Unit 2: Lesson 2 – Case Studies: Influenza and HIV

LESSON QUESTIONS

- What steps are involved in viral infection and replication?
- Why are some kinds of influenza virus more deadly than others?
- How do flu viruses and HIV overcome immune system defenses?

LESSON OBJECTIVES

- Create a model of viral infection and replication.
- Explain why some kinds of influenza virus are more deadly than others.
- Describe how flu viruses and HIV overcome immune system defenses.

OVERVIEW

In this lesson, students investigate the process of viral infection and replication. A hands-on activity provides a model for viral infection and replication, which is then applied to understand the concepts of genetic variation and genetic drift. Students use these concepts to explain why some kinds of influenza virus are more deadly than others. Students view a video describing the influenza pandemic of 1918, and analyze the video to explain how this flu strain overcame immune system defenses to become particularly deadly. Students investigate a model of the HIV life cycle to understand how HIV replicates.

LENGTH

Four to five 45-minute sessions

GLOSSARY TERMS

AIDS, antigenic drift, antigenic shift, budding, epidemic, genotypes, hemagglutinin, HIV, messenger RNA, neuraminidase, pandemic, point mutation, reassortment, reverse transcription

STANDARDS

- **Next Generation Science Standards**
    - HS-LS1-2.4.1 Models (e.g., physical, mathematical, computer models) can be used to simulate systems and interactions— including energy, matter, and information flows—within and between systems at different scales.

- HS-LS4-2 Construct an explanation based on evidence that the process of evolution primarily results from four factors: (1) the potential for a species to increase in number, (2) the heritable genetic variation of individuals in a species due to mutation and sexual reproduction, (3) competition for limited resources, and (4) the proliferation of those organisms that are better able to survive and reproduce in the environment.
- HS-LS4-4 Construct an explanation based on evidence for how natural selection leads to adaptation of populations.

- **Common Core State Standards**

  - RST.11-12.3 Follow precisely a complex multistep procedure when carrying out experiments, taking measurements, or performing technical tasks; analyze the specific results based on explanations in the text.

  - RST.11-12.4 Determine the meaning of symbols, key terms, and other domain-specific words and phrases as they are used in a specific scientific or technical context.

  - RST.11-12.7 Integrate and evaluate multiple sources of information presented in diverse formats and media (e.g., quantitative data, video, multimedia) in order to address a question or solve a problem.

  - WHST.9-12.2 Write informative/explanatory texts, including the narration of historical events, scientific procedures/ experiments, or technical processes.

  - WHST.9-12.9 Draw evidence from informational texts to support analysis, reflection, and research.

  - WHST.11-12.7 Conduct short as well as more sustained research projects to answer a question (including a self-generated question) or solve a problem; narrow or broaden the inquiry when appropriate; synthesize multiple sources on the subject, demonstrating understanding of the subject under investigation.

  - HSS.IC.B Make inferences and justify conclusions from sample surveys, experiments, and observational studies.

MATERIALS

- Student worksheet
- Computer with internet access
- Each student group will need the items listed for the activity Influenza – Antigenic Drift (Activity 1):
    - Influenza – Antigenic Drift activity sheet
    - 4 highlighter pens colored red, green, blue and yellow
    - Tape or glue
    - Scissors
    - Paper clips
    - 2 sheets copier paper
    - Timer or stopwatch
    - 4 envelopes for each group
- Causes and Consequences of an Influenza Pandemic activity sheet (Activity 2)
- The Life Cycle of the Human Immunodeficiency Virus activity sheet (Activity 3)

BACKGROUND FOR TEACHER

This lesson focuses on the mechanisms by which viruses infect cells and replicate. The lesson also covers genetic processes by which viruses are able to circumvent immune system defenses. The hands-on Activity 1 models how a virus infects a cell and replicates. The aim of the activity is to demonstrate how the process of replication results in mistakes in viral genetic material leading to genetic variation. Since these mistakes can also alter viral proteins (antigens), this variation is called antigenic variation. Over time, mutations can accumulate, resulting in a genetic makeup quite different from the original RNA sequence. The small changes that occur regularly in the viral genome are called antigenic drift. If two different strains of influenza viruses replicate in the same cell, their genes may combine to form a new strain. This dramatic change in the viral genome is called antigenic shift. The resulting change in viral protein structure results in high levels of susceptibility among populations. Antigenic shift is the reason that influenza can cause pandemics.

Influenza Virus

Influenza viruses are classified based on their membrane glycoproteins, hemagglutinin (H) and neuraminidase (N). Numbers after these letters indicate a particular viral strain, such as H1N5 (the notorious “bird flu”) or H1N1 (“swine flu”).

Influenza viruses contain segmented, negative strand RNA in a capsid enclosed in an envelope. The RNA has eight genes for eleven proteins. When the gene base sequences change, surface proteins may change, leading to antigenic drift. These genetic changes

enable a particular virus to repeatedly infect the same person, which is why we can get influenza one year even if we've had influenza or an influenza vaccine the previous year.

Influenza epidemics result when cases occur with higher than normal frequency. Seasonal patterns depend on the region and climate. In temperate regions, influenza season begins in late fall and extends into winter. During influenza ("flu") season, between 5% and 20% of the U.S. population may be infected with influenza virus.
When a new influenza strain arises, the immune system may not recognize novel surface proteins, so almost everyone could be susceptible. This widespread susceptibility is the basis for pandemics. Such strains commonly arise when two different influenza viruses infect a single organism. For example, pigs can be infected by both human and bird influenza viruses. If both viruses infect the same cell their genes may rearrange to form a new influenza virus. If the new virus can infect humans and is easily transmitted between people, a pandemic can occur because almost everyone will be susceptible to the new virus.

Human Immunodeficiency Virus (HIV)

HIV targets immune system cells, primarily CD4+ T-lymphocytes. For this lesson, it is sufficient for students to understand that HIV directly infects the immune system's cells. This strategy hinders the body's ability to defend itself against the virus, as well as other routine infections.

The virus continues to change as it replicates in an individual. Therefore, antibodies against the original HIV particles will not neutralize later generations of viruses. The virus uses a host cell receptor called CD4 to recognize host cells and gain entry. Early during HIV infection, the immune system produces inflammatory cytokines. These activate more T cells, providing more targets for the virus to infect. Infected T cells are killed by enzymatic degradation (necrosis) or rupture of the plasma membrane (cytolysis). The HIV replication cycle includes the following steps:

1. Attachment of HIV particles to cells via CD4 receptors.
2. The virus membrane fuses with the cell membrane, allowing it to enter into a host cell, where viral RNA and reverse transcriptase are released into the cell.
3. Reverse transcription occurs in the cytoplasm making viral RNA into double-stranded DNA. Mistakes during reverse transcription are common, which can cause changes to the virus that is produced.
4. The viral DNA is transported into the nucleus and the integrase enzyme facilitates integration of viral DNA into the host cell's DNA.
5. Integrated viral DNA is transcribed into messenger RNA during the cell's metabolism. The mRNA is exported into the cytoplasm where it is translated into viral proteins.
6. The newly formed viral proteins are transported to the plasma membrane.
7. Virus particles form and begin budding from the cells. These newly released particles go on to infect additional cells.

TEACHER NOTES

If you did not recently cover Unit 2, Lesson 1, you may want to review or introduce the idea that pathogens must find ways to survive evolutionarily. To do this, pathogens take different approaches. You can rely on figures from Unit 2, Lesson 1 to explore these ideas (refer to figures 1 and 2 in the file, Diagrams Related to the Development of Disease and Infection). If students are not familiar with the terminology in figure 2 and time doesn't allow for them to study these concepts, minimally they should understand that influenza relies on antigenic variation and HIV relies on resistance for survival.

LESSON RESOURCES

- Lesson animation
  - *Antigenic Drift: How the Influenza Virus Adapts* (https://vimeo.com/227179689)

- Lesson video
  - NOVA video segment about the influenza pandemic of 1918 (12:33) https://www.youtube.com/watch?v=hJM6M3AMwSs

- Lesson glossary

- AIDS info page with information about the HIV life cycle, NIH,
  - https://aidsinfo.nih.gov/education-materials/fact-sheets/19/73/the-hiv-life-cycle

- Additional resources that may be helpful:
  - Overview of the immune system, with sections on immune system function and location, NIH, https://www.niaid.nih.gov/research/immune-system-overview
  - Extensive descriptions of the immune system components, Immune Deficiency Foundation, https://primaryimmune.org/about-primary-immunodeficiencies/relevant-info/the-immune-system
  - Basic information on immune system function, How Stuff Works.com, http://science.howstuffworks.com/life/human-biology/immune-system2.htm

ENGAGE

1. Ask students to write down when they last had the flu, and then to write a short passage describing the symptoms, progress and treatment of the flu. (If a student has not had flu, he or she can write down their observations of someone else with the flu. They shouldn't disclose the identity of anyone they know who's had flu.)
2. Students work in small groups to share their descriptions and develop a list of common symptoms.
3. Choose one or two individual students and ask if they or anyone they know has had influenza ("flu") vaccine. (They should not disclose the identity of anyone they know who has had their influenza vaccine.)
4. Choose another couple of students and ask if they remember having vaccinations for other diseases. (Most students should have received vaccinations for measles and pertussis, also known as whooping cough.)
5. Explain to students that they will learn why people need yearly influenza vaccine whereas many other diseases require only one or a few vaccine doses.

EXPLORE 1

1. Students explore online sources and the lesson glossary to complete the vocabulary table in their worksheets.
2. Explain to students that their task is to determine how the influenza virus differs from other disease agents, and to explain why people need yearly flu vaccinations.
3. Propose a guiding question to students: *Why are some illnesses prevented by single vaccinations, but repeated vaccinations are needed to prevent flu?*
4. Students watch the animation, *Antigenic Drift: How the Influenza Virus Adapts* (https://vimeo.com/227179689).
5. Working in small groups, students complete Influenza- Antigenic Drift (Activity 1). The activity models the genetic processes underlying antigenic drift.
6. If time allows, students can complete a form of the activity modified to demonstrate antigenic shift.

EXPLAIN 1

1. Depending on student's understanding of the material, assign students to complete the Influenza- Antigenic Drift (Activity 1) activity questions either as a group or individually.
2. Working in groups, students develop an argument (hypothesize) related to why people need annual vaccinations against influenza. Ensure that the students' hypotheses account for why only one or a few vaccine doses are needed for some illnesses. Their arguments should include evidence to support their hypotheses.
3. Lead a class discussion on the groups' hypotheses, including how well the activity modeled antigenic drift and antigenic shift.

EXPLORE 2

1. Students work in small groups to research the influenza pandemic of 1918. (See for example, https://www.cdc.gov/flu/pandemic-resources/.)
2. Each group creates a concept map to illustrate features of the pandemic including origin and spread, death toll, death rate, local impacts, prevention, treatment and scientific understanding of influenza.
3. Students watch the NOVA video segment about the influenza pandemic of 1918: https://www.youtube.com/watch?v=hJM6M3AMwSs.

EXPLAIN 2

1. Working individually, students complete the Causes and Consequences of the Influenza Pandemic (Activity 2) activity questions.
2. Lead a class discussion on the role of antigenic drift and antigenic shift in the development of the Spanish influenza virus responsible for the 1918 pandemic.
3. Working individually students write a brief report on their investigation, including their answers to the guiding question.

ELABORATE

1. Refer students to The Life Cycle of the HIV Virus activity sheet (Activity 3).
2. Explain to students that their task is to investigate the life cycle of HIV and to identify key steps allowing cell infection, replication and reinfection.
3. Propose a guiding question to students such as: *What key steps in the HIV life cycle offer opportunities to develop treatments that would stop the virus from replicating?*
4. Working in small groups, students complete the Activity 3 questions.
5. Each group chooses one of the six drug classes of HIV treatments and creates a poster to explain the parts of the HIV replication cycle that the therapy is attempting to combat.

EVALUATE

1. Assess students based on their completion of the activity questions.

RUBRIC: STUDENT WORKSHEET

Vocabulary table

- Refer to the lesson glossary for correct definitions of terms.

RUBRIC - ACTIVITY 1: Influenza- Antigenic Drift

1. What does the yellow strip of paper represent?

    - The strip of paper represents a sequence of viral RNA bases.

2. What does step 1 of this activity represent? Include the term "virion" in your answer.

    - This step represents infection of the cell by the virion. The virion injects its RNA sequence into the cell.

3. When you compared the 10 green paper strips in the "Protein" envelope at the end of the activity, did the 10 strips have identical amino acid sequences? Quantify and explain your observations.

    - Answers may vary. In most cases, a mistake will have led to a change in the base sequence, and hence a change in the amino acid sequences. If students were particularly hasty, they may observe several differences between the first and last set of amino acids.

4. Explain how this activity models antigenic variation.

    - Answers may vary. Sample answer: Since the amino acid sequences in the later "Protein" strips of paper were different from the first amino acid sequence, the activity demonstrated antigenic variation.

5. Do your observations during the activity model antigenic drift? Explain your answer.

    - Answers may vary. Sample answer: As the amino acid sequences in the "Protein" strips diverged over successive cycles, the observations do model antigenic drift. Lack of divergence would indicate an absence of antigenic drift.

6. Describe how the activity could be modified to model antigenic shift, including the basis for your modification. (If time allows, complete your modified activity.)

    - Answers may vary. Sample answer: Antigenic shift occurs when two or more virus strains combine genetic material. This can happen when two different virus particles infect a cell at the same time. The changed genetic material presents a combination of viral surface antigens. We could modify the activity by combining the sequence from another group's yellow strips with

our group's yellow strips or introducing yellow strips with different combinations and cutting them in pieces before putting in the cell envelope then having transcriber 1 randomly choose pieces that equal the correct number of bases.

RUBRIC - ACTIVITY 2: Causes and Consequences of an Influenza Pandemic

1. What example was used to illustrate that the 1918 influenza was the deadliest flu of all time?
    - The 1918 influenza strain killed three times more people than were killed in action in World War 1.
2. What kind of virus caused the 1918 pandemic?
    - An ordinary bird flu that had changed.
3. What made the 1918 flu virus so deadly?
    - No one was immune because the strain was completely new and attacked a different part of the respiratory tract.
4. How did scientists recover the 1918 flu virus for direct study?
    - The genetic code was isolated from tissue samples of soldiers killed in WW1.
5. What cells do flu viruses infect?
    - Cells in the lungs and respiratory tract.
6. What protein is the "key" to accessing and infecting a cell?
    - Hemagglutinin
7. What protein enables the flu virus to get out of a cell?
    - Neuraminidase
8. What is the significance of the letters and numbers in flu strains identified by the letters H and N?
    - The letters H and N stand for hemagglutinin and neuraminidase respectively. The numbers signify different combinations of antigens.

9. How did researchers try to change the avian flu virus to make it more easily spread between humans?

    - Researchers introduced two changes (mutations) that were found to have made the 1918 strain lethal into a current avian flu virus. The experiment did not work as expected, so they think the avian flu will not easily adapt to infect people.

10. How did researchers change the seasonal flu to make it become more lethal?

    They took the hemagglutinin gene (or H gene) from the 1918 flu and put it in a seasonal flu virus, and it became more lethal. Then they did the reverse, and the 1918 virus became less lethal.

RUBRIC - ACTIVITY 3: The Life Cycle of the Human Immunodeficiency Virus

1. In Step 1, virus attaches (binds) to the host cell surface. What is the significance of the CD4 receptor?

    - The CD4 receptor allows the HIV particle to recognize a host cell.

2. In Step 2 the virus envelope fuses with the host cell membrane. How could a fusion inhibitor drug prevent HIV infection of the host cell?

    - The fusion inhibitor drug could prevent infection by stopping the HIV envelope from fusing with the cell, and stopping HIV molecules entering the cell.

3. What is the role of the reverse transcriptase enzyme molecule?

    - Reverse transcriptase converts the HIV RNA into DNA.

4. Which molecule enables HIV to integrate its DNA into the host cell's DNA?

    - Integrase

5. In Step 5, what is the role of the host cell in allowing replication of HIV DNA?

    - The HIV DNA uses the host cell's replication machinery to create long chains of HIV proteins.

6. Step 6 shows a process known as “assembly.” In what way is assembly similar to the process of fusion in Step 2?

    - During assembly, the HIV envelope fuses with the host cell membrane.

7. When the HIV particle first leaves the cell, it is inactive and cannot reinfect another host cell. What final step allows the HIV particle to become infectious?

    - After it leaves the host cell, the HIV releases an enzyme called protease. This enzyme breaks up the long protein chains in the noninfectious virus. These smaller proteins then combine, forming the infectious HIV particle.