Smallpox and the Immune System

OVERVIEW
This activity uses two short historically based stories about smallpox, told through comics, to motivate learning about the immune response, immune cells, and vaccines. Students also build a possible sequence of an immune response using illustrated cards, then relate their cards to graphs of immune responses and the comic.

Additional information related to pedagogy and implementation can be found on this resource’s webpage, including suggested audience, estimated time, and curriculum connections.

KEY CONCEPTS
- The immune response has two phases, the innate and the adaptive immune responses, that communicate with one another through immune cells.
- Immune cells have receptors that recognize and respond to antigens.
- Memory cells stay in the body even after a pathogen is gone, providing long-term protection from infection.
- Vaccines expose the body to antigens to stimulate an immune response and the production of memory cells.

STUDENT LEARNING TARGETS
- Identify the typical sequence of events in an immune response, including the roles of a subset of immune cells.
- Compare and contrast the innate and adaptive immune responses.
- Describe the relationship between the amount of virus and the immune response at various times during an infection.
- Explain why people may respond differently to an infection with the same virus.
- Describe how a vaccine protects from future infections.

PRIOR KNOWLEDGE
Before beginning this resource, students should be familiar with:
- what viruses are and that viruses infect cells
- cell structure (in particular, that cell membranes have protein receptors)

MATERIALS
- “Student Handout” (one per student or group of students)
- “Immune Cell Cards” (one set per group of students)
- “Smallpox Comic” and “Vaccine Comic”
- (optional) sticky notes for student questions in Part 1

TEACHING TIPS
- This activity can be completed as a combination of small group work and whole-class discussions.
- You may choose to distribute parts of the “Student Handout” separately. The “Procedure” section has suggestions for how to scaffold the information.
- Students can complete the handout individually or in their groups.
● The comics and photos in Figure 1 can be printed, shared digitally, or projected for students.
● The “Immune Cell Cards” can also be printed or shared digitally.
  ○ PDFs for both single-sided and double-sided printing are provided on this resource’s webpage. Print the cards, cut them out, and shuffle them. You may wish to laminate them for repeated use.
  ○ Individual card images (JPGs) are provided in the “Card Images” ZIP file. You can use a virtual whiteboarding or collaboration software (e.g., Google Slides, Miro, Mural, Whiteboard.fi) in which students can move and annotate card images.
● The topic of infectious diseases and the photos in Figure 1 (individuals with smallpox) may be upsetting to some students.
  ○ Let students know about this activity ahead of time. Allow them to talk with you about any concerns they might have.
  ○ Depending on your class, you may skip showing students Figure 1.

PROCEDURE
This activity consists of the parts outlined in this table:

<table>
<thead>
<tr>
<th>Part</th>
<th>Estimated Time</th>
<th>What Students Will Do</th>
<th>Purpose</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Read the “Smallpox Comic,” a short graphic narrative about smallpox infections.</td>
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<td>• Ask questions about the photos and comic.</td>
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<tr>
<td>Part 2: How Does the Body Respond to Smallpox?</td>
<td>20–40 min</td>
<td>• Build a possible sequence of an immune response using the “Immune Cell Cards.”</td>
<td>Build students’ vocabulary and understanding of the innate and adaptive immune responses.</td>
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<td>• Analyze a graph of a typical immune response to a viral infection.</td>
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<td>• Relate the cards and graph to the story in the comic.</td>
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<tr>
<td>Part 3: How Do Immune Responses Differ?</td>
<td>10–15 min</td>
<td>• Compare graphs of immune responses for two characters in the comic: one who recovered from smallpox infection and one who did not.</td>
<td>Continue to build students’ understanding of the immune response.</td>
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<tr>
<td>Part 4: How Does the Smallpox Vaccine Work?</td>
<td>15–20 min</td>
<td>• Read the “Vaccine Comic,” which is about the history of smallpox vaccines.</td>
<td>Apply students’ knowledge of the immune system to vaccines.</td>
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<td></td>
<td></td>
<td>• Answer questions about vaccines based on the comic.</td>
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<tr>
<td>Part 5: Reflection</td>
<td>5–15 min</td>
<td>• Answer several short reflection questions about the activity.</td>
<td>Have students reflect on their learning. Can serve as a final assessment.</td>
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The following sections outline several options for implementing each part of the activity.

PART 1: What Is Smallpox?
• Divide students into groups of two to four.
• Give groups the photos of individuals with smallpox (Figure 1 in the “Student Handout”). The photos can be printed, provided digitally, or projected on a screen for the whole class.

• Ask students to examine the photos and write at least two questions about them (Question 1 in the “Student Handout”). They can write their questions on sticky notes (one per question), on a whiteboard, in their handouts, or digitally.

• Have a member of each group read one of their two questions aloud and post it (on a wall, whiteboard, online whiteboard, etc.). Multiple groups will likely post similar questions.

• Once all the questions are posted, ask students to help you organize the questions into groups (for example, all questions about the cause of smallpox in one group, all questions about symptoms in another group, etc.).

• Provide students with copies of the “Smallpox Comic.”
  o Copies can be printed, read online, or projected on a screen and read aloud to the class.
  o Students can read the comic individually, in their groups, or as a class.

• Ask students whether the comic answered any of their questions (Question 2a); remove answered questions from where they were posted.

• Ask students for any new questions they have after reading the comic (Question 2b).

• Guide the discussion so that students eventually focus on the immune system and its response to infection.

PART 2: How Does the Body Respond to Smallpox?

• Review with students that viruses and other pathogens have proteins on their surfaces that can trigger an immune response. A molecule that triggers an immune response is called an antigen.
  o This information is in the “Student Handout” at the start of Part 2. You can also share this in other formats (e.g., slides) and allow students to ask questions if anything is unclear.

• Provide each student group with a set of the “Immune Cell Cards.”
  o Note that the cards show only some of the receptors on some immune cells. Cells have many kinds of receptor proteins that various stimuli can activate. The information in the cards is a very simplified version of the actual processes involved.

• Review the cards with students. Ask if they have heard of any of the cells on the cards or if they know any other types of immune cells. These questions provide a way to assess students’ prior knowledge.

• Have students work in pairs or small groups to arrange the cards to show what happens in the body in response to the variola virus (Question 3).
  o Students should put individual cards or groups of cards in a linear sequence. Note that there isn’t a single correct way to do it.
  o You can ask students to write or draw their sequence of cards in the handout or on a whiteboard. Alternatively, each group can verbally share with the class.

• Once each group is comfortable with their card arrangement, provide the graph illustrating Anne’s immune response to smallpox infection (Figure 2).
  o Students can analyze the graph individually or in small groups, or you can project the graph on a slide for the whole class to analyze.
  o If students have not had much practice reading graphs, you can use the Identify and Interpret (I²) strategy.
  o This graph was adapted from a graph that showed a successful immune response to SARS-CoV-2 (Mangge et al. 2021).

• Ask students to answer Questions 4–10 in the handout, either in class (by writing in the handout, as part of a class discussion, by working in small groups, as class polls, etc.) or as homework.
  o If pressed for time, you can delete Question 10 (filling out the table) or assign it as homework.
PART 3: How Do Immune Responses Differ?

- Provide students with the two graphs illustrating Anne’s and Mr. Conti’s immune responses to smallpox infection (Figure 3).
- Ask students to analyze the graphs and answer Questions 11–12 in the handout.
  - Students can analyze the graphs individually or in small groups.
  - They can view the graphs in their handouts, or you can project the graphs on a screen for the whole class to explore and discuss.
  - The questions could be answered as part of a class discussion, as homework, or in their groups.

PART 4: How Does the Smallpox Vaccine Work?

- You could introduce this last part of the activity by asking students:
  - Do you know anyone who has had smallpox?
  - Have you been vaccinated for smallpox? Do you know anyone who has?
- Possible responses include the following:
  - Students will likely say they don’t know anyone with smallpox. This is because the World Health Organization declared smallpox eradicated in 1980.
  - Students may bring up mpox (formerly known as monkeypox), which caused an outbreak in the United States in 2022. Mpox is caused by a virus closely related to the variola virus that caused smallpox. Mpox symptoms are milder than smallpox, and mpox is rarely fatal. Mpox and smallpox are not related to chickenpox.
  - Students may have family members who were vaccinated for smallpox. People are no longer vaccinated for smallpox because the virus was eradicated. However, the vaccine used to protect from smallpox also protects from mpox; some people may receive mpox vaccinations.
- Provide students with copies of the “Vaccine Comic.”
  - Copies can be printed, read online, or projected on a screen and read aloud to the class.
  - Students can read the comic individually, in their groups, or as a class.
- After reading the comic, have students answer Questions 13–15 in the handout in small groups or as a class discussion.

PART 5: Reflection

- Have students answer Questions 16–18 to reflect on their learning. You can have students hand in this part of the activity, so you can gain insights into their understanding of the topic and address any misunderstandings.
- You may change some of the questions or add your own. For example, you could include questions about:
  - how this activity is relevant to students’ lives
  - what is one thing they might share with a friend or family member

ASSESSMENT GUIDANCE

These sample answers for questions in the “Student Handout” may include more detail than would be provided by students. They are meant to give you additional information that you may want to discuss with students.

PART 1: What Is Smallpox?

1. Write down at least two questions you have about what you observed in Figure 1.
   *Answers will vary.*

2. Read the “Smallpox Comic.”
a. Which of your questions, if any, were answered by reading this comic?

b. Write down at least two new questions that you have.
   
   *Answers will vary. Students will learn more about smallpox and the immune response throughout the activity.*

### PART 2: How Does the Body Respond to Smallpox?

3. Using the information in the “Immune Cell Cards,” arrange the cards to show what happens in Anne’s body in response to the variola virus over time. Some cards could be in the same or multiple spots in the sequence. You can write or draw the sequence of cards in the space below.
   
   *Students’ sequences will vary. Two examples are shown below.*

<table>
<thead>
<tr>
<th>Example 1:</th>
<th>Example 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>● C (phagocytes)</td>
<td>● C (phagocytes) and F (NK cells) together</td>
</tr>
<tr>
<td>● F (NK cells)</td>
<td>● F (APCs)</td>
</tr>
<tr>
<td>● B (APCs)</td>
<td>● D (helper T cells), E (cytotoxic T cells), and A (B cells and plasma cells) together</td>
</tr>
<tr>
<td>● D (helper T cells) and E (cytotoxic T cells) together</td>
<td>● G (memory cells)</td>
</tr>
<tr>
<td>● A (B cells and plasma cells)</td>
<td></td>
</tr>
<tr>
<td>● G (memory cells)</td>
<td></td>
</tr>
</tbody>
</table>

4. Using the information on the “Immune Cell Cards,” list the cards for the cells that are part of the:

a. **innate immune response**
   
   B (APCs), C (phagocytes), F (NK cells)

b. **adaptive immune response**
   
   A (B cells and plasma cells), D (helper T cells), E (cytotoxic T cells), G (memory cells)

5. Based on your analysis and interpretation of Figure 2:

a. **Approximately when was Anne exposed to the virus that causes smallpox?** Indicate this point in the graph.
   
   *This is indicated in the graph below by the arrow labeled “Anne exposed to variola virus.”*

b. **After Anne is exposed, at which points in the graph does her body have the highest and lowest amounts of virus?** Indicate these two points in the graph and label them.
   
   *These are indicated in the graph below by the arrows labeled “Highest/lowest amount of virus.”*
c. Describe the relationship between the amount of virus and the immune response.

There is a positive relationship at first, meaning that the immune response increases as the amount of virus increases. Then, there is a negative relationship, meaning that the immune response increases, but the amount of virus decreases.

6. Using the information in Figure 2, make changes to your sequence of cards from Question 3 as needed. Write your revised sequence below or describe the changes that you made.

Answers will vary depending on students’ sequences.

7. The adaptive immune response is more powerful than the innate immune response. Based on the information on the “Immune Cell Cards,” what makes it more powerful?

Some of the reasons are that, during the adaptive immune response:

• T cells and B cells recognize and help destroy specific pathogens.
• Memory cells are produced, which provide long-lasting protection.
• Antibodies are produced, which target the pathogen for destruction and prevent it from infecting other cells.

8. Which type of immune cell is responsible for communicating between the innate and adaptive immune responses?

Antigen-presenting cells (APCs).

When a dendritic cell or macrophage (part of the innate immune response) ingests a pathogen, it displays a piece of the pathogen (an antigen) on its surface and becomes an APC. APCs activate T cells, which are part of the adaptive immune response.

9. Some immune cells stay in the body even after the virus is gone. What are these cells called?

Memory cells.

Memory cells are B and T cells that stay in the body long after an infection is over, allowing the immune system to respond more quickly to future infections with the same pathogen.

10. The table below shows some scenes from the “Smallpox Comic” in chronological order. Using the information from the “Immune Cell Cards” and Figure 2, identify the type(s) of immune cells involved at each stage of Anne’s infection. In the “Explanation” column, support your choice of immune cells by explaining what happens inside Anne’s body in each scene. The first row has been completed as an example.
The scenes are open to interpretation, so students may provide different answers from the examples shown below. The descriptions below are a lot more than what would be expected for most students to write. This is an opportunity to give feedback and clarify any misunderstandings.

<table>
<thead>
<tr>
<th>Stage of Infection</th>
<th>Immune Cells Involved</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phagocytes</td>
<td>Anne does not have any symptoms, but the virus is in her body. Phagocytes ingest the variola virus. They produce cytokines to call other cells to the scene.</td>
<td></td>
</tr>
<tr>
<td>Phagocytes, NK cells, and APCs</td>
<td>Anne is starting to feel sick. She may have chills and a fever. Phagocytes and NK cells respond to the virus by releasing cytokines, which cause fever and inflammation. Other innate immune cells (like APCs) are likely also active.</td>
<td></td>
</tr>
<tr>
<td>Phagocytes, NK cells, and APCs. Possibly helper T cells and cytotoxic T cells.</td>
<td>Anne is displaying more symptoms of infection. Innate immune cells (phagocytes, NK cells, and APCs) are probably still responding to the virus. APCs may also be activating T cells to begin the adaptive immune response.</td>
<td></td>
</tr>
<tr>
<td>Helper T cells, cytotoxic T cells, and B/plasma cells</td>
<td>Anne is recovering. She has probably moved into the adaptive immune response by this point, so mostly adaptive immune cells (T cells and B/plasma cells) are active.</td>
<td></td>
</tr>
<tr>
<td>Memory cells</td>
<td>Anne has recovered. Even though the infection is over, the memory cells will remain in her body and help protect her from future infections of smallpox.</td>
<td></td>
</tr>
</tbody>
</table>

**PART 3: How Do Immune Responses Differ?**

11. Examine Figure 3.

As you review students’ answers, you may want to point out to them whether something is an observation vs. an inference. For Parts a and b, they are being asked to make observations.
a. How are the two graphs similar?
    **Similarities include that, in both graphs:**
    • the innate immune response comes before the adaptive immune response
    • the amount of virus and phagocytes increased during the innate immune response
    • antibodies and T cells increased during the adaptive immune response

b. How are the two graphs different?
    **Differences include that:**
    • The innate immune response (represented by phagocytes in the graph) increases earlier in Anne’s graph than in Mr. Conti’s.
    • The amount of virus eventually goes to 0 for Anne but keeps increasing for Mr. Conti.
    • Mr. Conti’s innate immune response and amount of virus kept increasing, but Anne’s did not.
    • Mr. Conti’s adaptive immune response did not begin as quickly as Anne’s. He produced a lot of antibodies but few T cells.

c. Explain how the differences you observed could explain why Anne survived and Mr. Conti died.
   Anne may have survived because her adaptive immune response occurred relatively soon after she was infected. The T cells and antibodies she produced helped destroy the virus.
   Mr. Conti’s adaptive immune response did not occur as quickly, and he did not produce as many T cells. Though his innate immune response increased to eliminate the virus, the innate immune response is not as powerful as the adaptive immune response, so the virus kept increasing. By the time he began producing T cells and antibodies, it was too late.

   **Factors that could have contributed to these differences include the following:**
   • Mr. Conti may have been infected with a lot more virus than Anne.
   • Mr. Conti’s immune system may have been functioning less effectively than Anne’s. Stress, age, sleep, nutrition, and genetics all affect the functioning of the immune system.
   • Mr. Conti may not have received as much care or support for his health as Anne. For example, maybe he did not have access to a doctor or hospital like Anne did.

12. Is Anne likely to get sick if she is exposed to the variola virus again? Why or why not?
   She is less likely to get sick because she now has memory cells specific to the variola virus. These cells can help her body respond more quickly to future smallpox infections.

**PART 4: How Does the Smallpox Vaccine Work?**

13. Discuss the following questions with other students or as directed by your instructor.
   a. What do all three methods have in common?
      All three methods activate an immune response to protect the body from a specific virus. All three methods use some of either the variola virus or a related virus.

   b. What is one difference between the three methods?
      Methods 1 and 2 expose the vaccinated individual to small amounts of the variola virus, whereas Method 3 exposes the individual to a virus related to the variola virus.

   c. How would the immune response to smallpox infection be the same or different for these methods?
      All three methods will stimulate the innate and adaptive immune responses. If the vaccinated individual survives, they will have memory cells that recognize the variola virus. Memory cells will stay in the body and protect the individual from future smallpox infections.
      Students may question how the related cowpox virus can help the body generate memory cells specific to the variola virus. These viruses have antigens that are sufficiently similar. So B and T cells
that can recognize a specific antigen on the cowpox virus can also recognize a similar antigen on the variola virus.)

14. Explain how getting a disease (or a vaccination for a disease) such as smallpox protects a person from this disease in the future.

Getting a disease (such as smallpox) or vaccination for the disease stimulates the immune system to produce specialized immune cells that help destroy the pathogen. A few of these specialized cells (memory cells) remain in the recovered/vaccinated person's body. If they are infected by the same pathogen again, these memory cells multiply quickly. They stimulate the production of other specialized immune cells and antibodies specific to the pathogen in a relatively short period of time.

15. After receiving the smallpox vaccine, would a person also be protected from other infectious diseases, such as infection with the influenza virus? Why or why not?

They might be protected from a related virus, like the virus that causes mpox. This is because memory cells recognize a specific antigen, and related viruses may have similar antigens. However, they wouldn’t recognize, or help protect against, an unrelated virus or another type of pathogen.

PART 5: Reflection

16. List three things you learned about how the immune system responds to pathogens, such as the variola virus.

Responses will vary. For example, students may indicate that they learned:

● There are different types of immune cells. Some (innate immune cells) are generalists, and some (adaptive immune cells) are specialists.

● Memory cells are produced while a person is recovering from a disease, such as smallpox, or after vaccination. These cells help protect the person from future infections.

● Not everyone’s immune system responds to an infection in the same way. In some individuals, the adaptive immune response does not occur or occurs too late for the virus to be destroyed and the person to survive.

17. List two questions you still have about the immune system.

Responses will vary. If many students ask similar questions, particularly about how the immune system works, you should address these questions with the class. You may also ask students to research some of their questions as an extension activity.

18. List one thing you enjoyed learning while doing this activity.

Responses will vary.

OPTIONAL EXTENSIONS

● Have students go through The Immune System Click & Learn, which provides additional information about immune cells and vaccines.

● Have students read a news story about smallpox and the debate about whether all viral stocks should be destroyed.

● Have students read a news story about mpox or related viruses.

REFERENCES


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