Unit 3: Where are we heading?

Unit 1: Why should we care about infectious diseases?
Unit 2: What does it mean to have an infectious disease?

Unit 3: When does a microbe become a pathogen?
Unit 4: How do pathogens make us sick?
Unit 5: How do we get better?

Up until now we have focused on identifying infectious diseases. In this unit we turn our focus to the question: When does a microbe become pathogenic? At the heart of this question is the idea that pathogenicity is a host-microbe interaction and most microbes are not pathogenic! For example, we live in a microbe-filled world but we are rarely sick.

This unit will address questions like:

- What is the difference between a pathogen and a microbe?
- Can any microbe be pathogenic under the right circumstances?
- Are the same microbes pathogenic in all hosts?
In Lesson 1.5 we discussed how the immune system is a series of barriers that protect us from pathogenic microbes. We also learned that we are constantly surrounded by bacteria, and that they even play an important role in our health. So, when and how does a microbe become pathogenic? This unit focuses on two aspects of this question: first, we will explore how microbes enter the protected areas of the host, and second, the tools (adaptations) pathogenic microbes have evolved to infect us. We will also see that the capacity for a microbe to cause disease depends on the host and the microbe!

All pathogens are microbes but not all microbes are pathogens

Remember, not all microbes are pathogens — in fact most microbes don’t cause disease. Remember, the microbes on and in our bodies outnumber our own human cells by 10 to 1. In fact, there are thousands of different microbial species living on us all the time: on and in the skin, hair, mouth, nose, respiratory tract, vagina, and gastrointestinal tract. The gut alone has about 500 to 1,000 bacterial species! All the microorganisms living on and in us are called the human microbiota, and the combined genes they carry, the human microbiome. Some estimations even state that these microbes are about 1–3% of our body mass. Our microbiota are not bystanders, they actively play a role in our health, which is evident when diseases result from overuse of antibiotics. Understanding the human microbiota is an exciting area of research and we are just beginning to understand how they impact us. We know that some of...
**DEFINITIONS OF TERMS**

**Sequencing** — the process of determining the sequence of nucleotides in genes or whole genomes.

**Virulence factors** — tools (adaptations) that allow a microbe to evade the immune system and proliferate in the host.

For a complete list of defined terms, see the *Glossary*.

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**Workbook**

**Lesson 3.1**

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**LESSON READINGS**

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**Figure 1:** Diversity seems to matter — having microbiota with a low diversity is associated with type 1 and 2 diabetes and the metabolic syndrome.

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these microbes provide benefits to the host, such as aiding digestion of food, producing vitamins for us, and training our immune system to recognize 'good' from 'bad' bacteria. Some studies have indicated correlation between the type of microbes in our bodies and diseases including allergies, diabetes, and metabolic syndrome. The diversity seems to matter as well. The data so far suggests that a diverse microbiota is associated with better health, while lower diversity has been associated with a number of diseases among which diabetes type 1 and 2, and the metabolic syndrome. However, these correlations and potential causations are not well understood, and our knowledge of them is changing quickly!

One of the major research initiatives is the **sequencing** of the human microbiome or the Human Microbiome Project. The main goal behind this project is to study variations in the human microbiome, and to look for associations with good health or diseases.

However, under special circumstances some of these mostly friendly microbes can become pathogenic. For example, if a bacterium that is beneficial to us while in the gut migrates to the bloodstream during a surgery, it might cause a life-threatening infection. **So, does this mean that the bacterium is a pathogen?**

**What is the difference between a microbe and a pathogen?**

Most of the time, microbes are not harmful or are beneficial to the host, but there are some microbes that have the ability to cause disease and such microbes are called pathogens. To be pathogenic, a microbe needs a set of tools (adaptations) that allow it to bypass immune barriers and to proliferate in the host. These tools are called **virulence factors**. As we will see, a microbe with lots of virulence factors is usually very pathogenic. Examples of such tools include bacterial capsules, attachment pili, toxins, enzymes that damage host tissues, etc.

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1. Which of the following statements about microbes is true?
   a. All microbes are pathogens.
   b. All microbes can cause disease when an opportunity presents.
   c. There are just a few species of microbes within the human body.
   d. Microbes can provide benefits to the host.

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**Figure 2:** Virulence factors are tools used to invade the host.
**DEFINITIONS OF TERMS**

**Whooping cough** — a lung infection caused by the bacterium *Bordetella pertussis*, which manifests as a prolonged cough. The disease can be life-threatening to infants.

For a complete list of defined terms, see the **Glossary**.

**LESSON READINGS**

**How do these tools work?**

In general, the virulence factors help the microbe to hide from the immune system, or overcome barriers that allow a host to keep certain organs sterile. For example, bacteria that have capsules as an outside layer, look less ‘foreign’ to the host immune system because capsules contain sugar molecules that are similar to host sugar molecules. This way, the immune cells, responsible for recognizing pathogens, don’t recognize the bacterium and fail to attack and eliminate it.

Attachment pili (also called fimbriae) are another set of virulence tools. Pili are short, hair-like appendages on the surface of bacteria. They allow bacteria to attach to host cells or to each other. When bacteria have a way to attach to host structures they can prolong their stay in the host, especially on mucus membranes. For example, the pili (fimbriae) on the bacterium that causes whooping cough, *Bordetella pertussis*, is one of its most important virulence factors.

Many bacteria produce toxins that cause damage to host cells and tissues. For example, *Vibrio cholerae*, the bacterium that causes cholera, makes a toxin that causes intestinal cells to secrete huge amount of water and electrolytes in a short period. This results in severe diarrhea that can lead to life-threatening dehydration in the host. But the diarrhea allows the bacteria to exit the current host in search of new ones. Bacteria can also make enzymes that damage tissues and organs of the host. For example, *S. aureus* produces enzymes that can break intracellular connections in a host tissue allowing the bacteria to migrate through host tissues in search of a more nutritious environment.

**Figure 3:** Bacterial cells (dark pink rods) stained to visualize the capsules (white halos around the rods).

**Figure 4:** *S. aureus* produces enzymes to help it pass through host tissue allowing it to migrate towards nutrients.

2. Which of the following is an example of a microbe using an adaptation to bypass host defenses?

   a. Bacteria which developed a mechanism to survive in low pH conditions in order to live in the stomach.
   b. When a particular bacteria outcompetes other bacteria.
   c. When a microbe encounters a new host.
   d. all of the above
DEFINITIONS OF TERMS

Meningitis — inflammation of the membranes covering the brain and the spinal cord.

Immunocompromised — a person whose immune system has a deficiency. Such a person is more susceptible to infections.

Biofilms — a cluster of microorganisms that form a colony of cells sticking to each other on a surface.

Quinine — an antimalarial drug derived from the Cinchona tree. It is usually taken orally, but if the patient is very sick, it is administered intravenously.

For a complete list of defined terms, see the Glossary.

Workbook Lesson 3.1

There are essentially two major groups of pathogens: primary pathogens and opportunistic pathogens

Primary pathogens possess virulence factors that allow them to bypass host barriers and cause disease by damaging host tissues. Examples include Neisseria meningitides (causes meningitis), and C. tetani (causes tetanus). These bacteria cause disease in most people they infect even if the hosts are in good health!

Opportunistic pathogens can be pathogenic under select circumstances such as infecting an immunocompromised host. Examples include the bacterium Pseudomonas aeruginosa, which is usually harmless to healthy people but is the leading cause of death in patients with cystic fibrosis. Cystic fibrosis is a genetic disease and people with it have a mutated (changed) membrane protein needed for fluid secretion of cells such as sweat and mucus. This mutated version of the protein doesn't function properly, and causes normal body secretions, such as mucus, to become very sticky. This stickiness leads to plugging of ducts in crucial organs like the lungs. Pseudomonas aeruginosa is normally found in the environment and when it gets inhaled into the lungs of cystic fibrosis patients, it can't be easily expelled, and gets to stick around in a perfect environment. It even forms biofilms, which are very hard to treat with antibiotics.

What is Ebola?

Microbes have evolved to live in specific environments. What happens if humans enter a new environment and contact an unknown microbe? Unfortunately sometimes, it infects humans. This is the case with the Ebola virus.

On the 5th of September 1976, a school principle named Mabalo Lokela, was admitted to a mission hospital in the Democratic Republic of the Congo (formerly Zaire). At first, his symptoms resembled malaria, as he suffered an intense fever, headache, chest pain, and nausea. He was given a quinine shot, and other standard treatments for malaria.

Figure 5: Pseudomonas aeruginosa cells (brown rods), the leading cause of death among patients with cystic fibrosis.

Figure 6: Ebola viral particles (red fibers) leaving an infected cell (in beige).

3. Which of the following about Ebola is false?
   a. It is a virus.
   b. The symptoms of the disease resemble other diseases such as malaria.
   c. Bats seem to be a natural reservoir of Ebola.
   d. Humans are not its natural host.
   e. none of the above
LESSON READINGS

However, he quickly worsened, progressing to dizziness, bloody diarrhea, eventually vomiting blood, and bleeding out of his nose, mouth, and intestines. Lokela died on September 8th from multiple organ failure.

After his burial, the hospital staff could only watch in horror as more people, friends and family of Lokela came into the hospital with similar symptoms, and they themselves began to fall ill. Ultimately 318 people became sick and eighty-eight percent of them died.

The cause of this horrible disease was later identified as a virus named Ebola after the Ebola River which is nearby to one of the first villages with an outbreak.

Where did Ebola come from?

For years, the origin of the Ebola virus was a mystery. As you know, viruses are unable to reproduce outside of host cells. This means that the virus must have had a host in order to survive. Researchers from around the world tested animals, insects, and even plants to try to find the reservoir. When Ebola broke out, researchers suspected that humans were not the natural host because Ebola is too lethal to them! Think about it; if you require a living body in order to reproduce, killing your host quickly is counter-productive since you may not have the time to spread to the next host. This leaves the question: what is Ebola's natural host? The natural host of Ebola is still speculative, but as of 2005, three species of fruit bats were found to possibly harbor Ebola without showing symptoms, the classic characteristic of a reservoir. We will learn more about reservoirs in Lesson 3.2.

If the natural reservoir of Ebola is bats, why is it infecting humans?

Humans are encroaching on areas of the world that are far beyond our natural ecosystem, and so we are exposing ourselves to the microbes that normally reside there. Some of those microbes may already have adaptations that allow them to jump from their animal host to a human. In most cases this will also mean that the microbe will be easily controlled by the immune system, since the microbe will lack adaptations that will specifically allow it to avoid the human immune system. However, if the microbe has an adaptation that works in multiple species, these microbes may be able to infect humans. But remember, the microbe did not evolve to coexist with humans so, at least initially, it is likely to cause severe disease.
Why would encroaching on a new ecosystem increase exposure to pathogens?

Consider the different structures of bacteria and viruses introduced in Lessons 1.3 - 1.4. Which structures are especially helpful in infecting hosts? How are they helpful?

Explain how an opportunistic pathogen can exist stably (without causing disease) in our gut, but could cause disease under certain circumstances.
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<th>TERM</th>
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