indo-European term lap, which means the removal of scales, or the Greek word for "scales", lepia. Historically, people infected were often confined against their will in leper colonies and in Medieval Europe were required to carry a bell to identify their presence. Attempted treatments have included arsenic, elephants' teeth, creosote, and mercury.
The causative agent of leprosy, Mycobacterium leprae, was discovered by G. H. Armauer Hansen in Norway in 1873, making it the first bacterium to be identified as causing disease in humans. The first effective treatment (promin) became available in the 1940s. In the 1950s dapsone was introduced. The search for further effective anti-leprosy drugs led to the use of clofazimine and rifampicin in the 1960s and 1970s. Later, Indian scientist Shantaram Yawalkar and his colleagues formulated a combined therapy using rifampicin and dapsone, intended to mitigate bacterial resistance. Multidrug therapy (MDT) combining all three drugs was first recommended by the WHO in 1981. These three anti-leprosy drugs are still used in the standard MDT regimens.Leprosy was once believed to be highly contagious and was treated with mercury—all of which applied to syphilis, which was first described in 1530. It is possible that many early cases thought to be leprosy could actually have been syphilis. Effective treatment first appeared in the late 1940s. Resistance has developed to initial treatment. It was not until the introduction of MDT in the early 1980s that the disease could be diagnosed and treated successfully within the community. Japan still has sanatoriums (although Japan's sanatoriums no longer have active leprosy cases, nor are survivors held in them by law).

Society and culture

Treatment cost

Between 1995 and 1999, WHO, with the aid of the Nippon Foundation, supplied all endemic countries with free Multi-Drug Treatment (MDT) in blister packs, channelled through ministries of health. This free provision was extended in 2000 and again in 2005 with donations by the MDT manufacturer Novartis through WHO. In the latest agreement signed between the company and WHO in October 2010, the provision of free MDT by WHO to all endemic countries will now run until at least the end of 2015. At the national level, non-government organizations (NGOs) affiliated to the national programme will continue to be provided with an appropriate free supply of this WHO supplied MDT by the government.

Stigma in India

Leprosy patients in India, like many parts of the world, suffer under some of the worst conditions and stereotypes about their disease. Depending on the level of disfigurement, a leper could receive harsher stigma and ostracism. Leprosy sufferers are markedly disadvantaged with respect to income, with 16-44% of victims reporting a decrease in pay as a result of having leprosy. Women suffer greater restrictions and social stigma than men. Leprosy prevents mothers from getting too close to their children out of fear that they could infect them. In a report, 49% of women stopped breast-feeding their babies as a result of having leprosy. Doctors and other health care providers and NGOs are working hard to educate people about the disease. In one study when leprosy treatment and education were mixed in with the local healthcare program, the attitudes towards the disease were somewhat alleviated as people had a better understanding of it. Now the disease prevalence has been reduced to less than 1 per million populations in most parts of the country.

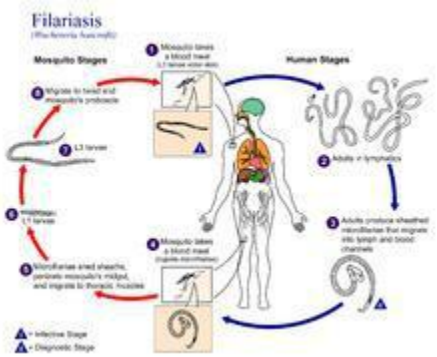
Notable cases

Saint Damien DeVeuster, a Roman Catholic priest from Belgium, ministered to the people with leprosy who had been placed under a government-sanctioned medical quarantine on the island of Molokaʻi in the Kingdom of Hawaiʻi.
Baldwin IV of Jerusalem was a Christian king of Latin Jerusalem, afflicted with leprosy. Baldwin, and the effects of his disease, were portrayed in the film Kingdom of Heaven.
Vietnamese poet Han Mac TuŌtani Yoshitsugu, a Japanese daimyo
In the Torah (also included within the Christian Old Testament), there are references to Moses and his sister Miriam being afflicted by a dreaded skin disease transliterated as tzaraath, which is widely but not exclusively understood to mean leprosy.
In the Books of Kings, included in the Jewish Nevi'im and Christian Old Testament, Naaman the Syrian and later the prophet Elisha's servant Gehazi were afflicted by a dreaded skin disease transliterated as tzaraath, which is widely but not exclusively understood to mean leprosy.
In the Books of Chronicles, included in the Jewish Ketuvim and Christian Old Testament, King Uzziah was suddenly struck

7. Filariasis

Filariasis

Classification and external resources



Life cycle of Wuchereria bancrofti, a parasite that causes filariasis

Filariasis (or **philariasis**) is a parasitic disease that is caused by thread-like roundworms belonging to the Filarioidea type. These are spread by blood-feeding black flies and mosquitoes.Eight known filarial nematodes use humans as their definitive hosts. These are divided into three groups according to the niche within the body they occupy:
Lymphatic filariasis is caused by the worms Wuchereria bancrofti, Brugia malayi, and Brugia timori. These worms occupy the lymphatic system, including the lymph nodes; in chronic cases, these worms lead to the disease elephantiasis.
Subcutaneous filariasis is caused by Loa loa (the eye worm), Mansonella streptocerca, and Onchocerca volvulus. These worms occupy the subcutaneous layer of the skin, in the fat layer. L. loa causes Loa loa filariasis, while O. volvulus causes river blindness.
Serous cavity filariasis is caused by the worms Mansonella perstans and Mansonella ozzardi, which occupy the serous cavity of the abdomen.The adult worms, which usually stay in one tissue, release early larval forms known as microfilariae into the host's bloodstream. These circulating microfilariae can be taken up with a blood meal by the arthropod vector; in the vector, they develop into infective larvae that can be transmitted to a new host.Individuals infected by filarial worms may be described as either "microfilaraemic" or "amicrofilaraemic", depending on whether microfilariae can be found in their peripheral blood. Filariasis is diagnosed in microfilaraemic cases primarily through direct observation of microfilariae in the peripheral blood. Occult filariasis is diagnosed in amicrofilaraemic cases based on clinical observations and, in some cases, by finding a circulating antigen in the blood.

Signs and symptoms
The most spectacular symptom of lymphatic filariasis is elephantiasis—edema with thickening of the skin and underlying tissues—which was the first disease discovered to be transmitted by mosquito bites. Elephantiasis results when the parasites lodge in the lymphatic system.
Elephantiasis affects mainly the lower extremities, while the ears, mucous membranes, and amputation stumps are affected less frequently. However, different species of filarial worms tend to affect different parts of the body; Wuchereria bancrofti can affect the legs, arms, vulva, breasts, and scrotum (causing hydrocele formation), while Brugia timori rarely affects the genitals.Those who develop the chronic stages of elephantiasis are usually amicrofilaraemic, and often have adverse immunological reactions to the microfilariae, as well as the adult worms.
The subcutaneous worms present with skin rashes, urticarial papules, and arthritis, as well as hyper- and hypopigmentation macules. Onchocerca volvulus manifests itself in the eyes, causing "river blindness" (onchocerciasis), one of the leading causes of blindness in the world. Serous cavity filariasis presents with symptoms similar to subcutaneous filariasis, in addition to abdominal pain, because these worms are also deep-tissue dwellers.

Diagnosis
Filariasis is usually diagnosed by identifying microfilariae on Giemsa stained, thin and thick blood film smears, using the "gold standard" known as the finger prick test. The finger prick test draws blood from the capillaries of the finger tip; larger veins can be used for blood extraction, but strict windows of the time of day must be observed. Blood must be drawn at appropriate times, which reflect the feeding activities of the vector insects. Examples are W. bancrofti, whose vector is a mosquito; night is the preferred time for blood collection. Loa loa's vector is the deer fly; daytime collection is preferred. This method of diagnosis is only relevant to microfilariae that use the blood as transport from the lungs to the skin. Some filarial worms, such as M. streptocerca and O. volvulus, produce microfilarae that do not use the blood; they reside in the skin only. For these worms, diagnosis relies upon skin snips, and can be carried out at any time.

Concentration methods
This section **needs additional citations for verification. Please help improve this article by adding citations to reliable sources. Unsourced material may be challenged and removed.**

arious concentration methods are applied: membrane filter, Knott's concentration method, and sedimentation technique.Polymerase chain reaction (PCR) and antigenic assays, which detect circulating filarial antigens, are also available for making the diagnosis. The latter are particularly useful in amicrofilaraemic cases. Spot tests for antigen are far more sensitive, and allow the test to be done any time, rather in the late hours.Lymph node aspirate and chylus fluid may also yield microfilariae. Medical imaging, such as CT or MRI, may reveal "filarial dance sign" in chylus fluid; X-ray tests can show calcified adult worms in lymphatics. The DEC provocation test is performed to obtain satisfying numbers of parasites in daytime samples. Xenodiagnosis is now obsolete, and eosinophilia is a nonspecific primary sign.

Cause

Human filarial nematode worms have complicated lifecycles, which primarily consists of five stages. After the male and female worms mate, the female gives birth to live microfilariae by the thousands. The microfilariae are taken up by the vector insect (intermediate host) during a blood meal. In the intermediate host, the microfilariae molt and develop into third-stage (infective) larvae. Upon taking another blood meal, the vector insect injects the infectious larvae into the dermis layer of the skin. After about one year, the larvae molt through two more stages, maturing into the adult worms.

Treatment

The recommended treatment for people outside the United States is albendazole (a broad-spectrum anthelmintic) combined with ivermectin. A combination of diethylcarbamazine and albendazole is also effective. All of these treatments are microfilaricides; they have no effect on the adult worms. Different trials were made to use the known drug at its maximum capacity in absence of new drugs. In a study from India, it has been shown that a formulation of albendazole has better anti-filarial efficacy than albendazole itself. In 2003, the common antibiotic doxycycline was suggested for treating elephantiasis. Filarial parasites have symbiotic bacteria in the genus Wolbachia, which live inside the worm and seem to play a major role in both its reproduction and the development of the disease. Clinical trials in June 2005 by the Liverpool School of Tropical Medicine reported an eight-week course almost completely eliminated microfilaraemia.

Other animals

Filariasis can also affect domesticated animals, such as cattle, sheep, and dogs.

Cattle

Verminous haemorrhagic dermatitis is a clinical disease in cattle due to Parafilaria bovicola.
Intradermal onchocercosis of cattle results in losses in leather due to Onchocerca dermata, O. ochengi, and O. dukei. O. ochengi is closely related to human O. volvulus

Stenofilaria assamensis and others cause different diseases in Asia, in cattle and zebu.

Horses

"Summer bleeding" is hemorrhagic subcutaneous nodules in the head and upper forelimbs, caused by Parafilaria multipapillosa (North Africa, Southern and Eastern Europe, Asia and South America).

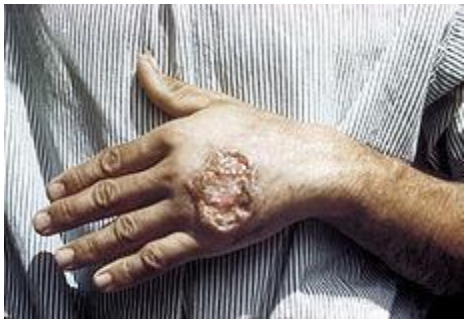
Dogs

Heart filariasis is caused by Dirofilaria immitis.

8.Leishmaniasis

Leishmaniasis

Classification and external resources

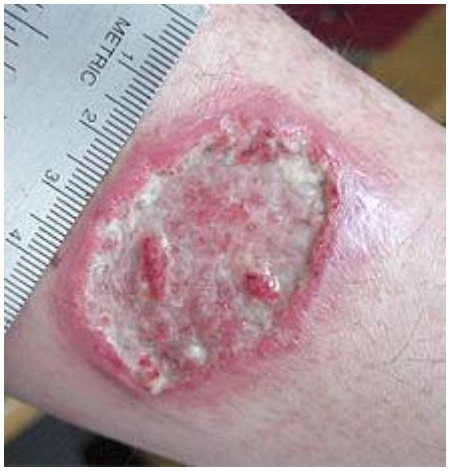


Cutaneous leishmaniasis in the hand of a Central

Leishmaniasis (/ˌliːʃməˈnaɪəsɪs/) **or leishmaniosis** (/liːʃˌmeɪnɪˈoʊsɪs/ **or** /liːʃˌmænɪˈoʊsɪs/) **is** a disease caused by protozoan parasites of the genus Leishmania and spread by the bite of certain types of sandflies. The disease can present in three main ways as: cutaneous leishmaniasis, mucocutaneous leishmaniasis and visceral leishmaniasis. The cutaneous form presents with skin ulcers, while the mucocutaneous form presents with ulcers of the skin, mouth and nose and the visceral form starts with skin ulcers and then later presents with fever, low red blood cells, and a large spleen and liver. Infections in humans are caused by more than 20 species of Leishmania. Risk factors include: poverty, malnutrition, deforestation and urbanization. All three types can be diagnosed by directly seeing the parasites under the microscope. Additionally visceral disease can be diagnosed via blood tests. Leishmaniasis can be partly prevented by sleeping under nets treated with insecticide. Other measures include: spraying insecticides to kill sandflies and treating people with the disease early to prevent further spread. The treatment needed is

determined by where the disease is acquired, the species of Leishmania and the type of infection. Some possible medications used for visceral disease include: liposomal amphotericin B, a combination of pentavalent antimonials and paromomycin, and miltefosine. For cutaneous disease paromomycin, fluconazole or pentamidine may be effective. About 12 million people are currently infected in some 98 countries there are about 2 million new cases and between 20 to 50 thousand deaths a year. About 200 million people in Asia, Africa, South and Central America and southern Europe live in areas where the disease is common. The World Health Organization has obtained discounts on some medications to treat the disease. The disease may occur in a number of other animals including dogs and rodents.

Signs and symptoms



Cutaneous leishmaniasis ulcer on left forearm

The symptoms of leishmaniasis are skin sores which erupt weeks to months after the person is bitten by infected sand flies.

Leishmaniasis may be divided into the following types:

Cutaneous leishmaniasis is the most common form, which causes an open sore at the bite sites, which heals in a few months to a year and half, leaving an unpleasant-looking scar. Diffuse cutaneous leishmaniasis produces widespread skin lesions which resemble leprosy, and may not heal on its own.

Mucocutaneous leishmaniasis causes both skin and mucosal ulcers with damage primarily of the nose and mouth.

Visceral leishmaniasis or kal-azar is the most serious form, and is potentially fatal if untreated. Other consequences, which can occur anywhere from a few months to years after infection, include fever, damage to the spleen and liver, and anemia.

Leishmaniasis is considered one of the classic causes of a markedly enlarged (and therefore palpable) spleen; the organ, which is not normally felt during examination of the abdomen, may even become larger than the liver in severe cases.

Life cycle of Leishmania

Leishmaniasis is transmitted by the bite of infected female phlebotomine sandflies which can transmit the infection Leishmania. The sandflies inject the infective stage, metacyclic promastigotes, during blood meals. Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophages and transform into amastigotes Amastigotes multiply in infected cells and affect different tissues, depending in part on which Leishmania species is involved

.These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sandflies become infected during blood meals on infected hosts when they ingest macrophages infected with amastigotes. In the sandfly's midgut, the parasites differentiate into promastigotes, which multiply, differentiate into metacyclic promastigotes, and migrate to the proboscis.

The genomes of three Leishmania species (L. major, L. infantum, and L. braziliensis) have been sequenced and this has provided much information about the biology of the parasite. For example, in Leishmania, protein-coding genes are understood to be organized as large polycistronic units in a head-to-head or tail-to-tail manner; RNA polymerase II transcribes long polycistronic messages in the absence of defined RNA pol II promoters, and Leishmania has unique features with respect to the regulation of gene expression in response to changes in the environment. The new knowledge from these studies may help identify new targets for urgently needed drugs and aid the development of vaccines.

Vector

Although most of the literature mentions only one genus transmitting Leishmania to humans (Lutzomyia) in the US, a 2003 study by Galati suggested a new classification for American sand

considered the vector of leishmaniasis.

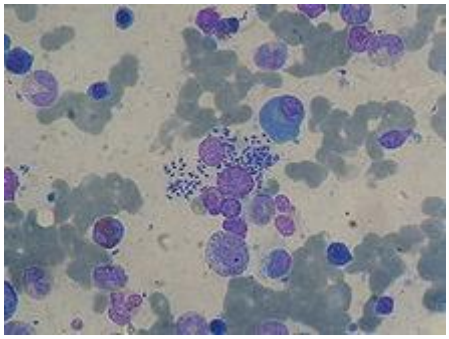
Organisms

Visceral disease is usually cause by Leishmania donovani, Leishmania infantum or Leishmania chagasi. But occasionally these species may cause other forms of disease. The cutaneous form of the disease is caused by more than 15 types of Leishmania.

Risk factors

Risk factors include: poverty, malnutrition, deforestation and urbanization.

Diagnosis

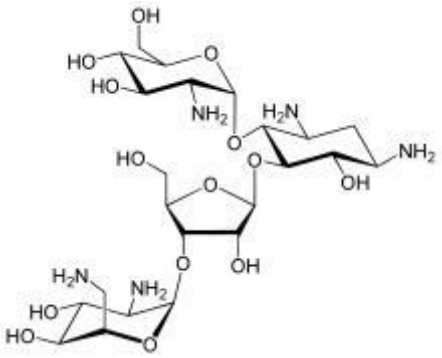


Bone marrow aspirate smear: visceral leishmaniasis

Leishmaniasis is diagnosed in the hematology laboratory by direct visualization of the amastigotes (Leishman-Donovan bodies). Buffy-coat preparations of peripheral blood or aspirates from marrow, spleen, lymph nodes, or skin lesions should be spread on a slide to make a thin smear and stained with Leishman's or Giemsa's stain (pH 7.2) for 20 minutes. Amastigotes are seen with monocytes or, less commonly in neutrophils, of peripheral blood and in macrophages in aspirates.

They are small, round bodies 2–4 μm in diameter with indistinct cytoplasm, a nucleus, and a small, rod-shaped kinetoplast. Occasionally, amastigotes may be seen lying free between cells. However, the retrieval of tissue samples is often painful for the patient and it can be difficult to identify the infected cells. For these reasons, other indirect immunological methods of diagnosis are developed. These methods include the enzyme-linked immunosorbent assay (ELISA), antigen coated dipsticks, and the direct agglutination test (DAT). Although these tests are readily available, they are not the standard diagnostic tests due to their insufficient sensitivity and specificity.There are several different polymerase chain reaction (PCR) tests for the detection of Leishmania DNA. With the PCR assay, a specific and sensitive diagnostic procedure is finally possible.Most forms of the disease are transmitted only from non-human animals, but some can be spread between humans. Infections in humans are caused by about 21 of 30 species that infect mammals: the different species look the same, but they can be differentiated by isoenzyme analysis, DNA sequence analysis, or monoclonal antibodies.

Treatment



Paromomycin is an inexpensive (US$10) and effective treatment for leishmaniasis.

The treatment is determined by where the disease is acquired, the species of Leishmania and the type of infection. For visceral leishmaniasis in India, South America and the Mediterranean liposomal amphotericin B is the recommended treatment and is often affected as a single dose. Rates of cure with a single dose of amphotericin have been reported as 95%. In India almost all infections are resistant to pentavalent antimonials. In Africa a combination of pentavalent antimonials and paromomycin is recommended. These, however, can have significant side effects. Miltefosine is an oral medication that is effective against both visceral and cutaneous leishmaniasis. Side effects are generally mild, though it can cause birth defects if taken within 3 months of getting pregnant. It does not appear to work for Leishmania major or L. braziliensis. The evidence around the treatment of cutaneous leishmaniasis is poor. A number of topical treatments may be used for cutaneous leishmaniasis. Which treatments are effective depends on the strain, with topical paromomycin effective for L. major, L. tropica, L. mexicana, L. panamensis and L. braziliensis. Pentamidine is effective for L. guyanensis. Oral fluconazole or itraconazole appears effective in L. major and L. tropica.

Epidemiology

Cutaneous leishmaniasis in North Africa; Leishmania infantum = green, Leishmania major = blue, Leishmania tropica = red

Disability-adjusted life year for leishmaniasis per 100,000 inhabitants. no data less than 20

20–30
30–40
40–50

50–60

60–70
70–80
80–100
100–120
120–150

150–200 More than 200

Leishmaniasis occurs in 88 tropical and subtropical countries. Approximately 350 million people live in these areas. The settings in which leishmaniasis is found range from rainforests in Central and South America to deserts in West Asia and the Middle East. It affects as many as 12 million people worldwide, with 1.5–2 million new cases each year. The visceral form of leishmaniasis has an estimated incidence of 500,000 new cases. More than 90 percent of the world's cases of visceral leishmaniasis are in India, Bangladesh, Nepal, Sudan, and Brazil. As of 2010 it caused about 52,000 deaths down from 87,000 in 1990. Different types of the disease occur in different regions of the world. Cutaneous disease is most common in Afghanistan, Algeria, Brazil, Colombia and Iran while mucocutaneous disease is most common in Bolivia, Brazil and Peru and visceral disease is most common in Bangladesh, Brazil, Ethiopia, India and Sudan.

Leishmaniasis is found through much of the Americas from northern Argentina to southern Texas, though not in Uruguay or Chile, and has recently been shown to be spreading to North Texas. Leishmaniasis is also known as papalomoyo, papa lo moyo, ulcero de los chicleros and "chiclera" in Latin America. During 2004, an estimated 3,400 troops from the Colombian army, operating in the jungles near the south of the country (in particular around the Meta and Guaviare departments), were infected with leishmaniasis. Apparently, a contributing factor was that many of the affected soldiers did not use the officially provided insect repellent, because of its allegedly disturbing odor. Nearly 13,000 cases of the disease were recorded in all of Colombia throughout 2004, and about 360 new instances of the disease among soldiers had been reported in February 2005.

The disease is found across much of Asia, and in the Middle East. Within Afghanistan, leishmaniasis occurs commonly in Kabul, partly due to bad sanitation and waste left uncollected in streets, allowing parasite-spreading sand flies an environment they find favorable. In Kabul, the number of people infected was estimated to be at least 200,000, and in three other towns (Herat, Kandahar and Mazar-i-Sharif) there were about 70,000 more, according to WHO figures from 2002.] Kabul is estimated as the largest center of cutaneous leishmaniasis in the world, with approximately 67,500 cases as of 2004. Africa, in particular the East and North, is home to cases of leishmaniasis. The disease is spreading to Southern Europe, but is not found in Australia or Oceania.Leishmaniasis is mostly a disease of the developing world, and is rarely known in the developed world outside a small number of cases, mostly in instances where troops are stationed away from their home countries. Leishmaniasis has been reported by U.S. troops stationed in Saudi Arabia and Iraq since the Gulf War of 1990, including visceral leishmaniasis. In September 2005, the disease was contracted by at least four Dutch marines who were stationed in Mazari Sharif, Afghanistan, and subsequently repatriated for treatment.

A 1917 case of cutaneous leishmaniasis in the Middle East, known then locally as "Jericho Buttons" for the frequency of cases near the ancient city of Jericho

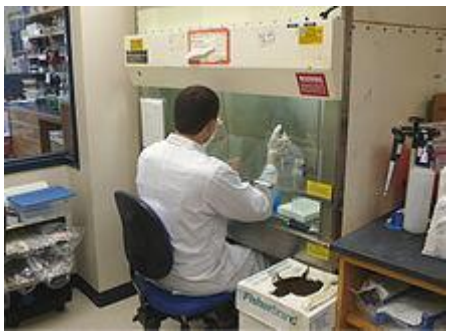
Descriptions of conspicuous lesions similar to cutaneous leishmaniasis (CL) appear on tablets from King Ashurbanipal from the seventh century BC, some of which may have derived from even earlier texts from 1500 to 2500 BC. Persian physicians, including Avicenna in the 10th century AD, gave detailed descriptions of what was called Balkh sore. In 1756, Alexander Russell, after examining a Turkish patient, gave one of the most detailed clinical descriptions of the disease. Physicians in the Indian subcontinent would describe it as kala-azar (pronounced kālā āzār, the Urdu, Hindi and Hindustani phrase for "black fever", kālā meaning black and āzār meaning fever or disease). In the Americas, evidence of the cutaneous form of the disease in Ecuador and Peru appears in pre-Inca potteries depicting skin lesions and deformed faces dating back to the first century AD. Some 15th- and 16th-century texts from the Inca period and from Spanish colonials mention "valley sickness", "Andean sickness", or "white leprosy", which are likely to be CL. It remains unclear who first discovered the organism. Surgeon Major Cunningham of the British Indian army possibly saw it first in 1885 without being able to relate it to the disease. Peter Borovsky, a Russian military surgeon working in Tashkent, conducted research into the etiology of oriental sore, locally known as "Sart sore", and in 1898 published the first accurate description of the causative agent, correctly described the parasite's relation to host tissues and correctly referred it to Protozoa. However, because his results were published in Russian in a journal with low circulation, his priority was not internationally acknowledged during his lifetime. In 1901, Leishman identified certain organisms in smears taken from the spleen of a patient who had died from "dum-dum fever" (Dum Dum is an area close to Calcutta) and proposed them to be trypanosomes, found for the first time in India. A few months later, Captain Charles Donovan (1863–1951) confirmed the finding of what became known as Leishman-Donovan bodies in smears taken from patients in Madras in southern India. But it was Ronald Ross who proposed that Leishman-Donovan bodies were the intracellular stages of a new

parasite, which he named Leishmania donovani. The link with the disease kala-azar was first suggested by Charles Donovan, but was conclusively demonstrated by Charles Bentley's discovery of Leishmania donovani in patients with kala-azar. The disease became a major problem for Allied troops fighting in Sicily during the Second World War; research by Leonard Goodwin then showed pentostam was an effective treatment.

Society and culture

The Institute for OneWorld Health has reintroduced the drug paromomycin for treatment of leishmaniasis, results with which led to its approval as an orphan drug. The Drugs for Neglected Diseases Initiative is also actively facilitating the search for novel therapeutics. A treatment with paromomycin will cost about $10. The drug had originally been identified in 1960s, but had been abandoned because it would not be profitable, as the disease mostly affects poor people. The Indian government approved paromomycin for sale in August 2006. The World Health Organization has gotten a reduced cost for liposomal amphotericin B at $18 a vial, however many vials may be needed for treatment and it must be kept cool.

Research



A parasitologist working on L. major in a biocontainment hood

Several potential vaccines are being developed, under pressure from the World Health Organization, but as of 2013 none are available. The team at the Laboratory for Organic Chemistry at the Swiss Federal Institute of Technology (ETH) in Zürich are trying to design a carbohydrate-based vaccine. The genome of the parasite Leishmania major has been sequenced, possibly allowing for identification of proteins that are used by the pathogen but not by humans; these proteins are potential targets for drug treatments.On February 2012, the nonprofit Infectious Disease Research Institute launched the world's first human clinical trial of the visceral leishmaniasis vaccine. The vaccine is a recombinant form of two fused Leishmania parasite proteins with an adjuvant. Two phase 1 clinical trials with healthy volunteers are to be conducted. The first one takes place in Washington (state) and is followed by a trial in India. In 2009, the Hebrew University of Jerusalem Kuvin Center for the Study of Infectious and Tropical Diseases, in a collaborative effort with Addis Ababa University, was awarded a grant by the Bill & Melinda Gates Foundation for research into visceral leishmaniasis in Ethiopia. The project will gather data to be analyzed to identify the weak links in the transmission cycle, and devise methods for control of the disease. HIV protease inhibitors have been found to be active against

controlled by nelfinavir and ritonavir in a human monocyte cell line and also in human primary monocyte-derived macrophages. Since September 2011 there exists a World Community Grid project called Drug Search for Leishmaniasis which has the goal to find new drugs against this disease.

Notable cases

Marguerite Higgins, Pulitzer Prize winning journalist, died in early 1966 from leishmaniasis contracted while on an assignment the previous year.Magazine photographer Joel Sartore was diagnosed with the disease after a skin lesion refused to heal following a photo shoot in the Bolivian wilderness. Following intensive IV treatment similar to chemotherapy, his infection has resolved. While filming the latest series of Extreme Dreams in Peru, UK television presenter Ben Fogle caught the disease. He was left bedridden for three weeks on his return home. Fogle was treated at London's Hospital for Tropical Diseases. During his two-and-a-half-year walk through the Amazon, Ed Stafford tested positive for cutaneous leishmaniasis in Oriximiná, Para, Brazil. He convinced the local doctor that he could not stay in one place for treatment due to his undertaking and was prescribed with 20 days of intravenous injection

9. Malaria

Malaria

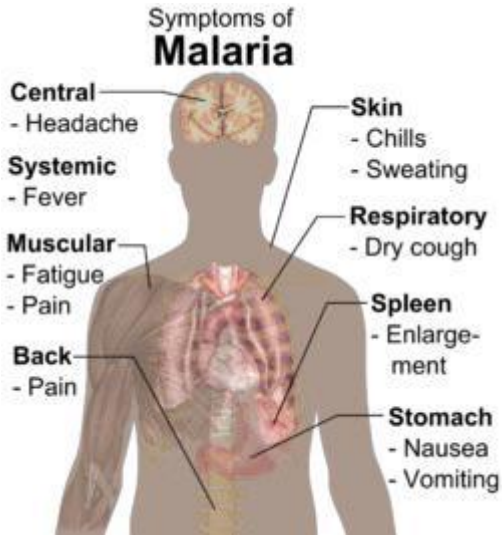
Classification and external resources

A Plasmodium in the form that enters humans and other vertebrates from the saliva of female mosquitoes (a sporozoite) traverses the cytoplasm of a mosquito midgut epithelial cell.

is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a type of unicellular microorganism) of the genus Plasmodium. Commonly, the disease is transmitted by a bite from an infected female Anopheles mosquito, which introduces the organisms from its saliva into a person's circulatory system. In the blood, the parasites travel to the liver to mature and reproduce. Malaria causes symptoms that typically include fever and headache, which in severe cases can progress to coma or death.Five species of Plasmodium can infect and be transmitted by humans. The vast majority of deaths are caused by P. falciparum and P. vivax, while P. ovale, and P. malariae cause a generally milder form of malaria that is rarely fatal. The zoonotic species P. knowlesi, prevalent in Southeast Asia, causes malaria in macaques but can also cause severe infections in humans. Malaria is common in tropical and subtropical regions because rainfall, warm temperatures, and stagnant waters provide an environment ideal for mosquito larvae. Malaria is typically diagnosed by the microscopic examination of blood using blood films, or with antigen-based rapid diagnostic tests. Modern techniques that use the polymerase chain reaction to detect the parasite's DNA have also been developed, but these are not widely used in malaria-endemic areas due to their cost and complexity.Disease transmission can be reduced by preventing mosquito bites by using mosquito nets and insect repellents, or with mosquito-control measures such as spraying insecticides and draining standing water. Despite a need, no effective vaccine exists, although efforts to develop one are ongoing. Several medications are available to prevent malaria in travellers to malaria-endemic countries. A number of antimalarial medications are available in those who have the disease. Severe malaria is treated with intravenous or intramuscular quinine or, since the mid-2000s, the artemisinin derivative artesunate, which is better than quinine in both children and adults and is given in combination with a second anti-malarial such as mefloquine. Resistance has developed to several antimalarial drugs; for example, chloroquine-resistant P. falciparum has spread to most malarial areas, and emerging resistance to artemisinin has become a problem in some parts of Southeast Asia.

The disease is widespread in tropical and subtropical regions in a broad band around the equator, including much of Sub-Saharan Africa, Asia, and the Americas. The World Health Organization estimates that in 2010, there were 219 million documented cases of malaria. That year, the disease killed between 660,000 and 1.2 million people, many of whom were children in Africa. The actual number of deaths is not known with certainty: data are unavailable in many rural areas, and many cases are undocumented. Malaria is commonly associated with poverty and may also be a major hindrance to economic development.

Signs and symptoms



Main symptoms of malaria

The signs and symptoms of malaria typically begin 8–25 days following infection; however, symptoms may occur later in those who have taken antimalarial medications as prevention. Initial manifestations of the disease—common to all malaria species—are similar to flu-like symptoms, and can resemble other conditions such as septicemia, gastroenteritis, and viral diseases. The presentation may include headache, fever, shivering, joint pain, vomiting, hemolytic anemia, jaundice, hemoglobin in the urine, retinal damage, and convulsions. The classic symptom of malaria is paroxysm—a cyclical occurrence of sudden coldness followed by shivering and then fever and sweating, occurring every two days (tertian fever) in P. vivax and P. ovale infections, and every three days (quartan fever) for P. malariae. P. falciparum infection can cause recurrent fever every 36–48 hours or a less pronounced and almost continuous fever. Severe malaria is usually caused by P. falciparum (often referred to as falciparum malaria). Symptoms of falciparum malaria arise 9–30 days after infection. Individuals with cerebral malaria frequently exhibit neurological symptoms, including abnormal posturing, nystagmus, conjugate gaze palsy (failure of the eyes to turn together in the same direction), opisthotonus, seizures, or coma.

Complications

There are several serious complications of malaria. Among these is the development of respiratory distress, which occurs in up to 25% of adults and 40% of children with severe

P. falciparum malaria. Possible causes include respiratory compensation of metabolic acidosis, noncardiogenic pulmonary oedema, concomitant pneumonia, and severe anaemia. Although rare in young children with severe malaria, acute respiratory distress syndrome occurs in 5–25% of adults and up to 29% of pregnant women. Coinfection of HIV with malaria increases mortality. Renal failure is a feature of blackwater fever, where hemoglobin from lysed red blood cells leaks into the urine.

Infection with P. falciparum may result in cerebral malaria, a form of severe malaria that involves encephalopathy. It is associated with retinal whitening, which may be a useful clinical sign in distinguishing malaria from other causes of fever. Splenomegaly, severe headache, hepatomegaly (enlarged liver), hypoglycemia, and hemoglobinuria with renal failure may occur.

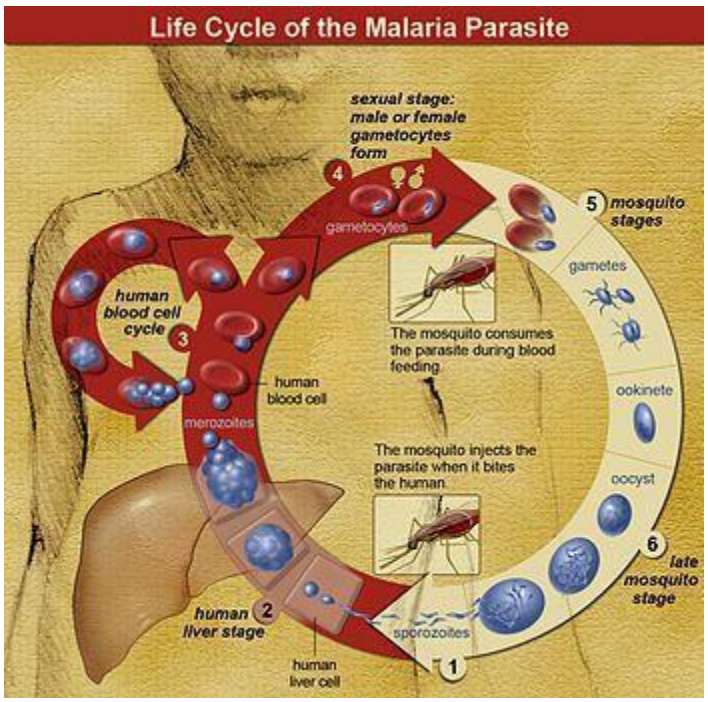
Malaria in pregnant women is an important cause of stillbirths, infant mortality and low birth weight, particularly in P. falciparum infection, but also with P. vivax.

Cause

Malaria parasites belong to the genus Plasmodium (phylum Apicomplexa). In humans, malaria is caused by P. falciparum, P. malariae, P. ovale, P. vivax and P. knowlesi. Among those infected, P. falciparum is the most common species identified (~75%) followed by P. vivax (~20%). although P. falciparum traditionally accounts for the majority of deaths, recent evidence suggests that P. vivax malaria is associated with potentially life-threatening conditions about as often as with a

diagnosis of P. falciparum infection. vivax proportionally is more common outside of Africa. There have been documented human infections with several species of Plasmodium from higher apes; however, with the exception of P. knowlesi—a zoonotic species that causes malaria in macaques—these are mostly of limited public health importance. Climate change is likely to affect malaria transmission, but the severity and geographic distribution of such effects is currently uncertain.

Life cycle



The life cycle of malaria parasites. A mosquito causes an infection by a bite. First, sporozoites enter the bloodstream, and migrate to the liver. They infect liver cells, where they multiply into

merozoites, rupture the liver cells, and return to the bloodstream. Then, the merozoites infect red blood cells, where they develop into ring forms, trophozoites and schizonts that in turn produce further merozoites. Sexual forms are also produced, which, if taken up by a mosquito, will infect the insect and continue the life cycle.In the life cycle of Plasmodium, a female Anopheles mosquito (the definitive host) transmits a motile infective form (called the sporozoite) to a vertebrate host such as a human (the secondary host), thus acting as a transmission vector. A sporozoite travels through the blood vessels to liver cells (hepatocytes), where it reproduces asexually (tissue schizogony), producing thousands of merozoites. These infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 24 new infective merozoites, at which point the cells burst and the infective cycle begins anew. Other merozoites develop into immature gametocytes, which are the precursors of male and female gametes. When a fertilised mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut. The male and female gametocytes fuse and form a ookinete—a fertilized, motile zygote. Ookinetes develop into new sporozoites that migrate to the insect's salivary glands, ready to infect a new vertebrate host. The sporozoites are injected into the skin, in the saliva, when the mosquito takes a subsequent blood meal. Only female mosquitoes feed on blood; male mosquitoes feed on plant nectar, and thus do not transmit the disease. The females of the Anopheles genus of mosquito prefer to feed at night. They usually start searching for a meal at dusk, and will continue throughout the night until taking a meal. Malaria parasites can also be transmitted by blood transfusions, although this is rare.

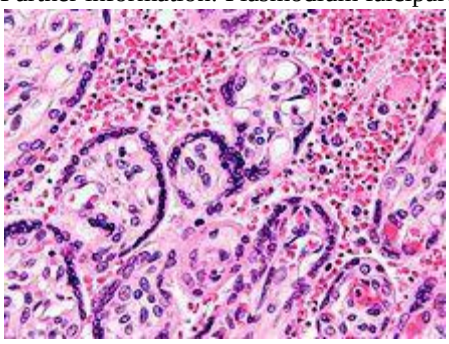
Recurrent malaria

Symptoms of malaria can recur after varying symptom-free periods. Depending upon the cause, recurrence can be classified as either recrudescence, relapse, or reinfection. Recrudescence is when symptoms return after a symptom-free period. It is caused by parasites surviving in the blood as a result of inadequate or ineffective treatment. Relapse is when symptoms reappear after the parasites have been eliminated from blood but persist as dormant hypnozoites in liver cells. Relapse commonly occurs between 8–24 weeks and is commonly seen with P. vivax and

P. ovale infections. P. vivax malaria cases in temperate areas often involve overwintering by hypnozoites, with relapses beginning the year after the mosquito bite. Reinfection means the parasite that caused the past infection was eliminated from the body but a new parasite was introduced. Reinfection cannot readily be distinguished from recrudescence, although recurrence of infection within two weeks of treatment for the initial infection is typically attributed to treatment failure. People may develop some immunity when exposed to frequent infections.

Pathophysiology

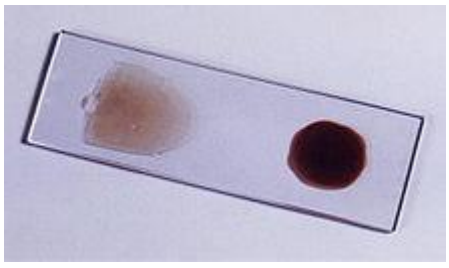
Further information: Plasmodium falciparum biology



Micrograph of a placenta from a stillbirth due to maternal malaria. H&E stain. Red blood cells are anuclear; blue/black staining in bright red structures (red blood cells) indicates foreign nuclei from the parasites.Malaria infection develop via two phases: one that involves the liver (exoerythrocytic phase), and one that involves red blood cells, or erythrocytes (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 where they infect hepatocytes, multiplying asexually and asymptomatically for a period of 8–30 days. After a potential dormant period in the liver, these organisms differentiate to yield thousands of merozoites, which, following rupture of their host cells, escape into the blood and infect red blood cells to begin the erythrocytic stage of the life cycle. The parasite escapes from the liver undetected by wrapping itself in the cell membrane of the infected host liver cell.Within the red blood cells, the parasites multiply further, again asexually, periodically breaking out of their host cells to invade fresh red blood cells. Several such amplification cycles occur. Thus, classical descriptions of waves of fever arise from simultaneous waves of merozoites escaping and infecting red blood cells. Some P. vivax sporozoites do not immediately develop into exoerythrocytic-phase merozoites, but instead produce hypnozoites that remain dormant for periods ranging from several months (7–10 months is typical) to several years. After a period of dormancy, they reactivate and produce merozoites. Hypnozoites are responsible for long incubation and late relapses in P. vivax infections, although their existence in P. ovale is uncertain. The parasite is relatively protected from attack by the body's immune system because for most of its human life cycle it resides within the liver and blood cells and is relatively invisible to immune surveillance. However, circulating infected blood cells are destroyed in the spleen. To avoid this fate, the P. falciparum parasite displays adhesive proteins on the surface of the infected blood cells, causing the blood cells to stick to the walls of small blood vessels, thereby sequestering the parasite from passage through the general circulation and the spleen. The blockage of the microvasculature causes symptoms such as in placental malaria. Sequestered red blood cells can breach the blood–brain barrier and cause cerebral malaria.

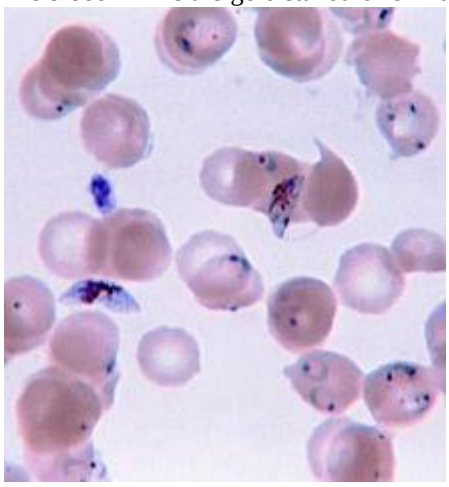
Liver dysfunction

Liver dysfunction as a result of malaria is uncommon and usually only occurs in those with other liver condition such as viral hepatitis or chronic liver disease. The syndrome is sometimes called malarial hepatitis. While it has been considered a rare occurrence, malarial hepatopathy has seen an increase, particularly in Southeast Asia and India. Liver compromise in people with malaria correlates with a greater likelihood of complications and death.



Diagnosis

The blood film is the gold standard for malaria diagnosis.



Ring-forms and gametocytes of Plasmodium falciparum in human blood

Owing to the non-specific nature of the presentation of symptoms, diagnosis of malaria in non-endemic areas requires a high degree of suspicion, which might be elicited by any of the following: recent travel history, enlarged spleen, fever, low number of platelets in the blood, and higher-than-normal levels of bilirubin in the blood combined with a normal level of white blood cells.Malaria is usually confirmed by the microscopic examination of blood films or by antigen-based rapid diagnostic tests (RDT). Microscopy is the most commonly used method to detect the malarial parasite—about 165 million blood films were examined for malaria in 2010. Despite its widespread usage, diagnosis by microscopy suffers from two main drawbacks: many settings (especially rural) are not equipped to perform the test, and the accuracy of the results depends on both the skill of the person examining the blood film and the levels of the parasite in the blood. The sensitivity of blood films ranges from 75–90% in optimum conditions, to as low as 50%. Commercially available RDTs are often more accurate than blood films at predicting the presence of malaria parasites, but they are widely variable in diagnostic sensitivity and specificity depending on manufacturer, and are unable to tell how many parasites are present. In regions where laboratory tests are readily available, malaria should be suspected, and tested for, in any unwell person who has been in an area where malaria is endemic. In areas that cannot afford laboratory diagnostic tests, it has become common to use only a history of fever as the indication to treat for malaria—thus the common teaching "fever equals malaria unless proven otherwise". A drawback of this practice is overdiagnosis of malaria and mismanagement of non-malarial fever, which wastes limited resources, erodes confidence in the health care system, and contributes to drug resistance. Although polymerase chain reaction-based tests have been developed, they are not widely used in areas where malaria is common as of 2012, due to their complexity.

Classification

Malaria is classified into either "severe" or "uncomplicated" by the World Health Organization (WHO). It is deemed severe when any of the following criteria are present, otherwise it is considered uncomplicated.

Decreased consciousness

Significant weakness such that the person is unable to walk Inability to feed

Two or more convulsions

Low blood pressure (less than 70 mmHg in adults and 50 mmHg in children) Breathing problems

Circulatory shock

Kidney failure or hemoglobin in the urine

Bleeding problems, or hemoglobin less than 50 g/L (5 g/dL) Pulmonary oedema

Blood glucose less than 2.2 mmol/L (40 mg/dL)

Acidosis or lactate levels of greater than 5 mmol/L

A parasite level in the blood of greater than 100,000 per microlitre (µL) in low-intensity transmission areas, or 250,000 per µL in high-intensity transmission areas

Cerebral malaria is defined as a severe P. falciparum-malaria presenting with neurological symptoms, including coma (with a Glasgow coma scale less than 11, or a Blantyre coma scale greater than 3), or with a coma that lasts longer than 30 minutes after a seizure.

Prevention

An Anopheles stephensi mosquito shortly after obtaining blood from a human (the droplet of blood is expelled as a surplus). This mosquito is a vector of malaria, and mosquito control is an effective way of reducing its incidence.Methods used to prevent malaria includes medications, mosquito elimination and the prevention of bites. There is no vaccine for malaria. The presence of malaria in an area requires a combination of high human population density, high anopheles mosquito population density and high rates of transmission from humans to mosquitoes and from mosquitoes to humans. If any of these is lowered sufficiently, the parasite will eventually disappear from that area, as happened in North America, Europe and parts of the Middle East. However, unless the parasite is eliminated from the whole world, it could become re-established if conditions revert to a combination that favours the parasite's reproduction. Furthermore, the cost per person of eliminating anopheles mosquitoes rises with decreasing population density, making it economically unfeasible in some areas. Prevention of malaria may be more cost-effective than treatment of the disease in the long run, but the initial costs required are out of reach of many of the world's poorest people. There is a wide difference in the costs of control (i.e. maintenance of low endemicity) and elimination programs between countries. For example, in China—whose government in 2010 announced a strategy to pursue malaria elimination in the Chinese provinces—the required investment is a small proportion of public expenditure on health. In contrast, a similar program in Tanzania would cost an estimated one-fifth of the public health budget.

Mosquito control

Man spraying kerosene oil in standing water, Panama Canal Zone 1912

Walls where indoor residual spraying of DDT has been applied. The mosquitoes remain on the wall until they fall down dead on the floor.

Vector control refers to methods used to decrease malaria by reducing the levels of transmission by mosquitoes. For individual protection, the most effective insect repellents are based on DEET or picaridin. Insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS) have been shown to be highly effective in preventing malaria among children in areas where malaria is common. Prompt treatment of confirmed cases with artemisinin-based combination therapies (ACTs) may also reduce transmission.

Mosquito nets create a protective barrier against malaria-carrying mosquitoes that bite at night.

Mosquito nets help keep mosquitoes away from people and reduce infection rates and transmission of malaria. Nets are not a perfect barrier and are often treated with an insecticide designed to kill the mosquito before it has time to find a way past the net. Insecticide-treated nets are estimated to be twice as effective as untreated nets and offer greater than 70% protection compared with no net. Between 2000 and 2008, the use of ITNs saved the lives of an estimated 250,000 infants in Sub-Saharan Africa. About 13% of households in Sub-Saharan countries own ITNs. In 2000, 1.7 million (1.8%) African children living in stable malaria-endemic conditions were protected by an ITN. That number increased to 20.3 million (18.5%) African children using ITNs in 2007, leaving 89.6 million children unprotected. An increased percentage of African households (31%) are estimated to own at least one ITN in 2008. Most nets are impregnated with pyrethroids, a class of insecticides with low toxicity. A recommended practice for usage is to hang a large "bed net" above the center of a bed to drape over it completely with the edges tucked in. Pyrethroid-treated nets and long-lasting insecticide-treated nets offer the best protection, and are most effective when used from dusk to dawn. Indoor residual spraying is the spraying of insecticides on the walls inside a home. After feeding, many mosquitoes rest on a nearby surface while digesting the bloodmeal, so if the walls of houses have been coated with insecticides, the resting mosquitoes can be killed before they can bite another person and transfer the malaria parasite. As of 2006, the World Health Organization recommends 12 insecticides in IRS operations, including DDT and the pyrethroids cyfluthrin and deltamethrin. This public health use of small amounts of DDT is permitted under the Stockholm Convention, which prohibits its agricultural use. One problem with all forms of IRS is insecticide resistance. Mosquitoes affected by IRS tend to rest and live indoors, and due to the irritation caused by spraying, their descendants tend to rest and live outdoors, meaning that they are less affected by the IRS. There are a number of other methods to reduce mosquito bites and slow the spread of malaria. Efforts to decrease mosquito larva by decreasing the availability of open water in which they develop or by adding substances to decrease their development is effective in some locations. Electronic mosquito repellent devices which make very high frequency sounds that are supposed to keep female mosquitoes away, do not have supporting evidence.

Other methods

Community participation and health education strategies promoting awareness of malaria and the importance of control measures have been successfully used to reduce the incidence of malaria in some areas of the developing world. Recognizing the disease in the early stages can stop the disease from becoming fatal. Education can also inform people to cover over areas of stagnant, still water, such as water tanks that are ideal breeding grounds for the parasite and mosquito, thus cutting down the risk of the transmission between people. This is generally used in urban areas where there are large centers of population in a confined space and transmission would be most likely in these areas. Intermittent preventive therapy is another intervention that has been used successfully to control malaria in pregnant women and infants, and in preschool children where transmission is seasonal. June has been marked as Anti-malaria month by National Vector Borne Disease Control Programme (NVBDCP) of India with an objective to increase multisectoral collaboration and community involvement in malaria control.

Medications

There are a number of drugs that can help prevent malaria while travelling in areas where it exists. Most of these drugs are also sometimes used in treatment. Chloroquine may be used where the parasite is still sensitive. Because most Plasmodium is resistant to one or more medications, one of three medications—mefloquine (Lariam), doxycycline (available generically), or the combination of atovaquone and proguanil hydrochloride (Malarone)—is frequently needed. Doxycycline and the atovaquone and proguanil combination are the best tolerated; mefloquine is associated with death, suicide, and neurological

and psychiatric symptoms. The protective effect does not begin immediately, and people visiting areas where malaria exists usually start taking the drugs one to two weeks before arriving and continue taking them for four weeks after leaving (with the exception of atovaquone/proguanil, which only needs to be started two days before and continued for seven days afterward). The use of preventative drugs is seldom practical for those who reside in areas where malaria exists, and their use is usually only in short-term visitors and travellers. This is due to the cost of the drugs, side effects from long-term use, and the difficulty in obtaining anti-malarial drugs outside of wealthy nations. The use of preventative drugs where malaria-bearing mosquitoes are present may encourage the development of partial resistance.

Treatment

Malaria is treated with antimalarial medications; the ones used depend on the type and severity of the disease. While medications against fever are commonly used, their effects on outcomes are not clear. Uncomplicated malaria may be treated with oral medications. The most effective treatment for P. falciparum infection is the use of artemisinins in combination with other antimalarials (known as artemisinin-combination therapy, or ACT), which decreases resistance to any single drug component. These additional antimalarials include: amodiaquine, lumefantrine, mefloquine or sulfadoxine/pyrimethamine. Another recommended combination is dihydroartemisinin and piperaquine. ACT is about 90% effective when used to treat uncomplicated malaria. To treat malaria during pregnancy, the WHO recommends the use of quinine plus clindamycin early in the pregnancy (1st trimester), and ACT in later stages (2nd and 3rd trimesters). In the 2000s (decade), malaria with partial resistance to artemisins emerged in Southeast Asia. Infection with P. vivax, P. ovale or P. malariae is usually treated without the need for hospitalization. Treatment of P. vivax requires both treatment of blood stages (with chloroquine or ACT) as well as clearance of liver forms with primaquine.
Recommended treatment for severe malaria is the intravenous use of antimalarial drugs. For severe malaria, artesunate is superior to quinine in both children and adults. Treatment of severe malaria involves supportive measures that are best done in a critical care unit. This includes the management of high fevers and the seizures that may result from it. It also includes monitoring for poor breathing effort, low blood sugar, and low blood potassium.[14]

Resistance
Drug resistance poses a growing problem in 21st century malaria treatment. Resistance is now common against all classes of antimalarial drugs save the artemisinins. Treatment of resistant strains became increasingly dependent on this class of drugs. The cost of artemisinins limits their use in the developing world. Malaria strains found on the Cambodia-Thailand border are resistant to combination therapies that include artemisinins, and may therefore be untreatable Exposure of the parasite population to artemisinin monotherapies in subtherapeutic doses for over 30 years and the availability of substandard artemisinins likely drove the selection of the resistant phenotype. Resistance to artemisinin has been detected in Cambodia, Myanmar, Thailand, Vietnam. and emerging resistance in Laos.

Prognosis
Disability-adjusted life year for malaria per 100,000 inhabitants in 2004

no data	2000–2500
<10	2500–2750
0–100	2750–3000
100–500	3000–3250
500–1000	3250–3500
1000–1500	≥3500
1500–2000	

When properly treated, people with malaria can usually expect a complete recovery. However, severe malaria can progress extremely rapidly and cause death within hours or days. In the most severe cases of the disease, fatality rates can reach 20%, even with intensive care and treatment. Over the longer term, developmental impairments have been documented in children who have suffered episodes of severe malaria. Chronic infection without severe disease can occur in an immune-deficiency syndrome associated with a decreased responsiveness to Salmonella bacteria and the Epstein–Barr virus. During childhood, malaria causes anemia during a period of rapid brain development, and also direct brain damage resulting from cerebral malaria. Some survivors of cerebral malaria have an increased risk of neurological and cognitive deficits, behavioural disorders, and epilepsy. Malaria prophylaxis was shown to improve cognitive function and school performance in clinical trials when compared to placebo groups.

Epidemiology
Distribution of malaria in the world:
- Elevated occurrence of chloroquine- or multi-resistant malaria
- Occurrence of chloroquine-resistant malaria
- No Plasmodium falciparum or chloroquine-resistance
- No malaria

The WHO estimates that in 2010 there were 219 million cases of malaria resulting in 660,000 deaths. Others have estimated the number of cases at between 350 and 550 million for falciparum malaria and deaths in 2010 at 1.24 million up from 1.0 million deaths in 1990. The majority of cases (65%) occur in children under 15 years old. About 125 million pregnant women are at risk of infection each year; in Sub-Saharan Africa, maternal malaria is associated with up to 200,000 estimated infant deaths yearly. There are about 10,000 malaria cases per year in Western Europe, and 1300–1500 in the United States. About 900 people died from the disease in Europe between 1993 and 2003. Both the global incidence of disease and resulting mortality have declined in recent years. According to the WHO, deaths attributable to malaria in 2010 were reduced by over a third from a 2000 estimate of 985,000, largely due to the widespread use of insecticide-treated nets and artemisinin-based combination therapies.

Malaria is presently endemic in a broad band around the equator, in areas of the Americas, many parts of Asia, and much of Africa; in Sub-Saharan Africa, 85–90% of malaria fatalities occur. An estimate for 2009 reported that countries with the highest death rate per 100,000 of population were Ivory Coast (86.15), Angola (56.93) and Burkina Faso (50.66). A 2010 estimate indicated the deadliest countries per population were Burkina Faso, Mozambique and Mali. The Malaria Atlas Project aims to map global endemic levels of malaria, providing a means with which to determine the global spatial limits of the disease and to assess disease burden. This effort led to the publication of a map of P. falciparum endemicity in 2010. As of 2010, about 100 countries have endemic malaria. Every year, 125 million international travellers visit these countries, and more than 30,000 contract the disease. the geographic distribution of malaria within large regions is complex, and malaria-afflicted and malaria-free areas are often found close to each other. Malaria is prevalent in tropical and subtropical regions because of rainfall, consistent high temperatures and high humidity, along with stagnant waters in which mosquito larvae readily mature, providing them with the environment they need for continuous breeding. In drier areas, outbreaks of malaria have been predicted with reasonable accuracy by mapping rainfall. Malaria is more common in rural areas than in cities. For example, several cities in the Greater Mekong Subregion of Southeast Asia are essentially malaria-free, but the disease is prevalent in many rural regions, including along international borders and forest fringes In contrast, malaria in Africa is present in both rural and urban areas, though the risk is lower in the larger cities.

History

Although the parasite responsible for P. falciparum malaria has been in existence for 50,000– 100,000 years, the population size of the parasite did not increase until about 10,000 years ago, concurrently with advances in agriculture and the development of human settlements. Close relatives of the human malaria parasites remain common in chimpanzees. Some evidence suggests that the P. falciparum malaria may have originated in gorillas.

References to the unique periodic fevers of malaria are found throughout recorded history, beginning in 2700 BC in China. Malaria may have contributed to the decline of the Roman Empire, and was so pervasive in Rome that it was known as the "Roman fever". Several regions in ancient Rome were considered at-risk for the disease because of the favourable conditions present for malaria vectors. This included areas such as southern Italy, the island of Sardinia, the Pontine Marshes, the lower regions of coastal Etruria and the city of Rome along the Tiber River. The presence of stagnant water in these places was preferred by mosquitoes for breeding grounds. Irrigated gardens, swamp-like grounds, runoff from agriculture, and drainage problems from road construction led to the increase of standing water.

British doctor Ronald Ross received the Nobel Prize for Physiology or Medicine in 1902 for his work on malaria.

The term malaria originates from Medieval Italian: mala aria — "bad air"; the disease was formerly called ague or marsh fever due to its association with swamps and marshland. Malaria was once common in most of Europe and North America, where it is no longer endemic, though imported cases do occur. Scientific studies on malaria made their first significant advance in 1880, when Charles Louis Alphonse Laveran—a French army doctor working in the military hospital of Constantine in Algeria—observed parasites inside the red blood cells of infected people for the first time. He therefore proposed that malaria is caused by this organism, the first time a protist was identified as causing disease. For this and later discoveries, he was awarded the 1907 Nobel Prize for Physiology or Medicine. A year later, Carlos Finlay, a Cuban doctor treating people with yellow fever in Havana, provided strong evidence that mosquitoes were transmitting disease to and from humans. This work followed earlier suggestions by Josiah C. Nott, and work by Sir Patrick Manson, the "father of tropical medicine", on the transmission of filariasis. In April 1894, a Scottish physician Sir Ronald Ross visited Sir Patrick

Manson at his house on Queen Anne Street, London. This visit was the start of four years of collaboration and fervent research that culminated in 1898 when Ross, who was working in the Presidency General Hospital in Calcutta, proved the complete life-cycle of the malaria parasite in mosquitoes. He thus proved that the mosquito was the vector for malaria in humans by showing that certain mosquito species transmit malaria to birds. He isolated malaria parasites from the salivary glands of mosquitoes that had fed on infected birds. For this work, Ross received the 1902 Nobel Prize in Medicine. After resigning from the Indian Medical Service, Ross worked at the newly established Liverpool School of Tropical Medicine and directed malaria-control efforts in Egypt, Panama, Greece and Mauritius. The findings of Finlay and Ross were later confirmed by a medical board headed by Walter Reed in 1900. Its recommendations were implemented by William C. Gorgas in the health measures undertaken during construction of the Panama Canal. This public-health work saved the lives of thousands of workers and helped develop the methods used in future public-health campaigns against the disease.
The first effective treatment for malaria came from the bark of cinchona tree, which contains quinine. This tree grows on the slopes of the Andes, mainly in Peru. The indigenous peoples of Peru made a tincture of cinchona to control fever. Its effectiveness against malaria was found and the Jesuits introduced the treatment to Europe around 1640; by 1677, it was included in the London Pharmacopoeia as an antimalarial treatment. It was not until 1820 that the active ingredient, quinine, was extracted from the bark, isolated and named by the French chemists

Pierre Joseph Pelletier and Joseph Bienaimé Caventou.

Artemisia annua, source of the antimalarial drug artemisin
Quinine become the predominant malarial medication until the 1920s, when other medications began to be developed. In the 1940s, chloroquine replaced quinine as the treatment of both uncomplicated and severe malaria until resistance supervened, first in Southeast Asia and South America in the 1950s and then globally in the 1980s. Artemisinins, discovered by Chinese scientist Tu Youyou and colleagues in the 1970s from the plant Artemisia annua, became the recommended treatment for P. falciparum malaria, administered in combination with other antimalarials as well as in severe disease. Plasmodium vivax was used between 1917 and the 1940s for malariotherapy—deliberate injection of malaria parasites to induce fever to combat certain diseases such as tertiary syphilis. In 1917, the inventor of this technique, Julius Wagner-Jauregg, received the Nobel Prize in Physiology or Medicine for his discoveries. The technique was dangerous, killing about 15% of patients, so it is no longer in use.
The first pesticide used for indoor residual spraying was DDT. Although it was initially used exclusively to combat malaria, its use quickly spread to agriculture. In time, pest control, rather than disease control, came to dominate DDT use, and this large-scale agricultural use led to the evolution of resistant mosquitoes in many regions. The DDT resistance shown by Anopheles mosquitoes can be compared to antibiotic resistance shown by bacteria. During the 1960s, awareness of the negative consequences of its indiscriminate use increased, ultimately leading to bans on agricultural applications of DDT in many countries in the 1970s. Before DDT, malaria was successfully eliminated or controlled in tropical areas like Brazil and Egypt by removing or poisoning the breeding grounds of the mosquitoes or the aquatic habitats of the larva stages, for example by applying the highly toxic arsenic compound Paris Green to places with standing water.
Malaria vaccines have been an elusive goal of research. The first promising studies demonstrating the potential for a malaria vaccine were performed in 1967 by immunizing mice with live, radiation-attenuated sporozoites, which provided significant protection to the mice upon subsequent injection with normal, viable sporozoites. Since the 1970s, there has been a considerable effort to develop similar vaccination strategies within humans.

Society and culture
Economic impact

Malaria clinic in Tanzania

Malaria is not just a disease commonly associated with poverty: some evidence suggests that it is also a cause of poverty and a major hindrance to economic development. Although tropical regions are most affected, malaria's furthest influence reaches into some temperate zones that have extreme seasonal changes. The disease has been associated with major negative economic effects on regions where it is widespread. During the late 19th and early 20th centuries, it was a major factor in the slow economic development of the American southern states. A comparison of average per capita GDP in 1995, adjusted for parity of purchasing power, between countries with malaria and countries without malaria gives a fivefold difference ($1,526 USD versus $8,268 USD). In the period 1965 to 1990, countries where malaria was common had an average per capita GDP that increased only 0.4% per year, compared to 2.4% per year in other countries.

Poverty can increase the risk of malaria, since those in poverty do not have the financial capacities to prevent or treat the disease. In its entirety, the economic impact of malaria has been estimated to cost Africa $12 billion USD every year. The economic impact includes costs of health care, working days lost due to sickness, days lost in education, decreased productivity due to brain damage from cerebral malaria, and loss of investment and tourism. The disease has a heavy burden in some countries, where it may be responsible for 30–50% of hospital admissions, up to 50% of outpatient visits, and up to 40% of public health spending. Cerebral malaria is one of the leading causes of neurological disabilities in African children. Studies comparing cognitive functions before and after treatment for severe malarial illness continued to show significantly impaired school performance and cognitive abilities even after recovery. Consequently, severe and cerebral malaria have far-reaching socioeconomic consequences that extend beyond the immediate effects of the disease.

Counterfeit and substandard drugs

Sophisticated counterfeits have been found in several Asian countries such as Cambodia, China, Indonesia, Laos, Thailand, and Vietnam, and are an important cause of avoidable death in those countries. The WHO said that studies indicate that up to 40% of artesunate-based malaria medications are counterfeit, especially in the Greater Mekong region and have established a rapid alert system to enable information about counterfeit drugs to be rapidly reported to the relevant authorities in participating countries. There is no reliable way for doctors or lay people to detect counterfeit drugs without help from a laboratory. Companies are attempting to combat the persistence of counterfeit drugs by using new technology to provide security from source to distribution. Another clinical and public health concern is the proliferation of substandard antimalarial medicines resulting from inappropriate concentration of ingredients, contamination with other drugs or toxic impurities, poor quality ingredients, poor stability and inadequate packaging. A 2012 study demonstrated that roughly one-third of antimalarial medications in Southeast Asia and Sub-Saharan Africa failed chemical analysis, packaging analysis, or were falsified.

War

World War II poster

Throughout history, the contraction of malaria has played a prominent role in the fates of government rulers, nation-states, military personnel, and military actions. In 1910, Nobel Prize in Medicine-winner Ronald Ross (himself a malaria survivor), published a book titled The Prevention of Malaria that included a chapter titled "The Prevention of Malaria in War." The chapter's author, Colonel C. H. Melville, Professor of Hygiene at Royal Army Medical College in London, addressed the prominent role that malaria has historically played during wars: "The history of malaria in war might almost be taken to be the history of war itself, certainly the history of war in the Christian era. ... It is probably the case that many of the so-called camp fevers, and probably also a considerable proportion of the camp dysentery, of the wars of the sixteenth, seventeenth and eighteenth centuries were malarial in origin." Malaria was the most important health hazard encountered by U.S. troops in the South Pacific during World War II, where about 500,000 men were infected. According to Joseph Patrick Byrne, "Sixty thousand American soldiers died of malaria during the African and South Pacific campaigns." Significant financial investments have been made to procure existing and create new anti-malarial agents. During World War I and World War II, inconsistent supplies of the natural anti-malaria drugs cinchona bark and quinine prompted substantial funding into research and development of other drugs and vaccines. American military organizations conducting such research initiatives include the Navy Medical Research Center, Walter Reed Army Institute of Research, and the U.S. Army Medical Research Institute

of Infectious Diseases of the US Armed Forces. Additionally, initiatives have been founded such as Malaria Control in War Areas (MCWA), established in 1942, and its successor, the Communicable Disease Center (now known as the Centers for Disease Control and Prevention, or CDC) established in 1946. According to the CDC, MCWA "was established to control malaria around military training bases in the southern United States and its territories, where malaria was still problematic".

Eradication efforts

Several notable attempts are being made to eliminate the parasite from sections of the world or to eradicate it worldwide. In 2006, the organization Malaria No More set a public goal of eliminating malaria from Africa by 2015, and the organization plans to dissolve if that goal is accomplished. Several malaria vaccines are in clinical trials, which are intended to provide protection for children in endemic areas and reduce the speed of transmission of the disease. As of 2012, The Global Fund to Fight AIDS, Tuberculosis and Malaria has distributed 230 million insecticide-treated nets intended to stop mosquito-borne transmission of malaria. The U.S.-based Clinton Foundation has worked to manage demand and stabilize prices in the artemisinin market. Other efforts, such as the Malaria Atlas Project, focus on analysing climate and weather information required to accurately predict the spread of malaria based on the availability of habitat of malaria-carrying parasites.The Malaria Policy Advisory Committee (MPAC) of the World Health Organization (WHO) was formed in 2012, "to provide strategic advice and technical input to WHO on all aspects of malaria control and elimination".In November 2013, WHO and the malaria vaccine funders group set a goal to develop vaccines designed to interrupt malaria transmission with the long-term goal of malaria eradication.

Malaria has been successfully eliminated or greatly reduced in certain areas. Malaria was once common in the United States and southern Europe, but vector control programs, in conjunction with the monitoring and treatment of infected humans, eliminated it from those regions. Several factors contributed, such as the draining of wetland breeding grounds for agriculture and other changes in water management practices, and advances in sanitation, including greater use of glass windows and screens in dwellings. Malaria was eliminated from most parts of the USA in the early 20th century by such methods, and the use of the pesticide DDT and other means eliminated it from the remaining pockets in the South in the 1950s. (see National Malaria Eradication Program) In Suriname, the disease has been cleared from its capital city and coastal areas through a three-pronged approach initiated by the Global Malaria Eradication program in 1955, involving: vector control through the use of DDT and IRS; regular collection of blood smears from the population to identify existing malaria cases; and providing chemotherapy to all affected individuals. Bhutan is pursuing an aggressive malaria elimination strategy, and has achieved a 98.7% decline in microscopy-confirmed cases from 1994 to 2010. In addition to vector control techniques such as IRS in high-risk areas and thorough distribution of long-lasting ITNs, factors such as economic development and increasing access to health services have contributed to Bhutan's successes in reducing malaria incidence.

Research

Immunity (or, more accurately, tolerance) to P. falciparum malaria does occur naturally, but only in response to years of repeated infection. An individual can be protected from a P. falciparum infection if they receive about a thousand bites from mosquitoes that carry a version of the parasite rendered non-infective by a dose of X-ray irradiation. An effective vaccine is not yet available for malaria, although several are under development. The highly polymorphic nature of many P. falciparum proteins results in significant challenges to vaccine design. Vaccine candidates that target antigens on gametes, zygotes, or ookinetes in the mosquito midgut aim to block the transmission of malaria. These transmission-blocking vaccines induce antibodies in the human blood; when a mosquito takes a blood meal from a protected individual, these antibodies prevent the parasite from completing its development in the mosquito. Other vaccine candidates, targeting the blood-stage of the parasite's life cycle, have been inadequate on their own. For example, SPf66 was tested extensively in endemic areas in the 1990s, but clinical trials showed it to be insufficiently effective. Several potential vaccines targeting the pre-erythrocytic stage of the parasite's life cycle are being developed, with RTS,S as the leading candidate; it is expected to be licensed in 2015. A US biotech company, Sanaria, is developing a pre-erythrocytic attenuated vaccine called PfSPZ that uses whole sporozoites to induce an immune response. In 2006, the Malaria Vaccine Advisory Committee to the WHO outlined a "Malaria Vaccine Technology Roadmap" that has as one of its landmark objectives to "develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year" by 2015.

Malaria parasites contain apicoplasts, organelles usually found in plants, complete with their own genomes. These apicoplasts are thought to have originated through the endosymbiosis of algae and play a crucial role in various aspects of parasite metabolism, such as fatty acid biosynthesis. Over 400 proteins have been found to be produced by apicoplasts and these are now being investigated as possible targets for novel anti-malarial drugs.

With the onset of drug-resistant Plasmodium parasites, new strategies are being developed to combat the widespread disease. One such approach lies in the introduction of synthetic pyridoxal-amino acid adducts, which are taken up by the parasite and ultimately interfere with its ability to create several essential B vitamins. Antimalarial drugs using synthetic metal-based complexes are attracting research interest.

A non-chemical vector control strategy involves genetic manipulation of malaria mosquitoes. Advances in genetic engineering technologies make it possible to introduce foreign DNA into the mosquito genome and either decrease the lifespan of the mosquito, or make it more resistant to the malaria parasite. Sterile insect technique is a genetic control method whereby large numbers of sterile males mosquitoes are reared and released. Mating with wild females reduces the wild population in the subsequent generation; repeated releases eventually eliminate the target population.

Genomics is now central to malaria research. With the sequencing of P. falciparum, one of its vectors Anopheles gambiae, and the human genome, the genetics of all three organisms in the malaria lifecycle can be studied.[175] Another new application of genetic technology is the ability to produce genetically modified mosquitoes that do not transmit malaria, potentially allowing biological control of malaria transmission. Researchers are encouraged by the findings of a study that commenced in 2002 involving the monitoring of the lives of 1,000 Tanzanian children. The study is one of many being explored in 2014 in the race to find a malaria vaccine.

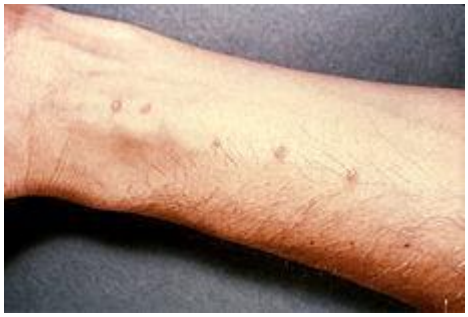
Other animals

Nearly 200 parasitic Plasmodium species have been identified that infect birds, reptiles, and other mammals, and about 30 species naturally infect non-human primates. Some of the malaria parasites that affect non-human primates (NHP) serve as model organisms for human malarial parasites, such as P. coatneyi (a model for P. falciparum) and P. cynomolgi (P. vivax). Diagnostic techniques used to detect parasites in NHP are similar to those employed for humans. Malaria parasites that infect rodents are widely used as models in research, such as P. berghei. Avian malaria primarily affects species of the order Passeriformes, and poses a substantial threat to birds of Hawaii, the Galapagos, and other archipelagoes. The parasite P. relictum is known to play a role in limiting the distribution and abundance of endemic Hawaiian birds. Global warming is expected to increase the prevalence and global distribution of avian malaria, as elevated temperatures provide optimal conditions for parasite reproduction.

10. Schistosomiasis

Schistosomiasis

Classification and external resources



Skin blisters on the forearm, created by the entrance of Schistosoma parasite.

Schistosomiasis /ˌʃistəsəˈmaɪəsəs/ **(also** known as **bilharzia**, **snail fever**, and **Katayama fever**) is a disease caused by parasitic worms of the Schistosoma type. It may infect the urinary tract or intestines. Symptoms may include abdominal pain, diarrhea, bloody stool, or blood in the urine.

In those who have been infected a long time, liver damage, kidney failure, infertility, or bladder cancer may occur. In children it may cause poor growth and learning difficulty. The disease is spread by contact with water that contains the parasites. These parasites are released from freshwater snails that have been infected. The disease is especially common among children in developing countries as they are more likely to play in infected water. Other high risk groups include farmers, fishermen, and people using infected water for their daily chores. Diagnosis is by finding the eggs of the parasite in a person's urine or stool. It can also be confirmed by finding antibodies against the disease in the blood. Methods to prevent the disease include improving access to clean water and reducing the number of snails. In areas where the disease is common entire groups may be treated all at once and yearly with the medication praziquantel. This is done to decrease the number of people infected and therefore decrease the spread of the disease. Praziquantel is also the treatment recommended by the World Health Organization for those who are known to be infected. Schistosomiasis affects almost 210 million people worldwide, and an estimated 12,000 to 200,000 people die from it a year. The disease is most commonly found in Africa, Asia and South America. Around 700 million people, in more than 70 countries, live in areas where the disease is common. Schistosomiasis is second only to malaria, as a parasitic disease with the greatest economic impact.

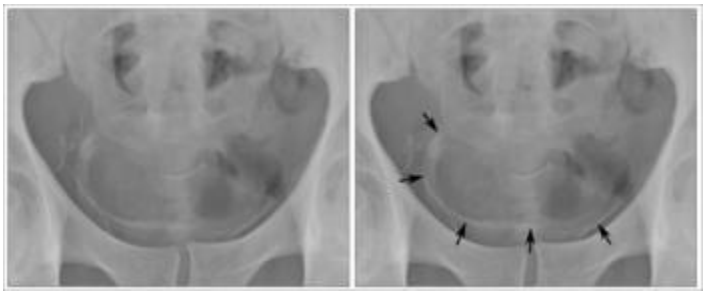
Classification

Species of Schistosoma that can infect humans:
Schistosoma mansoni (ICD-10 B65.1) and Schistosoma intercalatum (B65.8) cause intestinal schistosomiasis
Schistosoma haematobium (B65.0) causes urinary schistosomiasis
Schistosoma japonicum (B65.2) and Schistosoma mekongi (B65.8) cause Asian intestinal schistosomiasis
Avian schistosomiasis species cause swimmer's itch and clam digger itch
Species of Schistosoma that can infect other animals:
S. bovis — normally infects cattle, sheep and goats in Africa, parts of Southern Europe and the Middle East
S. mattheei — normally infects cattle, sheep and goats in Central and Southern Africa
S. margrebowiei — normally infects antelope, buffalo and waterbuck in Southern and Central Africa

S. curassoni — normally infects domestic ruminants in West Africa
S. rodhaini — normally infects rodents and carnivores in parts of Central Africa

Signs and symptoms

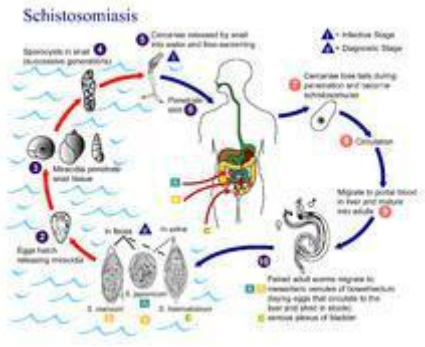
Above all, schistosomiasis is a chronic disease. Many infections are subclinically symptomatic, with mild anemia and malnutrition being common in endemic areas. Acute schistosomiasis (Katayama's fever) may occur weeks after the initial infection, especially by S. mansoni and
S. japonicum. Manifestations include:
T. Abdominal pain Cough
Diarrhea
Eosinophilia — extremely high eosinophil granulocyte (white blood cell) count. Fever
Fatigue
Hepatosplenomegaly — the enlargement of both the liver and the spleen.
Hepatic schistosomiasis is the second most common cause of esophageal varices worldwide.
Genital sores — lesions that increase vulnerability to HIV infection. Lesions caused by schistosomiasis may continue to be a problem after control of the schistosomiasis infection itself. Early treatment, especially of children, which is relatively inexpensive, prevents formation of the sores.
Skin symptoms: At the start of infection, mild itching and a papular dermatitis of the feet and other parts after swimming in polluted streams containing cercariae.
Occasionally central nervous system lesions occur: cerebral granulomatous disease may be caused by ectopic S. japonicum eggs in the brain, and granulomatous lesions around ectopic eggs in the spinal cord from S. mansoni and S. haematobium infections may result in a transverse myelitis with flaccid paraplegia.



Calcification of the bladder wall on a plain x-ray image of the pelvis, in a 44 year old sub-Saharan man. This is due to urinary schistosomiasis.Continuing infection may cause granulomatous reactions and fibrosis in the affected organs, which may result in manifestations that include:
Colonic polyposis with bloody diarrhea (Schistosoma mansoni mostly);
Portal hypertension with hematemesis and splenomegaly (S. mansoni, S. japonicum); Cystitis and ureteritis (S. haematobium) with hematuria, which can progress to bladder cancer;
Pulmonary hypertension (S. mansoni, S. japonicum, more rarely S. haematobium); Glomerulonephritis; and central nervous system lesions.
Bladder cancer diagnosis and mortality are generally elevated in affected areas.

Pathophysiology

Life cycle



Schistosoma life cycle. Source: CDC
Schistosomes have a typical trematode vertebrate-invertebrate lifecycle, with humans being the definitive host.

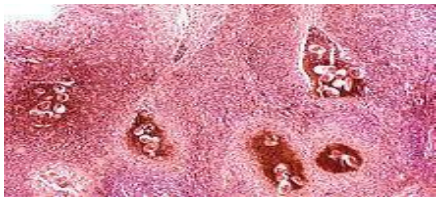
Snails

The life cycles of all five human schistosomes are broadly similar: parasite eggs are released into the environment from infected individuals, hatching on contact with fresh water to release the free-swimming miracidium. Miracidia infect freshwater snails by penetrating the snail's foot. After infection, close to the site of penetration, the miracidium transforms into a primary (mother) sporocyst. Germ cells within the primary sporocyst will then begin dividing to produce secondary (daughter) sporocysts, which migrate to the snail's hepatopancreas. Once at the hepatopancreas, germ cells within the secondary sporocyst begin to divide again, this time producing thousands of new parasites, known as cercariae, which are the larvae capable of infecting mammals.

Cercariae emerge daily from the snail host in a circadian rhythm, dependent on ambient temperature and light. Young cercariae are highly mobile, alternating between vigorous upward movements and sinking to maintain their position in the water. Cercarial activity is particularly stimulated by water turbulence, by shadows and by chemicals found on human skin.The most common way of getting schistosomiasis in developing countries is by wading or swimming in lakes, ponds and other bodies of water that are infested with the snails (usually of the genera Biomphalaria, Bulinus, or Oncomelania) that are the natural reservoirs of the Schistosoma pathogen.

Humans

Penetration of the human skin occurs after the cercaria have attached to and explored the skin. The parasite secretes enzymes that break down the skin's protein to enable penetration of the cercarial head through the skin. As the cercaria penetrates the skin it transforms into a migrating schistosomulum stage.



Photomicrography of bladder in S. hematobium infection, showing clusters of the parasite eggs with intense eosinophilia, Source: CDC

The newly transformed schistosomulum may remain in the skin for two days before locating a post-capillary venule; from here the schistosomulum travels to the lungs where it undergoes further developmental changes necessary for subsequent migration to the liver. Eight to ten days after penetration of the skin, the parasite migrates to the liver sinusoids. S. japonicum migrates more quickly than S. mansoni, and usually reaches the liver within eight days of penetration. Juvenile S. mansoni and S. japonicum worms develop an oral sucker after arriving at the liver, and it is during this period that the parasite begins to feed on red blood cells. The nearly-mature worms pair, with the longer female worm residing in the gynaecophoric channel of the shorter male. Adult worms are about 10 mm long. Worm pairs of S. mansoni and S. japonicum relocate to the mesenteric or rectal veins. S. haematobium schistosomula ultimately migrate from the liver to the perivesical venous plexus of the bladder, ureters, and kidneys through the hemorrhoidal plexus.

Parasites reach maturity in six to eight weeks, at which time they begin to produce eggs. Adult S. mansoni pairs residing in the mesenteric vessels may produce up to 300 eggs per day during their reproductive lives. S. japonicum may produce up to 3,000 eggs per day. Many of the eggs pass through the walls of the blood vessels, and through the intestinal wall, to be passed out of the body in feces. S. haematobium eggs pass through the ureteral or bladder wall and into the urine. Only mature eggs are capable of crossing into the digestive tract, possibly through the release of proteolytic enzymes, but also as a function of host immune response, which fosters local tissue ulceration. Up to half the eggs released by the worm pairs become trapped in the mesenteric veins, or will be washed back into the liver, where they will become lodged. Worm pairs can live in the body for an average of four and a half years, but may persist up to twenty years.

Trapped eggs mature normally, secreting antigens that elicit a vigorous immune response. The eggs themselves do not damage the body. Rather it is the cellular infiltration resultant from the immune response that causes the pathology classically associated with schistosomiasis.

Diagnosis

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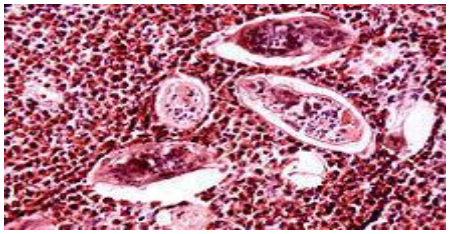
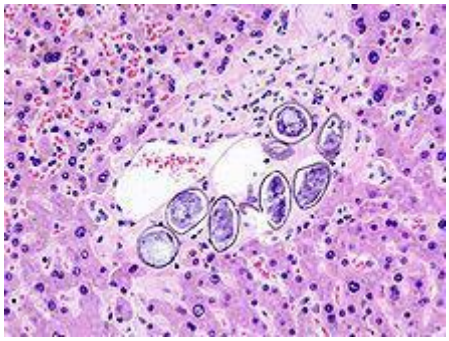


High powered detailed micrograph of Schistosoma parasite eggs in human bladder tissue



S. japonicum eggs in hepatic portal tract.

Contemporary diagnosis involves detection of parasitic antigens by ELISA; all that is required from the patient is a blood sample. This screening method is highly effective. Microscopic identification of eggs in stool or, less commonly, the urine is another way of arriving at a positive diagnosis. For the measurement of eggs in the feces of presenting patients the scientific unit used is eggs per gram (epg). Stool examination should be performed when infection with S. mansoni or S. japonicum is suspected, and urine examination should be performed if S. haematobium is suspected.
Eggs can be present in the stool in infections with all Schistosoma species. The examination can be performed on a simple smear (1 to 2 mg of fecal material). Since eggs may be passed intermittently or in small amounts, their detection will be enhanced by repeated examinations and/or concentration procedures (such as the formalin-ethyl acetate technique). In addition, for field surveys and investigational purposes, the egg output can be quantified by using the Kato technique (20 to 50 mg of fecal material) or the Ritchie technique.Eggs can be found in the urine in infections with S. japonicum and with S. intercalatum (recommended time for collection: between noon and 3 p.m.) Detection will be enhanced by centrifugation and examination of the sediment. Quantification is possible by using filtration through a nucleopore membrane of a standard volume of urine followed by egg counts on the membrane. Investigation of
S. haematobium should also include a pelvic x-ray as bladder wall calcification is highly characteristic of chronic infection.Recently a field evaluation of a novel handheld microscope was undertaken in Uganda for the diagnosis of intestinal schistosomiasis by a team led by Russell Stothard from the Natural History Museum of London, working with the Schistosomiasis Control Initiative, London. Tissue biopsy (rectal biopsy for all species and biopsy of the bladder for S. haematobium) may demonstrate eggs when stool or urine examinations are negative.The eggs of S. haematobium are ellipsoidal with a terminal spine, S. mansoni eggs are also ellipsoidal but with a lateral spine, S. japonicum eggs are spheroidal with a small knob.Antibody detection can be useful in both clinical management and for epidemiologic surveys.

Prevention

A few countries have eradicated the disease, and many more are working toward it. The World Health Organization is promoting these efforts. In some cases, urbanization, pollution, and/or consequent destruction of snail habitat has reduced exposure, with a subsequent decrease in new infections.

Snails

Prevention is best accomplished by eliminating the water-dwelling snails that are the natural reservoir of the disease. Acrolein, copper sulfate, and niclosamide can be used for this purpose. Recent studies have suggested that snail populations can be controlled by the introduction of, or augmentation of existing, crayfish populations.For many years from the 1950s onwards, vast dams and irrigation schemes were constructed, causing a massive rise in water-borne infections from schistosomiasis. The detailed specifications laid out in various UN documents since the 1950s could have minimized this problem. Irrigation schemes can be designed to make it hard for the snails to colonize the water, and to reduce the contact with the local population. This has been cited as a classic case of the relevance paradox because guidelines on how to design these schemes to minimise the spread of the disease had been published years before, but the designers were unaware of them.

Treatment

Ethiopian children treated for schistosoma mansoni
Schistosomiasis is readily treated using a single oral dose of the drug praziquantel annually. As with other major parasitic diseases, there is ongoing and extensive research into developing a schistosomiasis vaccine that will prevent the parasite from completing its life cycle in humans. In 2009, Eurogentec Biologics developed a vaccine against bilharziosis in partnership with INSERM and researchers from the Pasteur Institute. The World Health Organization has developed guidelines for community treatment of schistosomiasis based on the impact the disease has on children in endemic villages:
When a village reports more than 50 percent of children have blood in their urine, everyone in the village receives treatment.
When 20 to 50 percent of children have bloody urine, only school-age children are treated.
When fewer than 20 percent of children have symptoms, mass treatment is not implemented.

The Bill & Melinda Gates Foundation has recently funded an operational research program — the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) to answer strategic questions about how to move forward with schistosomiasis control and elimination. The focus of SCORE is on development of tools and evaluation of strategies for use in mass drug administration campaigns.Antimony has been used in the past to treat the disease. In low doses, this toxic metalloid bonds to sulfur atoms in enzymes used by the parasite and kills it without harming the host. This treatment is not referred to in present-day peer review scholarship; praziquantel is universally used. Outside of the U.S., there is a drug available exclusively for treating Schistosoma mansoni (oxamniquine) and one exclusively for treating S. hematobium (metrifonate). While metrifonate has been discontinued for use by the British National Health Service, a Cochrane review found it equally effective in treating urinary schistosomiasis as the leading drug, praziquantel. Mirazid, an Egyptian drug made from myrrh, was under investigation for oral treatment of the disease up until 2005. The efficacy of praziquantel was proven to be about eight times than that of Mirazid and therefore Mirazid was not recommended as a suitable agent to control schistosomiasis. Another agent, mefloquine, which has previously been used to treat malaria, was recognised in 2008-2009 to be effective against schistosoma. Mefloquine may be used in combination with praziquantel or artemisinins. Its mechanism of action is not known but it causes extensive and severe morphological, histopathological, and ultrastructural damage to adult and juvenile schistosomes, particularly, the worm tegument, musculature, gut, and vitelline glands of female worms.

Epidemiology
Disability-adjusted life year for schistosomiasis per 100,000 inhabitants. no data
less than 50 50-75 75-100 100-150 150-200 200-250 250-300 300-350
350-400
400-450
450-500 more than 500

The disease is found in tropical countries in Africa, the Caribbean, eastern South America, Southeast Asia and in the Middle East. In these areas as of 2010 it affects approximately
238 million people 85% of whom live in Africa. An estimated 600 million people worldwide are at risk from the disease. Worldwide an estimated 12,000 to 200,000 people die related to schistosomiasis yearly.
Schistosoma mansoni is found in parts of South America and the Caribbean, Africa, and the Middle East; S. haematobium in Africa and the Middle East; and S. japonicum in the Far East. S. mekongi and S. intercalatum are found locally in Southeast Asia and central West Africa, respectively.Among human parasitic diseases, schistosomiasis (sometimes called bilharziasis) ranks second behind malaria in terms of socio-economic and public health importance in tropical and subtropical areas. The disease is endemic in 74-76 developing countries. They live in rural agricultural and peri-urban areas. 20 million have severe consequences from the disease. In many areas, schistosomiasis infects a large proportion of children under 14 years of age.

History
Schistosomiasis is known as bilharzia or bilharziosis in many countries, after German physician Theodor Bilharz, who first described the cause of urinary schistosomiasis in 1851.
The first doctor who described the entire disease cycle was Brazilian parasitologist Pirajá da Silva in 1908. The first known case of infection was discovered in 2014, it belongs to a child who lived 6,200 years ago. It was a common cause of death for Ancient Egyptians in the Greco-Roman Period.

Society and culture
Schistosomiasis is endemic in Egypt, exacerbated by the country's dam and irrigation projects along the Nile. From the late 1950s through the early 1980s, infected villagers were treated with repeated injections of tartar emetic. Epidemiological evidence suggests that this campaign unintentionally contributed to the spread of hepatitis C via unclean needles. Egypt has

the world's highest hepatitis C infection rate, and the infection rates in various regions of the country closely track the timing and intensity of the anti-schistosomiasis campaign.

11.Onchocerciasis

Onchocerciasis

Classification and external resources

An adult black fly with the parasite Onchocerca volvulus coming out of the insect's antenna, magnified 100x

Onchocerciasis (/ˈɒŋkəsɜrˈsaɪ.əsɪs/ **or** /ˈɒŋkəsɜrˈkaɪ.əsɪs/), also known as **river blindness** and **Robles disease**, is a disease caused by infection with the parasitic worm Onchocerca volvulus. Symptoms include severe itching, bumps under the skin, and blindness. It is the second most common cause of blindness due to infection, after trachoma The parasite worm is spread by the bites of a black fly of the Simulium type. Usually many bites are required before infection occurs. These flies live near rivers therefore the name of the disease. Once inside a person the worms create larva that make their way out to the skin. Here they can infect the next black fly that bites the person. There are a number of way to make the diagnosis including: placing a biopsy of the skin in normal saline and watching for the larva to come out, looking in the eye for larva, and looking within the bumps under the skin for adult worms. A vaccine against the disease does not exist. Prevention is by avoiding being bitten by flies. This may include the use of insect repellent and proper clothing, as well as improving sanitation practices and water management to reduce the presence of the flies. Efforts to eradicate the disease by treating entire groups of people twice a year is ongoing in a number of areas of the world. Treatment of those infected is with the medication ivermectin every six to twelve months. This treatment kills the larva but not the adult worms. The medication doxycycline, which kills an associated bacteria called Wolbachia, appears to weaken the worms and is recommended by some as well. Removal of the lumps under the skin by surgery may also be done. About 17 to 25 million people are infected with river blindness, with approximately 0.8 million having some amount of loss of vision. Most infections occur in sub-Saharan Africa, although cases have also been reported in Yemen and isolated areas of Central and South America. In 1915, the physician Rodolfo Robles first linked the worm to eye disease.

Signs and symptoms

Adult worms remain in subcutaneous nodules, limiting access to the host's immune system. Microfilariae, in contrast, are able to induce intense inflammatory responses, especially upon their death. Wolbachia species have been found to be endosymbionts of O. volvulus adults and microfilariae, and are thought to be the driving force behind most of O. volvulus morbidity. Dying microfilariae have been recently discovered to release Wolbachia surface protein that activates TLR2 and TLR4, triggering innate immune responses and producing the inflammation and its associated morbidity. The severity of illness is directly proportional to the number of infected microfilariae and the power of the resultant inflammatory response. Skin involvement typically consists of intense itching, swelling, and inflammation. A grading system has been developed to categorize the degree of skin involvement:

Acute papular onchodermatitis – scattered pruritic papules

Chronic papular onchodermatitis – larger papules, resulting in hyperpigmentation Lichenified onchodermatitis – hyperpigmented papules and plaques, with edema

Lymphadenopathy, pruritus and common secondary bacterial infections

Skin atrophy – loss of elasticity, the skin resembles tissue paper, 'lizard skin' appearance Depigmentation – 'leopard skin' appearance, usually on anterior lower leg

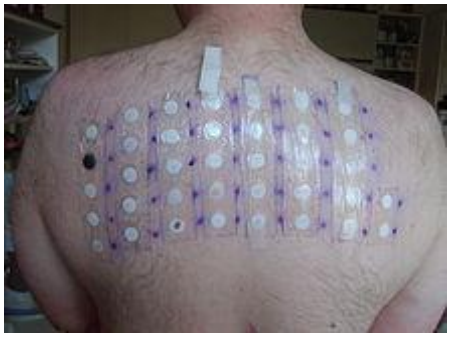
Glaucoma effect – eyes malfunction, begin to see shadows or nothing

Ocular involvement provides the common name associated with onchocerciasis, river blindness, and may involve any part of the eye from conjunctiva and cornea to uvea and posterior segment, including the retina and optic nerve. The microfilariae migrate to the surface of the cornea.

Punctate keratitis occurs in the infected area. This clears up as the inflammation subsides. However, if the infection is chronic, sclerosing keratitis can occur, making the affected area become opaque. Over time, the entire cornea may become opaque, thus leading to blindness. Some evidence suggests the effect on the cornea is caused by an immune response to bacteria present in the worms. The skin is itchy, with severe rashes permanently damaging patches of skin.

Mazzotti reaction

The Mazzotti reaction, first described in 1948, is a symptom complex seen in patients after undergoing treatment of onchocerciasis with the medication diethylcarbamazine(DEC). Mazzotti reactions can be life-threatening, and are characterized by fever, urticaria, swollen and tender lymph nodes, tachycardia, hypotension, arthralgias, oedema, and abdominal pain that occur within seven days of treatment of microfilariasis.



Patch test

The phenomenon is so common when DEC is used that this drug is the basis of a skin patch test used to confirm that diagnosis. The drug patch is placed on the skin, and if the patient is infected with O. volvulus microfilaria, localized pruritus and urticaria are seen at the application site.

Nodding disease

This is an unusual form of epidemic epilepsy associated with onchocerciasis. This syndrome was first described in Tanzania by L. Jilek-Aall during the 1960s. It occurs most commonly in Uganda and South Sudan.It manifests itself in previously healthy 5–15-year-old children, is often triggered by eating or cold temperatures and is accompanied by cognitive impairment. Seizures occur frequently and may be difficult to control.The electroencephalogram is abnormal but cerebrospinal fluid (CSF) and magnetic resonance imagining (MRI) are normal or show non specific changes. If there are abnormalities on the MRI they are usually present in the hippocampus. Polymerase chain reaction testing of the CSF does not show the presence of the parasite.

Classification

Onchocerciasis may be divided into the following phases or types:

Erisipela de la costa

An acute phase, it is characterized by swelling of the face, with erythema and itching. Onchocerciasis causes different kinds of skin changes, which vary in different geographic regions. This skin change, erisípela de la costa, of acute onchocerciasis is most commonly seen among victims in Central and South America.

Mal morando

This cutaneous condition is characterized by inflammation accompanied by hyperpigmentation.

Sowda

A cutaneous condition, it is a localized type of onchocerciasis.

Additionally, the various skin changes associated with onchocerciasis may be described as follows:

Leopard skin

The spotted depigmentation of the skin that may occur with onchocerciasis Elephant skin

The thickening of human skin that may be associated with onchocerciasis Lizard skin

The thickened, wrinkled skin changes that may result with onchocerciasis

Cause

The cause is Onchocerca volvulus

Life cycle

The life of the parasite can be traced through the black fly and the human hosts in the following steps:

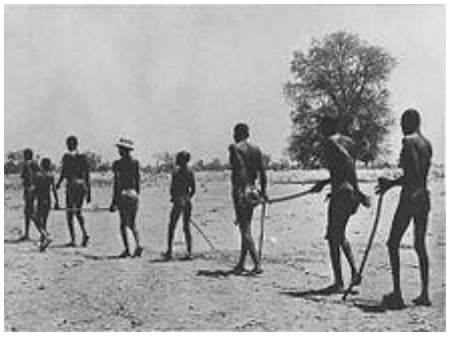
1. A Simulium female black fly takes a blood meal on an infected human host, and ingests microfilaria.
2. The microfilaria enter the gut and thoracic flight muscles of the black fly, progressing into the first larval stage (J1.).

3. The larvae mature into the second larval stage (J2.), and move to the proboscis and into the saliva in its third larval stage (J3.). Maturation takes about seven days.
4. The black fly takes another blood meal, passing the larvae into the next human host's blood.
5. The larvae migrate to the subcutaneous tissue and undergo two more molts. They form nodules as they mature into adult worms over six to 12 months.
6. After maturing, adult male worms mate with female worms in the subcutaneous tissue to produce between 700 and 1,500 microfilaria per day.
7. The microfilaria migrate to the skin during the day, and the black flies only feed in the day, so the parasite is in a prime position for the female fly to ingest it. Black flies take blood meals to ingest these microfilaria to restart the cycle.

Prevention

Various control programs aim to stop onchocerciasis from being a public health problem. The first was the Onchocerciasis Control Programme (OCP), which was launched in 1974, and at its peak, covered 30 million people in 11 countries. Through the use of larvicide spraying of fast-flowing rivers to control black fly populations, and from 1988 onwards, the use of ivermectin to treat infected people, the OCP eliminated onchocerciasis as a public health problem. The OCP, a joint effort of the World Health Organisation, the World Bank, the United Nations Development Programme, and the UN Food and Agriculture Organization, was considered to be a success, and came to an end in 2002. Continued monitoring ensures onchocerciasis cannot reinvade the area of the OCP. In 1992, the Onchocerciasis Elimination Programme for the Americas, which also relies on ivermectin, was launched. In 1995, the African Programme for Onchocerciasis Control began covering another 19 countries, mainly relying upon the use of ivermectin. Its goal is to set up a community-directed supply of ivermectin for those who are infected. In these ways, transmission has declined. On July 29, 2013, the Pan American Health Organization (PAHO) announced that after 16 years of efforts, Colombia had become the first country in the world to eliminate the parasitic disease onchocerciasi. No vaccine to prevent onchocerciasis infection in humans is available. A vaccine to prevent onchocerciasis infection for cattle is in phase three trials. Cattle injected with a modified and weakened form of O. ochengi larvae have developed very high levels of protection against infection. The findings suggest that it could be possible to develop a vaccine that protects people against river blindness using a similar approach. Unfortunately, a vaccine to protect humans is still many years off

Treatment



The burden of onchocerciasis: children leading blind adults in Africa

In mass drug administration (MDA) programmes, the treatment for onchocerciasis is ivermectin (trade name: Mectizan); infected people can be treated with two doses of ivermectin, six months apart, repeated every three years. The drug paralyses and kills the microfilariae causing fever, itching, and possibly oedema, arthritis and lymphadenopathy. Intense skin itching is eventually relieved, and the progression towards blindness is halted. In addition, while the drug does not kill the adult worms, it does prevent them for a limited time from producing additional offspring. The drug therefore prevents both morbidity and transmission for up to several months.Ivermectin treatment is particularly effective because it only needs to be taken once or twice a year, needs no refrigeration, and has a wide margin of safety, with the result that it has been widely given by minimally trained community health workers.

Antibiotics

For the treatment of individuals, doxycycline is used to kill the Wolbachia bacteria that live in adult worms. This adjunct therapy has been shown to significantly lower microfilarial loads in the host, and may have activity against the adult worms, due to the symbiotic relationship between Wolbachia and the worm. In four separate trials over 10 years with various dosing regimens of doxycycline for individualized treatment, doxycycline was found to be effective in sterilizing the female worms and reducing their numbers over a period of four to six weeks. Research on other antibiotics, such as rifampicin, has shown it to been effective in animal models at reducing Wolbachia both as an alternative and as an adjunct to doxycycline. However, doxycycline treatment requires daily dosing for at least four to six weeks, making it more difficult to administer in the affected areas.

Ivermectin

Ivermectin kills the parasite by interfering with the nervous system and muscle function, in particular, by enhancing inhibitory neurotransmission. The drug binds to and activates glutamate-gated chloride channels. These channels, present in neurons and myocytes, are not invertebrate-specific, but are protected in vertebrates from the action of ivermectin by the blood– brain barrier. Ivermectin is thought to irreversibly activate these channel receptors in the worm, eventually causing an inhibitory postsynaptic potential. The chance of a future action potential occurring in synapses between neurons decreases and the nematodes experience flaccid paralysis followed by death. Ivermectin is directly effective against the larval stage microfilariae of O. volvulus; they are paralyzed and can be killed by eosinophils and macrophages. It does not kill adult females (macrofilariae), but does cause them to cease releasing microfilariae, perhaps by paralyzing the reproductive tract.

Epidemiology

Disability-adjusted life year for onchocerciasis per 100,000 inhabitants no data
less than 10 10–50 50–
60 60–70 70–80 80–90
90–100 100–150 150–
200 200–300 300–400
more than 400

About 37 million people are infected with this about 300,000 of those had been permanently blinded. As of 2008, about 99% of onchocerciasis cases occured in Africa. Onchocerciasis is currently endemic in 30 African countries, and isolated regions of South America. Over 85 million people live in endemic areas, and half of these reside in Nigeria. Another 120 million people are at risk for contracting the disease. Due to the vector's breeding habitat, the disease is more severe along the major rivers in the northern and central areas of the continent, and severity declines in villages farther from rivers.
According to a 2002 WHO report, onchocerciasis has not caused a single death, but its global burden is 987,000 disability adjusted life years (DALYs). The severe pruritus alone accounts for
60% of the DALYs. Infection reduces the host's immunity and resistance to other diseases, which results in an estimated reduction in life expectancy of 13 years. According to the Panamerican Health Organization, on July 2013, Colombia became the first country to completely eliminate this disease from within its borders.

History

Using case studies of coffee plantation workers in Guatemala, Robles hypothesized the vector of the disease is a day-biting insect, and more specifically, two anthropophilic species of Simulium flies found to be endemic to the areas. He published his findings on a "new disease" from
Guatemala associated with subcutaneous nodules, anterior ocular (eye) lesions, dermatitis, and microfilariae in 1917.

Society and culture

Since 1988, ivermectin has been provided free of charge for use in humans by Merck through the Mectizan donation program (MDP). The MDP works together with ministries of health and nongovernmental development organisations, such as the World Health Organization, to provide free ivermectin to those who need it in endemic areas.

Research

Animal models for the disease are somewhat limited, as the parasite only lives in primates, but there are close parallels. Litomosoides sigmodontis , which will naturally infect cotton rats, has been found to fully develop in BALB/c mice. Onchocerca ochengi, the closest relative of O. volvulus, lives in intradermal cavities in cattle, and is also spread by black flies. Both systems are useful, but not exact, animal models. A study of 2501 people in Ghana showed the prevalence rate doubled between 2000 and 2005 despite treatment, suggesting the parasite is developing resistance to the drug. A clinical trial of another antiparasitic agent, moxidectin(manufactured by Wyeth), began on July 1, 2009 (NCT00790998).

12. Tuberculosis in relation to HIV

The **co-epidemic of tuberculosis (TB) and human immunodeficiency virus (HIV) is one of the major global health challenges in the present time. The World Health Organization (WHO) reports 9.2 million new cases of TB in 2006 of whom 7.7% were HIV-infected. Tuberculosis is the most common contagious infection in HIV-Immunocompromised patients leading to death.**
These both diseases become dreadful in combination as HIV declines the human immunity while tuberculosis becomes progressive due to defective immune system.This condition becomes more severe in case of multi-drug (MDRTB) and extensively drug resistant TB (XDRTB), which are difficult to treat and contribute to increased mortality. See Multi-drug-resistant tuberculosis. Tuberculosis can occur at any stage of HIV infection. The risk and severity of tuberculosis increases soon after infection with HIV. A study on gold miners of South Africa revealed that the risk of TB was doubled during the first year after HIV seroconversion. Although tuberculosis can be a relatively early manifestation of HIV infection, it is important to note that the risk of tuberculosis progresses as the CD4 cell count decreases along with the progression of HIV infection. The risk of TB generally remains high in HIV-infected patients above the background risk of the general population even with effective immune reconstitution with ART maintaining high CD4 cell counts.

Categories of tuberculosis and HIV infection

Tuberculosis is categorized into two types: active disease or latent infection. Active TB infection is symptomatic and contagious while latent TB infection is usually asymptomatic and non conatgious. Only 10% lifetime chances are there to progress the latent infection into active tuberculosis disease. If proper treatment is not given in case of active disease then death rate is up to 66%. See Tuberculosis/Research. HIV infection is also of two types: latent infection or active disease. After viral DNA integration into host genome, the virus may become latent, allowing the virus and its host cell to be in suspended stage so as to avoid detection by the immune system while in active infection, the virus transcribes, produces new RNA genomes and viral proteins which gets packaged and released from the cell as new virus particles thus allowing further replication process and producing more viral particles. See HIV

Pathogenesis of co-infection of HIV and tuberculosis

TB can develop either through progression of primary infection or through reactivation of latent infection. Infection with M. tuberculosis can occur when an individual is exposed to infectious tubercle bacilli. When the bacilli reach the pulmonary alveoli, they are ingested by alveolar macrophages while other surviving tubercle bacilli multiply within the macrophage and eventually undergo hematogenous spread to other areas of the host body. In HIV infection, defective macrophages function against the TB infection, leading to the progression of TB disease.

Treatment

It is currently recommended that HIV-infected individuals with TB receive combined treatment for both diseases, irrespective of CD4+ cell count. ART (Anti Retroviral Therapy)along with ATT (Anti Tuberculosis Treatment) is the only available treatment in present time. Though the timing of starting ART is the debatable question. The advantages of early ART include reduction in early mortality, reduction in relapses, preventing drug resistance to ATT and reduction in occurrence of HIV-associated infections other than TB. The disadvantages include cumulative toxicity of ART and ATT, drug interactions leading to inflammatory reactions are the limiting factors for choosing the combination of ATT and ART.

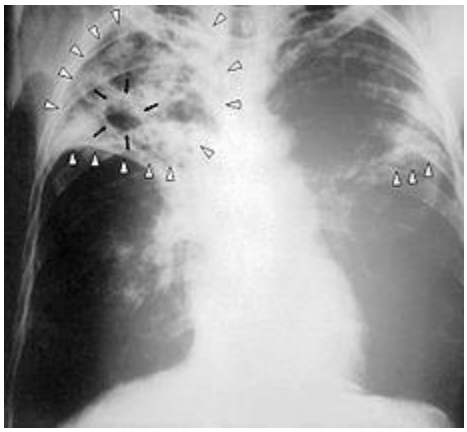
Research at molecular level

A study conducted on 452 patients revealed that the genotype responsible for higher IL-10 expression makes HIV infected people more susceptible to tuberculosis infection. Another study on HIV-TB co-infected patients also concluded that higher level of IL-10 and IL-22 makes TB patient more susceptible to Immune reconstitution inflammatory syndrome (IRIS). It is also seen that HIV co-infection with tuberculosis also reduces concentration of immunopathogenic matrix metalloproteinase (MMPs) leading to reduced inflammatory immunopathology.

13. Tuberculosis

Tuberculosis

Classification and external resources



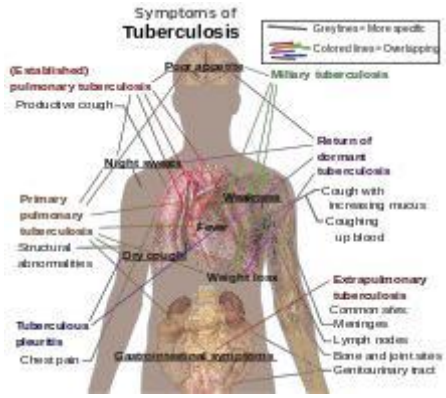
Chest X-ray of a person with advanced tuberculosis: Infection in both lungs is marked by white arrow-heads, and the formation of a cavity is marked by black arrows.

Tuberculosis, **MTB**, or **TB** (short for tubercle bacillus), in the past also called phthisis, phthisis pulmonalis, or consumption, is a widespread, and in many cases fatal, infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. Most infections do not have symptoms, known as latent tuberculosis. About one in ten latent infections eventually progresses to active disease which, if left untreated, kills **more** than 50% of those so infected.The classic symptoms of active TB infection are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss (the latter giving rise to the formerly common term for the disease, "consumption"). Infection of other organs causes a wide range of symptoms. Diagnosis of active TB relies on radiology (commonly chest X-rays), as well as microscopic examination and microbiological culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) and/or blood tests.

Treatment is difficult and requires administration of multiple antibiotics over a long period of time. Social contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in multiple drug-resistant tuberculosis (MDR-TB) infections. Prevention relies on screening programs and vaccination with the bacillus Calmette-Guérin vaccine.One-third of the world's population is thought to have been infected with M. tuberculosis, with new infections occurring in about 1% of the population each year. In 2007, an estimated 13.7 million chronic cases were active globally, while in 2010, an estimated 8.8 million new cases and 1.5 million associated deaths occurred, mostly in developing countries. The absolute number of tuberculosis cases has been decreasing since 2006, and new cases have decreased since 2002. The rate of tuberculosis in different areas

varies across the globe; about 80% of the population in many Asian and African countries tests positive in tuberculin tests, while only 5–10% of the United States population tests positive. More people in the developing world contract tuberculosis because of a poor immune system, largely due to high rates of HIV infection and the corresponding development of AIDS.

Signs and symptoms



The main symptoms of variants and stages of tuberculosis are given, with many symptoms overlapping with other variants, while others are more (but not entirely) specific for certain variants. Multiple variants may be present simultaneously.

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as **pulmonary tuberculosis**). Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, although extrapulmonary TB may coexist with pulmonary TB, as well.

General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue. Significant nail clubbing may also occur.

Pulmonary

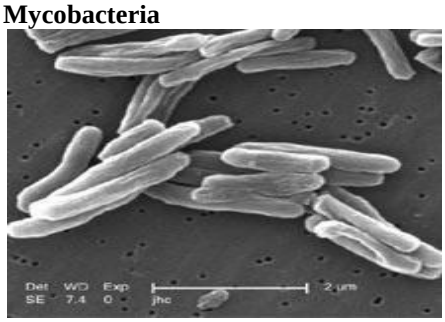
If a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases). Symptoms may include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain "asymptomatic"). Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery, resulting in massive bleeding (Rasmussen's aneurysm). Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones. The reason for this difference is not entirely clear. It may be due either to better air flow, or to poor lymph **drainage** within the upper lungs.

Extrapulmonary

In 15–20% of active cases, the infection **spreads** outside the lungs, causing other kinds of TB. These are collectively denoted as "extrapulmonary tuberculosis". Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV, this occurs in more than 50% of cases. Notable extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott disease of the spine), among others. When it spreads to the bones, it is also known as "osseous tuberculosis".a form of osteomyelitis. Sometimes, bursting of a tubercular abscess through skin results in tuberculous ulcer. An ulcer originating from nearby infected lymph nodes is painless, slowly enlarging and has an appearance of "wash leather".A potentially more serious, widespread form of TB is called "disseminated" TB, commonly known as miliary tuberculosis. Miliary TB makes up about 10% of extrapulmonary cases.

Causes

Mycobacteria



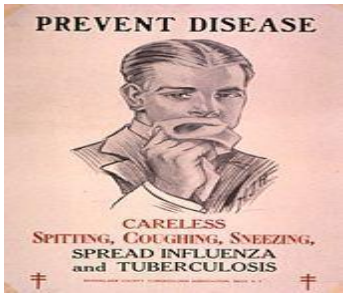
Scanning electron micrograph of M. tuberculosis

The main cause of TB is Mycobacterium tuberculosis, a small, aerobic, nonmotile bacillus. The high lipid content of this pathogen accounts for many of its unique clinical characteristics. It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour. Mycobacteria have an outer membrane lipid bilayer. If a Gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall. MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but M. tuberculosis can be cultured in the laboratory. Using histological stains on expectorated samples from phlegm (also called "sputum"), scientists can identify MTB under a regular (light) microscope. Since MTB retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus (AFB). The most common acid-fast staining techniques are the Ziehl–Neelsen stain, which dyes AFBs a bright red that stands out clearly against a blue background, and the auramine-rhodamine stain followed by fluorescence microscopy. The M. tuberculosis complex (MTBC) includes7des four other TB-causing mycobacteria: M. bovis, M. africanum, M. canetti, and M. microti. M. africanum is not widespread, but it is a significant cause of tuberculosis in parts of Africa. M. bovis was once a common cause of tuberculosis, but the introduction of pasteurized milk has largely eliminated this as a **public health** problem in developed countries. M. canetti is rare and seems to be limited to the Horn of Africa, although a few cases have been seen in African emigrants. M. microti is also rare and is mostly seen in immunodeficient people, although the prevalence of this pathogen has possibly been significantly underestimated. Other known pathogenic mycobacteria include M. leprae, M. avium, and M. kansasii. The latter two species are classified as "nontuberculous mycobacteria" (NTM). NTM cause neither TB nor leprosy, but they do cause pulmonary diseases that resemble TB.

Risk factors

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB are infected by the **virus**. This is a particular problem in sub-Saharan Africa, where rates of HIV are high. Of people without HIV who are infected with tuberculosis, about 5–10% develop active disease during their lifetimes; in contrast, 30% of those coinfected with HIV develop the active disease. Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the **principal** diseases of poverty. Those at **high risk** thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close **contact** with high-risk category patients, and health-care providers serving these patients. Chronic **lung disease** is another significant risk factor. Silicosis increases the risk about 30-fold. Those who smoke cigarettes have nearly twice the risk of TB compared to nonsmokers. Other disease states can also increase the risk of developing tuberculosis. These include alcoholism and diabetes mellitus (three-fold increase). Certain medications, such as corticosteroids and infliximab (an anti-αTNF monoclonal antibody), are becoming increasingly important risk factors, especially in the developed world. Also a genetic susceptibility element exists, for which the overall importance remains undefined.

Mechanism



Public health campaigns in the 1920s tried to halt the spread of TB.

Transmission

When people with active pulmonary TB cough, sneeze, speak, sing, or spit, they expel infectious aerosol droplets 0.5 to 5.0 µm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very small (the inhalation of fewer than 10 bacteria may cause an infection).

People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis may infect 10–15 (or more) other people per year. Transmission should only occur from people with active TB – those with latent infection are not thought to be contagious. The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the M. tuberculosis strain, the level of immunity in the uninfected person, and others. The cascade of person-to-person spread can be circumvented by effectively segregating those with active ("overt") TB and putting them on anti-TB drug regimens. After about two weeks of effective treatment, subjects with nonresistant active infections generally do not remain contagious to others. If someone does become infected, it typically takes three to four weeks before the newly infected person becomes infectious enough to transmit the disease to others.

Pathogenesis

About 90% of those infected with M. tuberculosis have asymptomatic, latent TB infections (sometimes called LTBI), with only a 10% lifetime chance that the latent infection will progress to overt, active tuberculous disease. In those with HIV, the risk of developing active TB increases to nearly 10% a year. If effective treatment is not given, the death rate for active TB cases is up to 66%.

TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within endosomes of alveolar macrophages. Macrophages identify the bacterium as "foreign" and attempt to eliminate it by phagocytosis. During this process, the entire bacterium is enveloped by the macrophage and stored temporarily in a membrane-bound vesicle called a phagosome. The phagosome then combines with a lysosome to create a phagolysosome. In the phagolysosome, the cell attempts to use reactive oxygen species and acid to kill the bacterium. However, M. tuberculosis has a thick, waxy mycolic acid capsule that protects it from these toxic substances. M. tuberculosis actually reproduces inside the macrophage and will eventually kill the immune cell.

The primary site of infection in the lungs, known as the "Ghon focus", is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe. Tuberculosis of the lungs may also occur via infection from the blood stream. This is known as a Simon focus and is typically found in the top of the lung. This hematogenous transmission can also spread infection to more distant sites, such as peripheral lymph nodes, the kidneys, the brain, and the bones. All parts of the body can be affected by the disease, though for unknown reasons it rarely affects the heart, skeletal muscles, pancreas, or thyroid.

Tuberculosis is classified as one of the granulomatous inflammatory diseases. Macrophages, T lymphocytes, B lymphocytes, and fibroblasts aggregate to form granulomas, with lymphocytes surrounding the infected macrophages. When other macrophages attack the infected macrophage, they fuse together to form a giant multinucleated cell in the alveolar lumen. The granuloma prevents dissemination of the mycobacteria and provides a local environment for interaction of cells of the immune system. Bacteria inside the granuloma can become dormant, resulting in latent infection. Another feature of the granulomas is the development of abnormal cell death (necrosis) in the center of tubercles. To the naked eye, this has the texture of soft, white cheese and is termed caseous necrosis.

If TB bacteria gain entry to the blood stream from an area of damaged tissue, they can spread throughout the body and set up many foci of infection, all appearing as tiny, white tubercles in the tissues. This severe form of TB disease, most common in young children and those with HIV, is called miliary tuberculosis. People with this disseminated TB have a high fatality rate even with treatment (about 30%).

In many people, the infection waxes and wanes. Tissue destruction and necrosis are often balanced by healing and fibrosis. Affected tissue is replaced by scarring and cavities filled with caseous necrotic material. During active disease, some of these cavities are joined to the air passages bronchi and this material can be coughed up. It contains living bacteria, so can spread the infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Upon cure, affected areas are eventually replaced by scar tissue.

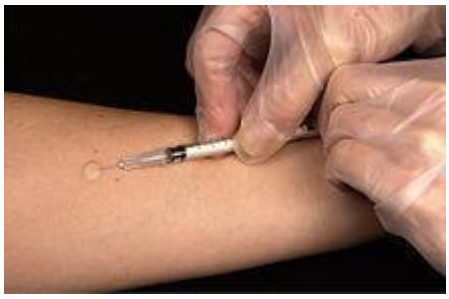
Diagnosis

M. tuberculosis (stained red) in sputum

Active tuberculosis

Diagnosing active tuberculosis based merely on signs and symptoms is difficult, as is diagnosing the disease in those who are immunosuppressed. A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting longer than two weeks. A chest X-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation. Interferon-γ release assays and tuberculin skin tests are of little use in the developing world. IGRA have similar limitations in those with HIV. A definitive diagnosis of TB is made by identifying M. tuberculosis in a clinical sample (e.g. sputum, pus, or a tissue biopsy). However, the difficult culture process for this slow-growing organism can take two to six weeks for blood or sputum culture. Thus, treatment is often begun before cultures are confirmed. Nucleic acid amplification tests and adenosine deaminase testing may allow rapid diagnosis of TB. These tests, however, are not routinely recommended, as they rarely alter how a person is treated. Blood tests to detect antibodies are not specific or sensitive, so they are not recommended.

Latent tuberculosis



Mantoux tuberculin skin test

The Mantoux tuberculin skin test is often used to screen people at high risk for TB. Those who have been previously immunized may have a false-positive test result. The test may be falsely negative in those with sarcoidosis, Hodgkin's lymphoma, malnutrition, or most notably, in those who truly do have active tuberculosis.[1] Interferon gamma release assays (IGRAs), on a blood sample, are recommended in those who are positive to the Mantoux test. These are not affected by immunization or most environmental mycobacteria, so they generate fewer false-positive results. However, they are affected by M. szulgai, M. marinum, and M. kansasii. IGRAs may increase sensitivity when used in addition to the skin test, but may be less sensitive than the skin test when used alone.

Prevention

Tuberculosis prevention and control efforts primarily rely on the vaccination of infants and the detection and appropriate treatment of active cases. The World Health Organization has achieved some success with improved treatment regimens, and a small decrease in case numbers.

Vaccines

The only available vaccine as of 2011 is bacillus Calmette-Guérin (BCG). In children it decreases the risk of getting the infection by 20% and the risk of infection turning into disease by nearly 60%.It is the most widely used vaccine worldwide, with more than 90% of all children being vaccinated. The immunity it induces decreases after about ten years. As tuberculosis is uncommon in most of Canada, the United Kingdom, and the United States, BCG is only administered to people at high risk. Part of the reasoning arguing against the use of the vaccine is that it makes the tuberculin skin test falsely positive, so of no use in screening. A number of new vaccines are currently in development.

Public health

The World Health Organization declared TB a "global health emergency" in 1993, and in 2006, the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between its launch and 2015. A number of targets they have set are not likely to be achieved by 2015, mostly due to the increase in HIV-associated tuberculosis and the emergence of multiple drug-resistant tuberculosis. A tuberculosis classification system developed by the American Thoracic Society is used primarily in public health programs.

Management

Treatment of TB uses antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which hinders the entry of drugs and makes many antibiotics ineffective. The two antibiotics most commonly used are isoniazid and rifampicin, and treatments can be prolonged, taking several months. Latent TB treatment usually employs a single antibiotic, while active TB disease is best treated with combinations of several antibiotics to reduce the risk of the bacteria developing antibiotic resistance. People with latent infections are also treated to prevent them from progressing to active TB disease later in life. Directly observed therapy, i.e.

having a **health care** provider watch the person take their medications, is recommended by the WHO in an effort to reduce the number of people not appropriately taking antibiotics. The evidence to support this practice over people simply taking their medications independently is poor. Methods to remind people of the importance of treatment do, however, appear effective.

New onset

The recommended treatment of new-onset pulmonary tuberculosis, as of 2010, is six months of a combination of antibiotics containing rifampicin, isoniazid, pyrazinamide, and ethambutol for the first two months, and only rifampicin and isoniazid for the last four months. Where resistance to isoniazid is high, ethambutol may be added for the last four months as an alternative.

Recurrent disease

If tuberculosis recurs, testing to determine to which antibiotics it is sensitive is important before determining treatment. If multiple drug-resistant TB is detected, treatment with at least four effective antibiotics for 18 to 24 months is recommended.

Medication resistance

Primary resistance occurs when a person becomes infected with a resistant strain of TB. A person with fully susceptible TB may develop secondary (acquired) resistance during therapy because of inadequate treatment, not taking the prescribed regimen appropriately (lack of compliance), or using low-quality medication. Drug-resistant TB is a serious public health issue in many developing countries, as its treatment is longer and requires more expensive drugs. MDR-TB is defined as resistance to the two most effective first-line TB drugs: rifampicin and isoniazid. Extensively drug-resistant TB is also resistant to three or more of the six classes of second-line drugs. Totally drug-resistant TB is resistant to all currently used drugs. It was first observed in 2003 in Italy, but not widely reported until 2012, and has also been found in Iran and India. Bedaquiline is tentatively supported for use in multiple drug-resistant TB.
XDR-TB is a term sometimes used to define extensively resistant TB, and constitutes one in ten cases of MDR-TB. Cases of XDR TB have been identified in more than 90% of countries.

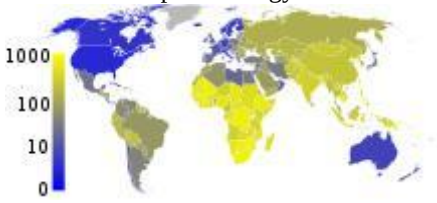
Prognosis

Age-standardized death from tuberculosis per 100,000 inhabitants in 2004.
no data
≤10 ≥10–25 ≥25–
50 ≥50–75 ≥75–
100 ≥100–250

Progression from TB infection to overt TB disease occurs when the bacilli overcome the immune system defenses and begin to multiply. In primary TB disease (some 1–5% of cases), this occurs soon after the initial infection. However, in the majority of cases, a latent infection occurs with no obvious symptoms. These dormant bacilli produce active tuberculosis in 5–10% of these latent cases, often many years after infection. The risk of reactivation increases with immunosuppression, such as that caused by infection with HIV. In people coinfected with M. tuberculosis and HIV, the risk of reactivation increases to 10% per year. Studies using DNA fingerprinting of M. tuberculosis strains have shown reinfection contributes more substantially to recurrent TB than previously thought, with estimates that it might account for more than 50% of reactivated cases in areas where TB is common. The chance of death from a case of tuberculosis is about 4% as of 2008, down from 8% in 1995.

Epidemiology

Main article: Epidemiology of tuberculosis



In 2007, the prevalence of TB per 100,000 people was highest in sub-Saharan Africa, and was also relatively high in Asia.

Roughly one-third of the world's population has been infected with M. tuberculosis, with new infections occurring in about 1% of the population each year. However, most infections with M. tuberculosis do not cause TB disease, and 90–95% of infections remain asymptomatic. In 2012, an estimated 8.6 million chronic cases were active. In 2010, 8.8 million new cases of TB were diagnosed, and 1.20–1.45 million deaths occurred, most of these occurring in developing countries. Of these 1.45 million deaths, about 0.35 million occur in those coinfected with HIV.

Tuberculosis is the second-most common cause of death from infectious disease (after those due to HIV/AIDS). The absolute number of tuberculosis cases ("prevalence") has been decreasing since 2005, while new cases ("incidence") have decreased since 2002. China has achieved particularly dramatic progress, with about an 80% reduction in its TB mortality rate between 1990 and 2010. Tuberculosis is more common in developing countries; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5– 10% of the US population test positive. Hopes of totally controlling the disease have been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine, the expensive and time-consuming diagnostic process, the necessity of many months of treatment, the increase in HIV-associated tuberculosis, and the emergence of drug-resistant cases in the 1980s in 2007, the country with the highest estimated incidence rate of TB was Swaziland, with 1,200 cases per 100,000 people. India had the largest total incidence, with an estimated 2.0 million new cases. In developed countries, tuberculosis is less common and is found mainly in urban areas. Rates per 100,000 people in different areas of the world were: globally 178, Africa 332, the Americas 36, Eastern Mediterranean 173, Europe 63, Southeast Asia 278, and Western Pacific 139 in 2010. In Canada and Australia, tuberculosis is many times more common among the aboriginal peoples, especially in remote areas. In the United States the Aborigines have a fivefold greater mortality from TB, and racial and ethnic minorities accounted for 84% of all reported TB cases. The incidence of TB varies with age. In Africa, it primarily affects adolescents and young adults. However, in countries where incidence rates have declined dramatically (such as the United States), TB is mainly a disease of older people and the immunocompromised (risk factors are listed above). Worldwide, 22 "high-burden" states or countries together experience 80% of cases as well as 83% of deaths.

History

Egyptian mummy in the British Museum – tubercular decay has been found in the spines of Egyptian mummies.

Tuberculosis has been present in humans since antiquity. The earliest unambiguous detection of M. tuberculosis involves evidence of the disease in the remains of bison in Wyoming dated to around 17,000 years ago. However, whether tuberculosis originated in bovines, then was transferred to humans, or whether it diverged from a common ancestor, is currently unclear. A comparison of the genes of M. tuberculosis complex (MTBC) in humans to MTBC in animals suggests humans did not acquire MTBC from animals during animal domestication, as was previously believed. Both strains of the tuberculosis bacteria share a common ancestor, which could have infected humans as early as the Neolithic Revolution. Skeletal remains show prehistoric humans (4000 BC) had TB, and researchers have found tubercular decay in the spines of Egyptian mummies dating from 3000–2400 BC. Genetic studies suggest TB was present in the Americas from about 100 AD. Phthisis is a Greek word for consumption, an old term for pulmonary tuberculosis; around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times. It was said to involve fever and the coughing up of blood, which was almost always fatal. Before the Industrial Revolution, folklore often associated tuberculosis with vampires. When one member of a family died from it, the other infected members would lose their health slowly. People believed this was caused by the original person with TB draining the life from the other family members.

Although the pulmonary form associated with tubercles was established as a pathology by Dr Richard Morton in 1689, due to the variety of its symptoms, TB was not identified as a single disease until the 1820s. It was not named "tuberculosis" until 1839, by J. L. Schönlein. During 1838–1845, Dr. John Croghan, the owner of Mammoth Cave, brought a number of people with tuberculosis into the cave in the hope of curing the disease with the constant temperature and purity of the cave air; they died within a year. Hermann Brehmer opened the first TB sanatorium in 1859 in Görbersdorf (now Sokołowsko), Silesia.

Dr. Robert Koch discovered the tuberculosis bacillus.

The bacillus causing tuberculosis, M. tuberculosis, was identified and described on 24 March 1882 by Robert Koch. He received the Nobel Prize in physiology or medicine in 1905 for this discovery. Koch did not believe the bovine (cattle) and human tuberculosis diseases were similar, which delayed the recognition of infected milk as a source of infection. Later, the risk of transmission from this source was dramatically reduced by the invention of the pasteurization process. Koch

announced a glycerine extract of the tubercle bacilli as a "remedy" for tuberculosis in 1890, calling it "tuberculin". While it was not effective, it was later successfully adapted as a screening test for the presence of pre-symptomatic tuberculosis. Albert Calmette and Camille Guérin achieved the first genuine success in immunization against tuberculosis in 1906, using attenuated bovine-strain tuberculosis. It was called bacille Calmette–Guérin (BCG). The BCG vaccine was first used on humans in 1921 in France, but only received widespread acceptance in the US, Great Britain, and Germany after World War II. Tuberculosis caused the most widespread public concern in the 19th and early 20th centuries as an endemic disease of the urban poor. In 1815, one in four deaths in England was due to "consumption". By 1918, one in six deaths in France was still caused by TB. After TB was determined to be contagious, in the 1880s, it was put on a notifiable disease list in Britain; campaigns were started to stop people from spitting in public places, and the infected poor were "encouraged" to enter sanatoria that resembled prisons (the sanatoria for the middle and upper classes offered excellent care and constant medical attention). Whatever the (purported) benefits of the "fresh air" and labor in the sanatoria, even under the best conditions, 50% of those who entered died within five years (circa 1916).

In Europe, rates of tuberculosis began to rise in the early 1600s to a peak level in the 1800s, when it caused nearly 25% of all deaths. By the 1950s, mortality had decreased nearly 90%. Improvements in public health began significantly reducing rates of tuberculosis even before the arrival of streptomycin and other antibiotics, although the disease remained a significant threat to public health such that when the Medical Research Council was formed in Britain in 1913, its initial focus was tuberculosis research. In 1946, the development of the antibiotic streptomycin made effective treatment and cure of TB a reality. Prior to the introduction of this drug, the only treatment (except sanatoria) was surgical intervention, including the "pneumothorax technique", which involved collapsing an infected lung to "rest" it and allow tuberculous lesions to heal. Because of the emergence of MDR-TB, surgery has been re-introduced as an option within the generally accepted standard of care in treating TB infections. Current surgical interventions involve removal of pathological chest cavities ("bullae") in the lungs to reduce the number of bacteria and to increase the exposure of the remaining bacteria to drugs in the bloodstream, thereby simultaneously reducing the total bacterial load and increasing the effectiveness of Hopes systemic antibiotic therapy. of completely eliminating TB (cf. smallpox) from the population were dashed after the rise of drug-resistant strains in the 1980s. The subsequent resurgence of tuberculosis resulted in the declaration of a global health emergency by the World Health Organization in 1993.

Society and culture

The World Health Organization, Bill and Melinda Gates Foundation, and US government are subsidizing a new fast-acting diagnostic test for use in low- and middle-income countries. This will reduce the cost from $16.86 to $9.98. Additionally the test can determine if there is resistance to the antibiotic rifampicin which may indicate multi-drug resistant tuberculosis and is accurate in those who are co-infected with HIV. Many resource-poor places as of 2011 still only have access to sputum microscopy.

India had the highest total number of TB cases worldwide in 2010, in part due to poor disease management within the private and public health care sector. Programs such as the Revised National Tuberculosis Control Program are helping to reduce TB levels amongst people receiving public health care. A 2014 EIU-healthcare report was released claiming a need to address apathy against tuberculosis, urging for increased funding. The report cites among others Dr Lucica Ditui of STOP TB Partnership; "[TB] is like an orphan. It has been neglected even in countries with a high burden and often forgotten by donors and those investing in health interventions.", and STOP TB Partnership suggests given the current pace of declining infection rate it will take 180 years before incidence in developing world will decrease to the level of the developed world. The World Bank claims incidence of TB has declined by 17% between 2004– 2014. Slow progress has led to frustration, expressed by executive director of the Global Fund to Fight AIDS, Tuberculosis and Malaria – Mark Dybul: "we have the tools to end TB as a pandemic and public health threat on the planet, but we are not doing it." Several international organizations are pushing for more transparency in treatment, and more countries are implementing mandatory reporting of cases to the government, although adherence is often sketchy. Commercial treatment-providers may at times overprescribe second-line drugs as well as supplementary treatment, promoting demands for further regulations. The government of Brazil provides universal TB-care, which reduces this problem this problem. Conversely falling rates of TB-infection may not relate to the number of programs directed at reducing infection rates, but may be tied to increased level of education, income and health of the population. Costs of the disease, as calculated by the World Bank in 2009 may exceed 150 billion USD per year in "high burden" countries alone. Lack of progress eradicating the disease may also be due to lack of patient follow-up – as among the 250M rural migrants in China – which frequently relocate in search of employment, and are often socially marginalized.

Stigma

Slow progress in preventing the disease may in part be due to stigma associated with TB. In large stigma has been linked to fear of transmission from affected individuals. Stigma may additionally be due to links between TB and poverty; and in Africa, AIDS. Such stigmatization may be both real and perceived, for example; in Ghana individuals suffering TB are banned from attending public gatherings; one study saw perceived stigma among Mexican Indians to be worse by non-sufferers than by sufferers. Stigma towards TB sufferers may result in delays when seeking treatment, lower treatment compliance, and family members keeping cause of death secret – allowing the disease to spread further. At odds is Russia, where stigma was associated with increased treatment compliance. TB stigma also affects socially marginalized individuals disproportionally, such as: migrants, women and poorly educated individuals, and also varies significantly between regions.

One way to fight TB stigma may be through the promotion of " TB clubs", where sufferers may share experiences and offer support, or through counseling.
Some studies have shown TB education programs to be effective in decreasing stigma, and may thus be effective in increasing treatment adherence. Despite this, studies on correlation between reduced stigma and mortality were lacking as of 2010, and similar efforts to decrease stigma surrounding AIDS have been minimally effective. Some have claimed the stigma to be than the disease itself, and healthcare providers may unintentionally reinforce stigma, as sufferers are often perceived as difficult.

Research
The BCG vaccine has limitations, and research to develop new TB vaccines is ongoing. A number of potential candidates are currently in phase I and II clinical trials. Two main approaches are being used to attempt to improve the efficacy of available vaccines. One approach involves adding a subunit vaccine to BCG, while the other strategy is attempting to create new and better live vaccines. MVA85A, an example of a subunit vaccine, currently in trials in South Africa, is based on a genetically modified vaccinia virus. Vaccines are hoped to play a significant role in treatment of both latent and active disease. To encourage further discovery, researchers and policymakers are promoting new economic models of vaccine development, including prizes, tax incentives, and advance market commitments. A number of groups, including the Stop TB Partnership, the South African Tuberculosis Vaccine Initiative, and the Aeras Global TB Vaccine Foundation, are involved with research. Among these, the Aeras Global TB Vaccine Foundation received a gift of more than $280 million (US) from the Bill and Melinda Gates Foundation to develop and license an improved vaccine against tuberculosis for use in high burden countries.
A number of medications are being studied for multi drug resistant tuberculosis including: bedaquiline and delamanid. Bedaquiline received U.S. Food and Drug Administration (FDA) approval in late 2012. The safety and effectiveness of these new agents are still uncertain, because they are based on the results of a relatively small studies. However, existing data suggest that patients taking bedaquiline in addition to standard TB therapy are five times more likely to die than those without the new drug, which has resulted in medical journal articles raising health policy questions about why the FDA approved the drug and whether financial ties to the company making bedaquiline influenced physicians' support for its use

Other animals
Mycobacteria infect many different animals, including birds, rodents, and reptiles. The subspecies Mycobacterium tuberculosis, though, is rarely present in wild animals. An effort to eradicate bovine tuberculosis caused by Mycobacterium bovis from the cattle and deer herds of New Zealand has been relatively successful. Efforts in Great Britain have been less successful.

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