- Inactive whole virus: Sinovac, Sinopharm
- Protein antigen: Novavax
- DNA: CanSino, AstraZeneca, and Johnson & Johnson
- mRNA: Pfizer, Moderna

- For the "Version 2" worksheet, consider relating student answers to Question 20 to the three tests (RT-PCR test, antigen test, and antibody test) discussed in the *Detection* video. Then discuss how these tests can avoid false positives from certain vaccines.
    - The RT-PCR test does not detect the genetic instructions (DNA or mRNA) vaccines because it detects a different region of the viral genome than the region that encodes the spike protein (which is delivered by these vaccines).
        - To understand the RT-PCR test, students may need additional background on PCR. For a brief summary of how PCR works, consider showing the *Polymerase Chain Reaction* animation. This animation does not show the first step for the RT-PCR test: reverse transcription (RT), in which the viral RNA is converted to DNA.
        - You may want to discuss the role of primers with students. As shown in the PCR animation, primers are short DNA sequences designed to bind a specific region of target DNA. In the RT-PCR test for SARS-CoV-2, the target region typically does not vary too much (or else the primers may not bind, causing false negatives) but varies enough to allow SARS-CoV-2 to be distinguished from other coronaviruses. A common target for primers is the nucleocapsid-encoding region of the viral genome; for more details on the structure of coronaviruses, refer to *Virus Explorer*.
    - Antigen tests typically detect the nucleocapsid protein, which is not present in either the antigen protein vaccines or the genetic instructions (DNA and mRNA) vaccines. Therefore, these vaccines would not be detected by the antigen tests.
    - Many antibody tests detect antibodies for the spike protein, which are produced in response to all the vaccines in the animation. However, antibody tests are not relevant to Question 20 because they should not be used to detect active viral infections, as antibodies remain long after the virus has been cleared.
    - Whether these tests detect the inactive whole virus vaccine varies. The virus is typically chemically inactivated with chemicals such as formalin and β-propiolactone. These chemicals can modify proteins, nucleotides, or both. Depending on the chemical used, certain tests may give false positives for the inactive whole virus vaccine and others may not.

TEACHING TIPS

- Consider conducting a formative assessment prior to watching the animations. Some ideas are as follows:
    - Before class, make a list of common misconceptions about SARS-CoV-2 or COVID-19 that you have become aware of in your community or seen on social media. Include several factual statements in the list as well.
        - Invite students to discuss which of these statements are accurate and which are not. Record their decisions.
        - Revisit the list after viewing the animations. Ask students if they have changed their earlier decisions about the accuracy of the statements.
    - Ask students to make a list of what they know about coronavirus infection, evolution, and detection. This can be done individually or in pairs.
        - Ask students to share one or two items from their lists with the class. Reinforce that, at this point, all ideas are to be accepted.
        - After viewing the animations, invite students to address misconceptions they had about SARS-CoV-2 and COVID-19. Ask students to discuss where some of these misconceptions may have originated.

- Consider discussing with students how they could become better informed about COVID-19 and other real-world issues and less prone to misconceptions.
    - For example, students may have seen news articles making false or misleading claims about COVID-19. Students could analyze these articles using the "Evaluating Science in the News" activity, in which they evaluate a science news article to determine whether it is trustworthy.
- Some examples in the worksheets are based on real research studies. You may wish to have students explore the original studies and data in more depth. A full list of references can be found at the end of this document. In particular:
    - In the **"Version 1"** worksheet:
        - Question 3, which describes SARS-CoV-2's ability to bind to cell receptors, is based on Wrapp et al. (2020).
        - Question 9, which describes a large deletion in some SARS-CoV-2 viruses, is based on Holland et al. (2020).
    - In the **"Version 2"** worksheet:
        - Questions 6 and 7, which discuss how the drug remdesivir could potentially treat SARS-CoV-2 infections, are based on Gordon et al. (2020).
        - Questions 10–14, which compare SARS-CoV-2 viruses in different states, use real sequence data from GenBank. GenBank links for all of these sequences are provided in the "References" at the end of this document.

STUDENT WORKSHEETS

There are two "Student Worksheets" that can be used to accompany the animations. "Version 1" was developed by a high school educator, and "Version 2" was developed by a college educator. Both worksheets were designed as learning assessments that probe students' understanding of the key concepts addressed in the animations. They can be used to assess students' understanding after watching the animations or to guide students as they watch the animations. You may modify the worksheets as needed (e.g., reducing the number of questions, adding explanations of vocabulary for English Language Learners, etc.) in order to better fit your learning objectives and your students' needs.

ANSWER KEY (VERSION 1)

PART 1: *Infection*

1. Explain how the terms COVID-19, SARS-CoV-2, and coronavirus mean different things.
COVID-19 is a disease, and SARS-CoV-2 is the virus that causes the disease. SARS-CoV-2 is a specific type of coronavirus. Coronaviruses are a family of viruses that infect humans and other animals.
2. The diagram below represents a SARS-CoV-2 virus. In the table below the diagram, identify each of the labeled structures. Write one or two sentences describing the role of each structure in the virus's replication process.

Label	Structure	Role in replication
1	***RNA genome***	***The RNA genome carries the virus's genetic information, including genes for proteins that the virus needs to make more copies of itself.***
2	***Protein spikes***	***The protein spikes attach to specific proteins on the surface of a cell. This allows the virus to enter the cell, release its RNA genome, and use the cell's machinery to make more copies of itself.***
3	***Envelope membrane***	***The envelope gives the virus its shape and protects the virus's genome so that it can be replicated. (Since the envelope is made from cell membranes, it helps protect the virus from the immune system. You may want to explain this to students since it is not explicitly explained in the animation.)***

3. Scientists discovered that SARS-CoV-2 is 10 to 20 times more likely to bind to these receptors than the other coronavirus was. Predict how this increased chance of binding has affected SARS-CoV-2's ability to replicate.
   A coronavirus must bind to receptors on a cell in order to enter that cell. Since SARS-CoV-2 is more likely to bind to the receptors, it is more likely to enter cells and produce copies of itself. So, this increased chance of binding probably improves SARS-CoV-2's ability to replicate.

4. Each of the following statements describes a step in the replication of SARS-CoV-2. These steps are listed in random order. Read through the steps and, in the spaces provided below, list them in the order they occur in the human body.
   a. The virus releases its RNA genome into the cell.
   b. Viral RNA polymerase helps transcribe more copies of the virus's RNA.
   c. The virus binds to a receptor on a human cell's membrane.
   d. New viruses travel to the cell membrane of the infected cell and are released outside the cell.
   e. The virus's RNA is translated into proteins by the cell's ribosomes.

   Correct order: ***c, a, e, b, d***

5. As shown in the animation, SARS-CoV-2 uses the ribosomes inside human cells to translate its RNA into viral proteins. According to the animation, what is one of the viral proteins made by the ribosomes, and how does that protein help SARS-CoV-2 make more copies of itself?
   One of the viral proteins made by the ribosomes is viral RNA polymerase, which is necessary to replicate the virus's genome. The polymerase makes copies of the virus's RNA, which are used to make new viral genomes and proteins that combine to make new viruses.

PART 2: ***Evolution***

6. The SARS-CoV-2 virus has an RNA genome made of 30,000 nucleotides. Identify the four different types of nucleotides found in the SARS-CoV-2 genome.
   A, U, C, and G. (A stands for the base adenine, U for uracil, C for cytosine, and G for guanine. The names of these bases are often used as the names of the nucleotides, though they are not technically the same.)
7. Could these mutations make the virus more deadly to humans? Support your answer in one or two sentences.
   Some mutations could make the virus more deadly, if they help the virus replicate or infect cells more easily. However, other mutations might make the virus less deadly or have no effect.
8. Based on the information above, explain why it may be possible to develop a SARS-CoV-2 vaccine that would *not* have to be modified as often as the flu vaccine.
   SARS-CoV-2 has a slower mutation rate than the virus that causes the flu. This means that SARS-CoV-2's genome, and the proteins it encodes, won't change as often. Vaccines frequently target specific viral proteins and may need to be modified if these proteins change in structure. Since SARS-CoV-2's proteins aren't changing as often, the SARS-CoV-2 vaccine probably won't need to be modified as often either.
9. Predict how the frequency of viruses with this deletion will change in the population over time. Use evidence to support your answer.
   This large deletion would most likely reduce or eliminate the protein's function, making it harder for the virus to escape the immune system. If so, viruses with this deletion would have a selective disadvantage (since they are more likely to be destroyed by the immune system) and would thus become less common in the population over time.

   (It is possible, although very unlikely with a deletion of this size, that the deletion could make the protein more effective at helping the virus escape the immune system. If so, the viruses with the deletion would have a selective advantage and would become more common in the population over time.)

10. How could sequencing many SARS-CoV-2 genomes be used to track how the virus has changed over time due to mutations?
    You could compare the genome sequences of SARS-CoV-2 samples taken from people in different locations over time. If there are variations among the genomes — such as more, fewer, or different nucleotides — you could track when and where these variations are present and determine when related mutations had occurred.

PART 3: ***Detection***

11. Imagine you are planning to visit a family member who is a nursing home resident. The nursing home requires that all visitors test negative for an active SARS-CoV-2 infection no more than two weeks before the visit. Which of the two tests shown above would you choose, or what other information would you want to learn before choosing? Use evidence from the table to support your answer.
    Student answers will vary; be open to a range of logical responses. If students prioritize speed, they may want to get the antigen test. If they prioritize accuracy and want fewer false negatives (e.g., because they are concerned about the risk of infecting a family member), they may want to get the RT-PCR test. Students may also discuss other information they'd want to know before choosing. This could include things like the availability of the tests, where they can get tested, how much each test would cost with/without health insurance, whether there are other tests they could get, etc.
12. In addition to the tests described above, people can also get tested for the presence of SARS-CoV-2 antibodies. Explain how an individual could test negative for an active SARS-CoV-2 infection and positive for SARS-CoV-2 antibodies.
    The individual could test negative for an active infection and positive for antibodies if they were infected in the past and have since recovered. Since they have recovered, they will no longer have the virus. But they will still have antibodies from having fought the virus before.

PART 4: ***Vaccination***

13. The animation describes the following types of SARS-CoV-2 vaccines. Briefly summarize how each type of vaccine triggers an immune response. (*Hint*: Remember that the immune system responds specifically to antigens.)
    a. Inactive whole virus
       The inactive virus in the vaccine contains antigens that trigger an immune response.
    b. Antigen proteins
       The antigen proteins (e.g., spike proteins) in the vaccine trigger an immune response directly.
    c. mRNA (genetic instructions)
       The mRNA in the vaccine is translated into antigen proteins, which trigger an immune response.
    d. DNA (genetic instructions)
       The DNA in the vaccine is transcribed into mRNA. The mRNA is then translated into antigen proteins, which trigger an immune response.

14. As shown in the animation, some SARS-CoV-2 vaccines deliver mRNA for the spike protein. Mark each of the following statements about this mRNA as either true or false.

Once the mRNA has entered a person's cells, it…	True (T) or False (F)
…is translated into spike proteins.	***T***
…is integrated into the cells' DNA.	***F***
…helps trigger the production of B cells.	***T***
…is eventually eliminated from the body.	***T***

15. Why would an unvaccinated person probably need more time to recover from a SARS-CoV-2 infection than a vaccinated person would?
Assuming that the unvaccinated person hasn't had a SARS-CoV-2 infection before, they wouldn't have memory B cells or antibodies that can quickly protect them from the virus. This person would need more time for their body to produce enough B cells and antibodies to fight the virus, and they might experience more serious disease in the meantime.

16. Why might people need another SARS-CoV-2 vaccination if the SARS-CoV-2 virus mutates?
Vaccines help the body produce B cells and antibodies that target specific antigens on the virus. If the virus's antigens change due to mutations, these B cells/antibodies may no longer be able to target the virus. You may need a new vaccine, one with antigens from the mutated virus, to produce new B cells/antibodies that target the mutated virus.

ANSWER KEY (VERSION 2)

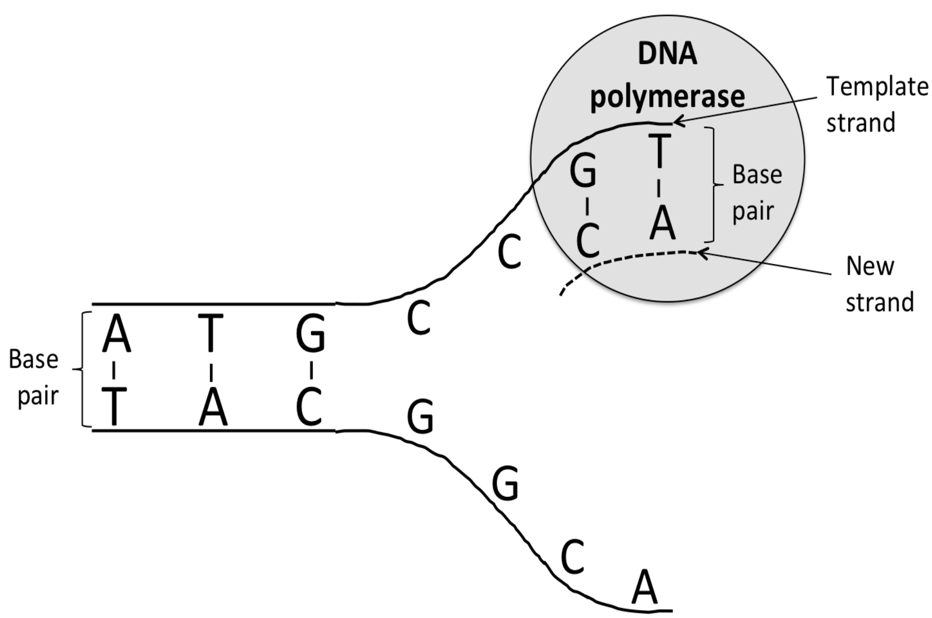
PART 1: ***Infection***

1. Describe the shape and location of SARS-CoV-2's protein spikes.
The animation shows that the protein spikes are shaped like clubs and stick out from the virus's surface (envelope).

2. What is the function of the spike protein?
The spike proteins bind to specific proteins on the surface of a cell, allowing the virus to enter the cell.

3. Predict how mutations in the gene that encodes the spike protein might affect the types of cells the virus infects.
Mutations in the gene that encodes the spike protein could change the amino acids encoded and therefore the shape and/or chemical properties of the spike protein. These changes may increase or decrease the spike protein's ability to bind to certain cell surface proteins. Different cell types have different cell surface proteins, so changes in the spike protein could affect which cell types the virus can bind to and thus infect.

4. Draw and label a model that shows how complementary base-pairing is used to create a new strand of DNA during cellular DNA replication. Your model should include the following labels: template strand, new strand, base pair, and DNA polymerase.
Student models will vary. An example is shown below.



5. List the similarities and differences between cellular DNA replication and the RNA genome replication process used by coronaviruses.
Student answers will vary depending on what they already know about DNA replication (which is not covered in the animation). Example responses are shown below.

Similarities	
• ***occurs in cells*** • ***uses the nucleotides A, C, and G*** • ***replicates nucleic acids from "template" strands using complementary base pairing***	
Differences	
DNA replication for cells	**RNA genome replication for viruses**
• ***replicates a double-stranded molecule (DNA)*** • ***uses T (thymine)*** • ***uses the enzyme DNA polymerase***	• ***replicates a single-stranded molecule (RNA)*** • ***uses U (uracil)*** • ***uses the enzyme RNA polymerase***

6. Figure 1 shows that remdesivir "mimics" an important component of RNA replication. Which component of RNA replication has a structure similar to that of remdesivir?
In Figure 1, remdesivir appears most structurally similar to the nucleotide A.

7. Propose a hypothesis about how remdesivir might inhibit the virus's replication process.
Student hypotheses may vary, but should be stated as testable, falsifiable statements.
Example 1: Remdesivir prevents the new RNA from fully elongating.
Example 2: Remdesivir introduces mutations into the new RNA.

PART 2: ***Evolution***

8. When SARS-CoV-2 replicates in cells, mutations can occur in the virus's genome. Explain how a mutation (insertion, deletion, or substitution) in one of the virus's genes might affect a protein it encodes.
Mutations may have no effect on the protein encoded by the gene, or they may cause changes in the protein's amino acids. These amino acid changes may affect the structure, size, and function of the protein.

9. What impacts might mutations have on the transmission of the virus?
Mutations that help the virus replicate or infect cells could increase the virus's transmission. Mutations that make the virus less effective at replication or infection could decrease its transmission. Other mutations may not affect the virus's transmission at all.

10. Which of the following types of mutations is represented in Table 1?
    a. ***Substitutions (correct answer)***
    b. insertions
    c. deletions

11. At which stage of viral infection did these mutations most likely occur?
They probably occurred during the virus's genome replication process, which is prone to errors.

12. Fill in the last column of Table 1 to indicate the number of nucleotide differences between the virus from Washington and the viruses from other states.

	Position in the sequence alignment							Number of differences
State	1059	3037	14408	18060	23403	25563	28144	
Washington	C	C	C	T	A	G	C	–
Utah	C	T	T	C	G	T	T	***6***
Colorado	C	C	C	C	A	G	T	***2***
Kansas	C	T	T	C	G	G	T	***5***
California	T	T	T	C	G	T	T	***7***

13. Knowing that the virus from Washington probably arose first, make a list below predicting the order, from first to last, in which the viruses from these states arose.
    a. Washington
    b. ***Colorado***
    c. ***Kansas***
    d. ***Utah***
    e. ***California***

14. Why did you select this order?
    Mutations accumulate over time. So, the viruses with more sequence differences from the Washington virus probably arose later. (For reference, the actual collection dates for these samples were as follows. Washington: January 19, 2020; Colorado: March 7, 2020; Kansas: March 10, 2020; Utah: April 13, 2020; California: April 30, 2020.)

PART 3: ***Detection***

15. List the three types of molecules detected by the tests in the animation.
    Viral RNA, viral antigens (proteins), and antibodies

16. Imagine that three individuals get all three tests. Propose a possible explanation for each individual's test results, as shown in the following table.

Individual	**RT-PCR test**	**Antigen test**	**Antibody test**	**Explanation**
1	Positive	Positive	Negative	***This individual's RT-PCR and antigen tests are positive because they have an active infection. Their antibody test is negative because their immune system hasn't made antibodies against the virus yet.***
2	Positive	Negative	Negative	***This individual's RT-PCR test is positive because they have an active infection. Their antigen test should also be positive but produced a false negative in this case. Their antibody test is negative because their immune system hasn't made antibodies against the virus yet.*** ***(Consider discussing with students why the antigen test is more likely to produce a false negative than the RT-PCR test. The RT-PCR test is much more sensitive than the antigen test***

				because it amplifies viral RNA, which makes the virus easier to detect. The antigen test detects only the antigens/proteins that are present, so the virus must be replicating at high levels before it can be detected by the antigen test.)
3	Negativ e	Negative	Positive	***This individual's RT-PCR and antigen tests are negative because they had a past infection and recovered, so the virus is no longer in their body. Their antibody test is positive because their body still has the antibodies that were made to fight the virus.***

PART 4: ***Vaccination***

17. Antigen protein vaccines deliver the spike protein directly into the body. The DNA and mRNA vaccines, however, make the cells of the body generate the spike protein. Briefly describe how the body generates spike proteins for each vaccine type.
    a. DNA vaccines
    DNA delivered by the vaccine is transcribed into mRNA, which is translated into protein.
    b. mRNA vaccines
    mRNA delivered by the vaccine is directly translated into protein.

18. Do the genetic instructions (DNA and mRNA) vaccines contain the virus's full genome? If not, what region(s) of the genome do they contain?
    These vaccines just contain the region that encodes the spike protein.

19. Do the antigen protein vaccines contain all the proteins in the virus? If not, which protein(s) do they contain?
    These vaccines just contain the spike protein.

20. For each vaccine type in the animation, propose a test that could detect an active viral infection *without* false positives from that vaccine. (*Hint*: It may help to review the tests for active infections in the *Detection* animation. Note that there may not be a good test in every case.)

Vaccine type	**Proposed test without false positives**
Inactive whole virus	***It depends on how the virus is inactivated, but there may not be a good test in this case.***
Antigen proteins	***You could use an antigen test that detects a different viral protein than the spike protein. Or you could use an RT-PCR test that detects any part of the virus's RNA genome, since no viral RNA is delivered by this type of vaccine.***
Genetic instructions (DNA or mRNA)	***You could use an RT-PCR test that detects a different part of the virus's genome than the region that encodes the spike protein.***

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