Unit 4:
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?

In the previous unit, we focused on adaptations that contribute to microbial pathogenicity. We emphasized the idea that pathogenicity is a host-microbe interaction and that highly pathogenic microbes have adaptations that make them virulent.

In this unit, we turn our focus to how a pathogen’s life cycle causes disease. This unit will address two major questions:

- How bacteria cause damage to the host?
- How viruses cause damage to the host?
DEFINITIONS OF TERMS

Disease — when an infection starts causing damage to host tissues and produces symptoms.

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

LESSON 4.1 WORKBOOK

Why we feel sick — How pathogens cause direct and indirect damage

This unit introduces the idea that illness is the result of host cell damage and dysfunction. Once a pathogenic microbe gains access to the body, it can cause damage in two main ways: either directly by infecting host cells or damaging them with toxins, or indirectly by provoking your immune system to turn on infected and ‘innocent’ bystander self-cells.

What is the difference between an infection and a disease?

As we learned in lesson 3.3, pathogens can gain access a host and begin to replicate. Sometimes, the body’s defenses clear these infections before they cause any damage. While other times pathogens go into a dormant state, again not causing host damage. However, when an infection leads to damage or the dysfunction of host tissues, we will experience the symptoms of disease.

Figure 1: Infections may or may not cause symptoms.
LESSON READINGS

The location of a pathogen impacts the symptoms of a disease

As we have seen, pathogens reproduce in distinct cellular locations at very different rates. Both the location of the infection and the rate of replication impact host cell damage, and hence symptoms. Some symptoms, such as fever and fatigue, are general. Meaning they are experienced during many infections because they are the body’s major alarm system. These symptoms are typically the result of the immune system’s response rather than a manifestation of the pathogen’s direct damage to the host.

However, other symptoms can be more distinct or even disease-specific and usually result from damage of cells at the location of the infection. For example, an ear infection results in pain in the ears because *Streptococcus pneumoniae* is actually damaging the cells there. Likewise, cholera causes diarrhea because the infection is damaging the epithelial cells lining the intestines. In these cases, the location of the symptoms can help to identify the location of the infection, which in turn may help to identify the pathogen. But keep in mind: symptoms alone are insufficient to identify a pathogen. In fact, most common illnesses - ear infections, pneumonia, stomach bugs, and more can be caused by viruses as well as bacteria but the symptoms will be very similar regardless of the infectious agent!

Pathogens cause host damage directly and indirectly

Direct damage

Pathogens can cause direct damage in a few ways. Viruses and intracellular bacteria cause direct damage as they live inside host cells. Both use the infected cells resources and/or lyse them when leaving. Another example of direct damage happens when pathogens produce toxins that damage cells or tissues. For example, Shiga toxin damages the kidneys and tetanus toxin causes irreversible damage to neurons.

1. Pathogens can cause illness by directly damaging host cells. Direct damage usually occurs when pathogens are
   a. replicating
   b. producing toxins
   c. mutating
   d. a and b

DEFINITIONS OF TERMS

Tetanus toxin — a toxin produced by *Clostridium tetani*, which can cause irreversible damage to neurons.

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

Another way that a pathogen can cause damage is indirectly, by triggering an immune response that damages host cells. In this case, immune cells may respond to molecules that pathogens release, such as toxins, or to the pathogens themselves. After the immune system has recognized an infectious agent it attempts to eradicate it. In the process, infected host cells or bystander cells are often killed. In fact, some pathogens use this response intentionally to gain access to new areas of the host. For example, *Streptococcus* bacteria in the lungs can trigger immune damage of epithelial cells to gain access to the bloodstream. In addition, endotoxins and exotoxins can trigger strong (sometimes disproportionate) immune responses that destroy surrounding healthy host cells, thereby allowing the infection to spread further in the host.

Both indirect and direct damage can be caused by pathogens that replicate intracellularly and extracellularly, but the patterns of symptoms tend to differ.

Extracellular pathogens generally cause a plethora of symptoms

Pathogens that replicate outside of cells are called extracellular (extra, outside). Extracellular pathogens may be among the most adaptable of all pathogens. For example, *Staph. aureus* can be found on a variety of objects and surfaces, such as bedding, clothing, and doorknobs. It also causes more frequent and varied types of diseases than any other human pathogen.

Since extracellular bacteria do not need a host cell to replicate, many of them can survive outside of a host until they find a new one. Hence, they may not require host-to-host contact to be transmitted but can instead be transmitted via water, food or contaminated surfaces. These pathogens are often difficult to eradicate, and are responsible for many community and hospital-associated infections.
LESSON READINGS

This ability to survive in diverse conditions also impacts the symptoms of the diseases they cause: if a pathogen can replicate in multiple locations in the body, it can cause a plethora of symptoms. Many bacteria that replicate extracellularly can cause infections in many different body locations. For example, *Staph. aureus* can cause: skin infection; bloodstream infection if it gains access to the interior of the body; pneumonia; infections at the site of surgical wounds; toxic shock syndrome (TSS)! This is why *Staph.* infections can present with a range of symptoms that depend on the location of an infection, and host cell damage.

**Intracellular pathogens cause more specific symptoms**

Pathogens that live and replicate inside host cells are called intracellular (intra, inside). If you look back at lesson 1.4, where viruses were introduced, you will probably remember that they are intracellular pathogens. Viruses are intracellular pathogens that don’t possess the structures needed to reproduce on their own. However, intracellular bacteria may require a host cell to replicate or they might just prefer to replicate in cells but can still replicate outside of host cells. Like viruses, intracellular bacteria often infect specific cell types. This means that these infections lead to damage of select cells and thereby, more disease-specific symptoms than extracellular pathogens.

*We will now focus on the life cycle of a very common intracellular pathogen, Chlamydia trachomatis, which causes chlamydia.*

Chlamydia is one of the most common STDs

*Chlamydiae* bacteria that cause the STD ‘chlamydia’ require host cells to replicate. They have much smaller genome compared to other bacteria because they lack the genes to make key enzymes needed for growth and reproduction. For example, *Chlamydiae* are unable to make the building blocks for DNA and RNA, the ATP that’s used to transfer energy, and they can’t synthesize several amino acids needed to make their own proteins. So, just like viruses, these bacteria use host cell resources to replicate, while camouflaging themselves inside the host cell to hide from the immune system.

3. Which is true about extracellular pathogens?
   a. they’re the most adaptable of all pathogens
   b. they doesn’t need a host cell to replicate
   c. they can survive in diverse conditions
   d. all of the above

**Figure 5:** Extracellular pathogens are usually more adaptable, infecting many organs and causing a plethora of symptoms.

**DEFINITIONS OF TERMS**

Toxic shock syndrome — a life-threatening illness caused by toxins produced by some bacteria such as *S. aureus*. It has been associated with the use of super absorbent tampons.

Enzymes — proteins or RNA molecules that speed up biological reactions.

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

**STD** — sexually transmitted disease.

**Cervix** — the lower, narrow portion of the uterus connecting the uterus with the vagina.

**Fallopian tubes** — two tubes that lead from the ovaries into the uterus.

**Peritoneum** — a thin membrane that covers the internal organs in the abdomen.

**Prostate gland** — small gland located between the bladder and the penis. It produces fluid needed for proper function of sperms.

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

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**Workbook**

**Lesson 4.1**

**LESSON READINGS**

Chlamydia infection produces very subtle symptoms, mostly a little inflammation that progresses from the uterine cervix to the Fallopian tubes, and finally to the peritoneum. By the time symptoms appear in the peritoneum, it is likely that the fallopian tubes have been severely affected, leading to infertility. These women are at risk for pregnancy in the fallopian tubes which is non-viable pregnancy that is a life-threatening condition. In addition, infants born vaginally to infected women can acquire chlamydia in their eyes, ears, nose, and mouth and develop mild conjunctivitis together with a chronic cough. In men, symptoms are less pronounced, and include inflammation of the urethra that progresses to the prostate gland.

**Chlamydiae replication goes through six main stages:**

1. Infection begins when the free-floating bacteria bind to the apical (outside) surface of the host epithelial cells.
2. The bacteria are then taken up in vesicles by the host cells.
3. Once inside the cell, the bacteria quickly modify the vesicles, thereby escaping from the pathway that normally targets foreign debris for destruction.
4. The bacteria begin to replicate. Bacterial replication can also be stopped to hide from the immune response.
5. Replication can also stop when the bacteria have consumed all of the host cell’s nutrients. The immune response causes indirect damage while the use of host nutrients causes direct damage.
6. The bacteria then lyse the host cell in search of more nutrients. This lysis may lead to further invasion of host cells or release to infect other people.

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**Workbook**

**Lesson 4.1**

**LES**

1. These factors greatly impact symptoms and host cell damage:
   a. rate of replication
   b. location of the infection
   c. damage of cells at the location of the infection
   d. all of the above

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**Workbook**

**Lesson 4.1**

**LES**
The rate of growth of a pathogen also impacts the symptoms of a disease

As we have learned, the driving force for bacteria to invade a host is to gain access to nutrients. The faster bacteria replicate, the faster they will need to migrate to a new source of nutrients. Hence, fast growing bacteria generally cause acute damage to a host because they work to gain access to new areas of the body quickly. But is faster necessarily better?

Fast growing pathogens generally causes acute disease

Cholera is caused by an intestinal bacterium *V. cholerae*. These bacteria produce toxins that cause the intestinal cells to lose water and electrolytes. This results in severe diarrhoeal often leading to massive dehydration for the host. In addition, the immune system responds vigorously because the bacteria are growing quickly, which in turn causes indirect damage that is also acute. Since the cholera bacteria grow so quickly, they exhaust the nutrients within days and need to migrate to a new host. In this way, fast growth of the bacteria leads to dramatic damage in a short period of time, hence acute disease.

Slow replication commonly causes chronic or latent infection

The bacterium that causes tuberculosis, *Mycobacterium tuberculosis*, is covered by a thick waxy coat, i.e., it is acid-fast. This coat makes it difficult for nutrients to diffuse in, and so it’s doubling time is much slower than normal pathogens: 15–20 hours at body temperature compared with less than one hour for most other pathogens. Because *M. tuberculosis* replicates slowly it does not need to migrate to new host cells frequently. In fact, it generally stays in a small number of cells that become surrounded by immune cells forming a granuloma. Since *M. tuberculosis* grows slowly, it causes very limited damage. This allows a host to be chronically infected, without symptoms of disease for months or even years!
Pathogenesis of tuberculosis

1. *M. tuberculosis* is exceptional because it can replicate both inside and outside of cells. When the bacteria first enter the lungs, they start dividing, and are ingested by macrophages. They carry on dividing inside the macrophages, eventually killing them, rather than vice versa.

2. At this point, the immune system moves in to wall-off the areas of infection from the rest of the lung by forming granulomas.

3. *M. tuberculosis* can survive for long periods without replicating in granulomas, thus not damaging the host and not being ‘seen’ by the immune system. This is why most people infected with TB have the latent form, meaning they often have no symptoms for decades! People with latent TB are considered non-contagious.

4. However, if the immune system becomes compromised, for example with aging or co-infection with another pathogen like HIV, the TB bacteria can become reactivated. In such case, the granulomas may burst, releasing bacteria, which then begin to divide, infecting other cells and potentially other people. The disease has now progressed to its contagious and dangerous acute form.
Why do many extracellular pathogens cause non-specific symptoms?

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A pathogen can cause two types of damage: direct vs. indirect. Give an example of each type — how are the effects different?

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Describe how a pathogen’s ability to acquire nutrients might affect the severity of symptoms caused by that pathogen.

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<thead>
<tr>
<th>TERM</th>
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<td>Disease</td>
<td>When an infection starts causing damage to host tissues and produces symptoms.</td>
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<td>Doubling time</td>
<td>The time needed for a microbial cell to divide into two daughter cells.</td>
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<td>Endotoxins</td>
<td>Toxins that are permanent part of a bacterium, and get released and activated once the cell lysis, e.g., LPS in Gram-negative bacteria.</td>
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<tr>
<td>Enzymes</td>
<td>Proteins or RNA molecules that speed up biological reactions.</td>
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<td>Exotoxins</td>
<td>Toxins that are produced by microbes that are secreted in the environment.</td>
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<td>Fallopian tubes</td>
<td>Two tubes that lead from the ovaries into the uterus.</td>
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<td>Granuloma</td>
<td>An inflammation center formed when the immune system is trying to wall-off pathogens it can't eliminate.</td>
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<td>Infection</td>
<td>It occurs when a pathogen enters one's body and starts replicating.</td>
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<td>Macrophages</td>
<td>Immune cells that inject and try destroy foreign particles such as pathogens.</td>
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