HARVARD MEDICAL SCHOOL
BRIGHAM AND WOMEN'S HOSPITAL

CASES IN GLOBAL HEALTH DELIVERY

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Clinical Background on HIV/AIDS, Malaria, and Tuberculosis

HIV/AIDS

Global Epidemiology of HIVAIDS

In 2015, 2.1 million individuals around the world were newly infected with HIV.[1] This was about 64% lower than at the peak of the epidemic in 1996. About 70% of all new infections in 2015 were in sub-Saharan Africa.[1,2] In 2015, an estimated 1.1 million people died from AIDS. That number was smaller than the number dying in 2004, the year that deaths from HIV/AIDS peaked, due to anti-retroviral therapies (ART). By the end of 2015, there were an estimated 36.7 million people living with HIV/AIDS—27% more than in 2000 and four times as many as in 1990.[1,3] This was due, in part, to a prolongation of life among HIV positive patients receiving and adhering to ART.

Though there are clear pockets where HIV is resurging, the epidemic appears to have stabilized in most regions. In 2015, over 17 million people were on ART of which 12.1 million people were from low- and middle-income countries, though this number represented only 35% of those in need of initiating ART.[1]

While poverty is usually associated with HIV/AIDS, individual behaviors and characteristics, such as having more concurrent sexual partners, geographic mobility, and urbanization are also associated with the disease. High risk groups also include men who have sex with men, commercial sex workers, and injection drug users.

The World Health Organization (WHO) reported that of the countries reporting complete data, 93% provided free HIV testing through public sector health facilities in 2008. In 39 countries the number of HIV tests performed had more than doubled from the year prior. Despite this, the majority of those living with HIV remain unaware of their HIV status.

Julie Rosenberg, Kileken ole-MoiYoi, and Michelle Morse prepared this note with assistance from Claire Donovan for the purposes of classroom discussion rather than to illustrate either effective or ineffective health care delivery practice.

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Pathogenesis and Transmission of HIV/AIDS

Human Immunodeficiency Virus (HIV) is a virus that causes the body's immune system or natural defense against disease to break down. HIV's lifespan is characterized by complex interactions with the host and a chronic disease course, meaning the disease is not curable, but manageable. Like other retroviruses, HIV copies its genetic material into the host cell's DNA. When the host cell divides, the virus is copied and released from the cell into the human, killing the host cell in the process[4]

The virus attached to cells that mediate the host's immune system response, CD4 T cells and macrophages. A CD4 cell is a type of white blood cell responsible for initiating immune responses.[5] (see **Exhibit 1** for life cycle of HIV).

The virus is present in low levels in the blood, semen, and vaginal secretions of infected individuals. HIV cannot live outside the human body for very long and is not transmitted through casual contact such as kissing (saliva), insect bites, or via water or food. The main mechanism responsible for 80% of transmission is sexual contact, with anal intercourse being a more efficient mechanism of spread than vaginal intercourse. Other major routes of spread include intravenous drug use with contaminated needles or exposure to blood products through transplanted tissue or needle sticks. Outside of the US, transmission often occurs from mothers to infants via breast milk and during labor and delivery.

Clinical Manifestations of HIV/AIDS

Three to six weeks after infection, an early or acute phase occurs in the majority of patients (see **Exhibit 2** for the course of HIV).[6] Symptoms include fever, pharyngitis (swollen pharynx which causes sore throat), lymphadenopathy (enlarged lymph nodes), headache, loss of appetite, and rash.

The host responds to infection by creating new proteins (antibodies) that bind to the surface of the virion to stop the virion from infecting new cells. This response is only partially effective, however, because the virus mutates, rendering the hosts' antibodies to the disease useless. As the host tries to suppress the virus by producing more immune cells, the virus is actually propagated and CD4 cells are destroyed. This is reflected by a measurable rise in viral load and reduced CD4 count. Symptoms usually resolve within one to two weeks, upon which time the patient develops partial immunity against the virus.

With the resolution of initial symptoms, HIV infection progresses from the acute to persistent phase. During this time, patients are largely asymptomatic. Without treatment this phase may last for 10–15 years (median 10),[6] during which time infected individuals may spread the virus to others. The virus continues to mutate under selection pressures provided by the immune system, and CD4 cell counts decline at a rate inversely proportional to viral load. Although this phase may be protracted, it invariably progresses to the symptomatic phase.

The most advanced stage of HIV, the symptomatic phase, is called acquired immune deficiency syndrome (AIDS). Clinically, AIDS is defined as either a CD4 count below 200/μl or the diagnosis of an AIDS defining illness. These illnesses are typically opportunistic infections not found as commonly in immunocompetent individuals, including pneumocystis pneumonia, disseminated tuberculosis, crypotococcal meningitis, and mycobacterium avium intracellulare.

HIV/AIDS Diagnoses

The confirmation of HIV at any disease stage relies upon finding antibodies to the viral proteins, which may not appear immediately after infection, or a high viral load. Typically patients develop antibodies within 4–8 weeks of infection; however, in as many as 5% of patients, antibodies do not

develop for up to six months. As a result, many individuals with HIV may actually test negative for HIV in the early months of infection.[7]

While acute HIV is infrequently recognized or diagnosed in clinical practice,[8] a diagnosis of AIDS can be made in the presence of AIDS-defining illnesses and is a common phenomenon. Because antibodies take so long to develop and because many people who are tested do not return to clinics to learn about their test results, researchers have worked to develop a better screening test. Several rapid HIV tests were developed by 2002 in which results could be obtained in 20 minutes.[9]

Debate surrounds the ethics of mandatory HIV testing and specific policy differs from country to country; certain countries only mandate such tests in situations such as immigration or military conscription while others mandate HIV testing before marriage and childbirth.[10] Leaders in HIV prevention tactics believe client-initiated requests to get tested are crucial for effective HIV prevention.[11] Voluntary counseling and testing (VCT) involves self-initiated HIV testing and prevention counseling. It is often offered in free-standing sites and may be integrated into health centers, mobile units, and community-based settings. HIV prevalence among VCT clients is usually higher than the national prevalence, and demand for VCT has increased with the availability of ARVs.[12]

Couple HIV counseling and testing (CHCT) involves two people in a sexual relationship receiving HIV testing and pre- and post-test counseling together. CHCT is especially important where HIV discordance is common. When partners test separately, disclosure rates are much lower, and they may hear different messages about prevention.[12]

Provider-initiated counseling and testing (PICT), recommended by the World Health Organization starting in 2007, integrates HIV testing into clinical services. Some providers offer "opt-in" services in which each patient must specifically consent to HIV testing, usually in writing. Others offer "opt-out" services in which patients are notified that HIV testing is routine and recommended and that they must specifically refuse the test. PICT requires much less time from providers (10 minutes for HIV-negative patients or 15 for positive) and utilizes existing personnel and infrastructure, facilitating linkages to care and treatment.[12]

HIV/AIDS Treatment

Although antiretroviral (ARV) therapies have been developed to halt progression of the disease, HIV is incurable. Treatment usually consists of a combination of ARVs. Taking at least two drugs is considered combination therapy, while taking at least three different highly active antiretroviral therapies (HAART), is preferred. Drug selection is complex, with more than 20 antiretroviral medications available in six major classes.

Effective HAART delays progression of HIV to AIDS, reduces opportunistic infections, hospitalizations, and deaths. It restores the immune function (as indicated by the CD4 cell count), reduces the risk of transmission, limits drug resistance (which occurs more often in monotherapy and combination therapy), and improves the quality of life for patients.

When to start therapy is highly debated. Not all studies have agreed on the same viral set point or a point in which the CD4 counts become low enough to warrant treatment. In 2013, The WHO guidelines for treating HIV recommend starting ART in all individuals with a CD4 cell count of 500 cells/mm3or less and giving priority to individuals with severe or advanced HIV disease and those with a CD4 cell count of 350 cells/mm3 or less. Meanwhile, in the United States ART regimens are started as soon as HIV is diagnosed and patient consent is obtained, regardless of the CD4 count.[13, 14] In 2015, the WHO revised their 2013 recommendation to align with evidence and programmatic experience and recommended initiating ART for all individuals regardless of CD4 count.[15] The risks of early treatment include higher

risk of long-term drug toxicities due to a longer duration of antiretroviral exposure and the evolution of drug resistance if therapy fails to completely suppress viral replication. Many programs also must consider the costs of treatment and available funding. Once treatment is initiated, HAART is often continued indefinitely.

While HAART can be highly effective, patient compliance is an important issue. Patients often stop taking medications, lose access to them, forget to take them, or cannot tolerate the side effects from medications. Noncompliance with prescribed drug regimens allows for the development of viral resistance to certain drugs and selects for mutant, drug resistant strains of HIV that can then be passed on to other individuals. It has been estimated that patients can only miss three days of medications per month before the risk of drug resistance becomes significant.[16]

The most common first-line antiretroviral drugs dropped 30–68% in price between 2004 and 2008 thanks to global activism and advocacy work, the emergence of competition from generic manufacturers, and direct negotiation with pharmaceutical companies. The combination was available for USD 64 per person per year in 2010[17] (although the WHO has now recommended against this combination). In 2013, the WHO's preferred line of treatment was a one-pill-a-day combination with three different drugs that costs USD 139 per patient per year, which is down from USD 179 in 2012 (10). Contrary, in the United States the most common first line drug regimen costs upwards of USD 15,000, although this too is expected to significantly drop when the patent runs up in 2018.[18] While first-line drugs have become more affordable, making them more accessible, second-line ARV drugs continue to be expensive. The WHO-recommended second-line treatment cost more than USD 300.[19] Projections show increasing costs as the HIV epidemic progresses and more patients require second-line treatment.[20]

HIV/AIDS Prevention

The risk of HIV transmission is directly related to the viral load in HIV-infected individuals and may vary according to viral subtype.[21] Monogamy, delaying sexual debut, and using condoms consistently are all behavioral-based methods to prevent sexual transmission of HIV. Biomedical approaches, such as male circumcision and treating sexually transmitted infections, also reduce the likelihood of sexual HIV transmission.[22] HIV is transmitted between 0.04%-0.08% of the time an infected individual engages in sexual intercourse, which means the likelihood of contracting HIV through sexual intercourse is between 1 in 1234 and 1 and 2830. Many studies attempt to figure out the transmission rate of HIV depending on the mode of transmission, but it is difficult to know exactly which HIV encounter transmitted the virus (see **Exhibit 4** for rates of transmission by activity).

Preventing HIV transmission due to blood exposure involves blood safety, reducing occupational risk, and harm reduction strategies among injecting drug users. Prevention of mother-to-child transmission involves primary HIV prevention in women, prevention of unintended pregnancies in HIV-positive women, use of HAART, and provision of treatment care and support to women with HIV and their families. In pregnant patients with high viral loads, cesarean section as a mode of delivery is an important strategy to prevent vertical transmission of disease. An important component of HIV prevention is treatment of HIV-positive patients, thus reducing the likelihood that they will transmit the virus.

HIV prevention is complex, and numerous obstacles have impeded effective, widespread HIV prevention programs. These obstacles include: shortfalls in funding, inadequate data,[23,24] disagreement over core prevention activities,[25] an overemphasis on individual-level interventions,[26] insufficient focus on operations research, and a failure to effectively target, select, and deliver services.[24]

We have written more comprehensively about HIV prevention in the Global Health Delivery *Concept Note: HIV Prevention*.

Further Reading on HIV/AIDS

1. Centers for Disease Control and Prevention.
https://www.cdc.gov/hiv/basics/index.html
This page answers some of the common questions about HIV such as where it came from, what is HIV-2, and how HIV tests work

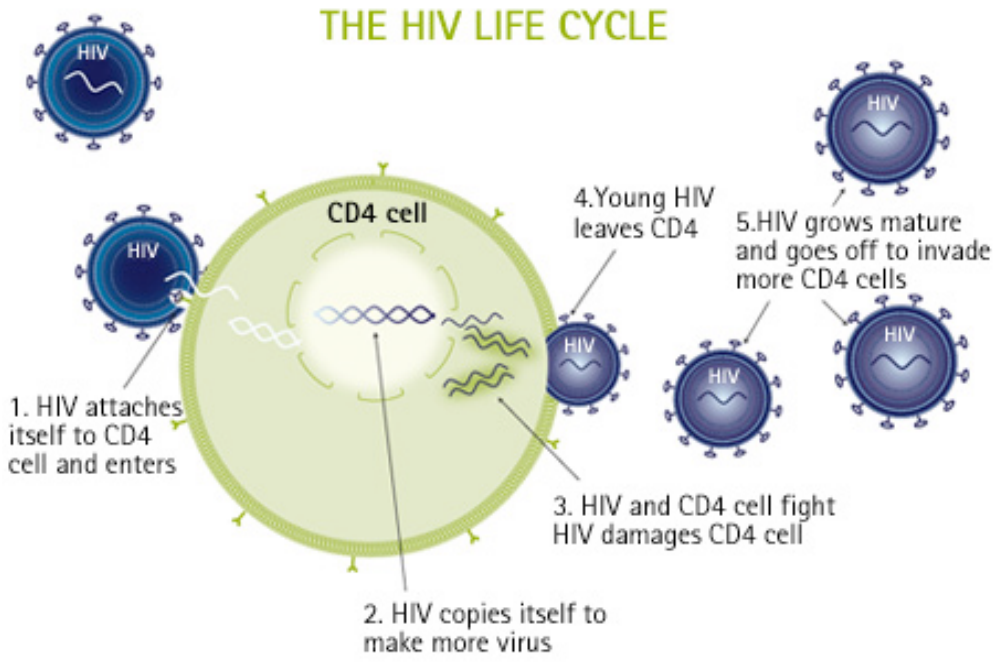
2. AIDS.gov
http://aids.gov/AIDS.gov
AIDS.gov has information on the latest US Federal resources as well as information on prevention, testing, research, risk, treatment options, and more, each broken down into many categories.

3. World Health Organization
http://www.who.int/topics/hiv_aids/en/
This page offers links to various resources on HIV/AIDS, including general information, technical information, guidelines, other WHO publications, statistics, and multimedia.
http://www.who.int/hiv/en/ offers the latest news on HIV and WHO guidelines.

4. UNAIDS
http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_en.pdf
The 2011 World AIDS Day Report describes the state of the epidemic globally, what has worked, and what needs improvement.

5. World Bank
siteresources.worldbank.org/INTAFRREGTOPHIVAIDS/Resources/The_Changing_HIV-AIDS_Landscape.pdf
The Changing HIV/AIDS Landscape: selected papers for the World Bank's Agenda for Action in Africa, 2007-2011 is an expansive (500 pp.) selection of background papers dealing with evidentiary matters, partnership relations, economic, financial and operational aspects of HIV/AIDS, and more.

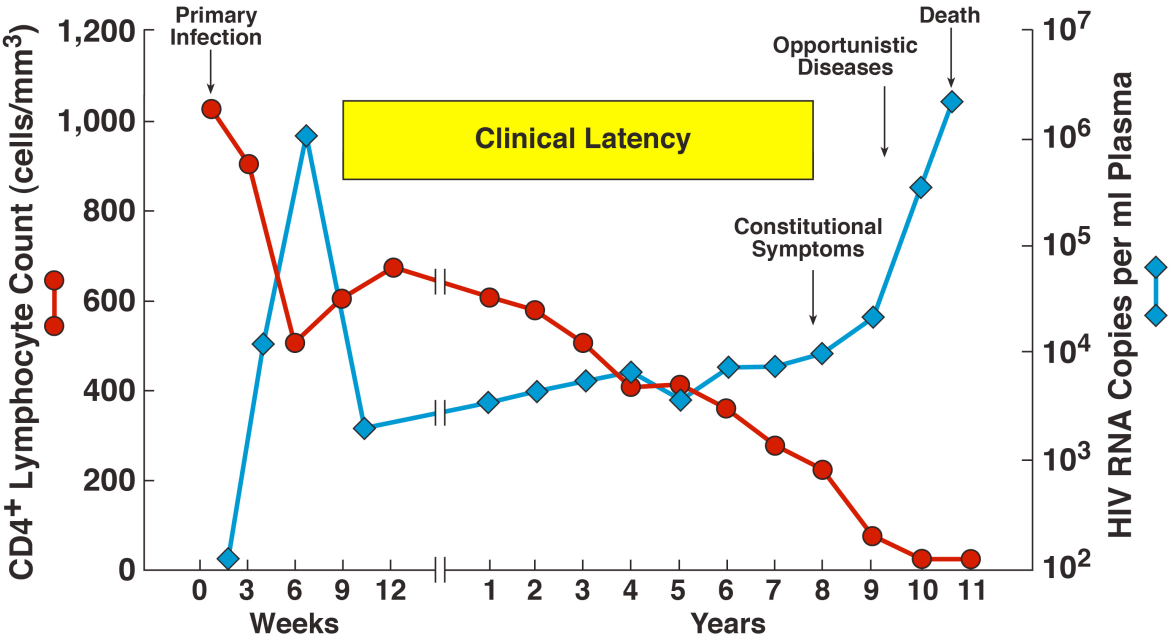
Exhibit 1 *HIV Life Cycle*



Note: The structural proteins and enzymes found in HIV allow for viral entry into host cells, replication, and characteristic spread of the disease. The virion (entire virus particle) is surrounded by multiple layers. The outer layer, the lipid envelope, has two important proteins that protrude from its surface.[27] The virus cannot infect other cells. The virus fuses with the CD4 T cell or macrophage cell and injects its core contents into the host cell's cytoplasm. The virion's RNA is incorporated into host DNA where it lays latent until a triggering event occurs, such as T-cell proliferation in response to a new infection. At that time, millions of new HIV virions are assembled that can infect new cells or be transmitted to others.[7]

Source: Terrence Higgins Trust. The immune system. 2014. http://www.tht.org.uk/myhiv/HIV-and-you/Simple-science/The-immune-system

Exhibit 2 *The Course of HIV*

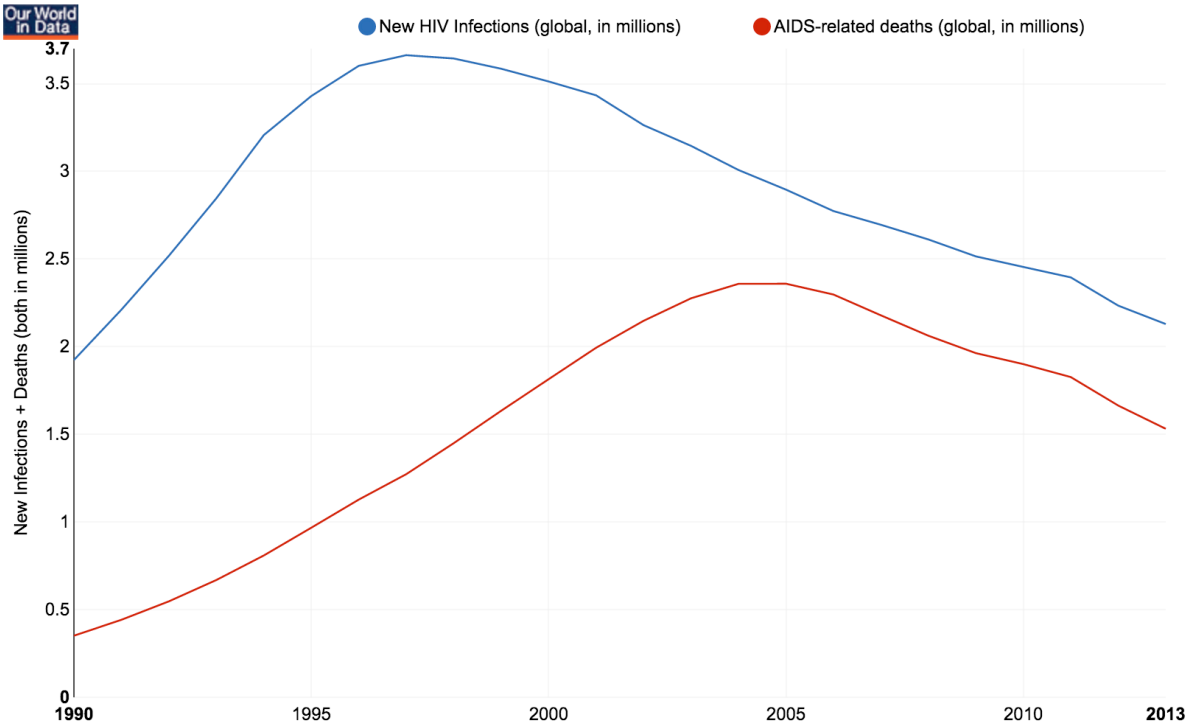


Modified From: Fauci, A.S., et al, Ann. Intern. Med., 124:654, 1996

During primary infection, HIV disseminates widely through the body, usually accompanied by an abrupt decrease in $CD4^+$ T cells. An immune response to HIV ensues, with a detectable decrease in viral load. Clinical latency follows but $CD4^+$ T cells slowly continue to decrease until they fall to a critical level below which there is a substantial risk of opportunistic infections.

Source: Adapted from NIAID website publication (3). NIAID website publication. Course of HIV infection. http://www.niaid.nih.gov/topics/hivaids/understanding/biology/Pages/clinicalCourse.aspx

Exhibit 3 *Annual global number of deaths due to AIDS and new HIV infections, 1990-2013*



Source: Max Roser, http://www.ourworldindata.org/data/health/hiv-aids Data source: AIDSinfoonline.org

Exhibit 4 *HIV Transmission by Activity*

Activity	Risk per exposure
Vaginal sex, female-to-male, studies in high-income countries	0.04% (1:2380)
Vaginal sex, male-to-female, studies in high-income countries	0.08% (1:1234)
Vaginal sex, female-to-male, studies in low-income countries	0.38% (1:263)
Vaginal sex, male-to-female, studies in low-income countries	0.30% (1:333)
Vaginal sex, source partner is asymptomatic	0.07% (1:1428)
Vaginal sex, source partner has late-stage disease	0.55% (1:180)
Receptive anal sex amongst gay men, partner unknown status	0.27% (370)
Receptive anal sex among gay men, partner HIV-positive	0.82% (1:123)
Receptive anal sex with condom, gay men, partner unknown status	0.18% (1:555)
Insertive anal sex, gay men, partner unknown status	0.06% (1:1666)
Insertive anal sex with condom, gay men, partner unknown status	0.04% (1:2500)
Receptive fellatio	Estimates range from 0.00% to 0.04% (1:2500)
Mother-to-child, mother takes at least two weeks antiretroviral therapy	0.8% (1:125)
Mother-to-child, mother takes combination therapy, viral load below 50	0.1% (1:1000)
Injecting drug use	Estimates range from 0.63% (1:158) to 2.4% (1:41)
Needlestick injury, no other risk factors	0.13% (1:769)
Blood transfusion with contaminated blood	92.5% (9:10)

Source**:** AidsMap. Estimated risk per exposure. http://www.aidsmap.com/Estimated-risk-per-exposure/page/1324038

Malaria

Global Epidemiology of Malaria

Malaria has plagued humanity for thousands of years, and many have suggested that humans coevolved with malaria. In 2015, there were an estimated 214 million cases of malaria, resulting in approximately 438,000 million deaths[28] (see **Exhibit 5** for map of malaria mortality over time). Children under the age of five and pregnant women are the most susceptible to developing severe malaria. Since the end of the 1970s, malaria has been largely classified as disease of poverty, restricted to the world poorest regions. Roughly 90% of malaria-attributed deaths occur in sub-Saharan Africa, and of those, 68% in children (see **Exhibit 7** for projected changes in malaria rates by country).[29]

Prior to the Malaria Eradication Program (MEP) of the 1950s and 1960s, malaria was found worldwide, as far North as Denmark and the northeast US. The US Centers for Disease Control and Prevention (CDC) was founded in 1942 as the Office of National Defense Malaria Control Activities and was located in Atlanta, GA due to the high burden of malaria in the southern US at the time. In 1949, the US was declared malaria-free and efforts were directed from elimination to surveillance.[30] Success in the US motivated public health policymakers and practitioners to replicate these efforts in other malaria-endemic countries.

In 1998, the Roll Back Malaria Partnership (RBM) was launched to draw attention to the increasing global burden of malaria and to improve efforts to combat the disease. Significant progress has been made since the founding of the RBM, particularly in increasing the availability of funds and coordinating malaria activities around the world. The 2008 Global Malaria Action Plan (GMAP) built on the RBM partnership by constructing a strategic outline for global malaria control and elimination. Despite the progress made by both RBM and GMAP, there is still much to be done to expand on and sustain the advances, which forms the basis of the 2016-2030 Global Technical Strategy for Malaria:

Malaria targets were outlined in the 2016-2030 Global Technical Strategy for Malaria:[31]

1. Reduce malaria mortality rates globally by at least 90% from 2015 to 2030
2. Reduce malaria case incidence globally by at least 90% from 2015 to 2030
3. Eliminate malaria from at least 35 countries in which malaria was transmitted in 2015 by 2030
4. Prevent re-establishment of malaria in all countries that are malaria-free

To achieve these targets, the document outlined a three-part global strategy with two supporting elements:

5. Ensure universal access to malaria prevention, diagnosis and treatment.
6. Accelerate efforts towards elimination and attainment of malaria-free status.
7. Transform malaria surveillance into a core intervention.
    a. Harnessing innovation and expanding research.
    b. Strengthening the enabling environment.

Malaria Transmission

Malaria is caused by one of five related parasites of the genus *Plasmodium*: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae, Plasmodium ovale,* and the recently discovered *Plasmodium knowlesii. Plasmodium falciparum* causes both the majority and the most severe cases of malaria; it is responsible for roughly 90% of malaria deaths. The parasites are primarily transmitted by female mosquitoes, primarily of the genus *Anopheles*. The mosquitoes are infected with reproductive malaria plasmodia (gametocytes) when they feed on an infected human. Once ingested by the mosquito, the gametocytes sexually reproduce and go through several developmental stages in the mosquito's gut eventually multiplying and migrating to the mosquito's salivary glands. Roughly a week later when the same mosquito takes a subsequent blood meal, it transfers the malaria plasmodia (now in the form of sporozoites) into the next human's bloodstream.

Once in the human host, the sporozoites are rapidly filtered out of the blood by the liver and subsequently infect liver cells. The sporozoites replicate and differentiate into merozoites eventually rupturing the liver cells to release merozoites into the bloodstream. The merozoites then repeatedly infect the red bloods cells and replicate causing severe malaise if untreated. The plasmodia spend most of the time in the protection of liver and red blood cells and are thus largely undetected by the body's immune system. Some of the merozoites in the human bloodstream differentiate into gametocytes, which can then be ingested by the next mosquito repeating the process (see **Exhibit 5** for lifecycle).

Malaria transmission typically increases following wet weather due to its dependence on the mosquito vector. Mosquitoes depend on relatively stagnant water to both lay their eggs and for the larval stage of development. High malaria transmission usually occurs in areas near bodies of water, swamps, or irrigated fields. Following wet weather, mosquito populations also increase in urban areas facilitated by the presence of standing water in potholes, ponds, industrial pits, and discarded tires or cans. High human and mosquito population densities facilitate malaria transmission both from mosquitoes to humans and from humans to mosquitoes.

Clinical Manifestations of Malaria

In the majority of malaria cases, infected individuals develop flu-like symptoms marked by fatigue, extreme head and muscle aches, chills caused by intermittent periods of high fever, and profound malaise. If untreated, some people will recover on their own while others progress to severe malaria marked by anemia, kidney failure, coma, and eventually death. People with stressed, underdeveloped, or previously unexposed immune systems such as women, young children, or migrants are the least likely to recover unassisted. People who continuously live in malaria endemic regions are known to develop a low level of immunity and may not exhibit extreme symptoms, while those who have never been exposed to the parasite present symptoms more intensely. Those who have developed immunity, however, may still transmit the disease to other people via the mosquito vector.

While long-term effects of malaria are minimal, people who were infected by *P. falciparum* and were not treated can suffer severe cerebral malaria, which can result in neurological damage. Being repeatedly infected by *P. falciparum*, even if treated, can lead to anemia. Other vectors, *P. ovale* and *P. vivax*, are known to remain dormant in the liver and can cause relapse years later.

Malaria Diagnosis

Of over 200 million suspected malaria cases in 2012, only 40 million cases were confirmed; an estimated 167 million cases (80%) were not clinically diagnosed.[32] Depending on the country, people infected with malaria often recognize the symptoms and seek treatment from private retail shops that

stock anti-malarials. Unfortunately, highly effective anti-malarials available in retail shops are expensive and because the majority of malaria victims are poor, they usually purchase less expensive and less effective anti-malarials. Self-diagnosis and treatment is thus a dangerous method for treating malaria.

When individuals present to hospitals or clinics with malaria-like symptoms, clinicians either symptomatically diagnosis malaria or take a blood sample for diagnosis. In many malaria endemic regions, when children present with malaria-like symptoms, anti-malarials may be prescribed before taking a blood sample. This method of diagnosis has resulted in a growing number of misdiagnosed cases in areas where malaria transmission is in decline. Misdiagnosis can result in wasted antimalarials and life threatening situations when other potentially fatal conditions such as sepsis are not immediately treated. As a result, clinicians are now advised to take blood samples whenever possible and identify malaria under the microscope or with rapid-diagnostic tests (RDTs) before prescribing anti-malarials. The effectiveness of these strategies varies from region to region and is dependent upon the presence of a trained microscopist or the availability of effective RDTs.

Malaria Treatment

Although not scientifically classified until the early 1900s, numerous treatments for the disease have been used around the world. Non-severe malaria is usually treated with over-the-counter oral medications. Severe malaria is usually treated with intravenous quinine or more recently artesunate. Artesunate is a derivative of artemisinin, which is extracted from the *Artemisia* plant and was used to treat malaria-like symptoms in China as early as 168 BCE.

Starting in the 1960s, quinine related compounds such as chloroquine were widely used to treat malaria. Chloroquine was the least expensive and most effective antimalarial available at the time. However, its widespread use until 1990 led to high levels of plasmodia resistance. Although it is still among the least expensive and widely available antimalarials, its use is strongly discouraged due to rampant resistance particularly in sub-Saharan Africa and Southeast Asia.

As of 2001, artemisinin-based combination therapy (ACT) became the treatment of choice for non-severe malaria. Artemisinin is extracted from *Artemisia annua*—a plant also known as sweet annie or wormwood used in Chinese traditional medicine—which was formally identified as an antimalarial compound in the late 1960s by scientists from the Chinese Academy of Military Medical Sciences. The Chinese team isolated four antimalarial derivatives (dihydroartemisinin, artesunate, arteether, and artemether) from artemisinin and created the first ACT, which was a combination of artemether and lumefantrine (AL).. Lumefantrine is an unrelated synthetic antimalarial. In an effort to make the AL combination available to victims of malaria in endemic countries, the Chinese scientists granted Novartis, a Swiss pharmaceutical company, license to market, manufacture, and sell the AL combination under the brand name of Coartem®. Novartis supplied Coartem® to the public sectors of developing countries at manufacturing cost provided that the drug was made available for free at public health facilities in malaria endemic countries. In 2015, Chinese scientist Youyou Tu received a Nobel Prize in Physiology or Medicine for her discovery of artemisinin.

There are currently several different forms of ACTs available at subsidized rates for the public sector in malaria endemic countries. However, because people in many malaria endemic countries are accustomed to seeking treatment from private retail shops, there are still major obstacles to ensuring access to inexpensive and effective antimalarials. The Affordable Medicines Facility for Malaria is a private sector subsidy for ACTs intended to undercut and substitute inexpensive but largely ineffective drugs such as chloroquine and sulphadoxine/pyrimethamine.

Malaria Prevention

In 2015, an antimalarial vaccine, RTS,S/ASO1 (RTS,S) completed Phase 3 testing and was awaiting its piloting[33] as a supplementary intervention to the existing malarial-prevention methods: prophylaxis, vector control, and limiting human exposure to mosquitoes.

Several drugs have been used for malaria prophylaxis over the past half century. Unfortunately, the plasmodia are quick to develop resistance to prophylaxis drugs due to the variable concentration of medication in the human blood stream. Various synthetic quinine-related compounds were used as prophylaxis. Quinine, an extract of Cinchona tree bark, was discovered by the Quechua people of Peru, who would mix it with sweetened water to reduce fever. Many European settlers purportedly drank tonic water (quinine and carbonated sweetened water) and gin as malaria prophylaxis during the early 1900s in Africa and Southeast Asia. Although the majority of quinine-related drugs are no longer recommended for prophylaxis due to high levels of plasmodia resistance, mefloquine is still used for both treatment and prophylaxis. Other medications used for prophylaxis (and treatment in some cases) include: quinacrine, chloroquine, primaquine, doxycyline and Malarone (atovaquone/proguanil). Prophylactic drugs are primarily manufactured for, and used by, people planning short visits to malaria endemic areas such as tourists, business travelers, or soldiers.

In the 1950s and 1960s, draining or treating mosquito breeding grounds and spraying insecticides to kill mosquitoes largely eliminated malaria from Europe, North America, and Australia. Vector control temporarily decreased malaria transmission in parts of Africa, but sustaining the progress proved to be challenging and expensive.

In addition to the logistical challenges of massive mosquito eradication campaigns, vector control can be hampered by mosquitos' ability to develop resistance quickly. Indoor residual spraying (IRS) of insecticides is a technique found in many parts of the world. Although several insecticides exist, dichloro-diphenyl-trichloroethane (DDT), an insect neurotoxin, is the most cost effective and was the insecticide of choice in the 1950s and 1960s. The WHO currently recommends 12 different insecticides for IRS, including DDT. However, due to highly debated concerns about the risk of environmental contamination and human consumption, DDT is banned in many parts of the world. Many countries in sub-Saharan Africa are agricultural economies, but the EU has issued statements that any agricultural products found with traces of DDT can be rejected from lucrative international markets. This not only poses economic risk to sub-Saharan Africa, but it also reignites the debate about the safety of DDT. Additionally, as with many vector control programs, there is a chance that by killing all mosquitoes that land on walls in houses, the mosquito population will adapt such that it is no longer vulnerable to IRS.

Mosquito bed nets have been an effective means for malaria prevention for many centuries. Malaria transmission can be greatly reduced with a physical barrier between mosquitos and their target blood meal. Because Anopheles mosquitoes largely feed at night, ensuring that people sleep under bed nets is a highly effective strategy for reducing malaria transmission. Nets currently in use present more than just a barrier and are often treated with insecticide; insecticides either coat the net or are slowly released through the net fiber. Initially, ITNs had to be retreated every six months by soaking the nets in an insecticide solution, however long-lasting insecticidal nets are now the preferred method and last 3–5 years. Most nets in the retail sector cost USD5–6. However, in the public sector or when distributed through campaigns, they are highly subsidized or distributed for free. ITNs not only protect those who sleep under them, but can also protect the community by killing and deterring mosquitoes that come into contact with the insecticides. However, ensuring effective net distribution, utilization, and replacement are significant obstacles to malaria control and elimination programs.

Treatment can also be used as a form of prevention to break the human-mosquito-human transmission cycle. Widespread education and risk reduction are also essential components of all the current strategies.

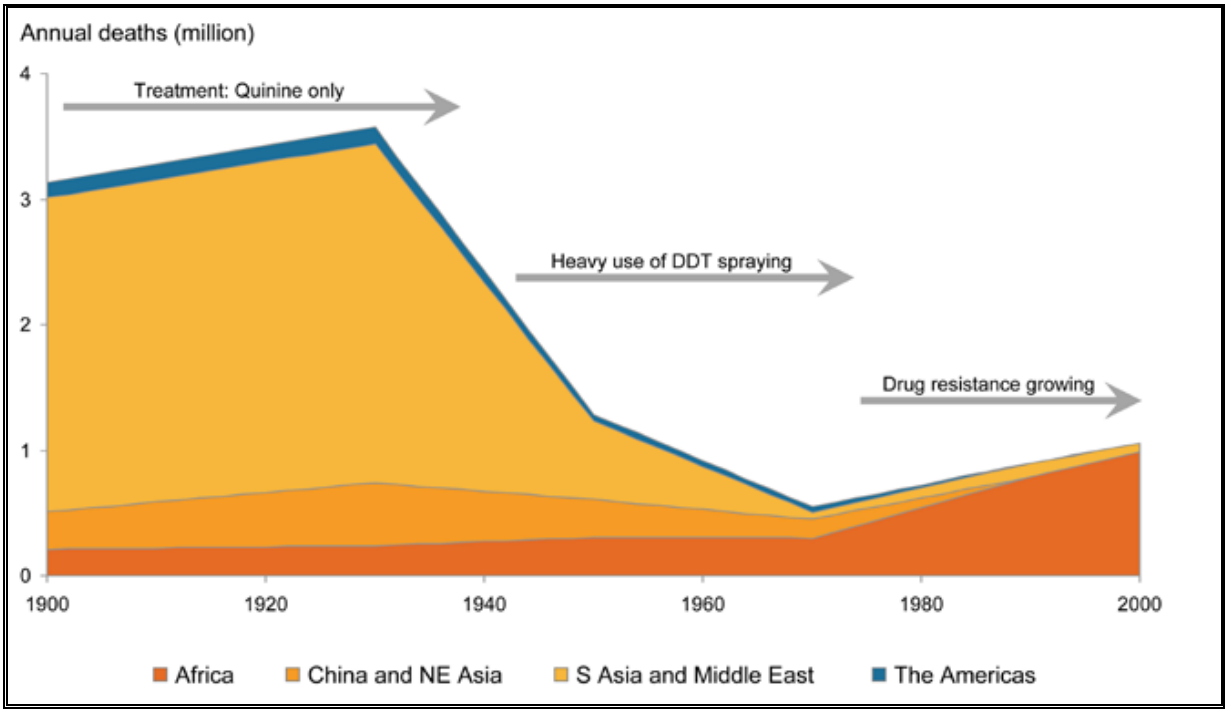
Further Reading on Malaria

1. The World Malaria Report, 2011. World Health Organization.
www.who.int/malaria/world_malaria_report_2011/en/
Comprehensive report detailing current data, policies, and strategies, including 99 country reports.

2. Vilaga, Jennifer. "Net Profit." Fast Company, Issue 92. March 2005.
Article touches on the complexity of developing and distributing bed nets as part of a public-private partnership.

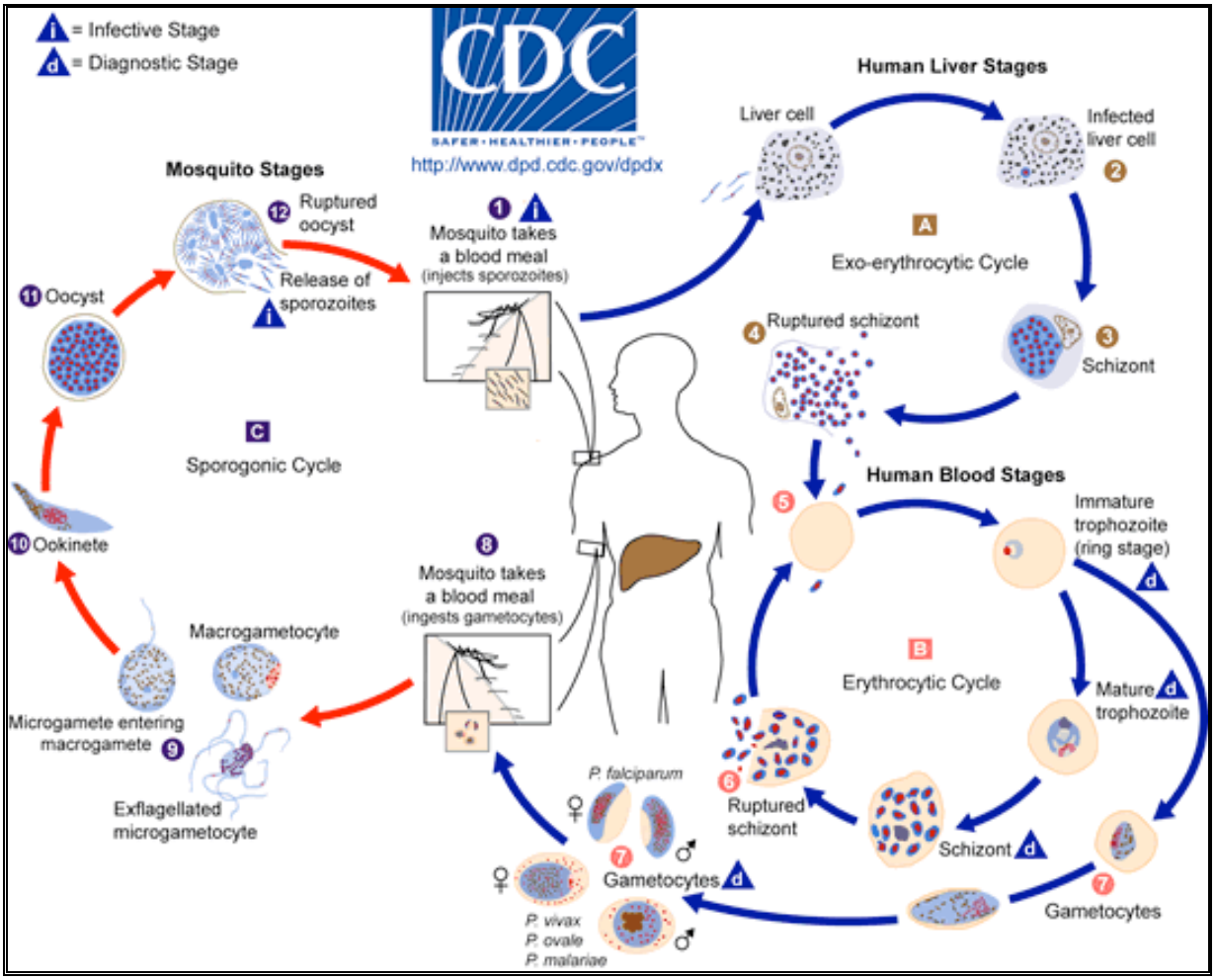
3. Malaria World or GHDonline.org
Online platforms that provide insight to the latest news and topics in malaria control and prevention. Malaria World provides scientific and other published materials while GHDonline is an active, member-driven professional virtual community.

Exhibit 5 *History of Malaria Mortality*



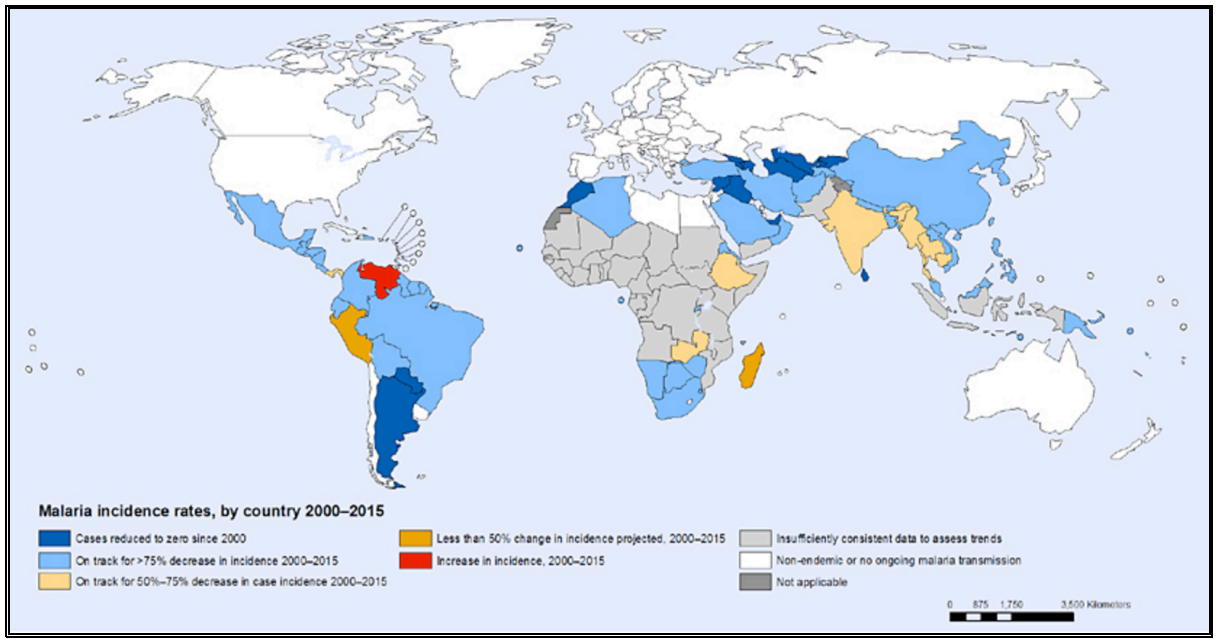
Source: Global Malaria Action Plan, RBM 2008. 29

Exhibit 6 Plasmodium Falciparum *Life Cycle*



Source: US Centers for Disease Control and Prevention. Malaria Biology. [accessed 12/4/2012] http://www.cdc.gov/malaria/about/biology/

Exhibit 7 Projected Changes in Malaria Rates by Country, 2000–2005



Source: WHO Malaria Map, 2015.

Tuberculosis

Global Epidemiology of Tuberculosis

Despite its presence for thousands of years and the presence of a known treatment, the global burden of tuberculosis (TB) is huge. More than 2 billion people (about one-third of the world population) are estimated to be infected with TB.[34] Global incidence rates of active TB peaked at 143 cases per 100,000 population in 2002. In 2014, an estimated 9.6 million new patients (equivalent to 133 cases per 100,000 population) developed active TB, and there were an estimated 1.5 million TB deaths, including the 390,000 additional deaths among those co-infected with HIV.[35] Of the patients with TB in 2015, it was estimated that 480,000 had multi-drug resistant TB (MDR-TB), a form of tuberculosis that does not respond to first-line anti-TB drugs.[35] While the notified or reported TB case numbers are significantly lower than estimates, 105 countries reported at least one case of Extensively drug-resistant TB (XDR-TB) by 2015, up from 58 in 2010. XDR-TB is a form of MDR-TB that is resistant to first-line anti-TB drugs and one or more second-line anti-TB drug.[36] HIV-positive individuals accounted for 12% of new TB cases that year.[35] The HIV/AIDS epidemic largely fueled the TB epidemic as immune-suppressed HIV patients more easily contracted, and subsequently spread, active TB infections. HIV-positive individuals, depending on the state of the epidemic, are 20 to 37 times more likely to contract TB than HIV negative individuals.[37]

The burden of TB varies dramatically around the globe (see **Exhibit 8** for map of burden). However, in 2015 there were 22 high-burden countries that contributed to 80% of all TB cases (see **Exhibit 9** for list of high-burden countries).[38] Sub-Saharan Africa, India, China, and the islands of Southeast Asia and Micronesia have some of the highest rates (100 per 100,000 or higher). Central and South America, Eastern Europe, and Northern Africa generally have intermediate rates (26 to 100 TB cases per 100,000). The US, Western Europe, Canada, Japan, and Australia have low rates (fewer than 25 cases per 100,000 inhabitants).

Tuberculosis Pathogenesis and Transmission

It is possible to be infected with TB and not show symptoms for many years. Known as latent TB, infected individuals do not feel sick nor can they spread the infection to others. Only 5%-10% of latent TB infections will become active, and half of those cases will occur within the first two years of exposure to the bacteria. In contrast, patients who present TB symptoms have active TB, or TB disease.[39] Patients with compromised immune systems, such as those with HIV, are more likely to develop active TB than others.[40] Patients whose active TB has spread through the lungs to other parts of the body through the blood or lymph system have disseminated TB. Although treatable, disseminated TB can cause permanent damage.[41]

Every person with untreated, active disease infects approximately 10 to 15 people per year. The bacilli travel through the air in microscopic droplets released by coughing, spitting, talking, singing, or sneezing. Droplets can remain airborne for prolonged periods of time with normal air currents. Close living quarters and repeated exposure increase the risk of transmission among family members of patients. Health care workers in facilities seeing patients before diagnosis and treatment, especially those in high prevalence communities, also have a recognized risk of nosociomial infection—infection at the health care facility.

Other risk factors identified include injection drug, tobacco, and alcohol use; poor nutritional status such as being underweight, having a vitamin D deficiency, or low iron; having systemic diseases such as a malignancy, diabetes, renal disease, or celiac disease; and being immunocompromised due to such

conditions as HIV, transplants, or daily doses of glucocorticoids such as prednisone. In the developing world, TB is most common among young adults and men because of their increased exposure in the community.

Clinical Manifestations of Tuberculosis

Active disease commonly produces cough with phlegm, fever, night sweats, fatigue, weight loss, and pain in the back, chest or kidneys. Other complications include hemoptysis (coughing up blood), pneumothorax (collapsed lung), bronchiectasis (widening of the airways which causes them to lose some function and can lead to infection and respiratory failure), and extensive pulmonary destruction (including pulmonary gangrene). A person with active, untreated disease may live up to five or ten years, and spontaneous remissions sometimes occur.

TB is much more difficult to diagnose in children as it does not present itself with obvious symptoms, in comparison to adult cases. Even when a sputum sample is able to be collected, a low bacteria count can result in a negative smear. Young children are at a higher rate of contracting extra pulmonary, or disseminated TB. Common symptoms of active TB in children include a chronic cough, fever, and weight loss.[42]

Tuberculosis Diagnosis

Epidemiologic evidence (exposure to an infectious individual or travel in a high-prevalence zone), clinical evidence (productive cough for over two weeks, fever, weight loss), or radiographic evidence (characteristic signs on an x-ray) suggest that a patient should be evaluated for active TB.

While chest radiograph (x-ray) cannot distinguish active pulmonary TB from latent (inactive) disease, it may be useful in the context of other clinical and epidemiologic information. Radiographies can be used to look for "pockets" of infection or to identify potential areas for surgical intervention with severe cases of TB.

For those at risk of TB but with no clinical signs of active disease, a tuberculin skin test can reveal previous exposure to TB and increased risk for future development of disease. The skin test involves the injection of tuberculin material (purified protein derivative [PPD] is used in North America) just under the skin layer, which stimulates a delayed hypersensitivity response and causes swelling within 48 to 72 hours if previous exposure to mycobacterial agents (including exposure to the Bacille Calmette-Guérin [BCG] TB vaccine) is present. The skin test cannot distinguish between active and latent TB infection.

Those suspected of having active pulmonary infection should have at least three sputum specimens, including one from the early morning, tested using acid-fast bacillus smears (AFB). Sputum is most easily obtained by coughing, though it may be induced by inhalation of irritants or retrieved by bronchoscopy. A sputum AFB smear involves staining for acid-fast bacteria on a slide under a microscope. Results from acid-fast smear microscopy should be available within 24 hours, making sputum smear testing the fastest and most inexpensive diagnostic tool for TB.

It is possible to have active TB and a negative sputum smear result, however. Culturing a sputum specimen, allowing it to grow for an allotted amount of time, provides a much more sensitive diagnosis. While at least 5000 to 10,000 bacilli per mililiter are needed to detect bacteria in sputum AFB smears, only 10 to 100 organisms are needed for a positive sputum culture. Culture allows for diagnosis of TB in patients with a lower mycobacterial load, which is more common in HIV. Sputum culture is positive in 85% to 90% of active pulmonary TB cases, however AFB smears are only positive in 60% of active TB cases.[43]

Traditional culture methods grow bacteria on solid media such as Lowenstein-Jensen and Ogawa. Solid media require less technology, but growth on solid media takes much longer than it takes on liquid media. The diagnosis of MDR-TB requires a specific type of culture, drug susceptibility testing (DST), in which prepared cultures are grown on media treated with various treatment compounds. If the cultures grow despite the presence of an anti-TB drug, there is resistance present. Drug susceptibility testing requires more skilled laboratory personnel and equipment to prepare and maintain the cultures over a longer period of time. Testing for first-line drug susceptibilities usually requires at least three weeks, and second-line drug testing can take four to six weeks at a minimum.

In 2010, the WHO endorsed the use of a new rapid testing and rifampicin resistance testing machine called the Xpert MTB/RIF. In less than two hours this machine can detect TB and see if the patient is resistant to rifampicin, which is the recommended drug to treat TB. In August of 2012, the public sector in 145 high-burden developing countries could purchase Xpert test cartridges for USD 9.98.[44]

By 2015, chest computed tomography, histopathological examination of biopsy samples, and new molecular diagnostic tests were available as faster and better TB diagnostic tools, especially for those patients whose pulmonary TB presented as smear-negative.[45] Improved DST methods have also been developed in order to address the prolonged wait time between testing and diagnosis, with the aim of initiating therapy as quickly as possible for patients.

After an original diagnosis, positive pulmonary TB patients should have their sputum samples tested at least monthly until at least two sequential, monthly samples are culture-negative, to ensure effective therapy. If a patient remains culture-positive for three months after initiating therapy or becomes culture-positive after being culture-negative, drug susceptibility testing should be repeated as this is a common sign of MDR-TB.

Tuberculosis Treatment

Treatment of pan susceptible (not resistant) TB involves taking four drugs for two months (izonaizid [INH], rifampin [RIF], pyrazinamide [PZA], and ethambutol [EMB]) followed by four months with just two drugs (INH and RIF). (See Cases in Global Health Delivery *Concept Note: TB Policy and Treatment* for more information.) Taking four drugs for significant amounts of time helps prevent the bacilli that spontaneously develop resistance to one drug from proliferating, which is important given TB bacteria are slow-growing.

MDR-TB treatment requires a much longer (up to two years), more expensive, complex, and toxic drug regimen. While individualized regimens designed to address each patient's resistance patterns according to drug susceptibility testing are ideal, such specialized treatment is not always possible. In this case (or while awaiting drug susceptibility results), patients can take an empirical treatment regimen based on expert advice or local resistance patterns. MDR-TB regimens usually contain at least five drugs from various classes of drugs including one injectable drug.

Latent tuberculosis can be treated to reduce the risk of developing active disease. For individuals without exposure to MDR-TB, ideal treatment involves INH daily for nine months, though there are several alternative regimens that can be used.

Tuberculosis Prevention

Reducing risk of transmission of TB, involves early identification of disease, isolation of infected patients, and effective treatment. Hospital and clinic policies to reduce the risk of exposing uninfected people to people with active TB are a key part of prevention. Engineering controls, including ventilation,

controlling airflow patterns, and using air filtration systems or ultraviolet irradiation, also reduce infectious droplets in the air. Masks can provide a barrier for protection as well, particularly when worn by coughing patients in waiting areas of clinics and hospitals.

The BCG vaccination is used for protection against TB, primarily in high-prevalence countries. It is prepared from an attenuated (weakened), live strain of Mycobacterium bovis. Though it does not affect the risk for TB infection, a BCG decreases the risk for developing disseminated TB. The vaccine is most effective in children.

TB treatment is, in itself, also a highly effective method of TB prevention due to the bacteria's contagious nature. Treating and curing TB among infected populations reduces the likelihood of bacterial transmission to other individuals. To this end, those who are in contact with patients presenting active TB should be screened and treated, if necessary.

Further Reading on Tuberculosis

1. Tuberculosis Coalition for Technical Assistance. *International Standards for Tuberculosis Care.* The Hague: The US Centers for Disease Control, American Thoracic Society, International Union Against Tuberculosis and Lung Disease, KNCV Tuberculosis Foundation, USAID, World Health Organization; 2009.

   http://www.who.int/tb/ISTC_Report_2ndEd_Nov2009.pdf

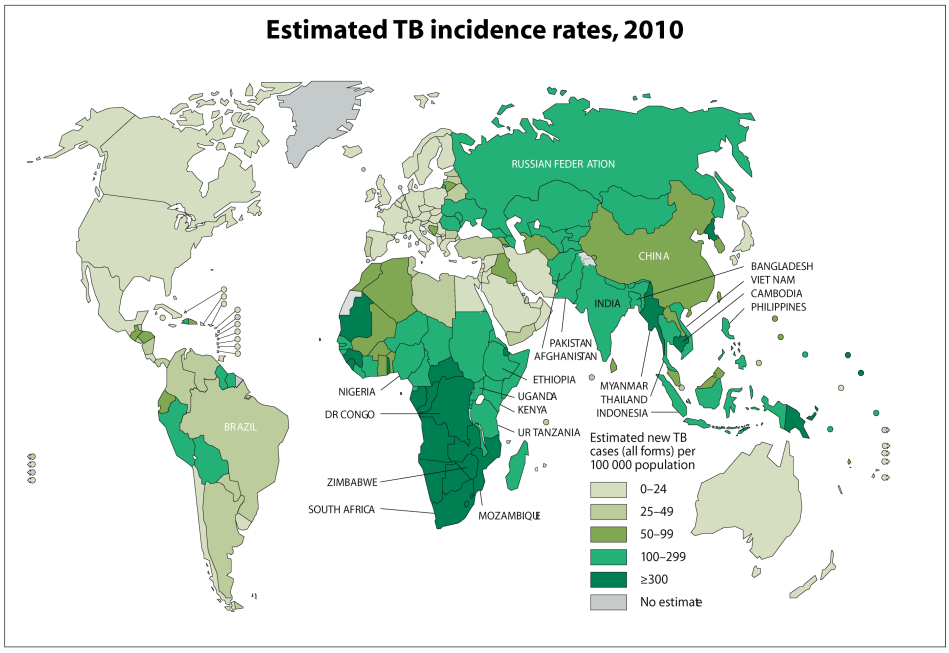
   Technical document outlining the fundamentals in TB clinical care and control measures and includes standards for diagnosis, treatment, addressing HIV infection and other co-morbidities, and public health.

2. Keshavjee S, Seung K. *Stemming the tide of multidrug-resistant tuberculosis: major barriers to addressing the growing epidemic.* Boston: Harvard Medical School, Partners in Health, François-Xavier Bagnoud Center for Health and Human Rights; 2008.

   http://www.ncbi.nlm.nih.gov/books/NBK45010/

   White paper examining complex issues surrounding the disease such as diagnosis, drug supply, and treatment delivery.

Exhibit 8 *Estimated TB Incidence Rates, 2010*



Source: World Health Organization, Global Tuberculosis Control Report 2011. 2011, WHO: Geneva, Switzerland.

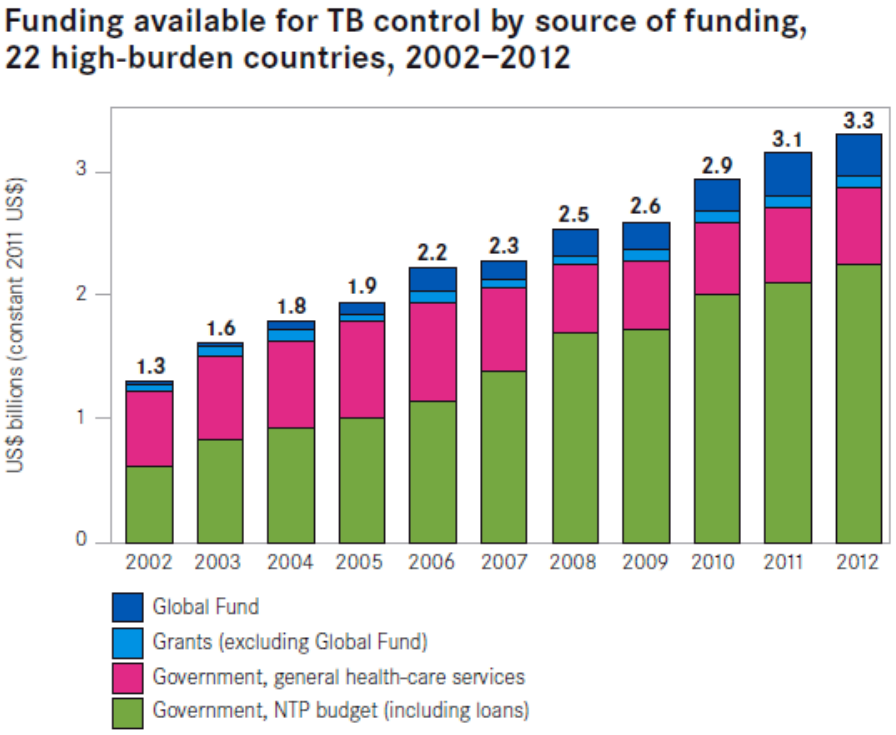
Exhibit 9 *The 22 High-burden TB Countries*

Estimated epidemiological burden of TB, 2012. Numbers in thousands.[a]

		MORTALITY[b]			HIV-POSITIVE TB MORTALITY			PREVALENCE			INCIDENCE			HIV-POSITIVE INCIDENT TB CASES		
	POPULATION	BEST[c]	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH
Afghanistan	29 825	11	4.6	20	< 0.1	< 0.1	0.3	110	54	180	56	47	67	0.3	0.2	0.5
Bangladesh[d]	154 695	70	29	130	< 0.1	< 0.1	0.1	670	340	1 100	350	290	410	0.2	0.2	0.3
Brazil	198 656	4.9	4.6	5.2	2.5	2.2	3	120	51	210	92	76	110	16	13	19
Cambodia	14 865	9.3	4.3	16	0.6	0.4	0.7	110	96	130	61	52	70	2.7	2.3	3.1
China	1 377 065	44	43	46	1.2	0.9	1.5	1 400	1 200	1 600	1 000	880	1 100	7.3	6.4	8.2
DR Congo	65 705	36	16	64	6.3	5.5	8.1	380	200	620	210	190	250	16	14	19
Ethiopia	91 729	16	12	21	5.6	4.6	7.3	210	170	250	230	170	290	23	17	30
India[e]	1 236 687	270	170	390	42	37	48	2 800	1 900	3 900	2 200	2 000	2 400	130	120	140
Indonesia	246 864	67	30	120	2.1	1.8	3	730	350	1 200	460	380	540	7.5	5.6	9.7
Kenya	43 178	9.5	5.4	15	7.7	6.6	8.9	130	71	210	120	110	120	45	44	47
Mozambique	25 203	13	1	41	45	35	53	140	28	340	140	96	190	83	58	110
Myanmar	52 797	25	12	44	4.6	3.8	5.3	260	200	320	200	170	230	19	16	21
Nigeria	168 834	27	1.6	86	19	11	25	270	43	710	180	85	310	46	21	80
Pakistan	179 160	62	27	110	1.2	0.8	1.3	670	320	1 100	410	340	490	3.8	3.1	4.6
Philippines	96 707	23	22	25	0.1	< 0.1	0.1	450	390	500	260	210	310	0.5	0.4	0.6
Russian Federation	143 170	19	18	20	1.8	1.5	2.2	170	73	320	130	110	150	9.3	7.9	11
South Africa	52 386	31	3.7	86	88	75	100	450	160	880	530	430	630	330	270	390
Thailand	66 785	9.2	3.8	17	2.2	1.9	2.8	110	47	190	80	66	95	12	10	14
Uganda	36 346	4.7	0.8	12	9.2	8	12	64	24	120	65	53	79	35	28	42
UR Tanzania	47 783	6.1	3.2	9.9	7	5.8	8	84	45	140	79	74	84	32	30	34
Viet Nam	90 796	18	12	25	2.1	1.8	2.7	200	78	370	130	99	170	9.3	6.9	12
Zimbabwe	13 724	4.6	0.2	16	18	15	20	59	13	140	77	60	97	55	42	69
High-burden countries	**4 432 959**	**780**	**630**	**940**	**270**	**250**	**280**	**9 600**	**8 200**	**11 000**	**7 000**	**6 700**	**7 400**	**880**	**810**	**960**
AFR	892 529	230	160	310	250	230	270	2 700	2 100	3 300	2 300	2 100	2 500	830	760	910
AMR	961 103	19	16	21	6.4	5.6	7.2	390	300	490	280	260	300	31	28	34
EMR	616 591	100	63	150	4.2	3.8	4.7	1 100	730	1 600	670	590	750	11	10	12
EUR	904 540	36	35	36	3.9	3.4	4.4	510	380	650	360	340	390	19	17	21
SEAR	1 833 359	450	330	590	51	46	56	4 800	3 700	6 100	3 400	3 200	3 700	170	160	180
WPR	1 845 562	110	96	120	4.8	4.2	5.4	2 400	2 100	2 600	1 600	1 500	1 800	24	21	27
Global	**7 053 684**	**940**	**790**	**1 100**	**320**	**300**	**340**	**12 000**	**11 000**	**13 000**	**8 600**	**8 300**	**9 000**	**1 100**	**1 000**	**1 200**

Source: World Health Organization, Global Tuberculosis Control Report 2012, WHO: Geneva, Switzerland.

Exhibit 10 *Funding for TB Control in the High-burden Countries, 2002 - 2011*



Source: World Health Organization, Global Tuberculosis Control Report 2011. 2011, WHO: Geneva, Switzerland.

References

1. UNAIDS. Fact sheet 2016 | UNAIDS. UNAIDS. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Published 2016. Accessed August 24, 2016.
2. UNAIDS and WHO. *Global Report 2013: UNAIDS Report on the Global AIDS Epidemic 2013*.; 2013. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf. Accessed May 29, 2014.
3. Global Estimates of People Living with HIV/AIDS, 1990-2014. http://kff.org/global-health-policy/slide/global-estimates-of-people-living-with-hivaids/. Published July 14, 2015. Accessed August 24, 2016.
4. Fauci AS, Desrosiers R. Pathogenesis of HIV and SIV - Retroviruses - NCBI Bookshelf. http://www.ncbi.nlm.nih.gov/books/NBK19359/. Accessed July 10, 2012.
5. AIDS Information, Education, Action, Awareness | CD4 (T-CELL) TESTS. http://www.aids.org/topics/aids-factsheets/aids-background-information/what-is-aids/hiv-testing/cd4-t-cell-tests/. Accessed May 29, 2014.
6. Fauci AS, Braunwald E, Kasper DL, et al. *Harrison's Principles of Internal Medicine, 17th Edition (Harrison's Principles of Internal Medicine*. 17th ed. McGraw-Hill Professional; 2008.
7. Murray PR, Rosenthal KS, Pfaller MA. *Medical Microbiology, 6th Ed.* 6th ed. Mosby; 2008.
8. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med*. 1996;125(4):257-264.
9. Greenwald J, Burstein GR, Pincus J, Branson B. A Rapid Review of Rapid HIV Antibody Tests. In: *Clinical Infectious Disease Reports 2006*. Vol 8. Current Science Inc.; :125-131. http://www.cdc.gov/hiv/topics/testing/resources/journal_article/pdf/rapid_review.pdf.
10. Open Society Institute. *Mandatory Premarital HIV Testing*. New York: Open Society Foundations; 2010:1-12. https://www.opensocietyfoundations.org/sites/default/files/mandatory-premarital-hiv-testing-20100513.pdf. Accessed August 24, 2016.
11. UNAIDS and WHO. UNAIDS/WHO Policy Statement on HIV Testing. June 2004. http://www.who.int/ethics/topics/hivtestingpolicy_who_unaids_en_2004.pdf?ua=1. Accessed May 29, 2014.
12. CDC Global AIDS Program. Types of Counseling and Testing. http://www.hiv.gov.gy/edocs/cdc_tl_types_ct.pdf. Accessed July 10, 2012.
13. *Consolidated Guidlines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Summary of Key Features and Recommendations*. World Health Organization, HIV/AIDS Programme; 2013. http://apps.who.int/iris/bitstream/10665/85322/1/WHO_HIV_2013.7_eng.pdf?ua=1. Accessed May 29, 2014.
14. Department of Health and Human Services. *Guidlines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Office of AIDS Research Advisory Council; 2014. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed May 29, 2014.
15. World Health Organization. *Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*. Geneva: World Health Organization; 2015:1-68. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1.

16. Katzung B, Masters S, Trevor A. *Basic and Clinical Pharmacology, 11th Edition*. 11th ed. McGraw-Hill Medical; 2009.

17. WHO/GPRM - Global Price Reporting Mechanism. *Transaction Prices for Antiretroviral Medicines and HIV Diagnostics from 2008 to March 2010: A Summary Report from the Global Price Reporting Mechanism*.; 2010.

18. First generic HIV drugs could save US at least $920 million a year. http://www.aidsmap.com/First-generic-HIV-drugs-could-save-US-at-least-920-million-a-year/page/2456184. Accessed May 29, 2014.

19. *Untangling the Web of Antiretroviral Price Reductions*. Medecins San Frontieres; 2013. http://d2pd3b5abq75bb.cloudfront.net/2013/09/11/10/25/44/896/MSF_Access_UTW_16th_Edition_2013.pdf. Accessed May 29, 2014.

20. Dutta A, Barker C, Kallarakal A. The HIV Treatment Gap: Estimates of the Financial Resources Needed versus Available for Scale-Up of Antiretroviral Therapy in 97 Countries from 2015 to 2020. *PLoS Med*. 2015;12(11). doi:10.1371/journal.pmed.1001907.

21. Hayes R, Kapiga S, Padian N, McCormack S, Wasserheit J. HIV prevention research: taking stock and the way forward. *AIDS*. 2010;24 Suppl 4:S81-92. doi:10.1097/01.aids.0000390710.04255.2b.

22. Padian NS, McCoy SI, Karim SSA, et al. HIV prevention transformed: the new prevention research agenda. *Lancet*. 2011;378(9787):269-278. doi:10.1016/S0140-6736(11)60877-5.

23. Piot P, Bartos M, Larson H, Zewdie D, Mane P. Coming to terms with complexity: a call to action for HIV prevention. *Lancet*. 2008;372(9641):845-859. doi:10.1016/S0140-6736(08)60888-0.

24. Bertozzi SM, Laga M, Bautista-Arredondo S, Coutinho A. Making HIV prevention programmes work. *The Lancet*. 2008;372(9641):831-844. doi:10.1016/S0140-6736(08)60889-2.

25. Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. *Lancet*. 2008;372(9639):669-684. doi:10.1016/S0140-6736(08)60886-7.

26. Gupta GR, Parkhurst JO, Ogden JA, Aggleton P, Mahal A. Structural approaches to HIV prevention. *Lancet*. 2008;372(9640):764-775. doi:10.1016/S0140-6736(08)60887-9.

27. Goldman L, Ausiello DA. *Cecil Medicine: Expert Consult Premium Edition, 23e*. 23rd ed. Saunders; 2007.

28. World Health Organization. WHO | 10 facts on malaria. World Health Organization. http://www.who.int/features/factfiles/malaria/en/. Accessed August 24, 2016.

29. WHO | Factsheet on the World Malaria Report 2013. WHO. http://www.who.int/malaria/media/world_malaria_report_2013/en/. Accessed May 29, 2014.

30. Centers for Disease Control and Prevention. CDC - Malaria - About Malaria - History - Elimination of Malaria in the United States (1947-1951). Centers for Disease Control and Prevention. https://www.cdc.gov/malaria/about/history/elimination_us.html. Accessed August 24, 2016.

31. World Health Organization. *Global Technical Strategy for Malaria 2016-2030*. Geneva: World Health Organization; 2015:1-29. http://apps.who.int/iris/bitstream/10665/176712/1/9789241564991_eng.pdf?ua=1. Accessed August 24, 2016.

32. WHO | Number of malaria cases. WHO. http://www.who.int/gho/malaria/epidemic/cases/en/index1.html. Accessed May 30, 2014.

33. World Health Organization. WHO | Questions and answers on RTS,S/ASO1 malaria vaccine. World Health Organization. http://www.who.int/immunization/research/development/malaria_vaccine_qa/en/. Accessed August 24, 2016.

34. Kim JY, Shakow A, Castro A, Vande C, Farmer P. The burden of tuberculosis: Population health burden. World Health Organization. http://www.who.int/trade/distance_learning/gpgh/gpgh3/en/index4.html. Accessed August 24, 2016.

35. World Health Organization. *Global Tuberculosis Report 2015*. Geneva: World Health Organization; 2015:1-155. http://www.who.int/tb/publications/global_report/gtbr15_main_text.pdf?ua=1. Accessed August 24, 2016.

36. Centers for Disease Control and Prevention. CDC | TB | Fact Sheets | Multidrug-Resistant Tuberculosis (MDR TB). Centers for Disease Control and Prevention. http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm. Published May 11, 2016. Accessed August 24, 2016.

37. Getahun H, Gunneberg C, Granich R, Nunn P. HIV Infection–Associated Tuberculosis: The Epidemiology and the Response. *Clinical Infectious Diseases*. 2010;50(s3):S201-S207. doi:10.1086/651492.

38. *Global Tuberculosis Report 2012*. World Health Organization; 2013. http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf. Accessed May 30, 2014.

39. Centers for Disease Control and Prevention. Latent TB Infection vs. TB Disease. Center for Disease Control and Prevention. http://www.cdc.gov/tb/publications/factsheets/general/ltbiandactivetb.htm. Accessed August 24, 2016.

40. The Difference Between Latent TB Infection and Active TB Disease. October 2008. http://www.ndhealth.gov/disease/tb/Documents/Fact%20Sheets/LTBIandActiveTB.pdf. Accessed June 6, 2014.

41. New York Times. Disseminated Tuberculosis - Symptoms, Diagnosis, Treatment of Disseminated Tuberculosis. NY Times Health Information. http://www.nytimes.com/health/guides/disease/disseminated-tuberculosis/overview.html. Published November 10, 2012. Accessed August 24, 2016.

42. TB & Children: Getting, diagnosing & preventing TB. TB Facts.org. http://www.tbfacts.org/tb-children/. Published 2016. Accessed August 24, 2016.

43. Tang Y-W, Meng S, Li H, Stratton CW, Koyamatsu T, Zheng X. PCR Enhances Acid-Fast Bacillus Stain-Based Rapid Detection of Mycobacterium tuberculosis. *J Clin Microbiol*. 2004;42(4):1849-1850. doi:10.1128/JCM.42.4.1849-1850.2004.

44. Tuberculosis Diagnostics Xpert MTB/RIF Test: WHO Recommendations. February 2013. http://who.int/tb/features_archive/factsheet_xpert.pdf. Accessed June 6, 2014.

45. Ryu YJ. Diagnosis of Pulmonary Tuberculosis: Recent Advances and Diagnostic Algorithms. *Tuberc Respir Dis (Seoul)*. 2015;78(2):64-71. doi:10.4046/trd.2015.78.2.64.