Chapter 4

World Health and Global Health Challenges

In Chapter 3 we examined measures which are used to assess the health of populations and to guide efforts to improve health throughout the world. In this chapter, we examine the leading causes of death in the developed and developing worlds. Before reading this chapter, you should visit A Tale of Two Girls on the World Health Organization website (http://www.who.int/features/2003/11/en/).[1] This brief presentation contrasts the lives of two baby girls, one born in Japan and the other in Sierra Leone, where the average life expectancy for women differs by 50 years.

Overview

We have seen that health data differ dramatically between developed countries and developing countries. In developing countries, infectious diseases, such as HIV/AIDS, tuberculosis, malaria and measles, are an important cause of mortality. In contrast, mortality in developed countries is more commonly associated with chronic diseases, such as cancer and heart disease. Figure 4.1 shows the percentage of deaths caused by infectious diseases, non-infectious diseases and injuries in developed and developing countries. [2] In this figure, Group 1 causes of mortality include infectious diseases, maternal and perinatal conditions, and nutritional deficiencies. Group 2 causes of mortality include non-communicable diseases such as cardiovascular disease, cancer, and mental disorders. Group 3 causes include both intentional injuries such as suicide, interpersonal violence and war as well as unintentional injuries such as motor vehicle accidents and accidental drowning. Throughout the world, Group 2 diseases account for most deaths; in developed countries they are responsible for more than 85% of deaths, while in developing countries Group 2 diseases account for just over half of all deaths. In contrast, Group 1 conditions account for only 6% of deaths in developed coun-
World Health and Global Health Challenges

**Figure 4.1**: Causes of death throughout the world:

**Group 1**: Communicable diseases, maternal/perinatal conditions, nutritional deficiencies;

**Group 2**: Non-communicable diseases (cardiovascular, cancer, mental disorders);

**Group 3**: Injuries.

Note that Group 1 causes account for a much larger portion of deaths in developing countries.[2]

Within a population, the mortality rate depends strongly on age. In general, mortality rate decreases from infancy to childhood, and then increases with increasing age throughout adulthood. Mortality rates in developing countries are higher than those in developed countries for all age groups (Figure 4.2); these differences are greatest for infants, children and young adults—the mortality rate for children under 5 years of age is more than 6 times higher in developing countries than in developed countries. [2]

The leading causes of mortality within a population also depend strongly on age. The incidence and mortality of cancer increase with increasing age, accounting for a large fraction of adult death. The infectious diseases pertussis, poliomyelitis, diphtheria, measles and tetanus are known as childhood cluster diseases and cause many deaths in children in developing countries. [2] In order to devise the most effective health interventions for different populations, it is important to understand how causes of morbidity and mortality vary with age and geographic region. In 1993, the Harvard School of Public Health began a collaboration with The World Bank and the WHO called the Global Burden of Disease Project to estimate the mortality and morbidity of diseases throughout the world. This study generated the most comprehensive and consistent set of estimates of mortality and morbidity by age, sex and region to quantify the burden of disease throughout the world.[3] The World Health Or-
Tessa and I were planning on working on some projects relating to nutrition.

Well, we’ve found a project. And it’s not just any project.

We have been dubbed, by Carrie (one of my favorite doctors here), directors of the initiation and direction of the World Food Programme food distribution at the clinic. It’s no small task; The World Food Programme (WFP) is very picky about who to give out food to, how much food to give out, and how often to give food out. They also want to make sure that every last kilogram of food is accounted for. So, Tessa and I are now in charge of creating a system to determine who is eligible to receive WFP food as well as organizing the quite complicated registration of each participant and then the doling out of food to each participant.

This is all quite tricky, as it seems the doctors and the administrative staff all have their own opinions about how the system should work and who should get food. It’s also complicated because we have to make it so that our WFP registration and distribution does not interfere with the normal going-ons of the clinic.

But everything seems to be going quite well—we have developed a quite meticulous and well-thought-out plan for the program—a triple-check system with three different ledger books to be filled out—which we hope to initiate next Thursday. And, I must say, our plan would never have been such a meticulous and well-thought-out one, if it were not for Tessa’s amazing planning skills and her relentless approach of not stopping until we had carefully looked at the program from every possible angle. Some day, I hope to be half as organized as she is. (Hey, I think it’s already starting to rub off a little. :))

The food that we are giving out is called Corn Soy Blend (CSB) and is pretty much what you would assume it to be—a mix of corn flour and soy flour (in order to get a healthy mix of both carbohydrates and protein), but with the added elements of some fat, vitamins and minerals to make it more of a complete meal.

We will also be working on creating a hand-out for the WFP participants to describe different ways to prepare the CSB to make beverages, porridge, breads, cakes, soups and even cookies. The purpose of this, besides just teaching them how to use this perhaps somewhat foreign food source, is to allow us to show them how they can add certain items (such as a tablespoon of oil or an avocado or some milk) in order to make the meal even more nutritionally complete. This is important to ensure that our young patients have the necessary dietary requirements for normal growth and development.

For now, however, we are mostly concentrating on rolling out the WFP distribution itself. And even though I feel like our plan is pretty much bullet-proof (okay, maybe I’m giving us too much credit), there will definitely be quite a bit of difficulty in getting everyone to agree that our solution is best, and there could be some problems that other members of the staff will bring up that we haven’t thought of yet. We will have to be ready to deal with those problems.

If all goes well, we hope to start training several members of the community to take over for us. It will be good for them because it gives them a job and will be great for us because it ensures that our program will continue after we’re gone and also frees us up to work on new and equally exciting projects.

I sincerely hope that everything goes well. There are so many patients that I’ve seen already that need this food so badly. Malnutrition is extremely common in Swaziland. It is even more common in our clinic as people with HIV/AIDS have increased caloric needs for a number of reasons. For example, the body’s metabolic rate increases in order to fuel the large immune system response to
fight off the infection. This food is also crucial to our patients because many have living situations that are altered by the infection. Many live with their grandmothers (gogos) due to the death of both of their parents as a result of AIDS. These grandmothers often take care of many other children who have been orphaned by AIDS (In clinic the other day, a gogo came in while I was there that was taking care of 11 children.) They have great difficulty in providing food for so many hungry mouths. Also, if the parents are living with HIV/AIDS they are likely to be weakened so much by their disease that they are unable to hold a job and therefore cannot afford to buy enough food for their children.

In terms of keeping patients healthy, making sure they have enough food to meet their needs is just as important, if not more so, than giving them ARVs. In fact, if they are not getting enough food, their immune systems will have a lessened ability to fight the infection, which will allow the virus to spread more quickly and thus hasten the onset of AIDS.

What it boils down to is that most of the patients seen at the Baylor Clinic are in desperate need of food. We need our program to work so that WFP will continue to give us more food to feed these patients.

I'm keeping my fingers crossed.
Table 4.1: Top ten causes of death in developed and developing countries for three age groups. Data from the WHO Global Burden of Disease Study, 2002.

<table>
<thead>
<tr>
<th>Ages 0-4</th>
<th>Developing Countries</th>
<th></th>
<th>Developed Countries</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause of Death</strong></td>
<td><strong># Deaths</strong></td>
<td><strong>% of Total Deaths</strong></td>
<td><strong>Cause of Death</strong></td>
<td><strong># Deaths</strong></td>
</tr>
<tr>
<td>Perinatal Conditions #1</td>
<td>2,378,099</td>
<td>23.2%</td>
<td>Perinatal Conditions #1</td>
<td>83,877</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>1,701,383</td>
<td>16.6%</td>
<td>Congenital anomalies #2</td>
<td>38,169</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>1,597,647</td>
<td>15.6%</td>
<td>Lower respiratory infections</td>
<td>32,872</td>
</tr>
<tr>
<td>Malaria</td>
<td>1,149,195</td>
<td>11.2%</td>
<td>Unintentional injuries #3</td>
<td>15,486</td>
</tr>
<tr>
<td>Measles</td>
<td>535,504</td>
<td>5.2%</td>
<td>Congenital anomalies #4</td>
<td>387,262</td>
</tr>
<tr>
<td>Congenital anomalies #5</td>
<td>387,262</td>
<td>3.8%</td>
<td>Lower respiratory infections</td>
<td>9,603</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>356,500</td>
<td>3.5%</td>
<td>Neuropsychiatric conditions</td>
<td>4,791</td>
</tr>
<tr>
<td>Pertussis</td>
<td>293,543</td>
<td>2.9%</td>
<td>Measles</td>
<td>4,712</td>
</tr>
<tr>
<td>Unintentional injuries #6</td>
<td>273,040</td>
<td>2.7%</td>
<td>Cardiovascular diseases</td>
<td>4,347</td>
</tr>
<tr>
<td>Tetanus</td>
<td>198,236</td>
<td>1.9%</td>
<td>Non-communicable respiratory disease</td>
<td>3,514</td>
</tr>
<tr>
<td>Protein-energy malnutrition</td>
<td>147,607</td>
<td>1.4%</td>
<td>HIV/AIDS</td>
<td>3,218</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>10,247,719</td>
<td></td>
<td>Total Deaths</td>
<td>230,861</td>
</tr>
<tr>
<td>Total Population</td>
<td>536,962,742</td>
<td></td>
<td>Total Population</td>
<td>81,206,312</td>
</tr>
<tr>
<td>Mortality Rate</td>
<td>1.9%</td>
<td></td>
<td>Mortality Rate</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ages 15-44</th>
<th>Developing Countries</th>
<th></th>
<th>Developed Countries</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause of Death</strong></td>
<td><strong># Deaths</strong></td>
<td><strong>% of Total Deaths</strong></td>
<td><strong>Cause of Death</strong></td>
<td><strong># Deaths</strong></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1,826,460</td>
<td>24.2%</td>
<td>Unintentional injuries #7</td>
<td>261,693</td>
</tr>
<tr>
<td>Unintentional injuries #8</td>
<td>1,212,096</td>
<td>16.0%</td>
<td>Cardiovascular diseases #9</td>
<td>172,194</td>
</tr>
<tr>
<td>Cardiovascular diseases #10</td>
<td>596,038</td>
<td>7.9%</td>
<td>Malignant neoplasms #11</td>
<td>129,897</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>591,316</td>
<td>7.8%</td>
<td>Self-inflicted injuries</td>
<td>106,759</td>
</tr>
<tr>
<td>Maternal conditions #12</td>
<td>488,346</td>
<td>6.5%</td>
<td>Ischaemic heart disease (IHD), cerebrovascular disease, other</td>
<td>55,043</td>
</tr>
<tr>
<td>Self-inflicted injuries</td>
<td>375,884</td>
<td>5.0%</td>
<td>Malignant neoplasms #11</td>
<td>449,127</td>
</tr>
<tr>
<td>Violence</td>
<td>330,313</td>
<td>4.4%</td>
<td>Digestive diseases #12</td>
<td>49,202</td>
</tr>
<tr>
<td>Digestive diseases #12</td>
<td>247,284</td>
<td>3.3%</td>
<td>HIV/AIDS</td>
<td>29,686</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>246,949</td>
<td>3.3%</td>
<td>Lower respiratory infections</td>
<td>16,739</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>7,555,885</td>
<td></td>
<td>Total Deaths</td>
<td>996,707</td>
</tr>
<tr>
<td>Total Population</td>
<td>2,312,272,679</td>
<td></td>
<td>Total Population</td>
<td>597,682,683</td>
</tr>
<tr>
<td>Mortality Rate</td>
<td>0.3%</td>
<td></td>
<td>Mortality Rate</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ages 45-59</th>
<th>Developing Countries</th>
<th></th>
<th>Developed Countries</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause of Death</strong></td>
<td><strong># Deaths</strong></td>
<td><strong>% of Total Deaths</strong></td>
<td><strong>Cause of Death</strong></td>
<td><strong># Deaths</strong></td>
</tr>
<tr>
<td>Cardiovascular diseases #10</td>
<td>1593447</td>
<td>27.3%</td>
<td>Cardiovascular diseases #10</td>
<td>569767</td>
</tr>
<tr>
<td>Malignant neoplasms #11</td>
<td>1051947</td>
<td>18.0%</td>
<td>Malignant neoplasms #11</td>
<td>495519</td>
</tr>
<tr>
<td>Unintentional injuries #7</td>
<td>455323</td>
<td>7.8%</td>
<td>Ischaemic heart disease (IHD), cerebrovascular disease, other</td>
<td>163503</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>386869</td>
<td>6.6%</td>
<td>Ischaemic heart disease (IHD), cerebrovascular disease, other</td>
<td>116643</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>362682</td>
<td>6.2%</td>
<td>Ischaemic heart disease (IHD), cerebrovascular disease, other</td>
<td>89668</td>
</tr>
<tr>
<td>Digestive diseases #12</td>
<td>340739</td>
<td>5.8%</td>
<td>Ischaemic heart disease (IHD), cerebrovascular disease, other</td>
<td>49873</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>283883</td>
<td>4.9%</td>
<td>Self-inflicted, violence</td>
<td>33114</td>
</tr>
<tr>
<td>Intentional injuries #13</td>
<td>215023</td>
<td>3.7%</td>
<td>Diabetes mellitus</td>
<td>26317</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>150126</td>
<td>2.6%</td>
<td>Diarrhoeal diseases</td>
<td>569767</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>145994</td>
<td>2.5%</td>
<td>HIV/AIDS</td>
<td>495519</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>5,844,812</td>
<td></td>
<td>Total Deaths</td>
<td>1,692,592</td>
</tr>
<tr>
<td>Total Population</td>
<td>600,316,766</td>
<td></td>
<td>Total Population</td>
<td>254,600,864</td>
</tr>
<tr>
<td>Mortality Rate</td>
<td>1.0%</td>
<td></td>
<td>Mortality Rate</td>
<td>0.7%</td>
</tr>
</tbody>
</table>
ganization now estimates the Global Burden of Disease for the years 2000 and beyond. Data from the Global Burden of Disease study can be used to identify the top 10 causes of mortality (Table 4.1) by age for developed and developing countries.\[2\] In the remainder of this chapter, we will examine the four leading causes of mortality by age group in more detail. We begin with the leading causes of child mortality.

**Leading Causes of Mortality, ages birth-4 years**

More than 10 million children under the age of 5 die every year throughout the world.\[4\] 98% of childhood deaths occur in developing countries—the number of children who die every year in developing countries is more than two times the number of children born each year in the US and Canada combined.\[5\] 90% of childhood deaths occur in just 42 countries, with nearly half occurring in sub-Saharan Africa and nearly one quarter in India.\[4\] Childhood mortality rates have dropped by nearly 50% throughout the world over the last 30 years (Figure 4.3).\[5\] However, progress to further reduce childhood mortality has slowed, and rates of decline have begun to level off, particularly in African countries.

Past efforts to reduce childhood mortality have been most successful for children over the age of 2 months. As we will see in Chapter 8, worldwide childhood immunization cam-

---

**Figure 4.3**: Childhood mortality rates over time for several regions of the world. Used with permission from [5].
Campaigns have reduced childhood mortality substantially; these vaccinations prevent diseases which typically affect older infants and children. Today, more than 40% of deaths to children under 5 occur during the first 28 days of life. This time is called the neonatal period, and more than 4 million babies die each year within their first month of life. The perinatal period refers to the period which extends from 22 weeks of pregnancy to the first 7 days of life. One quarter of deaths to children under 5 occur during childbirth and the first week of life. It has been estimated that 3.3 million babies are stillborn each year; these losses are not included in the estimates of the more than 10 million infants and children who die each year throughout the world.

Tragically, most childhood deaths, both in infancy and childhood, still occur as a result of preventable and treatable causes such as inadequate care during pregnancy, unsanitary childbirth conditions, pneumonia (lower respiratory infection), diarrhea and malaria. The underlying cause of most of these deaths is poverty and the associated malnutrition, crowded and unsanitary living conditions, and lack of access to healthcare (Figure 4.4). Undernutrition and malnutrition contribute to more than half of childhood deaths. Unsafe drinking water and poor sanitation are responsible for nearly 90% of deaths due to diarrheal diseases. In the 42 countries where most childhood deaths occur, many children do not have access to healthcare. For example, 60% of children with pneumonia failed to get the antibiotics they needed, and 70% of children with malaria did not receive treatment.

In this chapter, we will consider the pathophysiology of the four leading causes of mortality for children under the age of 5 in greater detail, along with potential interventions to address these conditions. For children in developing countries, the four leading causes of death are:

1. **Perinatal conditions** (conditions during childbirth and the first 7 days of life),
2. **Lower respiratory infections** (pneumonia),
3. **Diarrheal diseases**, and
4. **Malaria**.

For children in developed countries, the four leading causes of death are:

1. **Perinatal conditions**, 
2. **Congenital anomalies** (birth defects),
3. **Lower respiratory infections**, and
4. **Unintentional injuries**.

---

**Figure 4.4**: Infant mortality rates throughout the world in 2002.
Sad Story: June 13, 2007

Kim Malawi

At St. John’s yesterday on our rounds trying to find children to test, the nurses in the Pediatric Ward brought to our attention a 4-month-old orphan.

The infant lives in a residential orphanage, which is very rare in Malawi. Orphans are usually taken in by a member of their extended family. To be in a residential orphanage means this little girl has nobody left. She was breathing extremely rapidly and with great difficulty. They had her on oxygen.

By the time we saw her, they had already done a rapid test, which came back positive. This indicates that the little girl’s mother was certainly positive (and probably died of HIV) and that the baby was definitely exposed, if not infected. We managed to collect a dry blood spot sample to send to the lab, after a little difficulty. (She was so small and she was hard to put in the right position because of the oxygen connection.)

We’re pretty sure she has PCP pneumonia, which is really, really bad (and really specific to HIV infected individuals) because she hadn’t responded to 2 days of antibiotics. They put her on high-dose cotrimoxazole (the treatment for PCP) and hoped for the best. In this country, that’s the best they can do. That’s the limit of their options treatment-wise. It’s really distressing that they have so few options.

She died overnight.
**Perinatal Conditions:** Pregnancy, childbirth and the seven days after is a particularly dangerous time, both for babies and their mothers. More than 2.5 million children die as a result of perinatal conditions and more than 500,000 women die as a result of complications of pregnancy and childbirth each year.[6] These perinatal mortality statistics probably underestimate the scope of the problem, since the vast majority of these deaths occur in developing countries where rates of vital registration are lowest. Only about one fourth of the world’s births are registered and usually countries with the highest mortality rates have the lowest rates of vital registration.[6]

Most deaths in the first week of life result from inadequate access to healthcare during pregnancy, during childbirth and

**Fetal ultrasound** provides a window to examine gestational development. In developed countries ultrasound is routinely used to identify ectopic pregnancies (where the fertilized egg has implanted in the fallopian tube rather than the uterus), to determine the gestational age of the baby, to confirm the number of babies, to evaluate the baby’s growth and provide early evidence of delays in growth which might require intervention, to study the placenta which provides nourishment to the baby and identify any problems, and to help identify congenital abnormalities.

In an ultrasound imaging procedure, a transducer which emits and receives ultrasonic waves is placed in contact with the mother’s stomach. The transducer contains a quartz crystal called a piezoelectric crystal; when an oscillating electric current is applied to the piezoelectric crystal it changes shape rapidly and emits sound waves. Structures beneath the transducer reflect sound waves back toward the transducer; when these waves hit the crystal, it vibrates, producing an electric current. The time delay between incidence and detection depends on the speed of sound and the distance between the transducer and the reflecting surface. To provide a 2 dimensional image of a plane located in front of the transducer, we record the intensity of reflected sound as a function of time at each point along the transducer. Knowing the speed of sound in tissue, the time-dependent reflectance profile can be converted to yield the depth of reflective structures beneath each point of the transducer. These data can then be processed to yield an image of the structures underneath the transducer. Image resolution is determined by the frequency of the sound waves. Higher frequency waves have shorter wavelength, and thus better spatial resolution; however, higher frequency sound waves don’t penetrate through as much tissue. Generally, fetal ultrasound uses sound waves with a frequency of 3-7.5 MHz.

A new technology, 3D ultrasound, creates volumetric images of the structures beneath the ultrasound transducer; these can be processed to display detailed surface renderings of the fetus. To obtain 3D images, sound waves are sent in at different angles, and the position of objects in the pyramid shaped volume beneath the transducer are calculated based on the reflectance profile.
immediately afterward. As a result, many babies are born with low birth weight, many suffer asphyxia during birth or other birth trauma, and many acquire infections during childbirth; although these complications are frequently fatal, they are easy to prevent.[6]

Proper nutrition during pregnancy and prenatal care can substantially reduce the risk of premature delivery and low birth weight. A delivery attended by a skilled health care worker (midwife, nurse or physician) dramatically reduces the risks of birth asphyxia and birth trauma.[6] Birth asphyxia occurs when the baby does not initiate and sustain normal breathing at birth. Asphyxia can occur in cases when the umbilical cord is wrapped around the baby’s neck, or during a breech delivery. Skilled health care workers are trained to perform neonatal resuscitation to treat birth asphyxia. Birth trauma occurs during obstructed labor, when mechanical forces prevent descent of the baby through the birth canal. If the infant’s head is too large to pass through the bony birth canal (Figure 4.5), or the baby presents in a breech position (feet or bottom first), prolonged labor can result in severe trauma, both to mother and child.

Injuries to the baby can include intracranial hemorrhage, blunt trauma to internal organs such as the liver or spleen, and injury to the spinal cord or peripheral nerves– all of which can be fatal or result in lifelong disability.[6] Birth trauma is more common in developing countries. In these settings, a mother’s growth may be stunted by malnutrition or young mothers may bear children before pelvic growth is complete; in these cases, the infant’s head is frequently too large to pass through the birth canal.

The high perinatal mortality rate in developing countries is strongly related to conditions during childbirth. Most births in
developing countries are not attended by a skilled health care worker; Figure 4.6 shows the correlation between neonatal and maternal mortality rates and the fraction of births which are unattended. [5]

Unfortunately, there are no good screening tests to indicate those women who will need emergency medical care during childbirth and those who will not; thus, it is important that all births are attended by a trained health care worker. The effects of unattended birth extend beyond mortality; infants who survive traumatic birth frequently suffer lifelong disability such as cerebral palsy. [5]

The WHO has developed an important tool for healthcare workers to monitor and track the progress during labor – the partograph. Figure 4.7 shows a portion of a partograph, which graphs the progress of labor and helps anticipate the need for interventions, such as transfer to a hospital, before serious complications occur.[6]

Infection is another important source of mortality during the perinatal period. Infections during the first week of life are usually acquired from exposure to organisms in the maternal genital tract during birth. Infants born prematurely are at higher risk for developing sepsis (blood stream infection) as a result of this exposure. Sepsis is an extremely serious condition; left untreated, the fatality rate of sepsis is over 40%. [6] Because of high perinatal and neonatal mortality rates, in many cultures a child’s birth is not celebrated until he or she has survived the first weeks of life and mother and infant are isolated until this period has passed. This practice can be helpful to the child because isolation reduces exposure to infectious agents in the environment. However, it can also result in delays in seeking medical care needed for infections acquired during childbirth.

Infections of the umbilical cord are a common problem in developing countries where many births occur in the home. The use of non-sterile instruments to cut the umbilical cord can result in infections of the cord; these infections can lead to sepsis. The non-profit organization PATH develops and disseminates new health technologies for low resource settings. To reduce the incidence of infection following childbirth, PATH has supported the development of a delivery kit (Figure 4.8) in Nepal to create a clean childbirth environment for home births. PATH evaluated the impact of a similar clean delivery kit in Tanzania, which resulted in a 13 fold reduction in umbilical cord infection.[8]

**Lower Respiratory Infections:** Almost one million children
die every year as a result of infections of the lower respiratory tract, the most serious of which is pneumonia.[6] Pneumonia is an infection of the lung, and represents a group of infections caused by multiple organisms, including viruses, bacteria and fungi. Pneumonia is a particularly serious infection because it can interfere with the ability to oxygenate blood within the lungs. Ordinarily, when we breathe, oxygenated air is drawn into millions of alveoli, tiny sacs within the lung at the tips of the airways. As shown in Figure 4.9, alveoli are surrounded by capillaries which bring in deoxygenated blood from the right ventricle via the pulmonary artery. Oxygen diffuses across the alveolar membrane where it binds to hemoglobin within red blood cells, and the resulting oxygenated blood is collected in the pulmonary vein, where it travels to the left side of the heart to be pumped throughout the body. In attempting to fight off a lower respiratory infection, the body’s immune system produces fluid and pus that can fill the alveoli, interfering with crucial gas exchange. The symptoms of pneumonia include fever, cough, chest pain, and breathlessness. Treatment with antibiotics has since substantially reduced the mortality due to pneumonia; between 1936 and 1945 mortality due to pneumonia dropped 40% due to the widespread availability of antibiotics.[9] Current risk factors for child mortality due to pneumonia include living in poverty, low parental education level, environmental pollutants such as cigarette smoke or smoke from firewood burning in the house, low birth weight, malnut-

**SARS:**

Severe acute respiratory syndrome (SARS) is a viral respiratory illness that frequently leads to pneumonia. SARS is caused by a previously unrecognized virus called the SARS-associated coronavirus. Coronaviruses are a common cause of mild upper respiratory illnesses; the newly discovered virus causes a much more serious lower respiratory illness. Tests are currently underway to determine whether the SARS-associated coronavirus responds to antiviral drugs.

SARS first emerged in Southern China in November of 2002 and quickly spread to more than 24 countries throughout the world. Between November 2002 and July 2003 more than 8,000 people became ill with SARS and 774 died. By late July, 2003, the WHO declared the global outbreak to be over.
About half of pneumonias are produced by bacterial infection and about half by viral infection. The most common causes of bacterial pneumonia include Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and pertussis. The most common viral causes include respiratory syncytial virus (RSV), influenza virus, parainfluenza virus and measles. SARS is an emerging cause of pneumonia.

Bacterial pneumonias are treated with antibiotics; the choice

---

**Direct immunofluorescence assays:**

To rapidly determine whether the cause of a patient’s pneumonia is viral, a DFA test is used. DFA tests whether cells lining the upper respiratory tract are infected with viruses which cause many lower respiratory infections. If these cells are infected, it is assumed that the pneumonia is viral in origin.

In the test, nasal secretions are collected. A centrifuge is used to concentrate the cells into a small pellet. A drop containing these cells is placed on a slide and the cells are allowed to dry. The cells are immersed in alcohol to permeabilize the cell membranes. A solution containing monoclonal antibodies which bind tightly and specifically to viruses such as influenza, adenovirus, parainfluenza, and RSV is applied to the slide. These antibodies are coupled to a dye which shows bright green fluorescence when illuminated with blue light. The unbound antibody is washed from slide. The slide is examined under a fluorescence microscope. The DFA test will stain all virus infected cells bright apple green.

Results of DFA tests showing cells which stain positive for viral infection. The health care provider examines the cells under a fluorescence microscope. To yield accurate results, at least 20 cells must be examined.

http://www.chemicon.com/Featured/DFA.asp
of antibiotic depends on the causative factor. Viral pneumonias usually resolve on their own without treatment. In severe cases, oxygen can be administered, and antiviral drugs can be used. Therefore, in diagnosing pneumonia it is particularly important to ascertain whether the cause is viral or bacterial.

In developed countries, the presence and location of pneumonia can be confirmed by a chest x-ray (Figure 4.10). A complete blood count is performed to determine whether the infection is likely to be bacterial or viral; as we will see in Chapter 8, the types of immune cells present in blood differ with a bacterial or viral infection. To determine the cause of bacterial pneumonia, sputum produced when the patient coughs is examined under the light microscope to examine bacterial shape and staining characteristics (Figure 4.11).

In some cases, fluid is obtained directly from the lungs using a long, skinny needle which is advanced into the area of lung consolidation under the guidance of computed tomography. This fluid is cultured to determine which bacterial organisms are present and to determine which antibiotics they are responsive to. In addition, blood is obtained and cultured as well. Recently, rapid tests have been developed to identify the cause of viral pneumonias from nasal swabs. These tests are based on technology known as direct immunofluorescence assays (DFA) or enzyme-linked immunosorbent assays (ELISA). Accurate tests have been developed to detect influenza, RSV, parainfluenza, and other viruses.

In developing countries, diagnosis of pneumonia is made primarily on the basis of clinical signs and symptoms and sometimes a chest X-ray. Signs of particular importance include rapid breathing higher than 40 breaths/min in children over 1 year of age, chest indrawing, cyanosis (blue nailbeds), and poor feeding.[10] In mild pneumonia children will exhibit rapid breathing; chest indrawing is also present in moderate pneumonia. These symptoms are present in addition to cyanosis and poor feeding in severe pneumonia. In these settings, maternal education regarding when to seek medical care for pneumonia is particularly important.

Because of the difficulty in discriminating between viral and bacterial pneumonias on the basis of symptoms, the WHO recommends treating all pneumonias in children in developing countries with antibiotics.[10] This conservative approach ensures that all children who need therapy receive it and has proven to reduce mortality associated with pneumonia in developing countries. For example, in one trial in In-

Antibiotic resistance:
Widespread use of antibiotics began during World War II and led to dramatic reductions in the mortality of infectious diseases. Over the last 60 years, some bacteria have evolved resistance to commonly used antibiotics, and today, many physicians and scientists are concerned by the increasing difficulty of treating infections caused by antibiotic resistant strains of bacteria.

If you are admitted to the hospital in the US today, you have a 5-10% chance of acquiring an infection in the hospital. 70% of bacteria that cause hospital acquired infections are resistant to at least one drug. Resistant infections are more difficult and expensive to treat and more than 90,000 people die each year in the US from hospital acquired infections, up from only 13,300 deaths in 1992. Antibiotic resistance is not just a problem in hospitals; recently, multi-drug resistant strains of Staphylococcus aureus have been found in locker rooms.

Antibiotics kill bacteria which are sensitive to the drug; this efficiently selects out those bacteria resistant to the drug. Widespread use of antibiotics has spurred evolutionary changes in bacteria that allow them to resist the action of drugs. For example, penicillin kills bacteria by attaching to their cell walls and destroying a key part of the wall. In response, microbes can alter their cell walls so penicillin can't bind, enabling them to evade the action of the drug. Since bacteria are single celled organisms with a small number of genes, even a single random gene mutation can greatly affect the ability to cause disease. Bacteria divide every few hours, so they can evolve rapidly and a mutation that helps a bacterium to survive drug exposure can quickly become dominant in that population. Complicating the problem, bacteria can trade genes by exchanging plasmids—in effect, one strain of bacteria can develop resistance to one or more drugs and then efficiently transfer this resistance to other strains of bacteria.

The problem of drug resistance is exacerbated when antibiotics are overused or when patients don’t finish taking their prescription for antibiotics—drug resistant microbes can proliferate and be spread. Increases in antibiotic resistance have occurred in parallel with increased antibiotic use. Later in this chapter, we will see the worldwide problems associated with multi-drug resistant tuberculosis. Of particular concern today is the emergence of strains of bacteria resistant even to Vancomycin—the antibiotic of ‘last resort’ for treating resistant infections.
Chapter 4

**Dia:**
Child mortality rate due to pneumonia was 13.5% when untreated, and only 0.8% when treated with antibiotics.[10] However, one danger is that more resistant strains of bacteria will emerge from overuse of antibiotics.

A number of vaccines can prevent infections which cause pneumonia. For example, the Hib vaccine protects against Haemophilus influenzae. The WHO recommends worldwide Hib vaccination; unfortunately, only about 10% of world’s children have been vaccinated.[10] Pneumococcal vaccine protects against Streptococcus pneumoniae. Yearly flu vaccination can protect against pneumonias caused by the influenza virus.

**Diarrheal Diseases:** Diarrhea is a gastrointestinal disorder characterized by frequent watery stools. Diarrhea is caused by bacterial or viral infection of the gastrointestinal tract; the most common causes are infection with the Escherichia coli bacterium, Rotavirus and the Vibrio cholerae bacterium.[16] Diarrheal disease is uncommon in neonates who are often isolated and exclusively breastfed; instead it usually occurs in older infants and children, particularly in situations where safe sources of drinking water are not available.[4] Most children can recover from these gastrointestinal infections; however, diarrhea can lead to loss of substantial body fluids, sodium, chloride and other electrolytes. The symptoms of dehydration include low blood pressure, fainting, sunken eyes and fontanelle (soft spot in baby’s head).[17] This dehydration can quickly lead to death, particularly in babies and malnourished children. Diarrhea leads to 2.2 million deaths per year throughout the world, most in children in developing countries.[18] This is the equivalent of 20 jumbo jets crashing with no survivors every day.

How does diarrhea produce such rapid fluid loss? Ordinarily, during digestion, food is mixed with large quantities of water in the stomach. As the mixture passes through the colon, 98% of this water is reabsorbed along with electrolytes and nutrients, leaving solid waste to be eliminated.[19] Bacterial or viral infection interferes with the processes that control fluid reabsorption, leading to frequent, watery stools. The loss of just 10% of body fluids can prevent maintenance of adequate blood pressure and is enough to cause death.[17]

In the late 1960s, a simple new treatment was developed to prevent the fatal dehydration that frequently accompanies diarrheal disease. This inexpensive treatment, oral rehydration therapy, reduced mortality due to diarrhea from 4.6 million deaths per year to 1.5 million

---

**Cholera:**
Cholera is spread by drinking water or food contaminated with the cholera bacterium, Vibrio cholerae, or by coming in contact with feces of an infected person. Approximately 1 in 20 people infected with the cholera bacterium develop severe diarrhea. Without oral rehydration therapy, death can occur within a few hours. In countries with advanced water treatment and sanitation systems, cholera is rare. However, cholera can spread rapidly in crowded areas with inadequate sewage and water treatment. Today, cholera is prevalent in India, Bangladesh, Pakistan, Indochina, Indonesia, Afghanistan, Africa, South America and Mexico.

Outbreaks of violence or natural disasters often lead to conditions that cause cholera outbreaks. Beginning in April, 1994 the extremist Hutu militia slaughtered nearly one million Tutsis in Rwanda over a period of just 100 days. In July, the Tutsi led Rwandese Patriotic Front overthrew the genocidal Hutu government, resulting in a massive exodus of Hutus to the neighboring countries of Burundi and Zaire. More than 1 million Hutus entered Goma, Zaire over a 3-4 day period in July, 1994. Cholera spread rapidly in the refugee camp and at the height of the epidemic, more than 2,000 people died each day. Over the course of the epidemic, more than 46,000 lives were lost. Ironically, it was the cholera outbreak and loss of life amongst the genocidaires which captured the attention of the western world and aid agencies.

The book We Regret To Inform You Tomorrow We Will Be Killed With Our Families by Philip Gourevitch provides a compelling account of the factors that led to genocide in Rwanda, the events of 1994, and the world’s response.

The WHO publishes a short brochure to guide aid workers who suspect a cholera
Yay! I feel incredibly good about what I just did! I just finished creating a film! I’m so excited with having made it that I just need to write about it (get it all out) right away.

The film is only a short one, I’ll admit, but it fulfills a very important purpose here at the clinic. You see, now that the World Food Program distribution has taken off, Tessa and I spend every morning (from 7:15 to noon) registering patients, filling out record books to keep track of the amount of food we give out, and, of course, handing out food. We also have to somehow get across to the patients, who have never done this before, what exactly is going on. This is rather difficult as we have only a few choice Siswati vocabulary words and our patients’ English varies greatly and is often nonexistent. We have to explain who is eligible to receive food—people on ARVs are, people about to start ARVs aren’t, etc. We have to try to explain to each patient that they must bring the little green card we give them back to the clinic every time they come and that they must also bring a plastic bag in which to carry their food in. And on top of that, as Corn Soy Blend requires a different preparation than the food they are used to, we must explain to them the steps necessary to cook it.

Originally, we planned on just having one of the translators explain this to the patients several times each day. This approach worked quite nicely at first, but on busier days in the clinic, it is sometimes impossible to find a translator, as they are all at work in the exam rooms translating for the doctors. And, on top of that, it seems that more times I ask them, the less the translators are willing to give the same speech over again. (If I had a lot of work to do and was asked to yell the same instructions three times a morning, I wouldn’t be too happy either.)

It was this problem that sparked my idea of making a video. I thought that if I could make a video of the translators’ speeches and show it several times a day in the waiting-room, I would be able to kill two birds with one stone: it would make our jobs easier by making us less dependent on the translators to get our message across, and it would make the translators happy because they would be freed from their monotonous task. And, I happened to have exactly the bare minimum in terms of equipment that I would need to make it: my picture camera (which has a video option) and a computer.

So, I set to work.

I decided that the first thing I would need to do was get the approval of the translators. I needed their help—as they would be my actors—and I wanted to get their advice on what the film should say so that it would be effective and would come across clearly to the Swazi people. I sat down with them in the lobby and we talked for quite some time. As a group, they were quite willing to help out, but when it came to acting, none of them was very ready to volunteer (I think they were shy—about appearing on film). It took some work, but I finally convinced three of them—Lulu, Nomsa and Bongiwe to do it.

Then, I sat down right in the lobby, and, with my little camera, filmed Lulu (who seems to be Queen Bee of the lot) explaining the rules and regulations of the program. And Lulu did not fail me; a born star (you can tell she thinks so), with stage voice and lines memorized, she did it perfectly in one take. The second bit didn’t work out quite so well. I tried Nomsa at first. Nomsa, however, was a little bit too bashful for the big screen and kept forgetting what she was saying. Before I could attempt coaching her to success, she was called away to clinic duties. I was left with Bongiwe to finish the job. She, too, was shy, but Lulu urged her (somewhat forcefully) to conquer her fears and “just do it.” And so she did. The next day, however, when putting the movie together, I realized that Bongiwe’s voice was far, far too soft, and so I had to have Bongiwe try again. This time, we filmed in the board room in order to have fewer distractions. And boy was I surprised—I don’t know if it was the room or the timing or what, but Bongiwe laid it out like a professional. Go Bongiwe!

So, now that I had my film clips, I just had to put it all together. I uploaded the clips on to my computer and then into a program called Windows Movie Maker, which is a very primitive film editing
Chapter 4

program. Then, I spent quite a while discovering the ins-and-outs of the program and experimenting with different video effects. I put the clips in sequence, trimmed off the beginning “and GO!” or “ACTION!” parts that I had accidentally filmed, and created title pages. Then, to involve Nomsa (after her film debut didn’t work out as planned), I had her help me translate the titles into SiSwati.

Later, Sipho (pronounced See-po) came into the room and saw my project and was very excited about it. He told me that he had made a couple of movies in the past, so I, wanting input, had him watch my film. He loved it, but he had an idea to make it even better: what it really needed was a soundtrack!

I thought this was a wonderful idea, so we started looking for some music on my computer. But then, Sipho had another great idea: We needed to choose a song that our audience (Swazi patients from ages toddler to granny) would enjoy—and the best song to do that would certainly be an African one. And he knew just who to get it from! “Mlungisi,” he told me, “has all the best African music.”

So, we found Mlungisi in the filing room (he works at the clinic as a data clerk) and he was quite happy to have been thought of first when it came to good music taste. He helped us find a song that, he said “would be perfect.” The song he found was called “Mama ka Sibongile” by the Soul Brothers. Sipho and Mlungisi were both very satisfied with the choice because, apparently, the Soul Brothers are one of the best loved groups in Southern Africa. I hurried back to my computer to try it out.

The song worked wonderfully—it was quite up-tempo and peppy and was mostly instrumental (which is nice because lots of lyrics would have muddled Lulu and Sibongiwe’s words). I had to splice up the song according to the video segments and play with volume levels so that it would be louder during the titles and softer during the speaking parts. It took a while, but I got it eventually.

And, as no film is complete without the ending credits, I added those in too. Lulu, Sibongiwe, Mlungisi (whom I listed as musical director), and Sipho (whom I listed as technical support) were all quite excited to see their names scrolling boldly across the screen.

Finally, I had to transfer the movie from my computer to another and then burn it onto a DVD. Now this is where I would normally break down and want to give up (computers and I don’t often get along), but wonderful, amazing Sipho stayed with me (an hour past the time he usually goes home) and helped me every step of the way. And though we encountered quite a few difficulties, with Sipho’s help we were able to keep trudging forward and finally we had done it. We had our DVD.

With fingers crossed (so, so tightly), we walked downstairs and popped it into the DVD player. I think I might have even closed my eyes—I was really on pins and needles worrying that after all our work, something would go wrong.

But, when Sipho pressed play . . . there it was!!! My very short film in all its glory. I jumped in the air with excitement, and Sipho and I exchanged a very heartfelt high five.

I raced upstairs to find Carrie and Julia (two of the doctors who are my advisors-of-sorts) to have them come watch the film. On the way downstairs, Carrie stopped by Busi’s office and asked if she would like to come see the film. (Busi is the Executive Director, so everything in the clinic must be approved by her.) From the first title screen, they all had huge
smiles and were already talking about how impressed they were. After the film was over, they all congratulated me on my work. Busi said that she wished that I was here earlier so that I could have made a similar video of some of the patients speaking about living with HIV at an event they had at the clinic for the RED Campaign. She also asked me to make another video of the support group’s meeting on Saturday so that they can show it to other visitors. I felt quite honored by her request. The film wasn’t exactly Oscar material, but it was a good first attempt. (Hey, I’m sure even Spielberg wasn’t that good on the first go!) While watching the film on the TV, I saw quite a few things I would like to change. I thought about what I would do differently next time to make the film better. (Like using an actual video camera. ;))

What I love most about the entire experience is how inspired I now feel to do more. I feel like I’ve just opened the door to so many possibilities. I’ve realized that, using film, I can express all of the messages that I wanted to with the card project (discussed in an earlier blog)—proper hand-washing, hygiene, using clean water, proper infant feeding, etc.—and I can do it in a way the patients (who often cannot read) will be able to understand much more easily. And, if I do make films about these subjects, it will be incredibly helpful to the doctors. As it is, they must try to express all of these points to every patient they see. And, with so many patients, they are pressed for time. Perhaps with a detailed video, they would be able to really take these messages in. And, some of these basic messages are so important to get across. By using clean water, a mother can protect her baby from diarrhea (one of the major causes of infant mortality here). By adding just a teaspoon of oil to the baby’s porridge, a mother can prevent her child from improper brain development and stunting. These and many other problems have relatively simple solutions. Simple behavioral changes can prevent the loss of a child’s life.

I’m glad that I can do something that might actually help. I really can’t wait to do more. And I love that I can’t wait to do more.
Chapter 4

... deaths per year in 2000.[20] In 1978, the development of oral rehydration therapy was called the “most significant medical advance of the century” by the prestigious medical journal The Lancet.[21] To understand how a simple mixture of 1 liter of boiled water, 1 teaspoon of salt and 8 teaspoons of sugar can save so many lives, we must first understand some physiology of digestion.

The epithelial cells which line the colon are responsible for fluid reabsorption. Water moves from the lumen of the colon, across this epithelium and back into the blood vessels in response to osmotic gradients. In the upper gastrointestinal tract, the epithelium absorbs osmotically active products of digestion such as amino acids.[16] This reduces the tonicity of the solution in the lumen, and water passively leaves the lumen to equalize the osmotic pressure gradient. In the lower digestive tract, sodium is actively pumped out of the lumen, and again water follows.

There are several mechanisms by which colonic epithelial cells pump sodium out of the lumen. Toxins produced by bacteria which cause diarrhea (such as E. coli and V. cholerae) bind tightly to the luminal surface of the colonic epithelial cells and cause these cells to secrete chloride ions into the lumen; at the same time, these toxins interfere with one of the most important mechanisms of sodium reabsorption. [16] The reduced ability to pump sodium out of the lumen results in watery diarrhea (Figure 4.12).

Cholera is associated with a particularly severe diarrhea because the Vibrio cholerae bacterium produces a toxin which binds so tightly to epithelial cells in the gut that it remains active until the epithelium regenerates itself, which occurs every 5-7 days.[16]

Simply providing water or even salt water to cholera victims does not prevent dehydration, it simply adds to the volume of diarrhea. However, in the 1950s and 1960s researchers discovered a new mechanism of sodium reabsorption in the colon which was coupled to the transport of glucose.[16] This coupled glucose-sodium transporter was found to be unaffected by the cholera toxin, and in the presence of glucose, sufficient sodium reabsorption can occur to prevent dehydration. This is the basis for oral rehydration therapy. Researchers theorized that adding an oral rehydration solution containing both salt and sugar could enable sufficient sodium absorption to compensate for the effect of the toxins. This was confirmed in studies in the late 1960s in India and Bangladesh which showed that oral rehydration solutions containing glucose and sodium resulted in net reab-

---

**Figure 4.12:** Water secretion into the intestinal crypt space. a) Cl⁻ ions attract sodium ions Na⁺ into the crypt space, increasing the local osmotic pressure. b) As the osmotic pressure increases, water is pulled into the intestine. Used with permission from Merrick’s Inc.

http://www.merricks.com/intestinal.htm
sorption of fluid into the bloodstream of patients with cholera.[16] In 1975, the WHO and UNICEF agreed to promote a single oral rehydration solution containing 90 mM sodium, 20 mM potassium, 80 mM chloride, 30 mM bicarbonate, and 111 mM glucose.[25] Today, a packet of oral rehydration salts costs about ten cents (Figure 4.13).

While oral rehydration salts prevent dehydration, they don’t reduce the volume of diarrhea. This is because the glucose present in these solutions is absorbed as fast as it is delivered.[16] Newer solutions under development may act both to prevent dehydration and to reduce diarrhea volume. These new solutions contain glucose polymers. These polymers are not instantly reabsorbed—instead they are slowly broken down into glucose in the intestine. This glucose then permits sodium reabsorption in the same manner as today’s oral rehydration solutions. Solutions containing glucose polymers provide a continuous source of glucose to facilitate reabsorption, and can be thought of as a “glucose battery”.[16]

While diarrhea leads to far fewer deaths in developed countries, it is still an important cause of childhood morbidity. Diarrhea is the number two cause of visits to the pediatric emergency room in the US.[16] Although oral rehydration therapy is inexpensive, highly effective, and widely used throughout developing countries, many physicians in developed countries fail to use it to treat mild or moderate dehydration due to diarrhea. Instead, these physicians rely on rehydration using intravenous fluids, a method which is more painful and more expensive. In one survey, training directors in pediatric emergency medicine were asked to recommend treatment in 10 hypothetical scenarios. In each case, treatment with oral rehydration salts was the appropriate therapy; yet, only 17.2% of directors believed this was the best therapy and only 6.7% of directors said they would use oral rehydration salts in every case.[19] The reluctance to use oral rehydration therapy in the US is likely due to early experience with the first commercially available solutions in the US. A number of patients developed elevated sodium levels (hypernatremia); this occurred because the carbohydrate concentration was initially too high.[19] In addition, the initial product was dispensed in powder form and incorrect mixing exacerbated the problem. Most US physicians are still uncomfortable with oral rehydration therapy even though many clinical trials have shown that treatment with current solutions does not result in hypernatremia.

Vaccines to prevent infections such as rotavirus that cause
diarrheal diseases are under active development and testing. Infection with rotavirus causes 29-45% of all deaths due to diarrheal diseases. Rotavirus is found in every country and the incidence of rotavirus infection does not seem to go down as improvements are made in sanitation and hygiene. Rotavirus is highly contagious; almost every child will have one infection with rotavirus before they are 2 years old (Figure 4.14). In the US, 55,000 children are hospitalized each year due to rotavirus. Rotavirus infection causes explosive, watery diarrhea and sometimes is accompanied by vomiting. Although oral rehydration therapy is effective at preventing dehydration associated with rotavirus infection, parents and caregivers often stop giving it due to vomiting.

A vaccine called RotaShield designed to prevent rotavirus infection was approved by the US Food and Drug Administration in 1998. Prior to approval, clinical trials were carried out in the US, Venezuela, and Finland to test the safety and effectiveness of the rotavirus. These tests showed that the vaccine was 80-100% effective and found no evidence of statistically significant serious adverse side effects. After the vaccine came into widespread use in the United States a small number of infants who had been vaccinated developed a severe complication, bowel obstruction, which can be fatal. This complication developed in about one out of every 10,000 infants vaccinated and as a result the manufacturer withdrew the vaccine from the market in 1999. The decision to withdraw the vaccine in the US generated significant controversy. Researchers argued about whether it was ethical to continue trials of the rotavirus vaccine in developing countries and whether the high mortality associated with rotavirus infection could possibly justify the small risk of serious complications. It had been estimated that widespread use of the rotavirus vaccine in developing countries would result in 2,000-3,000 deaths per year due to vaccine-related complications, but could potentially save the lives of 500,000 children per year. We will revisit this debate in Chapter 9 when we consider the ethics of research involving human subjects.

Two new vaccines to prevent Rotavirus have just completed large clinical trials in more than 130,000 infants in the US, Latin America and Finland. These vaccines are based on a different technology, less likely to produce side effects, which we will examine in Chapter 8. Trial results show between 85-98% reduction in serious illness and 42-63% reduction in hospitalizations with no serious complications. While these results are very encouraging, current estimates

Figure 4.14: One of the author’s sons who developed a severe rotavirus infection as a baby in 1998, one month before the vaccine was commercially available.
place the cost of the vaccine at approximately $100 per dose—too expensive for developing countries where rotavirus causes the most mortality.[31]

**Malaria**: Malaria is a life threatening disease spread by mosquitoes which carry a parasite that can cause disease in humans. 40% of the world population lives in malaria endemic countries (Figure 4.15), and more than 300 million cases of malaria occur each year throughout the world.[32]

Each year on average, African children suffer between 1.6-5.4 episodes of malarial fever each year.[34] More than 1 million children under the age of 5 die as a result of malaria; the vast majority of these children live in sub-Saharan Africa.[32]

Malaria carrying mosquitoes harbor a parasite that can be transmitted to humans when bitten. There are four species of malaria parasite that infect humans. The most deadly of these, *plasmodium falciparum* (Figure 4.16) is the species most commonly found in mosquitoes in sub-Saharan Africa.[35]

Malaria parasites are capable of evading the human immune system; they initially travel to the liver where they infect liver cells and multiply. The infected liver cell bursts, and the daughter parasites can then attach to the surface of red blood cells, where they consume the hemoglobin and divide. The red blood cell then ruptures, releasing more daughter parasites which can go on to destroy other red blood cells. Symptoms of malaria first appear 9-14 days after infection when daughter parasites are released from liver cells and include fever, headache, vomiting, and flu-like symptoms.[32] Malaria kills by destroying oxygen carrying red blood cells; the destruction of these cells can lead to severe anemia. The debris produced when red blood cells...
are destroyed can clog the capillaries that carry blood to the brain (cerebral malaria) depriving the brain of crucial oxygen supply.[32] Many children who survive cerebral malaria are left with permanent neurological problems, including blindness and epilepsy.[34]

Pregnant women have increased susceptibility to malaria. The resulting maternal anemia can result in babies with low birth weight and malaria can be transmitted from mother to child across the placenta.[36] Insecticide treated bed nets offer a cost-effective solution to prevent malaria in pregnant women and infants. Since malaria carrying mosquitoes bite predominantly at night, encouraging mothers and infants to sleep under mosquito nets treated with insecticide can reduce malaria incidence, the incidence of low birth weight babies and malaria deaths in children.[36] In Kenya in the 1990s, residents were bitten 60-300 times a year by malaria carrying mosquitoes before control measures were put in place.[37] Providing insecticide treated nets (Figure 4.17) for pregnant women and their babies to sleep under resulted in a 25% reduction in low birth weight babies and a 20% reduction in deaths in young children.[34, 36] Insecticide treated bed nets cost about $1.70 however, they must be retreated with insecticide each year, which costs about 3-6 cents per treatment.[34] Long-lasting insecticide treated nets which are effective for up to 4 years are under development.[34]

Several drugs are available to treat malarial infection. The least expensive of these are chloroquine (13 cents/course), sulfadoxine-pyrimethamine (14 cents/course), and quinine ($2.68/7-day course).[37] Unfortunately, past inappropriate use of anti-malarial drugs has resulted in malaria parasites with high levels of resistance to drugs. The use of anti-malarials on a large scale, given as monotherapies, introduced in sequence, and continued use even in the face of high levels of resistance has made the treatment of malaria more difficult.[38] Resistance to chloroquine is common in Africa and resistance to sulfadoxine-pyrimethamine is increasing.[35] New treatments for resistant malaria include artemisinin containing drugs such as artesunate. These drugs are derived from a Chinese plant; currently, it takes 6-8 months to grow the plant, and another 2-5 months to process plant and yield drug.[38] Combination therapies including artemisinin cost about $1 per course. No resistance has been observed to these new therapies yet.

**Congenital Anomalies:** About 2-3% of all children are born with a birth defect and more than 400,000 children die...
As the health of a population improves, the proportion of mortality attributed to congenital anomalies increases. In developing countries, birth defects account for less than 4% of childhood deaths, whereas in developed countries they account for 16.9% of childhood deaths. Table 4.2 shows that the causes of congenital anomalies can be grouped into three categories: those caused by chromosomal abnormalities and single gene defects, those caused solely by environmental exposure or nutritional deficiencies, and those with complex or unknown causes which may include interaction between several genes and possibly environmental factors. Sporadic losses or rearrangements of genetic material have been estimated to affect 10% of conceptions and more than 90% of these events are incompatible with development and result in spontaneous abortion. Infants born with such defects can suffer congenital malformations and mental retardation. Advanced maternal age is a risk factor, and increases particularly after age 35. As a result, such defects are relatively more common in developing countries, where the fraction of births to women over 35 years of age is 11-15% compared to only 5-9% in developed countries.

Environmental causes of birth defects include exposure to infectious agents, exposure to teratogens in the environment, as well as maternal nutritional deficiencies. Exposure to infectious agents during gestation such as malaria or rubella can result in serious birth defects. Congenital rubella syndrome results from maternal infection with rubella in early pregnancy. This syndrome includes blindness, deafness, cardiovascular defects and severe mental retardation. Rubella epidemics occur every 4-7 years in populations that have not been immunized and are of particular concern in developing countries. Maternal consumption of alcohol, particularly binge drinking, can lead to fetal alcohol syndrome, which is characterized by altered facial features,

<table>
<thead>
<tr>
<th>Cause</th>
<th>Classification</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Chromosomal</td>
<td>Down syndrome</td>
</tr>
<tr>
<td></td>
<td>Single gene</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Environmental</td>
<td>Infectious disease</td>
<td>Congenital rubella syndrome</td>
</tr>
<tr>
<td></td>
<td>Maternal nutritional deficiency—folic acid</td>
<td>Neural tube defects</td>
</tr>
<tr>
<td>Complex</td>
<td>Congenital malformations involving single organ system</td>
<td>Congenital heart disease</td>
</tr>
</tbody>
</table>
fetal growth reduction, and cognitive defects.[6]

Several medicines are known to cause congenital anomalies. Thalidomide is still used to treat leprosy and HIV in developing countries and causes severe fetal limb and organ defects.[6] Some anticonvulsants can cause congenital heart defects.[6] Environmental pollutants such as heavy metals, pesticides and solvents, can also cause birth defects. For example, exposure to the fungicide methylmercury can cause central nervous system defects, mental retardation, cerebral palsy, deafness, and blindness.[6] In the 1970s, seed grain which had been treated with methylmercury was inadvertently used to make bread in Iraq, resulting in a number of fetal defects.[40] A range of nutritional deficiencies can also result in birth defects. Folate deficiency can cause neural tube defects (spina bifida, anencephaly) and iodine deficiency can cause mental retardation, hypothyroidism, goiter, and cretinism.[6]

Unintentional Injuries: In developed countries, unintentional injuries are the fourth leading cause of death for children under the age of 5.[2] Unintentional injuries result in the death of approximately 15,000 children under the age of 5 each year in developed countries and 273,000 children in developing countries. In both settings, the single largest cause of fatal unintentional injuries to children include drownings, which kill 82,000 children each year and road traffic accidents, which kill 58,000 children each year worldwide.[2] We will examine technologies to prevent injuries in road traffic accidents later in this chapter.

We saw in Chapter 1 that one of the UN Millenium Development Goals is to reduce childhood mortality by 2/3 by 2015. [41] Is this possible with today’s technology? A recent study estimated that 2/3 of childhood deaths could be prevented today if an essential set of currently available interventions which are feasible to implement in low income countries were made universally available to the populations in need. [42] The study authors conclude that, in most cases we have technology available to reduce child mortality, but children continue to die because the technology does not reach them.

Mortality rates for children under 5 years of age have dropped by 1/3 between the late 1970s and the late 1990s. [43] Over this same time period, neonatal mortality rates have dropped much more slowly. Future progress in reducing childhood mortality worldwide will require more progress in reducing infant and neonatal mortality. The island country of Sri Lanka, located off the southern tip of India, provides Read more about fetal alcohol syndrome:
The Broken Cord by Michael Dorris chronicles Dorris’ life as a single father after adopting a three year old child who suffered from fetal alcohol syndrome. Dorris was the first single male in America to adopt a child. His book was pivotal in encouraging Congress to pass laws regarding warnings about fetal alcohol syndrome on alcoholic beverage labels. The book won a National Book Critics Circle Award in 1989.

Implementing preventive interventions such as breastfeeding, insecticide treated materials, access to clean water, childhood vaccination, adequate nutrition, clean delivery, and therapeutic interventions such as oral rehydration therapy, antibiotics and antimalarial drugs can reduce childhood death by more than 2/3.


Read more about preventing childhood deaths:
an example of a successful approach. Sri Lanka has seen a dramatic drop in infant mortality rates over the past 50 years (Figure 4.18).

The infant mortality rate of 15 deaths per 1,000 live births in Sri Lanka is much lower than would be expected on the basis of its per capita GDP at PPP of $4600 in 2006.[45] Reductions in infant mortality are a result of substantial investments in health infrastructure and education. Health care is provided free of charge and the female literacy rate is nearly 90%. The first maternal hospital was established in 1879, and training of midwives began in 1926. The government began to promote institutional deliveries in 1948, and today more than 90% of deliveries occur in health care institutions. Since 1989, the partogram has been used to monitor labor, improved methods of resuscitating asphyxiated babies have been introduced, and neonatal tetanus has been eliminated by vaccinating mothers and by using aseptic procedures during delivery. Future challenges include providing equitable care throughout all provinces in the nation, particularly those affected by conflict.[46]

Developed countries also face challenges associated with infant mortality. In the US, infant mortality increased in 2002 to 7 per 1,000 live births for the first time in more than 40 years. Most of the rise occurred in the neonatal period and was related to the excess contribution of prematurity. While the causes of premature birth are not well understood, risk factors include maternal age, multi-fetal pregnancies, stress, smoking, and obesity.[47]
Leading Causes of Mortality, ages 15-44

Worldwide, more than 8.5 million people between the ages of 15 and 44 die each year, 88% in developing countries.[2] The death of a young adult can leave a family without a breadwinner and children without a parent, resulting in far-ranging social consequences. The leading causes of mortality for young adults differ substantially for those in developed and developing countries. For persons aged 15-44, the four leading causes of mortality in the developing world are:[2]

1) HIV/AIDS,
2) Unintentional injuries,
3) Cardiovascular diseases, and
4) Tuberculosis.

In the developed world, for persons aged 15-44, the four leading causes of mortality are:[2]

1) Unintentional injuries,
2) Cardiovascular diseases,
3) Cancer (malignant neoplasms), and
4) Self-Inflicted Injuries.

In developing countries, more than 1/3 of mortality in this age group is a result of two infectious diseases: HIV/AIDS and tuberculosis. In contrast, more than 1/3 of mortality in this age group in developed countries occurs as a result of injuries, both unintentional and self-inflicted. Here, we briefly review the epidemiology and pathophysiology of each of these causes of death.

**HIV and AIDS:** Globally, the burden of HIV/AIDS is staggering. HIV/AIDS is the leading cause of death among people aged 15-44.[2] Approximately 40 million people are living with HIV/AIDS worldwide and more than 20 million people have been killed by the disease. In 2003 alone, 3 million people died of AIDS and 5 million others became infected with HIV. The disease has been particularly devastating to the African continent. Two-thirds of those living with AIDS are in Africa, where 1 in 12 adults has HIV/AIDS. AIDS has reduced gains in life expectancy in sub-Saharan Africa which peaked in the late 1980s (Figure 4.19).[48]

There is worldwide concern over growing HIV/AIDS epidemics in eastern Europe and central Asia. In the United States today, it has been estimated that there are currently between 0.8-1.2 million people living with HIV/AIDS and between 30,000-40,000 new HIV infections per year occur in the US, most in African Americans and Hispanics.[48] The
The annual cost to treat HIV/AIDS is approximately $15 billion in the US.[49]

The clinical course of HIV/AIDS is characterized by initial infection with the HIV virus (Figure 4.20). HIV is spread by sexual contact with an infected person, by sharing needles for drug injection with someone who is infected, or by transmission from mother to child during pregnancy, childbirth or breastfeeding. The resulting acute infection can initially produce mononucleosis-like symptoms, including fever, sore throat, headache, muscle ache and nausea. This is followed by viral dissemination, eliciting an HIV-specific immune response. The virus continues to replicate, and begins to destroy an important component of the host’s immune system, the CD4+ lymphocyte.[50]

The rate of progression of HIV during the asymptomatic, latent period is correlated with the number of viruses present per unit volume of blood (viral load). During the latent phase the viral load remains low (Figure 4.21), but as disease progresses the viral load increases and CD4+ T lymphocytes decrease. Eventually the disease reaches the point where the resulting immunologic dysregulation produces AIDS. AIDS is characterized by a series of opportunistic infections and cancers, including Pneumocystis carinii pneumonia (PCP) and Kaposi’s sarcoma.[50] As more CD4+ lymphocytes are destroyed, the patient becomes increasingly susceptible to infections. Without treatment, within 10 years of infection, 50% of patients will develop clinical AIDS, 40% will develop illness associated with HIV, and 5-10% will remain asymptomatic.[49] Left untreated, the average AIDS patient dies within 1-3 years.[50]

The history of HIV/AIDS likely unfolded throughout your lifetime. In 1981, the Centers for Disease Control and Preven-
tion (CDC) reported cases of pneumonia caused by an unusual organism—*Pneumocystis carinii*—in 5 previously healthy, homosexual men and cases of a rare cancer—Kaposi’s sarcoma—in 26 previously healthy, homosexual men. In 1981-1982, it was noted that these findings were also associated with IV drug use, recipients of blood transfusions, and hemophiliacs. In 1983, the HIV virus was isolated, and in 1984 this virus was shown to be the causative agent of AIDS. In 1985, a simple blood test was developed to detect the virus— the ELISA test.[51] Initially AIDS was a rapidly fatal disease; however, in 1996 a breakthrough new treatment was developed—highly active antiretroviral therapy (HAART). Although HAART cannot cure AIDS, it has dramatically increased the lifespan of HIV infected persons, changing the management of HIV/AIDS from that of a fatal disease to that of a chronic, lifelong disease like diabetes. [53]

To understand how HAART works, we need to know more about the details of how the virus replicates within host immune cells. Figure 4.22 illustrates the process which occurs when the HIV virus infects CD4+ lymphocytes. The viral gp120 protein binds tightly to the CD4 receptor on T lymphocytes.[50] The gp41 viral protein helps the membranes of the two cells fuse, enabling the HIV RNA to enter the host cell.[50] The virus then uses the reproductive machinery of the host cell to reproduce. Viral RNA is transcribed to double stranded DNA by means of reverse transcriptase enzymes contained within the virus.[50] With the help of a viral enzyme, the viral DNA is then randomly incorporated into the host DNA. [50] This allows the host cell to produce new copies of viral RNA and viral coat proteins. Viral protease enzymes process these viral proteins so that the RNA and proteins can assemble into mature virus particles which then bud off the host cell membrane.[50]

**HIV Screening of Blood Donations:**

In 1985, it became mandatory to test donated blood for presence of antibodies to HIV. Before screening, more than 10,000 individuals in US acquired HIV/AIDS as a result of a transfusion; many of these individuals were hemophiliacs. Today, because of good screening procedures, the risk of acquiring HIV from a blood transfusion in the US is estimated to be between 1/725,000-1/835,000.

Donated blood is screened for the presence of antibodies to HIV, which usually develop within 2-8 weeks following infection. An enzyme linked immunosorbent assay (ELISA) test is used to screen blood for the presence of HIV antibodies. The ELISA principle was discovered in 1960 and is used to test many bodily fluids, including blood, urine and saliva, for the presence of antibodies, hormones, and proteins.

In an ELISA test for HIV antibodies, a small plastic well is coated with partially purified, inactivated HIV antigens. The sample to be tested is then incubated in the well; any antibodies against HIV will bind to the antigen and become immobilized. Unbound antibodies are then washed away. A second antibody which binds to all human antigens is then added. The second antibody is conjugated to an enzyme designed to react with dye added in the third step. Again, unbound antibody is washed away. In the third step, dye is added; in a positive test, the enzyme present on the captured antibody acts on the dye, producing a color change. The enzyme acts as an amplifier, so that even if only a few antibodies have been captured, the test generates a large enough color change to be detected. The optical absorption of the fluid is directly proportional to the concentration of the captured antigen.
**WFP and the Mbabane hospital: June 10, 2007**

**Tessa**  
**Swaziland**

Thursday—the long awaited WFP launching day—finally arrived! It was a whirlwind, of which I remember little. It was sooo busy, and Dave and I were running about and registering people all day. It actually went surprisingly well, but there are quite a few kinks for us to work out for Monday. The biggest problem was that there were about 30 patients that walked in (ie, they didn’t have an appointment). We had to look each one up to determine whether they were eligible before we could register them and give them food. That kind of threw our system off a bit (and compounded our struggle to communicate with some of the Saswati-speaking women), but it really wasn’t too difficult.

The greatest part of the day was actually giving the women and children their food. Most of them looked so happy to receive it. Some of them looked confused. And a few of them really didn’t seem like they needed it all. They were wearing nice clothes and seemed significantly less excited about the food than the others (although they still wanted it). It’s impossible to know for sure though because most of them dress up when they come into the clinic. I mean, we can’t say, “Um, no. I don’t think you need the food. Your outfit is too nice.” Of course not! There is really no way for us to know who is really poor and who isn’t. The majority of them are in dire need, though, so this food distribution program is really crucial for most of them.

I was able to interact a lot more with the patients than I had before, but because we were trying to register everyone and give out food and look people up all at once, I didn’t get to talk to very many of them for long. At the very end of the day, things slowed down, and Dave and I were able to talk to the women and play with the children a bit. One boy was so cute and had so much energy. He just kept walking around, climbing the stairs, following people out to the street…I couldn’t tell who he belonged to for awhile. He seemed to be friends with everyone.

Friday was equally busy. Dave and I presented on WFP and did boring stuff like fill out forms and fill bags of food. That afternoon, Eileen (another doctor and Dave’s mentor) took us to pick up a cabinet for the kitchen she is creating at the Mbabane hospital. They offered to deliver it right then, so we accompanied her to the children’s ward, where the kitchen was located. Surprisingly, I ran into someone I knew from the clinic. He was there with his nine-year-old daughter who was suffering from toxoplasmosis. I’m reading a book called *And the Band Played On* right now about the beginning of the HIV/AIDS epidemic. Many of the first men to suffer and die from AIDS came down with this exact disease. It is a disease that normally only infects cats, but when a person’s immune system is down, they can contract it as well. If a person doesn’t receive the medication he or she needs, he or she will die from it. The poor girl was clearly not receiving the treatment she needed. As Eileen hunted down a doctor from the hospital, Dave and I hung out in the children’s ward.

A group of women beckoned to me and started asking me all sorts of questions. After the usual exchange (where we’re from, what we do, what our family is like, why they want to go to the U.S., etc.), we started talking about why their children were sick. Mostly, they all had diarrhea and vomiting. I asked them if they boiled their water. They explained to me that they do occasionally, but most of the time electricity is too expensive (or firewood is too hard to gather) to boil water. I knew that saying, “Well, if you boiled your water every time, then your child probably wouldn’t be sick” would be way too critical and sweeping of a statement. So I kept my mouth shut. They clearly knew that they should boil their water but felt that they were unable to. I wondered what could be done to make it easier for them to do so. My mind wandered to Rice’s Engineers Without Borders group and thought that would be a good problem for them. Behavior change is so difficult. If something can be made automatic so that it is incorporated into their daily routine without adding any extra work, only then is it likely to make a difference.

Another interesting behavior-change problem we discussed dealt with the rapid spread of HIV/AIDS throughout Swaziland. I don’t remember how the topic came up, but they were telling me angrily how there are so many people who have AIDS yet still have sex. They say everyone knows that sex spreads the disease, but people continue to sleep with multiple partners, often without protection. They also told me that girls usually start having sex when they are 13!
I asked them if they all knew each other from home or if they had met there in the hospital. One woman responded that they had met there and had become very close. They were there to support each other and comfort each other when one of their children dies. She said it so matter-of-factly. Most of them had already lost at least one child.

As we walked out, Eileen explained to us how frustrating it was to come to this hospital. It always ran out of medicines, and as a result, people died. People that could easily be saved died because the hospital had no medicine to give them. I thought of the still, silent figure of the nine-year-old with toxoplasmosis. She was so skinny and looked way younger than nine. I wondered if my friend’s daughter would be dead next week when he came to work, and I felt sick to my stomach. I am so lucky to live where there are clean hospitals with more medicine than they need. I am so lucky that not every family I know has lost a child.
HAART drugs act to block several steps in the viral reproduction process. One type of HAART drug inhibits the reverse transcriptase enzymes that enable replication of the viral RNA. Without reverse transcriptase, the virus cannot replicate, preventing further infection of other cells. This enzyme is specific to HIV so that inhibition does not affect other normal cellular processes.[50] Two classes of reverse transcriptase inhibitor therapies are currently used in patients—nucleoside reverse transcriptase inhibitors which were first approved to treat patients in 1987 and non-nucleoside reverse transcriptase inhibitors which were first approved in 1996.[54] Another type of HAART drug inhibits HIV proteases, so that the viral product cannot leave the infected cell to spread to other cells. HIV proteases are distinct from mammalian proteases, so their inhibition does not affect other normal cellular processes.[50] Protease inhibitors were first approved for use in humans in 1995.[54] Another strategy under active investigation is the development of drugs which inhibit the initial fusion of HIV to the cell membrane. This is an area of active new research. Fusion inhibitors were approved for use in humans in the US in 2003, but only for patients who have failed other therapies.[55] Other drugs under development include those that may block integration of viral DNA into host genome.[50]

HIV can rapidly mutate, so that it can quickly develop resistance to either type of reverse transcriptase inhibitor or protease inhibitor if given alone. However, resistance develops much more slowly when patients take all three types of drugs simultaneously. This combination therapy is what is known as Highly Active Antiretroviral Therapy (HAART), and represents the most significant advance yet in the treatment of HIV/AIDS. The use of HAART greatly reduces the risk of disease progression and deaths due to AIDS. The clinical
impact of HAART is dramatic, the use of antiretroviral therapeutics decreased death rates due to HIV/AIDS by up to 80% in Europe and the Americas (Figure 4.23).[48] Figure 4.24 shows the probability of survival for patients who acquired an HIV infection in the years 1986-1996 (pre-HAART period) and the years 1997-1998 (HAART period).[56] Long term survival has significantly increased as a result of this important advance.

While HAART dramatically prolongs survival, it does not cure HIV/AIDS. The goal of HAART is to reduce viral loads to an undetectable level, which is usually attained although the virus is not eliminated. Patients must have their viral load and CD4 counts tested every few months to monitor for resistance, which can develop to individual drugs within the HAART regimen. When resistance develops, then the drug regimen must be changed or the typical patient will develop AIDS within 3 years. New combinations of drugs should include at least 2 drugs that the patient has not taken before. There are more than 20 approved antiretroviral drugs.[57] HAART regimens are complex—patients must take 2-13 pills a day and they must continue HAART for the rest of their lives.[53] Many of the HAART medicines have serious side effects.

It has been estimated that there are 6.5 million people living with HIV/AIDS in developing countries in need of HAART; 90% of these people can be found in just 34 countries.[48] Figure 4.25 documents the discrepancies between the need for and the availability of antiretroviral therapy (HAART) throughout the world.

Figure 4.23. Trends in annual rates of death due to leading causes of death among persons 25-44 years, USA, 1987-2000.

Figure 4.24: The long term probability of survival following an HIV infection acquired after the development of HAART is much greater than that for patients who acquired an HIV infection pre-HAART.
In the Americas, HAART is available to meet over ¾ of the need, while in Africa drugs are available to meet only 10% of the need. As a result in late 2003, the WHO launched the 3x5 Initiative, a program whose goal was to provide antiretroviral (ARV) treatment for three million people by 2005. However by June of 2005, roughly only a third of this goal was reached (Table 4.3). The 3x5 program is part of a greater global effort to provide universal HIV prevention and treatment as a basic human right, with an expansion goal of universal access to ARV treatment by 2010.

Developing effective tools to prevent future HIV infections has proven to be very difficult. There is active research to develop vaccines to prevent and/or control HIV infection. Pre-clinical work in animals is promising and we will examine these vaccines in detail in Chapter 8. Another approach is to educate and counsel patients about the risks of HIV infection and the steps they can take to reduce their risk, an approach that proved very successful in the US for homosexual men. Globally, the most common means of transmission of HIV infection is unprotected sexual intercourse between men and women. Transmission rates are as high as 45% without treatment. Prevention of mother-to-child transmission (MTCT) is also an area of targeted educational efforts; with 700,000 children infected by MTCT each year. Antiretroviral drugs drastically reduce transmission. In Africa, less than 5% of women and neonates who need interventions to prevent
MTCT receive them.[48]

Efforts to prevent the spread of HIV are complicated by the fact that individuals may not realize they are infected; more than 90% of HIV positive individuals do not know they are infected.[62] The reality is that stigma and discrimination—at home, at work, in health care settings, etc.—continue to deter people from having an HIV test, particularly if there is fear of violence, social isolation, and no guarantee of treatment availability for those who test positive.

**Unintentional Injuries:** Unintentional injuries are the second leading cause of death for people in developing countries between the ages of 15-44, killing more than 1 million in this age group each year.[2] In developed countries, unintentional injuries are the leading cause of death, and more than 260,000 people aged 15-44 die each year as a result. [2] The leading cause of fatal unintentional injury worldwide is road traffic accidents (Figure 4.26), which kill more than 500,000 people aged 15-44 every year. 90% of road traffic deaths occur in low income and middle income countries. [43] In developing countries most deaths involve pedestrians, bicyclists, motorcyclists and occupants of buses, while in developed countries most fatalities are occupants in cars. [43] Road traffic injuries are also a major cause of severe disability; 50 million people are injured each year in traffic accidents.[63] While traffic fatality rates have decreased in developed countries, traffic fatalities are expected to rise 65% worldwide between 2000-2020.[63]

In the United States, traffic fatality rates have decreased steadily over the last thirty years (Figure 4.27), yet automobile accidents still represent the leading cause of potential years of life lost. In 2005, 43,443 Americans were killed in road traffic accidents and 2,699,000 Americans suffered

<table>
<thead>
<tr>
<th>Geographical Region</th>
<th>Number of people receiving ARV therapy</th>
<th>Estimated need</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>500,000</td>
<td>(425,000 - 575,000)</td>
<td>4,700,000</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>290,000</td>
<td>(270,000 - 310,000)</td>
<td>465,000</td>
</tr>
<tr>
<td>East, South and South-East Asia</td>
<td>155,000</td>
<td>(125,000 - 185,000)</td>
<td>1,100,000</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>20,000</td>
<td>(18,000 - 22,000)</td>
<td>160,000</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>4,000</td>
<td>(2,000 - 6,000)</td>
<td>75,000</td>
</tr>
<tr>
<td>Total</td>
<td>970,000</td>
<td>(840,000 - 1,100,000)</td>
<td>6.5 million</td>
</tr>
</tbody>
</table>

**Table 4.3:** ARV therapy coverage in low and middle income countries, June 2005

![Figure 4.26: Road traffic accidents](image-url) are a leading cause of death throughout the world. Used with permission from NHTSA.
A Day with the Social Workers: July 4, 2007

Sophie       Lesotho

I spent most of yesterday trying to collect voice recordings of the adherence counseling sessions at the clinic. One of our projects is to develop a group ARV adherence counseling module. We wanted to know what is being said in the individual counseling sessions that the clinic currently has. The doctors said that this would be a good idea since they were finding that many of the patients did not know enough about their condition and ARVs when they came to them to start treatment even after finishing the adherence counseling sessions. One of the problems is that the current module places too little emphasis on educating the patient, but rather focuses mostly on counseling.

In one of the screening sessions, a mother came in with her 8-year-old girl to have the child tested. The girl was obviously ill – she appeared weak and was not expressive. Her eyes were sunken in and her cheeks and ankles were swollen. One of the doctors told me that these were signs of severe malnourishment - most likely due to protein deficiency. Many times when I’ve been around Basotho children, they just stare at you without any expression on their faces. Then, when you smile or wave at them, all of a sudden their faces uncover joyous smiles that nearly overwhelm you and give you an amazing sense of happiness and pleasure. When I smiled at this young girl who was being tested, she also revealed to me that same sweet smile, yet it seemed that it took effort. Another interesting thing about Basotho children is that they can be surprisingly stoic, which is a characteristic not often seen in children. They hardly flinch or show any emotion on their faces when they get their fingers pricked during HIV testing. This child was no exception.

The mother was also with the young girl, but she explained to the social worker that she did not want to be tested because she was afraid of knowing what the result might be. The social worker explained that it was worse not to know her status since the virus would continue to replicate in her body until she ended up with AIDS and then would die. At this explanation, she became even more afraid and was persuaded into being tested.

There is about a 5-minute wait for getting the results of an HIV rapid test. While we were in the room, I saw several cold sores on the mother’s mouth and was reminded of a powerpoint I had seen on some common symptoms of HIV infection. While we were waiting, I was anticipating that both the mother and child would be HIV positive. As we looked at the test results, the mother’s test result had two lines, while the child’s only had one. My face flushed with heat as I saw the result - only the mother came out positive. The mother did not show emotion when she was told her status – she remained calm and was quiet as she was referred to Senkatana clinic, which is the HIV clinic that treats adults. Maybe a positive test result is not as shocking for the Basotho seeing as they live in a country where 1/4th of the population is infected with HIV.
injuries in road accidents. Persons between the ages of 16 and 20 suffered the highest mortality rate. The fatal accident rate of male drivers is almost three times higher than for females. Mortality rates for motorcycles are even higher, with a death rate per mile nearly 40 times higher than that of automobiles. In the US, 39% of fatal crashes are related to alcohol use and the deadliest time on the road is midnight to 3 am Saturday and Sunday.[64]

Successful prevention of road accidents and resulting death and injury has focused legislation, education and engineering to reduce conditions which lead to crashes and keep occupants safer during crashes. Throughout the United States, laws regulate maximum driving speed on roadways. All 50 states in the US have laws requiring seat belt usage and the use of child safety restraints up to a certain age.[65] Twenty states require motorcycle drivers to wear helmets, and another 27 states require helmet usage with some provisions for exceptions; 3 have no requirements.[66] In 45 states it is illegal to drive with a blood alcohol concentration in excess of 0.08 g/dl.[67] New cars sold in the US must be manufactured to meet certain safety standards which protect occupants in the event of a crash.

To understand how these laws reduce the number of road accidents and the number and severity of accident-related injuries we need only consider Newton’s laws. Newton’s second law tells us that that the force, \( F \), acting on an object is a product of its mass, \( m \), and its acceleration, \( a \):

\[ F = ma. \]
Acceleration describes how rapidly velocity, \( v \), changes with time \( t \), and can be described as the rate of change of velocity with time:

\[
a = \frac{dv}{dt}.
\]

We can approximate the acceleration in a crash as the change in velocity divided by the time over which it occurs:

\[
a = \frac{\text{initial velocity}}{\text{time to come to rest}}.
\]

In a crash, velocity decreases to zero in a very short time leading to large accelerations and large forces. If these large forces are transmitted to passengers, fatal injuries can result. There are primarily two ways to reduce the forces that impact passengers—we can (1) reduce the initial velocity of impact and (2) extend the time that it takes the passenger comes to rest.

*Reducing initial crash velocity:* High velocity at initial impact leads to higher forces in crashes. This can be caused by traveling at excessive speeds. Figure 4.28 shows the risk of pedestrian death as a function of impact speeds above 40 km/h. Excessive speed contributes to 30% of deaths due to road accidents in developed countries, and 50% in developing countries.\[63\] Drivers traveling at higher speeds have less time to stop and avoid the crash or slow and reduce the speed of impact.

When drivers can anticipate a crash, they have time to react and begin to brake in order to reduce the velocity of initial impact. Factors that slow driver reaction times can increase the likelihood of injury and death. A number of factors slow driver reaction time, including alcohol use, cell phone use, and poor visibility.\[63\] In addition, driver inexperience can contribute to poor judgment and slowed reaction times.

Alcohol impaired drivers have 17 times increased risk of being involved in a fatal crash relative to drivers who have zero blood alcohol. The effects of alcohol increase risks more in younger, less experienced drivers. Figure 4.29 shows the risk of crash as a function of blood alcohol concentration. A study carried out in the US in the 1960s established the basis for the 0.08 g/dl limit on blood alcohol content; this study showed that at this level, drivers had a two fold increase in the risk of crash. New data indicates that the original study probably underestimated the risk of crash, and that the limit should be reduced to 0.05 g/dl for all drivers and 0.02 g/dl for young drivers. Data indicate that raising the minimum legal drinking age reduces the rates of alcohol-related crashes. Enforcement of these laws is also impor-
Chapter 4


tant; a low expectation of getting caught increases the risk of alcohol related crashes. Alcohol also increases the risk of pedestrian death in traffic accidents; studies show that 50-60% of pedestrians killed in traffic accidents had been drinking.[63]

The use of mobile phones is of growing concern; at any given daylight moment in the US it is estimated that 10% of drivers are using a cell phone.[68] Driver reaction times increase by 0.5-1.5 seconds when talking on the phone. The risk of crash increases four times when using a mobile phone; the equivalent effect of driving with a blood alcohol concentration of 0.09 g/dl. 35 countries have now banned use of hand held phones while driving. Hands free phones present less risk than hand held phones, but still distract drivers.[63] Only three states, New York, New Jersey and Connecticut, and the District of Columbia, ban the use of hand held mobile phones while driving.[68]

Increased visibility can enable time for driver reaction and reduce crash risk. The use of daytime running lights reduces car crashes by 10-15%.[63] High mounted brake lights reduces rear end crashes by 15-50%.[63]

Finally, inexperienced drivers have increased risk of fatal crashes. In the US and Canada, graduated drivers license systems have reduced crashes of new drivers by 9-43%.[63]

**Extending time for passengers to come to rest:** If we lengthen the time that it takes for passengers to come to rest during a crash we can also reduce the risk of injury and death. The front end of new cars are designed to crumple in a controlled manner, allowing the passengers additional time to decelerate and directing the energy absorbed in the

**Videos of crash tests:**
These crash test videos contrast what happens to occupants who are restrained with seat belts to those who are not wearing belts. In all three crashes, the crumple zone slows the deceleration of the passenger compartment.

Unbelted occupants rapidly accelerate into the dashboard:
http://www.regentsprep.org/Regents/physics/phys01/accident/nobelt.htm

Belted occupants are held with the passenger compartment:
http://www.regentsprep.org/Regents/physics/phys01/accident/withbelt.htm

Airbags can help protect unbelted occupants in the front seat, but unbelted rear occupants are not protected:

Airbags can help provide additional protection beyond seatbelts:
http://www.accidentreconstruction.com/movies/5thper.mov

This video illustrates the importance of child restraints. During the crash, a child seated in his unbelted mother’s lap effectively serves as an air bag for his mother:

Figure 4.29: The risk of crash as a function of blood alcohol concentration relative to a driver with zero blood alcohol concentration.

- Compton et al., 2002 (82); Moskowitz et al. 2002 (84)
- Borkenstein et al., 1964 (78); Allsop, 1966 (83)
crash away from the passenger compartment. In order for crumple zones to protect occupants, they must be wearing seat belts. Seat belts restrain occupants so that they remain in the passenger compartment; in addition, seat belts stretch during an impact, further slowing deceleration of passengers.[69] In a frontal collision, occupants not wearing seat belts will fly forward and decelerate rapidly when they come into contact with the dashboard, steering wheel or windshield. Air bags provide an additional cushion which slows the deceleration of occupants. Airbags inflate rapidly upon frontal impact; as occupants move forward, they strike the inflated airbag which slows their deceleration. In the US, a national car assessment program, begun in 1978, tests the safety of a car’s design—determining crash-worthiness in certain types of crashes—which consumers can consider when buying cars.[63] Videos of crash tests conducted by the National Highway Traffic Safety Administration provide a dramatic illustration of the effects of these safety measures.

The use of seat belts reduces the risk of death in a crash by 40-65%. Seat belts are most effective in roll overs and rear and frontal collisions. Numerous studies have shown that seat belt usage rates increase in areas where they are required by legislation and where these laws are enforced. Seat belt usage rates are much lower in developing countries, where half of all vehicles may lack functioning seat belts. When combined with seat belts, air bags have been shown to reduce the risk of fatal injury by 68%. The use of child restraints, such as car safety seats, reduces infant death by 71% and toddler death by 54%. Mandatory child restraint laws in the US have led to a 13% increase in usage rates and a 35% reduction in fatal injuries.[63]

Head injuries are a major cause of death for users of two wheel vehicles. This is of growing concern in Asia, where two wheelers are commonly used as family vehicles. Non-helmeted users are three times more likely to sustain head injuries in a crash of a two wheeler.[63] When the skull receives an impact, crucial nerves and blood vessels can be torn, leading to bleeding within the brain and neurologic damage. Helmets contain a layer of foam which is designed to crush upon impact. In a crash the foam collapses and extends the time over which the head comes to rest, thus reducing the force of impact. Helmet laws reduce fatal injuries by 20% and serious head injuries by 45%. Mandatory helmet laws in the US have reduced injuries by motorcycle drivers by 20-30%.[63]

**Cardiovascular disease:** Cardiovascular diseases are the profile of bioengineer Albert King:

The College of Engineering at Wayne State University has been a pioneer in the field of impact biomechanics since 1939. Two researchers in particular, Lawrence Patrick and Albert King, have made a number of significant contributions to the field of automotive safety. Dr. Patrick, who assumed the position of director of the Biomechanics Research Center in 1965, was known as a courageous researcher, volunteering himself for a number of different impact tests in the name of scientific advancement. In the image below, Dr. Patrick is shown preparing to ride the crash sled; a task usually reserved for cadavers and dummies. Dr. Patrick’s research led to the development of the Wayne State Tolerance Curve (an index of head-injury tolerance) as well as many automotive design improvements including the airbag. In 1976, Dr. Albert King took over the position of director, carrying on Patrick’s legacy. Dr. King’s research attempts to numerically model human bone structure from head to foot in order to predict injuries that might result from a crash. These models are verified in the laboratory experimentally using both crash test dummies and cadavers and then used to help design safer cars. Dr. King’s work has contributed to the regulations and design specifications of vehicles in the area of safety, resulting in safer steering columns, high penetration resistance windshields, tempered glass side windows, three-point belt restraint systems, and airbags.

Source: http://www.eng.wayne.edu/page.php?id=266
second leading cause of death for people aged 15-44 in developed countries and the third leading cause of death in this age group in developing countries.\[2\] Worldwide, more than 768,000 people aged 15-44 die every year as a result of cardiovascular diseases.\[2\] The most common cause of fatal cardiovascular disease in this age group is ischemic heart disease, which kills more than 286,000 people aged 15-44 every year.\[2\] Cerebrovascular disease is the second leading cause of cardiovascular mortality in this age group, killing 159,000 people aged 15-44 yearly.\[2\] Here, we will consider the pathophysiology of both ischemic heart disease and cerebrovascular disease.

In the United States more than 12 million people have ischemic heart disease.\[51\] This disease causes more deaths, disability and economic cost than any other illness in the US. The risk factors for developing ischemic heart disease include a positive family history, diabetes, hyperlipidemia (high cholesterol), hypertension (high blood pressure), and smoking.\[51\]

Ischemic heart disease is also called coronary artery disease (CAD) because it develops in the coronary arteries which supply blood to the heart. Throughout your lifetime, cardiac muscle cells in the heart contract rhythmically in order to supply the rest of your body with oxygenated blood. In fact, your body’s total volume of blood is pumped through the heart each minute. In order to maintain its function, the heart itself requires a continuous supply of oxygenated blood. The coronary arteries are responsible for supplying blood to heart muscle. Figure 4.30 shows the two main coronary arteries, the right main coronary artery and the left main coronary artery. These arteries branch directly from the aorta, and are about 3 mm in outer diameter at their maximum point. They branch and encircle the heart to supply oxygenated blood throughout.

In coronary artery disease, the lumen of the coronary arteries becomes obstructed in a process known as atherosclerosis (Figure 4.31). As the atherosclerotic narrowing obstructs blood flow in the coronary arteries, the oxygenated blood flow to the heart muscle is decreased. The most common symptom of CAD is angina, or chest pain. A typical angina patient is a man over 50 years of age or a woman over 60 years of age who suddenly experiences a sense of heaviness, pressure, squeezing, smothering or choking which is localized to the chest and may radiate to the left shoulder or both arms.\[51\] Angina attacks typically last 2-5 minutes. When atherosclerosis initially develops, the resid-
ual coronary artery circulation provides sufficient oxygenated blood to perfuse the heart. However, as the blockage grows to occupy more than 75% of the lumen diameter, during periods of exertion there is an insufficient supply of oxygenated blood to the heart and angina results.[51] As the degree of coronary blockage increases, patients may develop unstable angina, with severe pain of increasing frequency and, as the obstruction occupies more than 80% of the lumen, angina at rest.

The lumen of a blood vessel is lined by a specialized layer of endothelial cells. These endothelial cells serve an important role; they control the transport of many substances between blood and the surrounding tissue. When this layer of cells is damaged, as can occur with high blood pressure or due to high serum nicotine levels, cholesterol from the blood can deposit at the site of injury. The blood vessel reacts to this injury by producing large amounts of fibrous tissue; this fibrous cap covers the lesion. The center of the lesion generally contains dead cells and cholesterol debris and is known as the necrotic core. Some atherosclerotic plaques remain stable over time and simply reduce the size of the lumen available for blood flow. However, in some plaques the fibrous cap ruptures and the material in the necrotic core is exposed to the blood within the lumen. These plaques are known as unstable plaques. The material within the necrotic core is very thrombogenic and can rapidly cause a blood clot to form. The blood clot can lead to complete occlusion of the coronary artery, so that none of the tissue downstream from the blockage receives oxygenated blood. Without rapid treatment, the heart muscle supplied by the blocked artery will die. This event is known as a myocardial infarction, or heart attack. In the US, approximately 30% of patients do not survive a first heart attack; more than half

**Figure 4.31:** The series demonstrates the process and growth of an atherosclerotic plaque, and the development of a blood clot at the site of a ruptured plaque.
Coronary Arteriography:

Coronary arteriography is a non-surgical diagnostic procedure used to evaluate patients who exhibit chest pain. In this procedure, which is also called cardiac catheterization, thin catheters are threaded through blood vessels and into the heart. Contrast dye which absorbs x-rays is injected into the catheters to allow physicians to see inside the heart and the vessels using x-rays. This procedure is often used to determine if there are any blockages in the arteries surrounding the heart.


die before reaching a hospital. If the patient survives the myocardial infarction, the dead heart muscle is replaced with a fibrous scar. The scar tissue does not contract in the same way as healthy cardiac muscle, and the function of the heart can be severely compromised.[51]

The diagnosis of ischemic heart disease is usually made by listening to the patient’s history. Physical examination may reveal other disorders, including lipid disorders, hypertension, and diabetes. Diagnostic tests performed include an electrocardiogram to measure the electrical activity of the heart at rest and during activity (stress test), and coronary arteriography. In coronary arteriography, x-rays are used to take a picture of the lumen of the coronary arteries, also known as an angiogram. A radio-opaque dye is injected into the coronary circulation, and x-ray movies of the flow of the dye are obtained. For 50% of patients, their first symptom of CAD is a heart attack.[51]

Treatment of ischemic heart disease includes giving drugs such as nitrates or calcium channel agonists; these drugs increase the supply of blood to the heart by increasing the diameter (dilating) of the coronary arteries.[51] Other drugs, such as beta blockers, can be given to reduce the oxygen demand of the heart. While these drugs can relieve symptoms of CAD, they do not reduce the coronary artery blockage.

Treatments which increase coronary artery blood flow include drugs which dissolve the blood clot precipitating a myocardial infarction, such as tissue plasminogen activator.
In addition, there are two invasive procedures which directly treat blockages in coronary arteries—coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA). Figure 4.32 provides an overview of these two therapies, which we will consider in much more detail in Chapter 15.

159,000 persons between the ages of 15-44 die each year as a result of cerebrovascular disease, more commonly known as a stroke.[2] Cerebrovascular disease is the most prevalent neurologic disorder in the US. The vast majority of strokes (approximately 87%) are caused by ischemia and resulting infarction.[75] Ischemic strokes are a consequence of atherosclerosis in arteries which supply oxygenated blood to the brain (Figure 4.33). An ischemic stroke occurs when a blood vessel supplying the brain is blocked, depriving tissue downstream of oxygenated blood. This blockage can occur in a manner similar to that which occurs in a heart attack. If an atherosclerotic lesion within a brain vessel ruptures, blood in the vessel can come in contact with thrombogenic material within the plaque. A clot quickly forms in the vessel, closing off all blood flow. A stroke can also occur when a large clot formed elsewhere in the blood stream breaks loose and lodges in a blood vessel within the brain. Additionally, vessels within the brain can undergo transient vasoconstriction or spasm, resulting in stroke.

Because the occlusion forms suddenly, a stroke is characterized
Chapter 4

by the abrupt onset of a focal neurologic deficit. The maximal deficit typically occurs within hours of vessel occlusion. Often, patients awaken with neurologic deficit following a completed stroke. A small fraction of patients (approximately 15%) experience warning signs before a stroke called transient ischemic attacks (TIA).[75] While a TIA has traditionally been defined as a neurological deficit that resolves within 24 hours, imaging studies have revealed that nearly 2/3 of patients with a diagnosis of TIA have actually suffered an ischemic stroke. As a result, a new definition has been proposed that is based on tissue evidence of infarction rather than a set time interval.[76]

Diagnosis of cerebrovascular disease is frequently based on the patient’s history. Physical examination will include imaging studies such as computed axial tomography (CT) scan, magnetic resonance imaging (MRI) and MR angiography (MRA) to examine blood flow in the brain (Figure 4.34). These tests can be used to diagnose ischemic stroke, hemorrhagic stroke, and other problems involving the brain, brainstem, and spinal cord. MRI uses magnetic fields and CT scans use x-rays to produce 3-D images. MRA is a special type of MRI used to see the blood vessels in the neck or brain. Used with permission from the Internet Stoke Center (http://www.strokecenter.org/).

Figure 4.34. MRI (top), CT scan (bottom left), and MR angiography (bottom right).

Treatment of cerebrovascular disease includes the use of drugs to dissolve blood clots, or thrombolysis. Rehabilitation of stroke patients includes physical therapy, occupational therapy and speech therapy to provide encouragement and instruction for the patient and their family to overcome the resulting neurologic deficit.[51]

Tuberculosis: More than 600,000 people between the ages of 15-44 die each year as a result of tuberculosis (TB).[2] Worldwide in 2004, 9 million new cases of TB occurred, 80% in just 22 countries; in this same year, TB caused 2 million deaths, 98% in the developing world.[77, 78] It is estimated that 2 billion people—1/3 of the world’s population—are presently infected with TB bacilli, the causative agent of the disease. The global burden of TB continues to grow by 1% a year, primarily due to rapid increases in Africa

Figure 4.35:
Based on surveillance and survey data, there were an estimated 8.9 million new cases of TB in 2004 (140 per 100,000), including 3.9 million (62 per 100,000) new smear-positive cases.
WFP Update: June 25, 2007

Tessa

Just a quick update on what has been going on with the WFP project this past week...

We want to be sure that there will be someone to continue the WFP food distribution after Dave and I leave. So we are trying to find volunteers among the clinic patients. Before we could bring volunteers in to train, we had to find a way to cover their transportation costs (and perhaps a little extra as an incentive to volunteer). I managed to get a local grocery store to donate food vouchers. This is enough to cover the next month, and while it is very exciting, I need to see if we can get enough (perhaps from other grocery stores) to cover a few months more. It is difficult to get funds here at the clinic (even if it is a measly 400 rand—about 55 dollars—a month). At least now that we have the vouchers, we can bring in some women and start training them. The process of deciding on the trainees was interesting as well. I basically got a list from the clinic social worker of women she thought would be appropriate for the job (and who were in desperate need of food). During the process of choosing, I asked her if these women were literate. The ability to read and write is clearly crucial to being able to register the patients. Unfortunately she didn’t know, so now we basically have to bring them in one at a time and see how capable they are. One woman today actually approached me and asked about volunteering. She had completed high school and lived close by. She also seemed like she would be easy to train and like she would be capable of training other women after I leave. Despite all these factors, the clinic staff (the social worker and several other women met to discuss whom I should train) decided that I should try the other women first since their need was much greater. At first I wasn’t sure about the decision, but the more I think about it, the more I like how they made the decision. It shows how much the people here care about their patients. And if these women don’t work out, I think there will be enough time to train someone more capable.
Chapter 4

Figure 4.35: Transmission of tuberculosis and progression from latent infection to reacti-vated disease. Among persons who are seronegative for the human immunodeficiency virus (HIV), approximately 30 percent of heavily exposed persons will become infected. In 5 percent of persons with latent infection, active disease will develop within two years, and in an additional 5 percent, progression to active disease will occur later. The rate of pro-gression to active disease is dramatically increased among persons who are co-infected with HIV. Used with permission from [79].

Copyright © 2003 Massachusetts Medical Society. All rights reserved.

(Figure 4.35). It has been estimated that TB will kill another 35 million people in next 20 years if the current situation does not change.[78]

TB is a bacterial infection of the lungs caused by Mycobac-terium tuberculosis.[51] Not all people who are infected with TB have symptoms of the disease; most have what is known as latent TB. In latent TB, the patient's immune sys-tem has walled off the TB bacilli within a thick waxy coat to form granulomas. Latent TB can thus lie dormant for years before becoming active and causing symptoms (Figure 4.36).[51] Only 5-10% of people with normal immune sys-tems who are infected with TB will go on to develop active TB.[79]

However, a much higher fraction of people with weak im-mune systems who are infected with TB will develop active TB. For this reason, TB is particularly problematic in people with weak immune systems, including those with AIDS, ba-bies, and young children. In fact, people with AIDS are 100 times more likely to develop active TB once infected; HIV positive individuals have a 50% lifetime risk for developing active disease compared to a 5-10% lifetime risk for HIV negative individuals.[80, 81] The result is an escalation of TB incidence in countries with a high prevalence of HIV (Figure 4.37).[77] Furthermore, TB is the leading cause of death among HIV positive individuals, accounting for 13% of AIDS deaths worldwide.[82]

Skin and Serum Tests for TB:

The Mantoux tuberculin skin test, also known as the purified protein derivative (PPD) test, is the most accurate and thus preferred type of skin test. For the test, tuberculin—protein derived from tubercle bacilli that have been killed by heating—is injected between the layers of the skin, usually on the forearm. 2-3 days later, swelling at the injection site is assessed. Whether a reaction is classi-fied as positive depends on the diameter of the swelling, as well as the person's risk factors for TB. Most people with TB infection have an immune reaction to the tuberculin, as it resembles the tubercle bacilli causing their infection.

The QuantiFERON-TB Gold (QFT-G) blood serum test—approved by the FDA in 2005—measures a blood sample’s response to the presence of TB proteins. QFT-G can be used in all circumstances in which tuberculin skin tests are used. Additionally it may be used with persons who test false-positive with a tuberculin skin test, e.g. those vaccinated against TB with Bacille Calmette Guerin (BCG) and those who undergo serial evaluation for TB.
In active TB, the bacteria usually affect the lungs. Symptoms of active pulmonary TB include a persistent bad cough, chest pain, coughing up blood or sputum, weight loss, weakness, chills, fever, and night sweats. Hence TB is spread through the air from a person with active infection to another. If untreated, each person with active TB infects on average 10-15 people every year. Left untreated, active pulmonary TB results in lung tissue necrosis. This severe lung damage leads to hypoxia and death within 5 years in 65% of all cases. Additionally, highly fatal TB can result from bacilli dissemination to and destruction of a host of organs, such as the spleen, liver, kidneys, bone marrow and central nervous system.

Latent infection of TB is indicated by a positive skin or serum test with a negative chest x-ray. However, in HIV positive persons with TB infection or disease, skin tests often elicit no reaction due to their compromised immune response and sputum tests are often read as negative due to the unusual, difficult to diagnose strains of TB that HIV infected persons tend to contract. Nevertheless, annual TB screening is recommended for these high risk individuals. In all patients suspected of TB infection or disease, diagnosis of active TB is made by a chest x-ray (Figure 4.38) which shows nodules in the lungs, and is confirmed by positive sputum culture for *M. tuberculosis*.

It is important to treat patients for both latent and active TB. Drugs which cure TB have been available since the 1940s. Patients with a latent TB infection are treated with the antibiotic isoniazid; this treatment will prevent them from developing active TB. Active TB can almost always be cured by taking several antibiotics in combination, including isoniazid, rifampin, ethambutol and pyrazinamide. Active TB patients remain contagious during the first few weeks of antibiotic therapy and it is important for them to stay isolated for several weeks until they are no longer infectious. After several weeks of treatment, symptoms subside and patients begin to feel better. However, to completely cure the TB infection, patients must take drugs for 6 months. If patients discontinue medication before this period, it is much more likely that the TB will relapse and the TB bacilli will develop resistance.

Drug resistant TB is a particularly serious form of the disease and must be treated with special medicines. Because of the risk of resistant disease, poorly supervised therapy for TB is worse than no therapy at all. A simple clinical protocol has been shown to dramatically increase TB cure rates. Directly observed treatment short-course (DOTS) is the process of administering TB medicine daily under the watch of a health care worker. The use of DOTS can achieve cure rates of up to 95%.
even in the poorest countries. A 6 month supply of DOTS costs only $10.[82] More than 20 million TB patients worldwide have been treated with DOTS since 1995. However, approximately 20% of the world’s population still does not have access to DOTS.[77]

Multi-drug resistant TB (MDR-TB) is TB disease that arises from bacilli resistant to two or more TB medicines. MDR-TB is present in all countries surveyed by WHO and is a growing concern.[82] The prevalence of resistance in new TB cases is as high as 21.7% (7% median) for a single drug and as high as 17.8% (2.2% median) for two drugs.[85] Today, more than 450,000 new cases of MDR-TB occur each year. The problem is of particular concern in the Russian Federation, India, and China, where up to two-thirds of new MDR-TB cases occur (Figure 4.39).[83]

**Cancer:** Cancer is the third leading cause of death in developed countries for persons aged 15-44, killing more than 129,000 people each year. Worldwide, more than 580,000 people aged 15-44 die of cancer each year. The leading causes of cancer death for people in this age group include liver cancer (68,000 deaths/year), leukemias (65,000 deaths/year), stomach cancer (58,000 deaths/year) and breast cancer (57,000 deaths/year).[2] Nearly half of all men in US and 1/3 of women in the US will develop cancer at sometime in their lives. [86]

Cancer is a complex group of diseases, all of which are characterized by uncontrolled cell growth. Cancer cells usually form an abnormal mass called a tumor (some blood cancers like leukemia are exceptions).[86] The tumor grows more rapidly than the surrounding normal tissue and can damage adjacent normal structures. Tumors are characterized as benign or malignant based on the ability of tumor cells to break away from the main lesion and spread (metastasize) to other parts of the body. Benign tumors cannot metastasize, and are usually not life threatening. Malignant tumors can spread to distant sites; it is this metastasis that is responsible for more than 90% of deaths caused by cancer.[87]
I spent today making presentations, reading about nutrition, and checking up on some patient files for Dr. Eric. And, while that was interesting, all that sitting at a desk and staring into a computer all day can get quite tiresome. So at the end of the day, I decided to change things up a bit—get a little reality check—and step into a Dr.’s room and observe a check-up.

The room I chose was Dr. Amy’s.

I absolutely love Amy, by the way. She, very kindly, offered to take Tessa and I to Mlilwane this weekend, which we of course accepted, and I got to know her pretty well along the way. I also had the pleasure of meeting her daughter, Molly—a darling two-year-old with curly blonde hair who is quite afraid of strangers (she covers her eyes with her hands whenever she meets one) but is quite talkative and friendly once she warms up to you. Molly accompanied us for the ride in her carseat. Before hitting the road for good, we had to make an emergency stop at Amy and Molly’s in order to make about 50 tunafish sandwiches for a meeting she had to go to afterwards (for which she had to be a good little Swazi wife and bring a meal—despite the fact that, unlike the rest of the wives that would be attending just as wives, she, as a doctor, was actually going to present). Oh, and I plan on trying her special tuna fish sandwich recipe which involves apple slices as soon as possible.

So, I went in to Dr. Amy’s room and asked her if it would be alright for me to observe, and she said she was quite happy to have me come in. She was just starting her last check-up of the day with an adorable four-year-old boy named Clement.

Clement is HIV positive. However, because the Baylor Clinic has been able to provide him with free ARVs for a year now he is now quite healthy. His CD4 count has risen since he began ARV treatment from around 500, which is quite low, to a now very normal level of about 1,100.

Clement came in today with his gogo (grandmother) because of a cough he has had for about 4
weeks now. Amy treated him about two weeks ago with antibiotics, but it failed to help. The reasons for this, as Amy told me, could be that the prescribed antibiotic wasn’t the right one, the cough could be caused by a virus rather than bacteria, or that it could be tuberculosis. Apparently, Swaziland holds the record right now for the country with the highest percentage of its population infected with tuberculosis. Because of the prevalence of the disease here, it was very important for Amy to find out if this was Clement’s problem and treat it as quickly as possible. So, in order to check for TB, she had to administer a skin test.

A skin test, unfortunately, involves a needle, and when Amy reentered the room with needle in hand . . . you should have heard Clement’s screams! I had no idea that a child that small could produce a noise that big. Or, quite frankly, that unnerving.

I was a bit shell-shocked, but, of course, to Amy, the seasoned pediatrician, Clement’s screams were nothing out of the ordinary. She proceeded without hesitation. It took the combined effort of Gogo, Amy, and even Lulu (the translator) to hold Clement’s thrashing body still long enough for Amy to inject him for the test.

After the shot (which was given with a needle so small that I doubt he was able to even feel it much) Clement continued to cry a bit, but it was a more resigned “Oh, I guess that didn’t hurt too badly but I’m still mad at you for making me do something I didn’t want to do” kind of cry.

Besides the screaming part, I had a fantastic time observing. Amy did a wonderful job of teaching me about all kinds of things like what she looks for during a check-up, what different symptoms mean, and how she uses the medical records. In Clement’s case, it was the medical records that Amy and I found most interesting. While showing me the medical records, she noticed a very strange doctor’s note: Apparently, Clement’s house had recently burnt down.

And, apparently, somehow adorable little Clement did it.

Poor guy!
A cancer cell develops as a result of non-lethal damage to DNA; this damage can accrue as a result of environmental exposure to carcinogens, hereditary defects or a combination of both.[86] In any case, the cancer cell multiplies and unless eradicated by the host immune system, a tumor arises from the expansion of a single progenitor cell that has incurred genetic damage.

As tumors grow and become more aggressive, tumor cells can detach from the primary tumor, and secrete enzymes to degrade the matrix of connective tissue which surrounds them. This process is known as local invasion and enables the tumor to infiltrate the organ where it originated. In some cases, tumor cells migrate to blood vessels or lymphatic vessels. From there, tumor cells can circulate throughout the body, lodge in distant organs and form a metastasis.[88] Figure 4.41 illustrates the steps that occur during tumor formation and metastasis.

The most effective therapy to treat cancer is surgical removal. Generally, the patient’s prognosis is excellent if all of a tumor can be resected. However, in many cases, cancers are not diagnosed until there has been extensive tumor growth and metastasis, preventing complete surgical removal. In these cases, chemotherapeutic agents or radiation therapy or a combination of the two, generally after surgery removing the majority of the tumor mass, can be used to kill elusive tumor cells. Because early lesions are so much easier to treat, improvements in early detection can play a large
role in improving survival rates for cancer patients. Methods for the early detection of cancer are as varied as the sites in which they develop. Screening for early cancers generally occurs as a part of population-based programs and frequently leads to a biopsy of the suspected tumor site for microscopic examination.

**Figure 4.42** shows the 5 year survival rate for colorectal cancer, skin cancer, oral cancer, bladder cancer, and cervical cancer as a function of the stage of the tumor when it is initially detected. When a tumor is detected at a stage when only local invasion has occurred, the 5 year survival rates are on average over 90%. If regional metastasis has occurred, 5 year survival rates drop to 50-70%. However, when metastasis to distant organ sites has occurred, the 5 year survival rates are only 5-30%. Later in this chapter, we will consider the pathophysiology of lung cancer in more detail. One reason that lung cancer is so deadly is that it is frequently not detected until distant metastasis has occurred.

**Self-Inflicted Injuries:** The fourth leading cause of death for people aged 15-44 in developed countries is suicide – worldwide, more than 480,000 people between the ages of 15 and 44 years take their own lives, nearly as many as die from cancer in this age group.[2]

In 2003, the US reported a suicide rate of 10.8/100,000 people. The rate was 17.6/100,000 for men and 4.3/100,000 for
Firearms are used in nearly 60% of suicides; hanging and drug overdose are the second leading means of suicide for men and women respectively. Alcohol intoxication is associated with 25-50% of suicides.

The causes of suicide are complex - including interactions between personal, family, community and societal problems. The major risk factors include ready availability of weapons, inadequate social problem solving skills, abuse of alcohol and drugs, psychiatric illness, and affective, personality and other mental disorders. Other contributing risk factors include social adjustment problems, serious medical illness, living alone, recent bereavement, personal history of suicide attempt, divorce or separation, and unemployment.

Several of the risk factors for suicide could be screened for in the physician’s office. In fact 50-66% of all suicide victims visit a physician within 1 month before the event and 10-40% of victims visit their physician in the preceding week, suggesting the potential for screening and prevention. However, it is difficult to identify who is at risk. Direct questioning, including general questions about sleep disturbance, depressed mood, guilt and hopelessness, has been found to have low yield. Similarly, different survey instruments have not been shown to be good at predicting what will happen.

Leading Causes of Mortality, ages 45-60

For persons aged 45-60, the four leading causes of death in the developing world are:

1. Cardiovascular diseases,
(2) Cancer (malignant neoplasms),
(3) Unintentional injuries, and
(4) HIV/AIDS.

In the developed world, the four leading causes of death in this age group are:[2]

(1) Cardiovascular diseases,
(2) Cancer (malignant neoplasms),
(3) Unintentional injuries, and
(4) Digestive Diseases.

**Cardiovascular Diseases:** In both developed and developing countries, cardiovascular diseases are the leading cause of death for people aged 45-59, killing more than 2 million people in this age group every year.[2] Ischemic heart disease is the single leading cause of cardiovascular death in this age group, and is responsible for 1 million of these deaths.[2] Cerebrovascular disease is the second leading cause of cardiovascular death, killing nearly 625,000 people between the ages of 45 and 59 years worldwide.[2]

**Cancer:** Cancer is the second leading cause of death in both developed and developing countries for people aged 45-59.[2] More than 1.5 million people of this age die every year as a result of cancer. Lung cancer is by far the leading cause of cancer death in this age group, killing 263,000 people aged 45-59 each year throughout the world.[2] After lung cancer, stomach cancer (185,000 deaths/year), liver cancer (179,000 deaths/year) and breast cancer (148,000 deaths/year) account for most cancer mortality among this age group.[2]

Lung cancer is the leading cause of cancer death in men in the United States. An estimated 89,510 males and 70,880 females in the US will die of lung cancer in 2007.[92] Only 16% of patients with lung cancer survive 5 years or more after the original diagnosis.[92] The survival rate of lung cancer is so low because it is usually not detected until it is at a very advanced and untreatable stage. Only 16% of patients are diagnosed with localized disease, when treatment is most effective.[92] The most important risk factor for the development of lung cancer is smoking. Patients who actively smoke increase their risk of developing lung cancer by 13-fold, while patients exposed to passive smoke increase their risk by 1.5 times.[51]

The signs and symptoms of lung cancer include coughing, chest pain, difficulty breathing, and recurrent pneumonia.[92] A chest x-ray can document advanced lung cancer. The diagnosis of lung cancer is usually confirmed by a biopsy, obtained

**Figure 4.43:** Biopsies taken to detect the presence of cervical cancer, viewed as histological sections. The above are examples of a) normal tissue; early stage precancerous changes, b) CIN II, c) CIN I, d) CIN III; e) micro-invasive cancer; f) cancer.
under the guidance of CT or obtained through a bronchoscope.[51]

Small lung tumors can be removed surgically, usually resulting in good prognosis. Larger tumors which are confined to the lung are usually treated with chemotherapy or radiation therapy and surgery. Metastatic lung tumors are treated with a combination of chemo- and radiation therapy.[51]

It is usually difficult to detect lung cancer at an early stage when it is most easily treatable. By the time patients experience symptoms, the disease has usually spread to other organs.[51] A number of technologies have been tested to determine if they are useful to screen the general population for early lung cancer. However, clinical trials of chest x-ray and sputum cytology, (two of the most promising technologies), have not proven adequate to screen for early disease. [92]

Unintentional injuries: Unintentional injuries are the third leading cause of death in both developed and developing countries for people between the ages of 45 and 59 years, and are responsible for 618,000 deaths per year in this age group.[2] Road traffic accidents are by far the leading cause of death by unintentional injury in this age group, accounting for more than 222,000 deaths per year.[2]

HIV/AIDS: The fourth leading cause of death in developing countries is HIV/AIDS, which kills 386,000 persons aged 45-59 in developing countries each year.[2]

Digestive Diseases: The fourth leading cause of death in developed countries for persons aged 45-59 is digestive diseases. Worldwide, 456,000 people in this age group die each year as a result of digestive diseases.[2] Cirrhosis of the liver is by far the most common fatal digestive disease, killing 250,000 people each year between the ages of 45 and 59.[2]

The liver is the largest organ in the body and performs a number of crucial physiologic functions (Figure 4.44).[93] All blood that leaves the stomach and intestines passes to the liver through the hepatic portal vein; in addition, blood from the peripheral tissues enters the liver via the hepatic artery. [93] This blood contains nutrients as well as drugs and foreign substances that have been ingested. The liver metabolizes fat and glucose for energy storage and helps to remove toxic substances from the blood, transferring wastes to the kidney to be excreted. [93] The liver is the body’s largest chemical factory, producing bile to help absorb fats, proteins that regulate blood clotting, and immune agents.[93]
Loss of liver function can produce severe disease and death.

In cirrhosis, normal liver is replaced with scar tissue as a result of chronic injury, interfering with liver function.[94] There are several causes of cirrhosis, the two most common are chronic alcoholism and viral hepatitis infection.[94]

Alcoholic cirrhosis usually develops after more than a decade of heavy drinking. Heavy drinkers include those who drink between 8-16 ounces of hard liquor per day; about 1/3 of those who drink this much will develop cirrhosis within 15 years.[95] However, some social drinkers will develop alcoholic cirrhosis; this is much more likely in women for reasons that are not well understood. Alcohol injures the liver by blocking protein, fat and carbohydrate metabolism.[94]

Hepatitis is a viral infection which can also produce cirrhosis. In the United States, hepatitis C is the most common cause of infectious hepatitis; however, worldwide, hepatitis B is the most common cause.[94] Both infections cause liver inflammation and injury that can lead to cirrhosis over several decades. Acute hepatitis B infection leads to chronic hepatitis in approximately 1-5% of patients, a fraction of whom will develop cirrhosis.[51] Acute hepatitis C becomes chronic in 85-90% of patients. Approximately 20-50% of these patients will develop cirrhosis.[51]

The symptoms of cirrhosis include exhaustion, loss of appetite, nausea, vomiting blood, weakness, weight loss, and abdominal pain.[94] Patients bruise and bleed easily and become highly sensitive to medicines with increasing loss of liver function.

The diagnosis of cirrhosis is made by a liver biopsy done through a needle. It is currently not possible to reverse the liver damage associated with cirrhosis.[51] Discontinuing use of alcohol can prevent further damage as can treatment of hepatitis with medicines to boost immune response. In advanced cases, liver transplant is currently the only treatment which can restore liver function.

**Leading Causes of Morbidity and Mortality:**

In this chapter, we have considered the leading causes of mortality throughout the world. In examining global health, it is important to consider both causes of mortality and morbidity. As we saw in Chapter 3, the number of DALYs lost to disease measures the combined effects of morbidity and mortality. Table 4.4 shows the ten diseases which result in the greatest number of disability free years of life lost by age.
for developed and developing countries. In comparing Table 4.1 to Table 4.4, it is evident that the leading causes of mortality are not necessarily the same as the leading causes of morbidity. For example, unipolar depressive disorders are the leading cause of morbidity in the developed world and the second leading cause of morbidity in the developing world for ages 15-44. Despite the prevalence of these disorders and their significant contribution to the worldwide burden of disease, they are not listed as a leading cause of mortality. In assessing the state of health throughout the world it is important to consider not only the causes of death, but also those conditions, such as mental illness, that significantly impact a person’s quality of life.

Global Health Challenges

Can technology address the health challenges that are faced by citizens in the developing world? In January 2003, the Bill and Melinda Gates Foundation announced a $200 million medical research initiative to solve medical issues identified as ‘grand challenges’ in global health. This initiative is designed to encourage scientific and technological solutions to diseases that disproportionately affect the developing world. The initiative seeks scientific or technical innovations that remove a critical barrier to solving an important health problem in developing world, with a high likelihood of global impact and feasibility. The Foundation solicited ideas for Grand Challenges in May 2003 and received 1048 submissions from scientists and institutions in 75 countries. The Foundation’s Scientific Board heard proposals in August 2003 and identified 7 long range goals and 14 grand challenges (Table 4.5). These are heavily oriented toward infectious disease, largely because infectious diseases account for the most profound discrepancies between advanced and developing economies, and because the causes of infectious diseases are well-known and scientists can more easily understand and address technical and scientific obstacles to progress.
**Chapter 4**

### Table 4.4: Top ten causes of morbidity by age in developed and developing countries.[2]

#### Ages 0-4

<table>
<thead>
<tr>
<th>Cause of Disability</th>
<th># DALYs</th>
<th>% of Total DALYs</th>
<th>Cause of Disability</th>
<th># DALYs</th>
<th>% of Total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory infections</td>
<td>60,236,694</td>
<td>14.3%</td>
<td>Low birth weight</td>
<td>1,337,103</td>
<td>10.3%</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>55,543,326</td>
<td>13.2%</td>
<td>Congenital heart anomalies</td>
<td>1,327,944</td>
<td>10.2%</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>44,997,007</td>
<td>10.7%</td>
<td>Birth asphyxia and birth trauma</td>
<td>1,310,241</td>
<td>10.1%</td>
</tr>
<tr>
<td>Malaria</td>
<td>42,244,747</td>
<td>10.0%</td>
<td>Lower respiratory infections</td>
<td>1,138,923</td>
<td>8.8%</td>
</tr>
<tr>
<td>Birth asphyxia and birth trauma</td>
<td>33,133,613</td>
<td>7.9%</td>
<td>Diarrhoeal diseases</td>
<td>537,438</td>
<td>4.1%</td>
</tr>
<tr>
<td>Measles</td>
<td>18,618,263</td>
<td>4.4%</td>
<td>Iodine deficiency</td>
<td>495,378</td>
<td>3.8%</td>
</tr>
<tr>
<td>Protein-energy malnutrition</td>
<td>14,718,970</td>
<td>3.5%</td>
<td>Mental retardation, lead-caused</td>
<td>467,625</td>
<td>3.6%</td>
</tr>
<tr>
<td>Congenital heart anomalies</td>
<td>12,851,427</td>
<td>3.1%</td>
<td>Meningitis</td>
<td>367,109</td>
<td>2.8%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>12,264,915</td>
<td>2.9%</td>
<td>Down syndrome</td>
<td>367,281</td>
<td>2.8%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>12,181,146</td>
<td>2.9%</td>
<td>Asthma</td>
<td>259,845</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Total DALYs: 420,827,539 | Total DALYs: 13,003,994
Total Population: 536,962,742 | Total Population: 81,206,312

#### Ages 15-44

<table>
<thead>
<tr>
<th>Cause of Disability</th>
<th># DALYs</th>
<th>% of Total DALYs</th>
<th>Cause of Disability</th>
<th># DALYs</th>
<th>% of Total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>59,392,428</td>
<td>13.3%</td>
<td>Unipolar depressive disorders</td>
<td>10,484,105</td>
<td>13.7%</td>
</tr>
<tr>
<td>Unipolar depressive disorders</td>
<td>35,978,376</td>
<td>8.1%</td>
<td>Alcohol use disorders</td>
<td>6,308,519</td>
<td>8.3%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>19,848,813</td>
<td>4.5%</td>
<td>Road traffic accidents</td>
<td>3,804,331</td>
<td>5.0%</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>19,151,250</td>
<td>4.3%</td>
<td>Self-inflicted injuries</td>
<td>3,144,909</td>
<td>4.1%</td>
</tr>
<tr>
<td>Violence</td>
<td>14,923,499</td>
<td>3.3%</td>
<td>Violence</td>
<td>2,285,286</td>
<td>3.0%</td>
</tr>
<tr>
<td>Self-inflicted injuries</td>
<td>12,189,495</td>
<td>2.7%</td>
<td>Bipolar disorder</td>
<td>2,209,104</td>
<td>2.9%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>12,074,350</td>
<td>2.7%</td>
<td>Drug use disorders</td>
<td>2,037,084</td>
<td>2.7%</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>10,977,659</td>
<td>2.5%</td>
<td>Schizophrenia</td>
<td>1,944,628</td>
<td>2.5%</td>
</tr>
<tr>
<td>Alcohol use disorders</td>
<td>10,664,330</td>
<td>2.5%</td>
<td>Ischaemic heart disease</td>
<td>1,916,252</td>
<td>2.5%</td>
</tr>
<tr>
<td>Hearing loss, adult onset</td>
<td>9,186,758</td>
<td>2.1%</td>
<td>Hearing loss, adult onset</td>
<td>1,523,616</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Total DALYs: 445,613,527 | Total DALYs: 76,416,610
Total Population: 2,312,272,679 | Total Population: 597,682,683

#### Ages 45-59

<table>
<thead>
<tr>
<th>Cause of Disability</th>
<th># DALYs</th>
<th>% of Total DALYs</th>
<th>Cause of Disability</th>
<th># DALYs</th>
<th>% of Total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>12,050,270</td>
<td>7.6%</td>
<td>Ischaemic heart disease</td>
<td>5,286,352</td>
<td>11.3%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10,212,640</td>
<td>6.4%</td>
<td>Cerebrovascular disease</td>
<td>3,123,891</td>
<td>6.7%</td>
</tr>
<tr>
<td>Cataracts</td>
<td>9,735,678</td>
<td>6.1%</td>
<td>Unipolar depressive disorders</td>
<td>3,006,141</td>
<td>6.4%</td>
</tr>
<tr>
<td>Unipolar depressive disorders</td>
<td>8,374,876</td>
<td>5.3%</td>
<td>Hearing loss, adult onset</td>
<td>1,884,097</td>
<td>4.0%</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>7,267,981</td>
<td>4.6%</td>
<td>Trachea, bronchus, lung cancers</td>
<td>1,770,453</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hearing loss, adult onset</td>
<td>6,891,572</td>
<td>4.3%</td>
<td>Chronic obstructive pulmonary disease</td>
<td>1,762,640</td>
<td>3.6%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>6,793,167</td>
<td>4.2%</td>
<td>Osteoarthritis</td>
<td>1,645,250</td>
<td>3.3%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6,504,266</td>
<td>4.1%</td>
<td>Cirrhosis of the liver</td>
<td>1,450,096</td>
<td>3.1%</td>
</tr>
<tr>
<td>Vision disorders, age-related</td>
<td>4,787,811</td>
<td>3.0%</td>
<td>Diabetes mellitus</td>
<td>1,388,386</td>
<td>3.0%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4,045,375</td>
<td>2.5%</td>
<td>Alcohol use disorders</td>
<td>1,086,926</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Total DALYs: 159,380,182 | Total DALYs: 46,615,959
Total Population: 600,316,766 | Total Population: 254,000,864

---

[2] For the full data, see the source or further research.
<table>
<thead>
<tr>
<th>GOAL: To improve childhood vaccines:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC #1 Create effective single-dose vaccines that can be used soon after birth</td>
</tr>
<tr>
<td>GC#2 Prepare vaccines that do not require refrigeration</td>
</tr>
<tr>
<td>GC#3 Develop needle-free delivery systems for vaccines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOAL: To create new vaccines:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC#4 Devise reliable tests in model systems to evaluate live attenuated vaccines</td>
</tr>
<tr>
<td>GC#5 Solve how to design antigens for effective, protective immunity</td>
</tr>
<tr>
<td>GC#6 Learn which immunological responses provide protective immunity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOAL: To control insects that transmit agents of disease:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC#7 Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population</td>
</tr>
<tr>
<td>GC#8 Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOAL: To improve nutrition to promote health:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC#9 Create a full range of optimal, bioavailable nutrients in a single staple plant species</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOAL: To improve drug treatment of infectious diseases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC#10 Discover drugs and delivery systems that minimize the likelihood of drug resistant micro-organisms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOAL: To cure latent and chronic infections:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC#11 Create therapies that can cure latent infections</td>
</tr>
<tr>
<td>GC#12 Create immunological methods that can cure chronic infections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GOAL: To measure disease and health status accurately and economically in developing countries:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC#13 Develop technologies that permit quantitative assessment of population health status</td>
</tr>
<tr>
<td>GC#14 Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point-of-care</td>
</tr>
</tbody>
</table>

*Table 4.5: Grand Challenges in Global Health.*[96]
Bioengineering and Global Health Project

Project Task 1: Define a public health problem facing a particular country or region of the world. You may select your topic from a wide range of health issues - you must simply demonstrate that the chosen issue significantly and adversely affects the lives of people in the country or region you have selected. Write a one-page summary of your disease including: epidemiology, prevalence, and incidence in the region you have selected; pathophysiology of the disease; physical signs and symptoms of the disease.

Chapter 4 Homework

1. List the four leading causes of death in developed and developing countries for the following age groups:
   a. Ages 0-4
   b. Ages 15-44
   c. Ages 45-59
   d. Compare the differences in causes of mortality in these settings. What is responsible for the differences?
   e. Compare the leading causes of morbidity to the leading causes of mortality in each case. What differences do you note?

2. Road traffic accidents are a leading cause of death for young people.
   a. How do motorcycle helmets work to save lives?
   b. Why do factors which slow driver reaction time lead to increased crash frequency and crash severity? Name three factors which slow driver reaction times.
   c. Compare trends in motor vehicle related mortality rates in developed and developing countries over the past ten years. What factors do you think contribute to these differences?

3. Cholera can produce severe diarrhea. The associated fluid loss can lead to dehydration and death if untreated.
   a. How does cholera produce such severe fluid loss?
   b. What is oral rehydration therapy and how does it prevent dehydration associated with severe diarrhea?

4. The AIDS pandemic is a worldwide problem. An estimated 40 million people are living with HIV/AIDS and over 20 million deaths have been associated with this disease.
   a. Which component of the immune system is selectively targeted and destroyed by HIV?
   b. Sketch a plot showing (1) the viral load and (2) blood count of the cell type specified in part (a), over the time course of the disease. On the plot identify the acute phase of the infection, the latent period, and full-blown AIDS.
   c. What is the approximate length of the latent period? Can HIV be transmitted during this time?
   d. Draw a diagram which indicates the process of retrovirus replication inside a human cell.
   e. Combination drug therapies have been successful in suppressing viral levels. What is the name of the current treatment strategy and why is it so effective?
   f. There are several potential strategies for preventing retrovirus replication. On your diagram for part d, draw arrows to indicate the three stages targeted in current combination therapies. Name the type of each type of inhibition.
   g. Discuss the WHO 3x5 initiative and comment on the current progress and challenges

   a. According to the report, which species of *Plasmodium* parasites have developed drug resistance?
   b. Which region of the world is experiencing the most significant problem with drug resistance?
   c. What would be the yearly cost of treating every malaria infection on earth with the least expensive single-agent antimalarial? (Note: use the WHO’s low-end estimate of global incidence, and assume that one treatment per patient will suffice)
   d. What is the yearly cost for the least expensive combination therapy?
   e. In one sentence each, describe three strategies to prevent anti-malarial drug resistance.

6. The use of combinations of antiretroviral drugs has proven remarkably effective in controlling the progression of human immunodeficiency virus (HIV) disease and prolonging survival, but these benefits can be compromised by the development of drug resistance. Resistance is the consequence of mutations that emerge in the viral proteins targeted by antiretroviral agents. In the United States, as many as 50 percent of patients receiving antiretroviral therapy are infected with viruses that express resistance to at least one of the available antiretroviral drugs. ([NEJM 350:1023-35, 2004](http://www.nejm.org)). One new technology developed to decrease the development of resistance is described in the following NPR report: [http://www.npr.org/templates/story/story.php?storyId=5554167](http://www.npr.org/templates/story/story.php?storyId=5554167). How might this particular development reduce the risk of drug resistance in the developing and developed world?


   a. Define MDR and XDR tuberculosis.
   b. In 2004, which two regions of the world had the highest percentage of TB isolates classified as Multi-Drug Resistant?
   c. In 2004, which countries had more MDR isolates classified as XDR than any other?
   d. How does one attempt to treat MDR-TB? (Hint: Refer to the Weekly Report’s Editorial Note).

8. The Framingham Heart Study was a monumental project not only for cardiovascular disease, but for all of science, health, and medicine. Answers to the following questions may be found at the study’s website: [http://www.nhlbi.nih.gov/about/framingham/](http://www.nhlbi.nih.gov/about/framingham/).

   a. What was the initial purpose of the Framingham study?
   b. List 5 definite risk factors for heart disease, and the year in which they were found to be associated with an increased risk.


   a. What non-surgical therapies are alternatives to CABG?
   b. What vessels are used to form the “bypass”? What are the specific side effects associated with harvesting these vessels?

10. Cancer is the second leading cause of death in the United States and annually costs the health care system more than 100 billion dollars.

    a. What type of cancer is responsible for the greatest number of deaths worldwide?
    b. Why is the mortality rate so high for this type of cancer?
    c. Describe the stages of malignant tumor formation and metastasis.
References

[23] Gourevitch P. We wish to inform you that tomorrow we will be killed with our families: stories from Rwanda. 1st ed. New York: Farrar, Straus, and Giroux 1998.


Health Organization; 2005 June 29.
[70] National Transportation Safety Board. Crash tests without seatbelts. Regents Exam Prep Center.
[81] WHO Regional Office for South-East Asia. TB/HIV.