

Teacher Notes for “Coronavirus Evolution and the Covid-19 Pandemic”¹

In this analysis and discussion activity, students learn that the coronavirus responsible for the current pandemic very probably originated in bats. Students analyze how mutations and natural selection can produce a spillover infection. Next, students learn how natural selection increased the frequency of a mutation that made the coronavirus more contagious. Finally, students analyze how mutations contributed to the spread of the Omicron variant and its subvariants.

You could use this activity to introduce coronaviruses and natural selection. However, some students may find it helpful to complete the following analysis and discussion activities before they begin this activity.

- “Coronaviruses – What They Are and How They Can Make You Sick” (includes an introduction to how coronaviruses are replicated)
(<https://serendipstudio.org/exchange/bioactivities/coronavirusintro>)
- “What is natural selection?”
(<https://serendipstudio.org/exchange/bioactivities/NaturalSelectionIntro>).

Learning Goals

In accord with the Next Generation Science Standards (NGSS)²:

- This activity helps students to prepare for Performance Expectation HS-LS4-3. “Apply concepts of statistics and probability to support explanations that organisms with an advantageous heritable trait tend to increase in proportion to organisms lacking this trait.”
- This activity helps students to understand the Disciplinary Core Ideas:
 - LS4.B “Natural selection occurs only if there is both (1) variation in the genetic information between organisms in a population and (2) variation in the expression of that genetic information – that is, trait variation – that leads to differences in performance among individuals. The traits that positively affect survival are more likely to be reproduced, and thus are more common in the population. The traits that positively affect survival are more likely to be reproduced, and thus are more common in the population.”
 - LS4.C “Natural selection leads to adaptation, that is, to a population dominated by organisms that are... well suited to survive and reproduce in a specific environment. That is, the differential survival and reproduction of organisms in a population that have an advantageous heritable trait leads to an increase in the proportion of individuals in future generations that have the trait into a decrease in the proportion of individuals that do not.”
- Students engage in the Scientific Practices:
 - “Constructing Explanations. Apply scientific ideas, principles and/or evidence to provide an explanation of phenomena and solve design problems...”
 - “Developing and Using Models. Develop and/or use a model (including mathematical and computational) to generate data to support explanations, predict phenomena, analyze systems, and/or solve problems.”
- This activity helps students to understand the Crosscutting Concept, “Stability and Change. Much of science deals with constructing explanations of how things change and how they remain stable.”

¹ By Dr. Ingrid Waldron, Department of Biology, University of Pennsylvania, 2022. These Teacher Notes and the related Student Handout are available at <https://serendipstudio.org/exchange/bioactivities/coronavirusOrigin>.

² Quotations are from NGSS "High School Life Sciences" at <http://www.nextgenscience.org/sites/default/files/HS%20LS%20topics%20combined%206.13.13.pdf>

Instructional Suggestions and Biology Background

To maximize student participation and learning, I suggest that you have your students work individually or in pairs to complete each group of related questions and then have a class discussion after each group of questions. In each discussion, you can probe student thinking and help them develop a sound understanding of the concepts and information covered before moving on to the next group of related questions.

If your students are learning online, I recommend that they use the Google Doc version of the Student Handout available at <https://serendipstudio.org/exchange/bioactivities/coronavirusOrigin>. To answer questions 2a, 3 and 6, students can either print the relevant pages, draw on them and send pictures to you, or they will need to know how to modify a drawing online. To answer online, they can double-click on the relevant drawing in the Google Doc to open a drawing window. Then, they can use the editing tools to answer the questions.³ You may want to revise the GoogleDoc or Word document to prepare a version of the Student Handout that will be more suitable for your students; if you do this, please check the format by viewing the PDF.

A key is available upon request to Ingrid Waldron (iwaldron@upenn.edu). The following paragraphs provide additional instructional suggestions and background information – some for inclusion in your class discussions and some to provide you with relevant background that may be useful for your understanding and/or for responding to student questions.

The novel coronavirus that is causing the current global pandemic is called SARS-Cov-2 because of its similarity to SARS-Cov, a coronavirus that caused an epidemic of Severe Acute Respiratory Syndrome in 2002-2004, mainly in Asia. The disease caused by SARS-Cov-2 is called Covid-19. “Co” stands for corona, “vi” stands for virus and “d” stands for disease; 19 stands for 2019, the year in which this disease was first identified. As of August 8, 2022, the estimated number of Covid-19 deaths was 1.03 million in the US and 6.42 million in the world (<https://coronavirus.jhu.edu/region/united-states> and <https://coronavirus.jhu.edu/map.html>; you may want to use these sources to check the number of deaths at the time you use this activity). Globally, reported Covid-19 deaths accounted for roughly 10% of all deaths during the pandemic, and actual Covid-19 deaths were almost certainly substantially higher than reported deaths (<https://www.nature.com/articles/d41586-022-00104-8>).

Covid-19 survivors often experience long-term symptoms and new diagnoses of other illnesses. Patients who had recovered from severe Covid-19 had a 2.5 times higher chance of dying during the next year than those who have not had Covid-19 (<https://www.frontiersin.org/articles/10.3389/fmed.2021.778434/full>). Even for patients who had mild Covid-19, roughly a quarter experienced long-term symptoms such as fatigue or brain fog (<https://www.reuters.com/business/healthcare-pharmaceuticals/almost-third-people-report-lingering-symptom-6-12-months-after-covid-19-study-2022-03-04/>; <https://health.ucdavis.edu/news/headlines/studies-show-long-haul-covid-19-afflicts-1-in-4-covid-19-patients-regardless-of-severity/2021/03>).

³ To draw a shape

1. At the top of the page, find and click Shape.
2. Choose the shape you want to use.
3. Click and drag on the canvas to draw your shape.

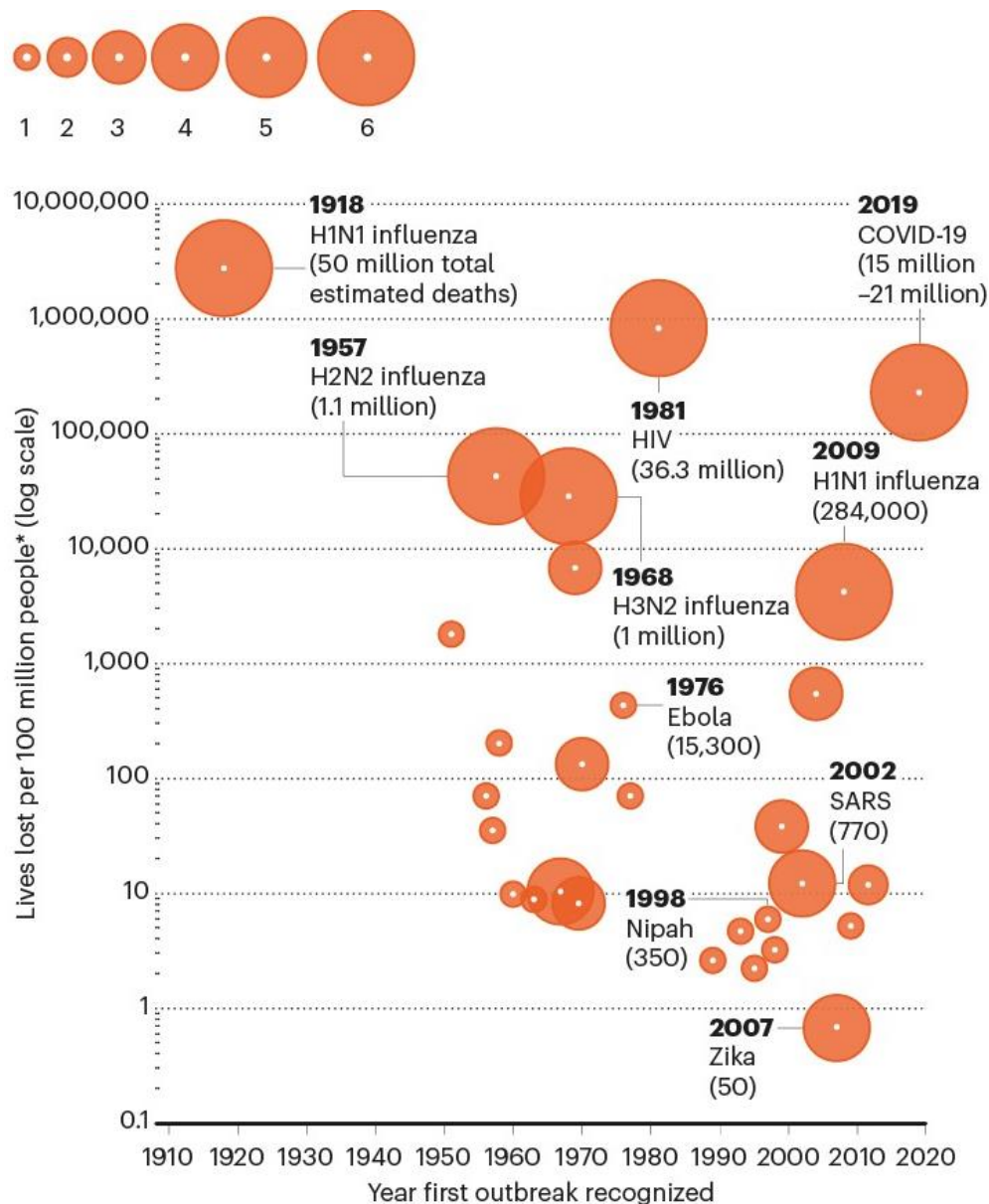
To insert text, at the top of the page, click Insert and then click Text Box, type your text, and drag the text box to where you want it.

When you are done, click Save and Close.

Where did the new coronavirus come from?

The recommended 9-minute video, “Where do new viruses come from?”

(<https://www.youtube.com/watch?v=NJLXdsO1GBI>) is generally very accurate, but at one point the narrator incorrectly refers to the virus, rather than the disease, as Covid-19. As explained in the video, spillover infections (the transmission of a pathogen from one type of animal to another) have been responsible for multiple human diseases caused by viral infections, including HIV-AIDS (Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome), Ebola, West Nile virus, Zika, influenza A, Middle East respiratory syndrome (MERS), and the first SARS outbreak. Spillover infections are also called zoonotic diseases.



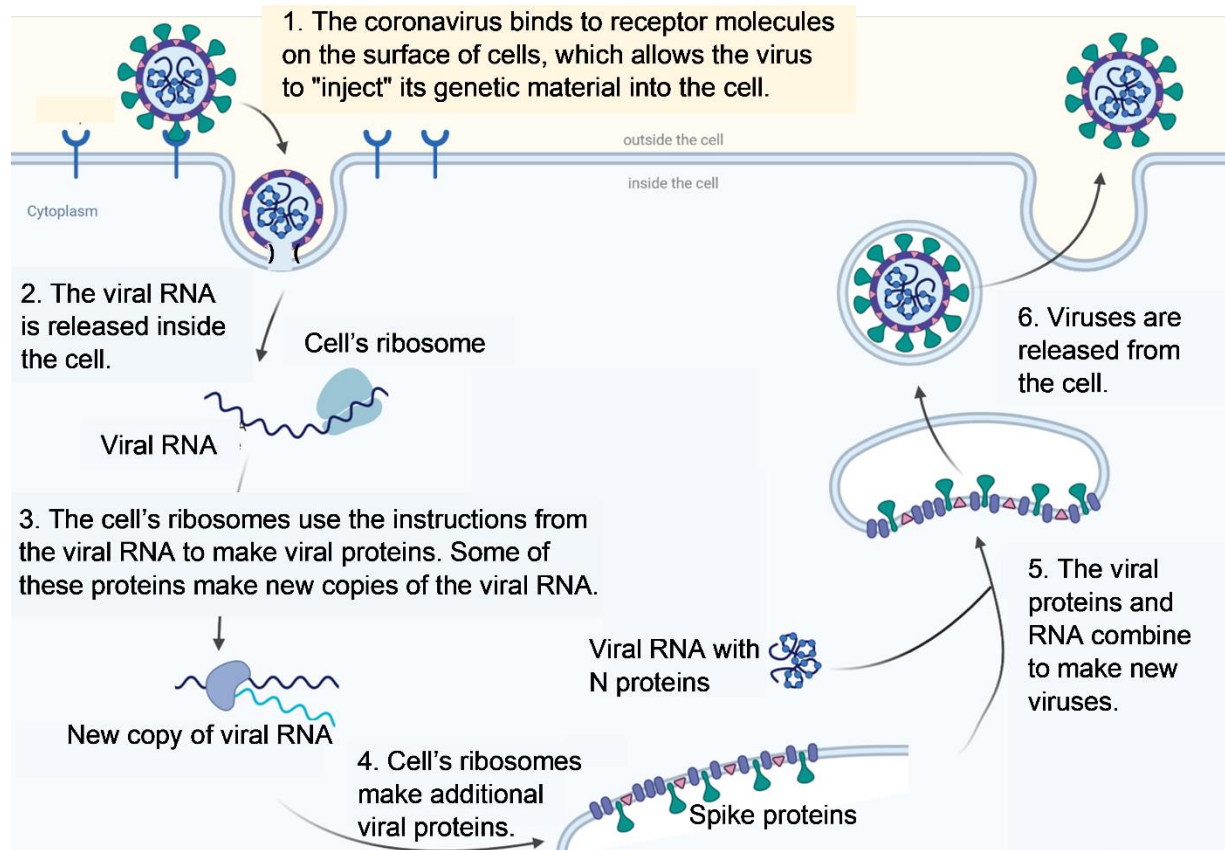
*Data are from viral outbreaks of zoonotic origin that resulted in ten or more deaths; figures in parentheses are total estimated deaths spread over multiple years (and over multiple outbreaks, in some instances) rounded to the nearest ten.

(The number of estimated deaths takes into account the underreporting of COVID-19 deaths, especially in developing countries; <https://www.nature.com/articles/d41586-022-01312-y>)

The recommended video may prompt students to inquire about the effectiveness of travel restrictions to stop or slow the spread of Covid-19 and similar pandemics. The available evidence suggests that border closings usually fail to reduce rates of infection because they are

enacted too late and they are insufficiently comprehensive and strict (e.g., they do not require strict quarantine for everyone entering the country).

The coronavirus spike protein binds to the ACE2 molecular receptor on the surface of cells in the nose, lungs, and multiple other parts of the body. This allows the viral RNA to enter the cell. Coronavirus RNA serves as mRNA, and the cell's ribosomes translate the viral RNA to make viral proteins. The viral RNA is copied by a viral enzyme. The viral proteins and RNA assemble to form new viruses that are released from the infected cell, which typically dies. The viruses that the cell releases can infect other body cells; they may be inactivated by the person's immune system; or they may be released to the air when the infected person coughs, sneezes, shouts, sings or breathes, and then the coronaviruses in the air may infect other people.



(Adapted from <https://enviraltech.com/wp-content/uploads/2020/05/SARS-CoV-2-replication-2.png>)

The recommended video and pages 1-2 of the Student Handout provide a simplified introduction to how spillover infections result from mutations and natural selection. Mutations are caused by random errors in copying the viral RNA, so most mutations will either have little or no effect on fitness or reduce the fitness of the virus (as exemplified by the hypothetical N version of the spike protein gene on page 2 of the Student Handout). Students may need to be reminded that mutation is random, but natural selection is not random.

The recommended video mentions recombination, but the Student Handout does not discuss this additional source of genetic variation. When two genetically different coronaviruses infect the same cell, recombination can combine parts of the RNA from these two coronaviruses to produce a coronavirus with a new combination of mutations. Recent research has supported the contribution of recombination to the origin of SARS-Cov-2 and has identified coronaviruses from bats in Laos that may have contributed a crucial segment of the SARS-Cov-2 RNA; these

bat coronaviruses have a spike protein gene that codes for a spike protein that has a high affinity for human ACE2 molecular receptors (<https://www.nature.com/articles/s41586-022-04532-4>).⁴

Recent evidence indicates that the most likely origin of SARS-CoV-2 was a spillover infection that originated in bats and reached humans via an intermediate host such as pangolins or raccoon dogs which were sold live in a market in Wuhan, China. (These animals are sold for meat, fur, or use in traditional medicine.) (<https://www.webmd.com/lung/news/20220727/more-evidence-covid-started-in-marketplace>; <https://www.science.org/doi/10.1126/science.abp8715>; <https://www.nature.com/articles/d41586-022-00584-8>) The evidence for this hypothesis is much stronger than the evidence for the alternative hypotheses that the SARS-CoV-2 virus was accidentally released from a lab or spilled over directly from bats in Southeast Asia to humans (e.g., when farmers enter a bat roosting site to collect bat guano for fertilizer).

The following sequence of events is required for a spillover infection to cause an epidemic.

- A mutation or mutations must result in a virus that can bind to molecules on the surface of the cells of a new host.
- This mutated virus must come in contact with an appropriate cell in the new host.
- The virus needs to be reproduced by the cells of the new host. Efficient reproduction in the new host usually requires additional mutations and natural selection.
- The virus must also be able to spread from person to person.

The history of spillover infections provides evidence that this rare combination of events has occurred repeatedly in the past, which is understandable when you consider the trillions of animal viruses and billions of people in the world

(<https://www.nationalgeographic.com/science/2020/04/factors-allow-viruses-infect-humans-coronavirus/>; <https://www.medrxiv.org/content/10.1101/2021.09.09.21263359v1>).

You may want to add the following question at the end of page 2 of the Student Handout.

8. Researchers have made several recommendations for preventing new spillover infections in humans. These recommendations include:

- Reduce human contact with wild animals (e.g., by banning the sale of wild animals).
- Regularly test the blood of people who are exposed to viruses in bats or other animals to detect exposure to any new or unusual viruses and take prompt action to prevent spread of these viruses.
- Monitor hospital patients to detect clusters of cases with unusual symptoms that may indicate a new spillover infection and act promptly to prevent wider spread of any new infectious disease.

What are the pros and cons of these recommendations?

The strategies recommended in this question would reduce the likelihood of a future pandemic. However, previous experience suggests that many people may be reluctant to comply with the behavioral changes recommended in the first strategy. The second and third strategies would require a substantial investment of resources.

⁴ After more than a decade of research on the origins of the 2002-2004 SARS epidemic, scientists identified a cave where many horseshoe bats roosted; parts of the RNA in the coronaviruses that infected these bats were very similar to parts of the RNA in the coronavirus that caused this earlier SARS epidemic. The scientists found evidence of frequent recombination of RNA from different coronaviruses, and they have argued that recombination in bat coronaviruses probably contributed to the origin of the SARS-CoV virus that caused the 2002-2004 SARS epidemic (<https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006698>). Additional evidence indicates that this bat coronavirus caused a spillover infection in civets which caused the spillover infection in humans.

How has the coronavirus changed during the Covid-19 pandemic?

Many of the more than 585 million recorded cases of Covid-19 have been confirmed by testing for coronavirus RNA in a sample collected from the nose (or saliva). For some of these samples, scientists have checked the sequence of the nearly 30,000 nucleotides in the RNA of the coronavirus. Scientists have found many differences in the nucleotide sequence, but research has focused on the mutations and combinations of mutations that have become widespread.

Mutations refer to changes in the nucleotide sequence relative to the original strain of coronavirus that spread around the world in late 2019 and early 2020.

Page 3 of the Student Handout analyzes how one mutation spread worldwide in the first half of 2020. The graph of the spread of the G mutation is based on sequencing over 52,000 samples of SARS-CoV-2, collected globally during the first half of 2020

(<https://media.nature.com/original/magazine-assets/d41586-020-02544-6/d41586-020-02544-6.pdf>). The scientific name of the G mutation is D614G because it results in the amino acid glycine (G) instead of aspartic acid (D) in the 614th amino acid position of the spike protein. Molecular evidence, cell experiments, and epidemiological evidence indicate that this mutation makes it easier for the coronavirus to enter human respiratory system cells and thus increases the transmission of coronaviruses from person to person.

The figure in the bottom half of page 3 of the Student Handout is an example of a simplified model that helps us to understand a complex phenomenon. This figure shows an unrealistically regular spread of coronavirus infections. The actual spread of coronavirus infections shows much more variation. On the one hand, many infected people don't pass their coronavirus infection to anyone else. At the other extreme, superspreader events, where a single infected person infects many other people, have played a significant role in the spread of coronavirus infections (<https://www.nature.com/articles/d41586-021-00460-x>).

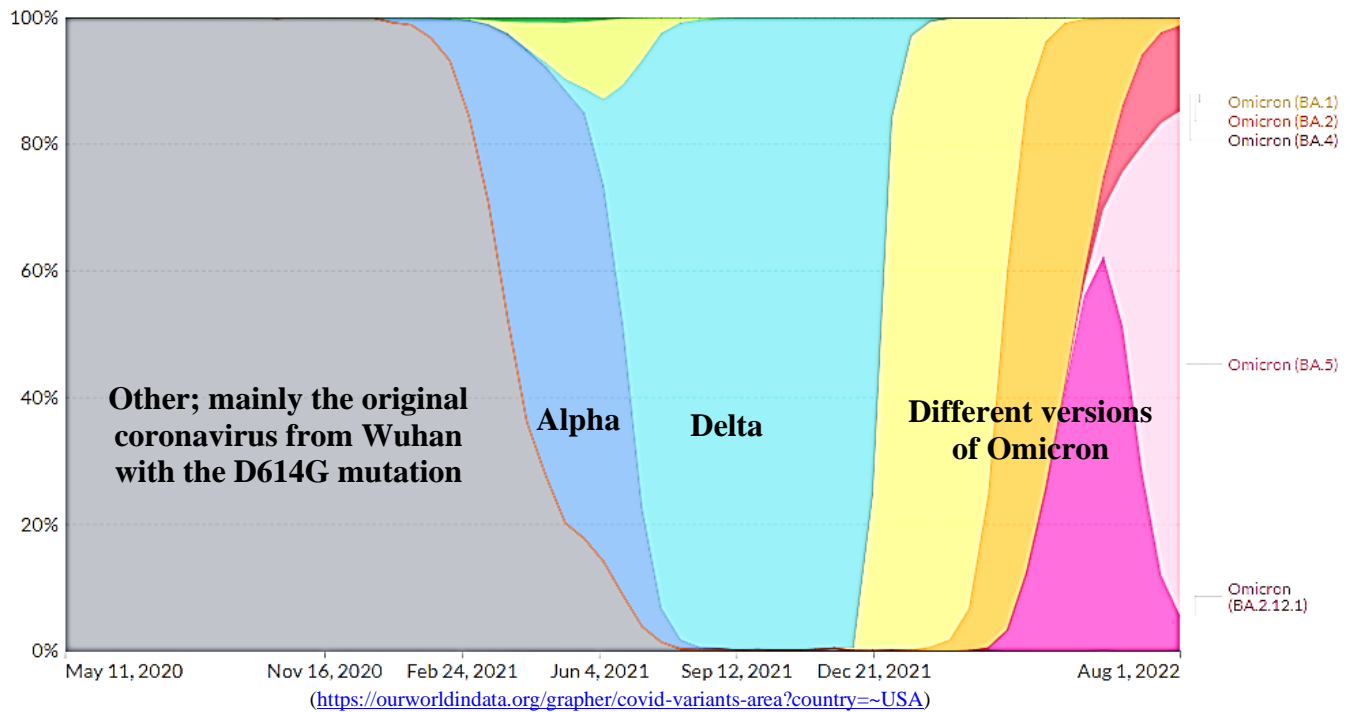
The last page of the Student Handout focuses on the Omicron variant and subvariants. A variant is a group of viruses that share the same set of inherited mutations and have become relatively common in a region or country. The millions of coronavirus infections during the pandemic have provided many opportunities for new mutations and natural selection for advantageous combinations of mutations, which has resulted in the repeated spread of new variants.⁵ Scientists believe that a variant may develop in a patient with a compromised immune system. This type of patient may have a prolonged coronavirus infection that allows the accumulation of multiple mutations in the patient's coronavirus population. This highly mutated version of the coronavirus may then spread to other people and become a new coronavirus variant. Other hypotheses propose that a variant may have accumulated multiple mutations in a wild animal population or possibly in a human population in a part of the world where genetic testing is so rare that the variant could have accumulated multiple mutations undetected

(<https://www.nature.com/articles/d41586-022-00215-2>).

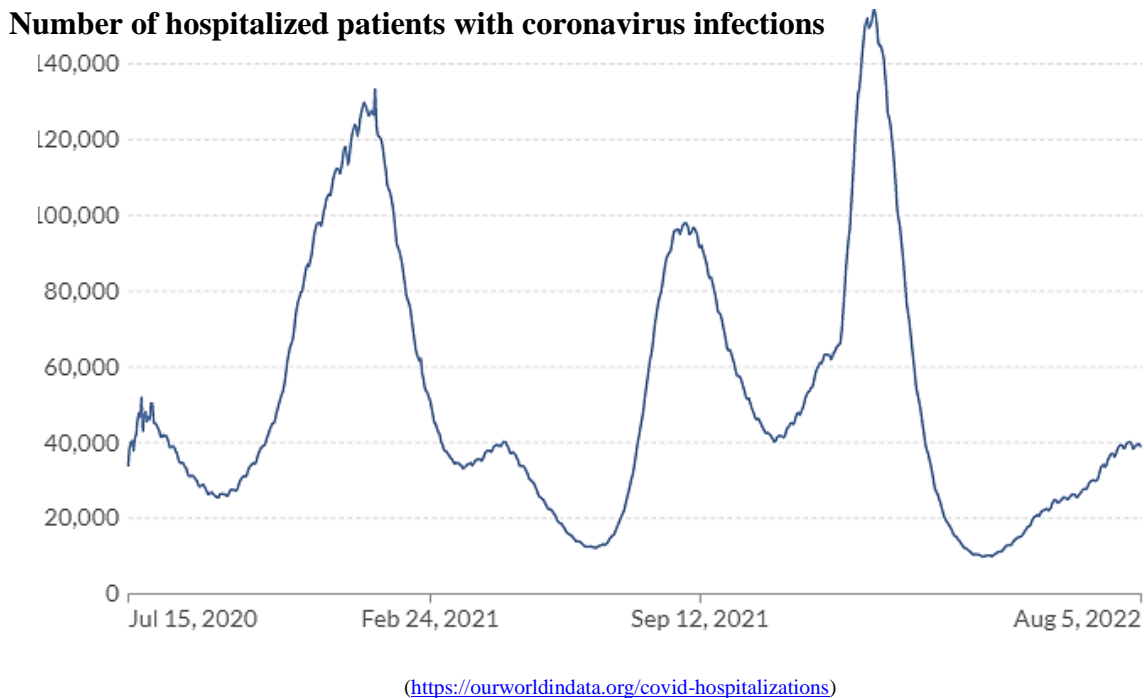
The Omicron variant was first detected in southern Africa in November 2021, and it soon became the fifth WHO-designated Variant of Concern. The percent of US coronavirus samples that were the Omicron variant increased from 0.06% on November 29, 2021, to 50% by

⁵ The Appendix on pages 12-13 of these Teacher Notes provides information on the first four Variants of Concern – Alpha, Beta, Gamma, and Delta (<https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html>); for the WHO definition of Variants of Concern, see [https://www.who.int/news/item/26-11-2021-classification-of-omicron-\(b.1.1.529\)-sars-cov-2-variant-of-concern](https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern)).

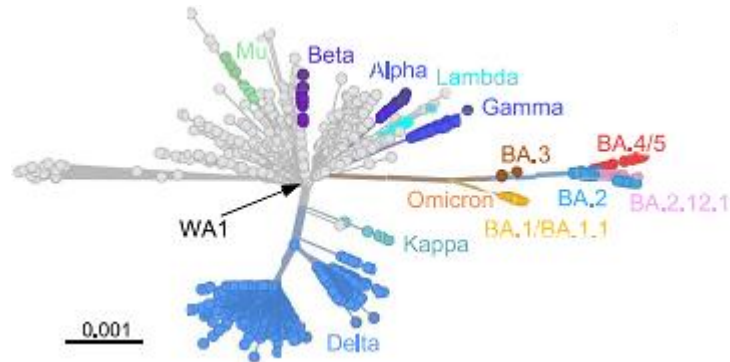
December 27, to 98% by January 2022 (<https://covid.cdc.gov/covid-data-tracker/#variant-proportions>; see figure below).



The graph below shows US trends in the number of hospitalized patients with coronavirus infections. Notice that the spread of the Delta and Omicron variants (shown above) corresponded to steep increases in the number of hospitalized patients with coronavirus infections (shown below).

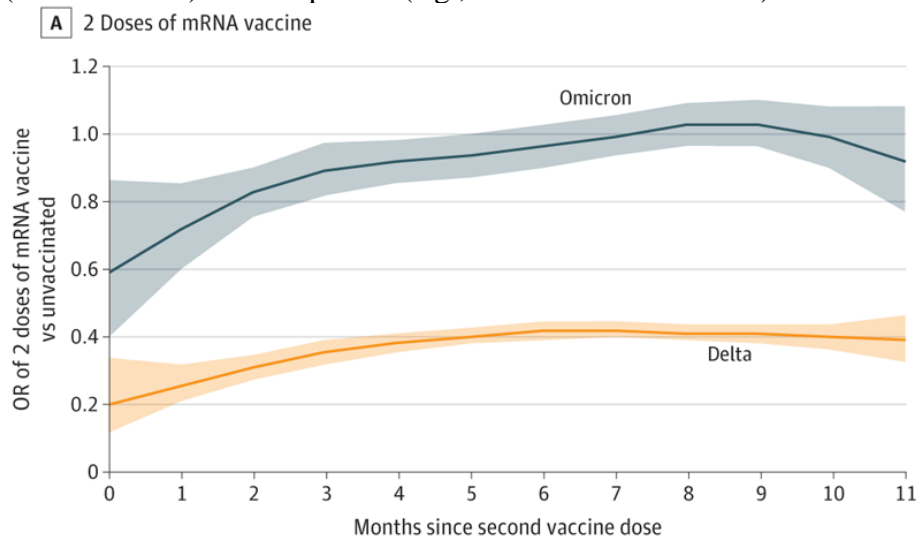


The Omicron variant has more than 50 mutations relative to the original version of SARS-CoV-2, including more than 30 mutations in the gene for the spike protein.⁶ Subvariants of Omicron are evolutionarily descended from the original Omicron virus (see figure below). Subvariants BA.4 and BA.5 have additional mutations that contribute to enhanced ability to evade immune defenses (<https://media.nature.com/original/magazine-assets/d41586-022-01730-y/d41586-022-01730-y.pdf>).



(Phylogenetic tree of SARS-CoV-2; https://www.nature.com/articles/s41586-022-05053-w_reference.pdf)

The ability to evade antibody defenses appears to be due to mutations in the spike protein gene that result in decreased binding of the spike protein to antibodies (<https://www.scientificamerican.com/article/omicrons-surprising-anatomy-explains-why-it-is-wildly-contagious/>). Evidence that immune defenses are less effective against Omicron comes from in vitro neutralization assays of antibody effectiveness and from observational studies of the risk of symptomatic SARS-CoV-2 infection by vaccination status. In the figure below, an odds ratio of 1 indicates that, by six months after vaccination, two doses of mRNA vaccine do not protect against infection by Omicron (although two doses of vaccine do protect against severe infection). The lower odds ratios for the Delta variant indicate that vaccination results in relatively strong and persistent protection against infection by the Delta variant. Two doses plus a booster provide better protection than two doses alone (https://jamanetwork.com/journals/jama/fullarticle/2788487?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jama.2022.0470). Notice that the effectiveness of immune defenses against SARS-CoV-2 depends on characteristics of the coronavirus (which variant) and the person (e.g., time since vaccination).



(https://jamanetwork.com/journals/jama/fullarticle/2788485?guestAccessKey=ccd57888-8fd5-4d31-9a19-82ee2b987521&utm_source=silverchair&utm_campaign=jama_network&utm_content=covid_weekly_highlights&utm_medium=email)

⁶ Some of the mutations observed in the Omicron variant have also been observed in some of the previous Variants of Concern.

Question 11a introduces the concepts of reinfection and breakthrough infections. Students may argue that breakthrough infections show that the vaccines are not working. To counteract this opinion, you may want to show the ~1-minute video, “What are vaccine breakthrough cases?” (available, about halfway down at <https://www.health.state.mn.us/diseases/coronavirus/stats/vbt.html>), which explains how to correctly interpret statistics about breakthrough cases.

In discussing student answers to question 11b, the most important point is as follows. When many people have already been vaccinated or infected with the original version of the novel coronavirus, then the ability to evade immune defenses has a considerable selective advantage.

The major components of the immune defenses include antibodies and T cells.⁷

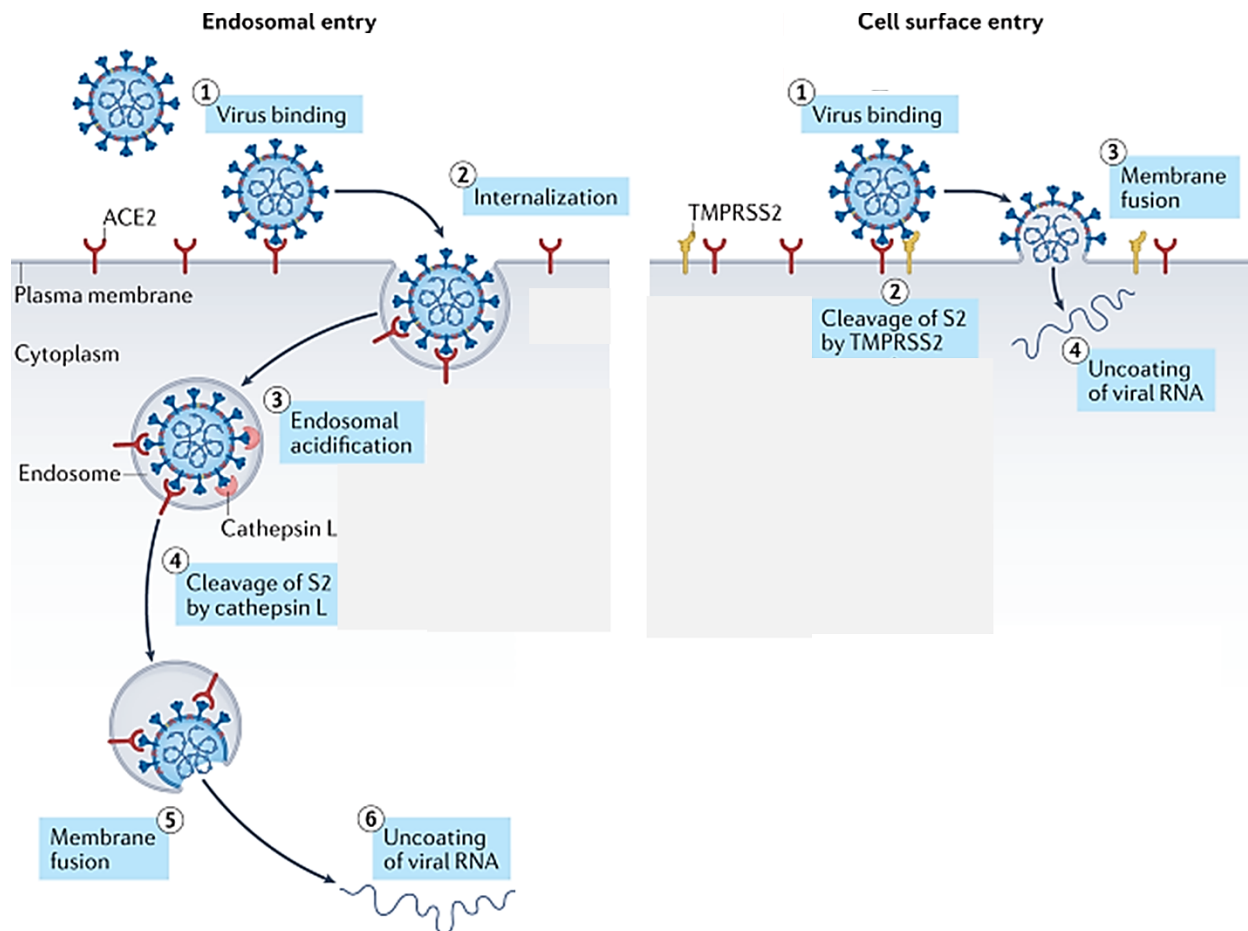
- Neutralizing antibodies bind to viral proteins in a way that blocks the virus from infecting the cell. In vitro, the Omicron variant has substantially reduced sensitivity to neutralizing antibodies from vaccinated people or people infected with earlier versions of the coronavirus. This helps to explain why vaccination and/or previous infection provide much reduced protection against infection with the Omicron variant.
- Cytotoxic T cells kill infected cells, which minimizes replication of the coronavirus. Most T cells from vaccinated or previously infected people continue to defend against the Omicron variant. This helps to explain why previous infection and/or vaccination (particularly with a booster shot) continue to protect against severe illness due to the Omicron variant.
(<https://www.medrxiv.org/content/10.1101/2022.01.03.21268111v1>;
<https://www.medrxiv.org/content/10.1101/2021.12.26.21268380v1>).

The Omicron variant has generally produced less severe disease than the Delta variant did. To some extent, disease has been less severe because so many people have been vaccinated (and boosted) and/or previously infected. However, to some extent less severe disease reflects differences between the Omicron and Delta variants. To understand why, it is helpful to understand the two different ways that coronavirus RNA can enter cells. Both routes of entry require an enzyme that cuts the S2 unit of the spike protein to expose a fusion peptide which forms a fusion pore that allows the viral RNA to enter the cell cytoplasm.

- Most nasal cells do not have an S2-cutting enzyme on their cell surface; coronavirus RNA enters these nasal cells via an endosome that has an S2-cutting enzyme (shown on the left in the figure below). The Omicron variant of the coronavirus preferentially uses the endosomal entry route, which may help to explain why it readily infects nasal epithelial cells and has been so highly contagious.
- Many lung cells have an enzyme on the cell surface that can make the needed cut in the S2 unit of the spike protein; coronavirus RNA enters these lung cells via cell surface entry (shown on the right in the figure below). The Delta variant efficiently uses this cell surface entry route, which explains why it easily infected lung cells and more often caused serious illness.⁸ (<https://www.nature.com/articles/d41586-022-00428-5>;
<https://www.medrxiv.org/content/10.1101/2022.01.03.21268111v1>)

⁷ A more complete description of immune defenses against coronavirus infections is available in the Student Handout and Teacher Notes for "Covid-19 Vaccines – How do they work?" (<https://serendipstudio.org/exchange/bioactivities/coronavirusvaccine>).

⁸ For an explanation of how infections of lung cells result in severe Covid-19, see "Coronaviruses – What They Are and How They Can Make You Sick" (<https://serendipstudio.org/exchange/bioactivities/coronavirusintro>).



(Adapted from <https://www.nature.com/articles/s41580-021-00418-x>)

There is a broad consensus that SARS-Cov-2 will continue to circulate in the human population for the foreseeable future, because:

- it is so widespread and capable of mutations;
- there are many people who are vulnerable to infection (e.g., because they are immunosuppressed or haven't yet been vaccinated);
- there are some animal reservoirs of infection (e.g., mink, deer and guinea pigs) and these animals may re-infect humans.

Beyond the conclusion that SARS-Cov-2 won't be eliminated, the future of the pandemic is unknown at the present time. One possibility would be that the illness caused by SARS-Cov-2 will become more like the common cold; some colds are caused by other types of coronaviruses. Unfortunately, it is also possible that future variants may cause more serious illness (<https://www.nature.com/articles/d41586-021-03619-8>).⁹ To reduce the risk of new, more dangerous variants emerging in the future, it will be important to adopt policies that reduce the number of coronavirus infections, e.g., widespread vaccination (including in poor countries), using masks, reducing indoor contact with people outside the family, and improving ventilation of indoor spaces. These policies would need to be adopted globally, because more dangerous variants that emerge in one part of the world can spread rapidly worldwide.

⁹ Some infectious diseases have become less severe over time, both because more people have developed some immunity and because natural selection may favor milder versions that allow people to maintain their usual activities and spread the disease more widely. However, much of the transmission of SARS-CoV-2 occurs before people develop symptoms or in people who never develop symptoms, so there is little selection for variants of SARS-CoV-2 that cause milder disease.

You may want to add the following question at the end of the activity.

12. What can you do to protect yourself against Covid-19 now and in the future?

The best ways to protect yourself against Covid-19 include:

- vaccination (which is especially effective in preventing severe illness)
- wearing a mask (when indoors with people outside your family or when with an infected or recently exposed family member)
- reducing the time spent indoors with people outside your family (especially minimizing the time spent in crowded, poorly ventilated indoor spaces where people are shouting or singing).

Washing your hands thoroughly with soap after contact with people outside your family may also help. The first two learning activities listed below provide additional relevant information.

Follow-Up Activities and Additional Resources

Covid-19 Vaccines – How do they work?

<https://serendipstudio.org/exchange/bioactivities/coronavirusvaccine>

Students begin by proposing a hypothesis to explain why the risk of severe Covid-19 is substantially lower for people who have been vaccinated and for people who have previously had Covid-19. Next, students analyze the immune system response to a coronavirus infection and learn how this response differs after a first vs. second exposure to the coronavirus. Finally, students analyze the biological effects of an mRNA vaccine and develop an evidence-based hypothesis about how a vaccine protects against severe Covid-19.

How to Reduce the Spread of Covid-19

<https://serendipstudio.org/exchange/bioactivities/coronavirusprev>

In this learning activity, students analyze information about how the coronavirus is transmitted and how to reduce the risk of coronavirus infection. Several questions engage students in thinking about how their behavior influences the risk of Covid-19 for more vulnerable individuals.

Resources for Teaching about Coronavirus

<https://serendipstudio.org/exchange/bioactivities/coronavirus>

This webpage has compiled information about learning activities and other resources for teaching high school biology students about the coronavirus and Covid-19.

If your students have additional questions about the novel coronavirus and the Covid-19 pandemic, you may want to encourage them to research these questions using the following sources of reliable information.

- Coronavirus (COVID-19) (<https://www.cdc.gov/coronavirus/2019-ncov/index.html>)
- Science (<https://www.sciencenews.org/editors-picks/2019-novel-coronavirus-outbreak>)
- New York Times (<https://www.nytimes.com/news-event/coronavirus>)

For additional information and learning activities about natural selection, see “Resources for Teaching and Learning about Evolution”

(<https://serendipstudio.org/exchange/bioactivities/evolrec>). For an additional learning activity about mutations, see "Mutations and Muscular Dystrophy"

(<https://serendipstudio.org/exchange/bioactivities/mutation>).

Sources for Student Handout Figures

- Figure of coronavirus structure, adapted from https://viralzone.expasy.org/resources/nCoV_SARS_virion.png
- Figure of translation and mutation, adapted from <https://i.pinimg.com/564x/1d/6b/e9/1d6be9580a00ace750b472953a2bd77f--point-mutation-ap-biology.jpg>
- Figure of trends in G mutation, adapted from <https://www.nature.com/articles/d41586-020-02544-6>
- Figure of coronavirus with antibodies, adapted from <https://www.nature.com/articles/d41586-020-01816-5>

Other figures were made by the author.

Appendix – The Beta, Gamma, Alpha and Delta Variants

The Beta variant was first detected in South Africa, where it spread rapidly in early December 2020. This variant had eight mutations in the spike protein gene, including:

- N501Y, which helped to make this variant more contagious, and
 - E484K and K417N, which decreased the effectiveness of immune defenses that developed after an initial infection with the original strain or after vaccination with a vaccine developed to protect against the original strain.
- (<https://www.washingtonpost.com/health/2021/02/05/virus-variant-reinfection-south-africa/>)

The Gamma variant, which was first detected in Brazil, had 21 mutations, including at least three that were observed in the Beta variant (N501Y, E484K and K417N/T). These mutations increased the rate of transmission of coronavirus infections and decreased the effectiveness of immune defenses developed during earlier infections. Because immune defenses were less effective against the Gamma variant, this variant was able to infect individuals who had already been infected once. (<https://www.nytimes.com/2021/03/01/health/covid-19-coronavirus-brazil-variant.html>)

The Alpha variant, which was first detected in the UK, has multiple mutations, including the N501Y mutation found in the Beta and Gamma variants. Also, the E484K mutation has been found in some cases of the Alpha variant (<https://www.newscientist.com/article/2266429-uk-coronavirus-variant-gets-nastier-as-south-african-variant-spreads/>; <https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e2.htm>).¹⁰ The Alpha variant was more transmissible. The figure on page 7 of these Teacher Notes shows the rapid spread of this variant in the US during the early months of 2021. The Alpha variant increased the risk of dying of Covid-19 in two ways:

- The risk of infection was increased because the rate of transmission of coronavirus infections was increased by roughly 50% for this variant.
- The risk that a coronavirus infection would result in death appears to have been ~30-50% higher for this variant. (<https://www.nature.com/articles/d41586-021-00299-2>).

The Delta variant was first detected in Maharashtra, India in December 2020. In the US, the Delta variant increased from 0.3% of coronavirus samples on April 19, 2021, to 51% by June 28

¹⁰ The fact that the same mutations were found in multiple variants that developed independently indicates that natural selection favored coronavirus variants that had these mutations, e.g., because they increased transmission and/or decreased the effectiveness of immune defenses. This is an example of convergent evolution, a more general phenomenon that has occurred frequently; a familiar example is the wide, thin shape of the wings of birds, bats and insects.

to 99% by August 23. The figure on page 7 of these Teacher Notes shows the increase of the Delta variant in the US.

The Delta variant was more contagious than previous variants. On average, a person infected with the Delta variant transmitted the virus to 5-9 other people vs. 2-4 for the original version of the coronavirus (<https://www.nytimes.com/2021/06/22/health/delta-variant-covid.html>). In people exposed to the coronavirus, viruses could be detected approximately two days sooner after exposure to the Delta variant vs. the original 2019 coronavirus strains, and the viral load in the nose was approximately 1000 times higher for the Delta variant (<https://www.medrxiv.org/content/10.1101/2021.07.07.21260122v1>). In cultures of human alveolar lung cells, the Delta variant resulted in about 10 times as many viral particles as the Alpha variant (<https://www.researchsquare.com/article/rs-637724/v1>).

In vitro, the Delta variant showed approximately six-fold reduced sensitivity to antibodies from people infected with earlier strains of the coronavirus and approximately eight-fold reduced sensitivity to vaccine-elicited antibodies (<https://www.researchsquare.com/article/rs-637724/v1>). At least some vaccines had lower effectiveness against the Delta variant, with higher rates of symptomatic “breakthrough” infections and transmission. However, it is important to note that the mRNA vaccines continued to protect well against hospitalization and death due to infections with the Delta variant (<https://www.researchsquare.com/article/rs-637724/v1>; <https://www.nytimes.com/2021/06/22/health/delta-variant-covid.html>).

These characteristics of the Delta variant could be due to mutations in the gene for the spike protein that increased binding of the spike protein to receptors on human airway cells and decreased binding of the spike protein to antibodies. The specific mutations in the Delta variant were generally different from the specific mutations in the Alpha, Beta and Gamma variants, but they tended to affect similar parts of the spike protein of the coronavirus.