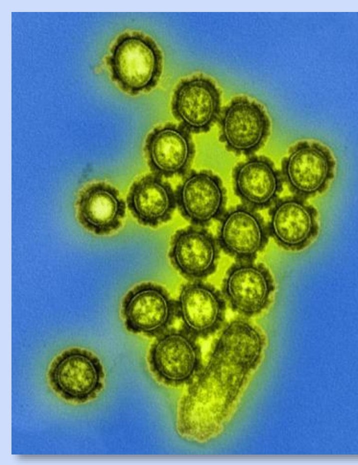
# Investigating Influenza

Influenza is an infectious disease commonly known as the flu. Seasonal outbreaks of influenza occur annually across the globe, leading to the deaths of tens of thousands of people. Additionally, severe outbreaks of pandemic influenza throughout history have caused the deaths of millions.

## Terms to Know

| | |
|---|---|
| **Control Group** | in a research study, the group that does not receive interventions |
| **Epidemic** | an increase in the number of cases of a disease above what is normally expected in that population in that area |
| **Experimental group** | in a research study, the group that does receive interventions to measure their effectiveness |
| **Public Health** | science of protecting and improving the health of people and their communities |
| **Surveillance** | ongoing, systematic collection, analysis, and interpretation of health-related data |
| **Vaccine** | a preparation that provides a trigger to help the immune system build immunity to a disease; allows the immune system to recognize a **virus** or bacterium as a threat |
| **Virus** | type of microbe (organisms too small to be visible to the naked eye) that causes **infectious** diseases; has a core of genetic material but no way to reproduce on its own; uses infected cells' reproductive machinery |

## What is Influenza?



Influenza (flu) is a contagious respiratory illness caused by influenza **viruses** that infect the nose, throat, and lungs. There are two main types of influenza **viruses** that cause **epidemics**: types A and B. These **viruses** that routinely spread in people (human influenza viruses) are responsible for seasonal flu **epidemics** each year. About 8% of the U.S. population gets sick from flu each season.

Most experts believe that flu **viruses** spread mainly by tiny droplets made when people with flu cough, sneeze, or talk. These droplets can land in the mouths or noses of people who are nearby. Less often, a person might get flu by touching a surface or object that has flu **virus** on it and then touching their own mouth, nose or possibly their eyes.

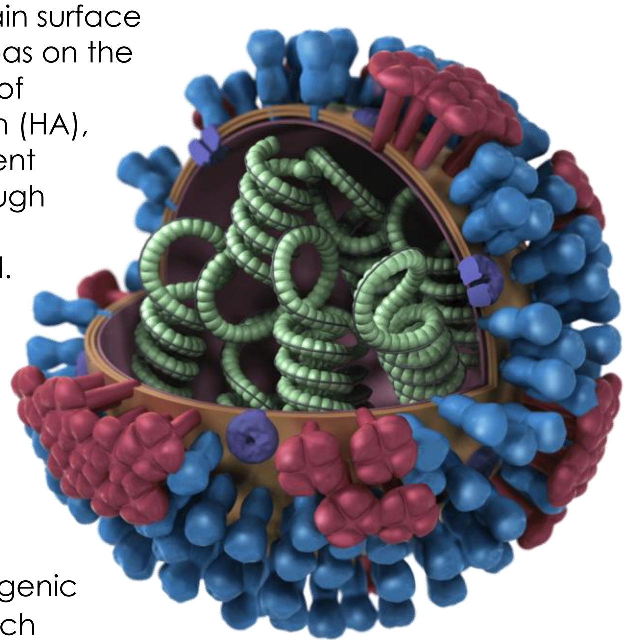
## Think About It

1. Do you or any of your family members get a yearly flu **vaccine**? Why or why not?
2. Have you ever had the flu? How did it feel? *Note: The "stomach flu" isn't a flu! It's a type of unrelated gastrointestinal illness.*
3. Do you think having the flu is a big deal? Why or why not?

## Influenza and the Centers for Disease Control and Prevention (CDC)

At the simplest level, **viruses** are made of nuclear material like RNA or DNA that is surrounded by a protein coat called a capsid. They come in shapes like helical, spherical, icosahedral, and complex. **Viruses** are incredibly small and can be viewed only by specialized high power electron microscopes. The image below shows the different features of a generic influenza **virus**.

Influenza **viruses** are spherical and contain surface proteins that allow them to attach to areas on the cell membranes of their hosts. One type of influenza surface protein is hemagglutinin (HA), pictured here in blue. There are 18 different hemagglutinin subtypes, named H1 through H18. Another surface protein is neuraminidase (NA), pictured here in red. There are 11 different neuraminidase subtypes named N1 through N11.




Following influenza infection or receipt of the influenza **vaccine**, the body's immune system develops antibodies that recognize and attach to antigenic sites, which are regions found on the surface proteins. By binding to these antigenic sites, antibodies neutralize flu **viruses**, which prevents them from causing further infection.

The M2 ion channels, pictured in purple, allow materials and signaling molecules to move in and out of the capsid. The ribonucleoprotein complex (RNP), in green, is the genetic material of the influenza **virus** that provides the information that will be replicated by the host's cells.

### Types of Influenza Viruses

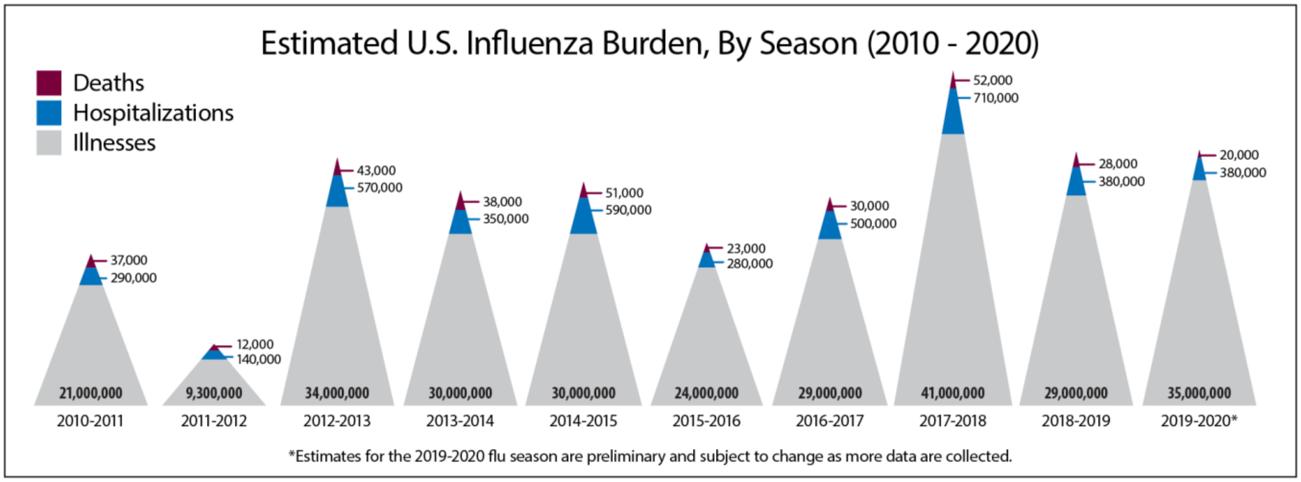
There are four types of influenza **viruses**: A, B, C, and D. Only types A and B cause flu **epidemics**.

- Influenza A viruses are divided into subtypes based on two antigen proteins on the surface of the virus: hemagglutinin (H) and neuraminidase (N). Current subtypes of influenza A viruses that routinely circulate in people include H1N1 and H3N2.
- Influenza B viruses are not divided into subtypes, but instead are further classified into two lineages: B/Yamagata and B/Victoria. Influenza B viruses generally change more slowly than influenza A viruses do. Influenza **surveillance** data from recent years shows co-circulation of influenza B viruses from both lineages in the United States and around the world.
- Influenza C viruses are rarely reported as a cause of human illness.
- Influenza D viruses primarily affect cattle and are not known to cause illness in people.

Influenza **viruses** are found in many different animals, including ducks, chickens, pigs, whales, horses, seals, bats, dogs, and cats. Infectious particles in saliva, mucus, and droppings can spread the **virus** from animal to animal. While most variants are not transmitted from these animals to people, there are documented outbreaks of certain avian and swine flus in people. When an infectious agent is transmitted from other animals to humans, this is known as a zoonotic infection. This can happen when the **virus** particles are in the air or when a person touches something that has the **virus** on it and then touches their nose, eyes, or mouth. Transmission between species is cause for concern due to the possibility it will cause an influenza pandemic.

## Monitoring Influenza

The Global Influenza Surveillance and Response System (GISRS) was established by the World Health Organization (WHO) in 1952 to monitor influenza cases, trends, and variants. CDC's Influenza Division has worked with WHO since 1956 to help control seasonal and pandemic influenza. CDC also helps establish and maintain **surveillance** and laboratory capacity in more than 50 countries around the world. CDC's FluView is a weekly influenza **surveillance** report that provides up-to-date information, including interactive data visualization tools, to monitor U.S. flu cases and deaths.




An important aspect of influenza **surveillance** is the use of gene sequencing to identify currently circulating strains of influenza, particularly any novel strains. **Viruses** mutate over time as small changes occur in the genes. These changes often result in changes to the surface proteins of the **virus**. When these antigen proteins change, it is known as antigenic drift and usually results in minor changes to the surface proteins. A person's immunity to one strain of flu **virus** will usually extend to other similar flu **viruses** and provide cross-protection. However, the small changes due to antigenic drift over time ultimately produces **viruses** that are substantially different from previous strains. All types of influenza exhibit antigenic drift. This is one reason why the composition of the flu **vaccine** must change yearly to match **viruses** that are currently in circulation.

Antigenic shift is another type of change that is far more abrupt and serious, potentially resulting in novel flu subtypes. This occurred in 2009 when an H1N1 flu virus resulted from the merger of different genes from North American swine, Eurasian swine, humans, and birds. Because it was a novel strain, it spread quickly due to the lack of immunity in the population. Only type A influenza **viruses** demonstrate antigenic shift, which is why these infections are closely monitored.

## Think About It

1. Why is antigenic shift potentially much more dangerous than antigenic drift?
2. Novel influenza **viruses** (viruses different from those currently in circulation) must be reported immediately to CDC. Why do you think this requirement exists?
3. Use HHMI's Virus Explorer to examine the characteristics of common **viruses**. What do you notice about the sizes, shapes, and structures of the **viruses** shown? https://media.hhmi.org/biointeractive/click/virus-explorer

## From the Expert:

Influenza (flu) is a potentially serious disease that can lead to hospitalization and sometimes even death. Every flu season is different, and influenza can affect people differently, but millions of people get flu every year, hundreds of thousands of people are hospitalized and thousands to tens of thousands of people die from flu-related causes every year. Flu can mean a few days of feeling bad and missing work or it can result in more serious illness. Complications of flu can include bacterial pneumonia, ear infections, sinus infections and worsening of chronic medical conditions, such as congestive heart failure, asthma, or diabetes.

Watch this video to hear Dr. Joe Bresee with CDC's Influenza Division address common questions and misconceptions about the flu and the flu **vaccine**. https://youtu.be/f86mImyhaoc

## Call to Action

In order to understand the dangers associated with influenza, it is essential that people understand the difference between preconceptions about influenza and the realities shown in the data. You can help people by following these three steps:

**1. Investigate common myths around influenza.** Myths about the flu and flu **vaccines** persist in today's world. Choose one you've heard before and design an experiment that would allow you to investigate whether there is any truth to it.

**2. Analyze influenza data.** CDC collects and publishes influenza data weekly. Use data provided to analyze trends in influenza cases, hospitalizations, and death. Make recommendations to help people in your community avoid the flu.

**3. Share your findings.** One of the ways CDC communicates information is through social media. Your explorations can help CDC communicate the work they have done and are doing to decrease influenza cases, hospitalizations, and deaths worldwide.

## Why Participate? A Message from CDC

An annual seasonal flu **vaccine** is the best way to help protect against flu. Vaccination has been shown to have many benefits, including reducing the risk of flu illnesses, hospitalizations and even the risk of flu-related death in children. While some people who get a flu **vaccine** may still get sick, flu vaccination has been shown in several studies to reduce severity of illness. Everyone 6 months of age and older should get an influenza **vaccine** every season, with rare exceptions.

You can help your community by getting an annual flu **vaccine** and talking to others about getting vaccinated. Even if you are a healthy young person who is not worried about facing serious flu complications, vaccination can benefit you by helping to prevent the spread of illness to people in your life who are more vulnerable to serious illness or death.

## Think About It

1. Many flu-related deaths occur because of secondary pneumonia infections that occur in weakened or damaged lungs. How can vaccines help prevent this?
2. A high dose **vaccine** containing 4 times the flu **virus** antigen is generally given to adults 65 and older. What effect do you think this has on the immune system? Why is this recommended for older adults?
3. Do you think you should wear a mask when sick to prevent spreading flu? Explain.

## Scientific Method Overview

The scientific method is a great tool to use to create and test a hypothesis. Use the flow chart below to think out your plan.

### Ask a question

Describe the question you are trying to answer. There are several questions you could use to guide your investigation:

- What myth do you want to investigate?
- Pose an investigative question.

### Do background research

Use the internet to find reference materials about the topic.

- What information would you need to research?
- Use videos and webpages from credible sources (.gov, .edu)

### Construct a hypothesis

Make a prediction about the results from an experiment. Try using an if/then statement format.

- If ___________ (I do this), then _______ (this) will happen.
- Ex: If I soak fruit for 15 min, it will destroy harmful bacteria.

### Test with an experiment

Conduct your experiment.

- How do you design an experiment to test this hypothesis?
- How many people? Where? What exactly will you do?
- What are your **control** and **experimental** groups?

### Analyze data

Examine your data and look for patterns in the results.

- How would you analyze the data for patterns?
- What would you expect to see?

### Draw conclusions

Interpret the patterns in the data to determine what it means.

- What story does your data tell?
- Go back to your hypothesis and either accept or reject it.

### Communicate results

Share your information with others!

- Use social media to share with CDC accounts listed.
- Tell others about your experimental results!

## Investigate Common Myths Around Influenza

Up until around 1890, the predominant belief was that diseases were caused by "bad air" stemming from pollution and rotting organic matter. This was known as the miasma theory. Though many scientists over the centuries had theorized that diseases were caused by invisible particles and could spread from person to person, it wasn't until the mid-19$^{th}$ century that the current germ theory began to take hold. Physician John Snow proposed that cholera was made of cellular units and solved an 1854 London cholera outbreak by blocking a contaminated water pump. In the 1860s, Louis Pasteur conducted experiments proving that bacteria were present in the air. Shortly thereafter, Robert Koch demonstrated that diseases are caused by specific microorganisms. Joseph Lister imposed sanitation requirements for surgeries and hospitals, resulting in dramatically lower rates of infection and death. The idea that diseases were caused by germs took hold, forever changing the face of **public health** and medicine.

It goes without saying that in the centuries leading up to the development of germ theory, incorrect ideas about the causes and cures of disease were plentiful. "Old wives' tales" represent the oral tradition by which home remedies and superstitions were transmitted through communities and generations. Though many of these tales have no basis in fact, they provided people with a sense of control in situations where they had none. Many of those false ideas persist today, despite plenty of evidence to the contrary. In this activity, you will be thinking about some of the things you've heard about sickness, including causes, treatments, and cures.

**What myths, sayings, or old wives' tales have you heard about the flu?**

Here are some examples to get you started:

- Feed a fever; starve a cold.
- If you're outside in the cold for too long, you'll get sick.
- Don't drink milk if you're sick.
- A flu shot can give you the flu.

How do you feel about these? Is there any truth to any of these wives' tales? Why do they persist?

### Design an Experiment

Choose one of your myths to investigate. You may also choose one of the given examples if it inspires you! If you were going to attempt to prove or disprove this statement, how would you do it? Before you get into this task, here is some information about experimental design.

## Setting Up Research Studies

### Control Group

Receives a placebo instead of the treatment. Placebos are usually made of sugar, starch, or some other substance that should have no effect on the subject.

### Experimental Group

Receives the treatment. At the end of the study, the results of this group will be compared to the control group to measure the treatment's effectiveness.

## Types of Research Studies

| Single Blind | Double Blind |
|---|---|
| Experimental group receives treatment. Control group receives a placebo. | Experimental group receives treatment. Control group receives a placebo. |
| Patients are "blind" because they do not know if they received the placebo or the treatment. | Patients are "blind" because they do not know if they received the placebo or the treatment. |
| Researchers are not "blind" because they know which group subjects are in. | Researchers are also "blind" because they do not know which group a subject is in. |

### Placebo Effect

Sometimes people begin feeling better after receiving a placebo for purely psychological reasons. For instance, someone with a headache might begin feeling better after taking an aspirin, even if it has no physical effect. The placebo effect should be considered when looking at the results of any experiment

When designing an experiment, it is important that you have a **control** group and an **experimental** group. The **experimental** group will receive whatever treatment or variable is being tested in the experiment, but the **control** group will not. By examining the different outcomes of the two groups, researchers can then determine whether a treatment is effective or not. Experiments can be conducted as single-blind experiments where the test subjects do not know which group they are in, but the researchers do. A better model is a double-blind experiment where the groups are hidden from both the test subjects and the researchers who are directly conducting the tests. Researchers who know what groups subjects are in might unconsciously give clues to subjects that impact their perception and outcomes, so using a double-blind model helps eliminate that bias.

As you design your experiment, it may be helpful to focus on your independent and dependent variables. An independent variable, sometimes called a manipulated variable, is the thing you will be changing. The dependent variable, sometimes called a responding variable, is the thing you will be measuring or observing to look for a change.

Here is a simple example of how these principles are used to design an experiment investigating treatments for influenza. If you are investigating the claim that vitamin C helps you recover from flu faster, you cannot simply give everyone vitamin C and note that they all got better. It could be that all participants would have gotten better in the same time frame regardless of whether they received the vitamin C or not. Instead, you would need two groups: a vitamin C group (**experimental**) and a placebo group (**control**). Both groups would receive doses of a substance they believe is vitamin C, but only one group would actually get the vitamin. The other would get an inactive placebo pill usually made of starch or sugar. The test subjects should have no idea which they are receiving. In a single-blind experiment, the people handing out the pills would know whether they were vitamin C or placebo, but in a double-blind experiment they would not. If the vitamin C group showed a faster recovery, it could indicate that taking vitamin C helps to decrease duration of illness. If both groups fared the same, it likely has no effect. Having the two groups allows for the effects of vitamin C to be better isolated and compared.

### Example Experiment

Carrying forward with the same vitamin C experiment, here is what the general **experimental** design would look like:

- **Ask a question:** How does vitamin C affect the duration of flu symptoms?
- **Do background research:** What is vitamin C? How does it affect the immune system? How much vitamin C is recommended? What are the safety considerations with using vitamin C? What do current studies about vitamin C indicate as far as its effectiveness in helping to fight disease?
- **Construct a hypothesis:** If flu patients are given 500 mg daily vitamin C doses, the duration of flu infection will decrease. The independent variable in this experiment is whether or not a person is given vitamin C, while the dependent variable is how long their flu lasts.
- **Test with an experiment:** Find a population of people with influenza through a health clinic or doctor's office. Provide patients with vitamin C or a placebo using a double-blind **experimental** model. Have patients record symptoms and temperature readings every 24 hours for 10 days.
- **Analyze data:** Determine how long severe illness lasted for each person and determine average duration for both groups to look for differences between **control** and **experimental** groups.
- **Draw conclusions:** Look for any differences in outcomes between the two groups.
- **Communicate results:** Publish findings in a scientific journal or in CDC's *MMWR* (*Morbidity and Mortality Weekly Report*) for other health care professionals to review.

| | |
|---|---|
| **Ask a Question**<br>What myth do you want to investigate? Pose an investigative question. | |
| **Do Background Research**<br>What information would you need to research to understand the topic better? | |
| **Construct a Hypothesis**<br>What will you be testing? An easy hypothesis format is "If ______, then ______." | |
| **Test with an Experiment**<br>How would you design an experiment that would test this hypothesis? How many people? Where? What exactly will you do? What are your **control** and **experimental** groups? Be as specific as possible here. | |
| **Analyze Data**<br>How would you analyze the data collected in the experiment to look for patterns? What would you expect to see? | |
| **Draw Conclusions**<br>What story does your data tell? Go back to your hypothesis and either accept or reject it. | Since you're not actually conducting this experiment or collecting data, you won't be able to analyze anything here. You can take a second and think about what different results would mean though! Plus, you'll be analyzing data in the next activity. |
| **Communicate Results**<br>Summarize your findings so that others may benefit from your knowledge or independently verify your results (peer review). | You won't really be able to communicate the results for an experiment you haven't conducted, but it is good to think about how researchers use scientific publications to present their findings to others in the field. Publishing your research is a really big deal in science and requires a wide variety of high-level skills to accomplish! |

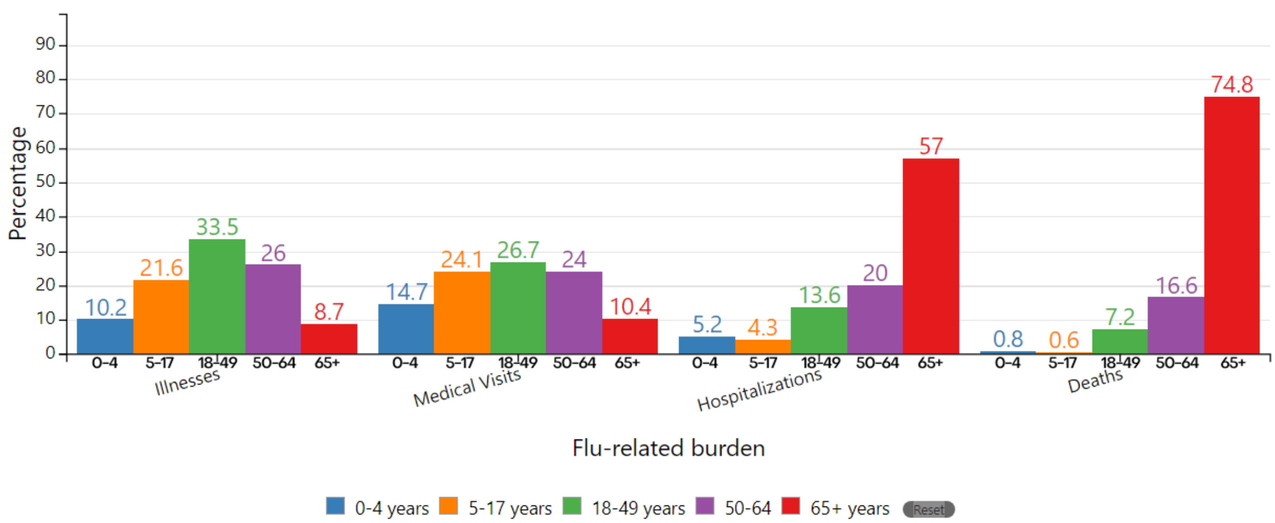
## Analyze Influenza Data

CDC tracks instances of about 120 diseases through the National Notifiable Disease Surveillance System, including infectious diseases, bioterrorism agents, sexually transmitted diseases, and noninfectious conditions. About 3,000 **public health** departments send disease data to 60 state, territorial, and other **public health** departments, who then send the data to CDC.

### What story does the data tell?

If you collected the data below during routine disease **surveillance**, what would you do with them? The three graphs below are some examples of data CDC collects. Using the data to make recommendations to health officials and the general public is one of CDC's most important duties.

Percentage of flu-related illnesses, medical visits, hospitalizations, and deaths by age group, 2018–2019 Influenza Season




Examine the x-axis, y-axis, graph title, units, and color key. What are some things you notice about this graph?

________________________________________

________________________________________

________________________________________

What health recommendations would you make based on the information presented above?

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A single graph cannot tell the full story of a disease outbreak. What questions do you have after looking at the data above? What do you want to know more about?

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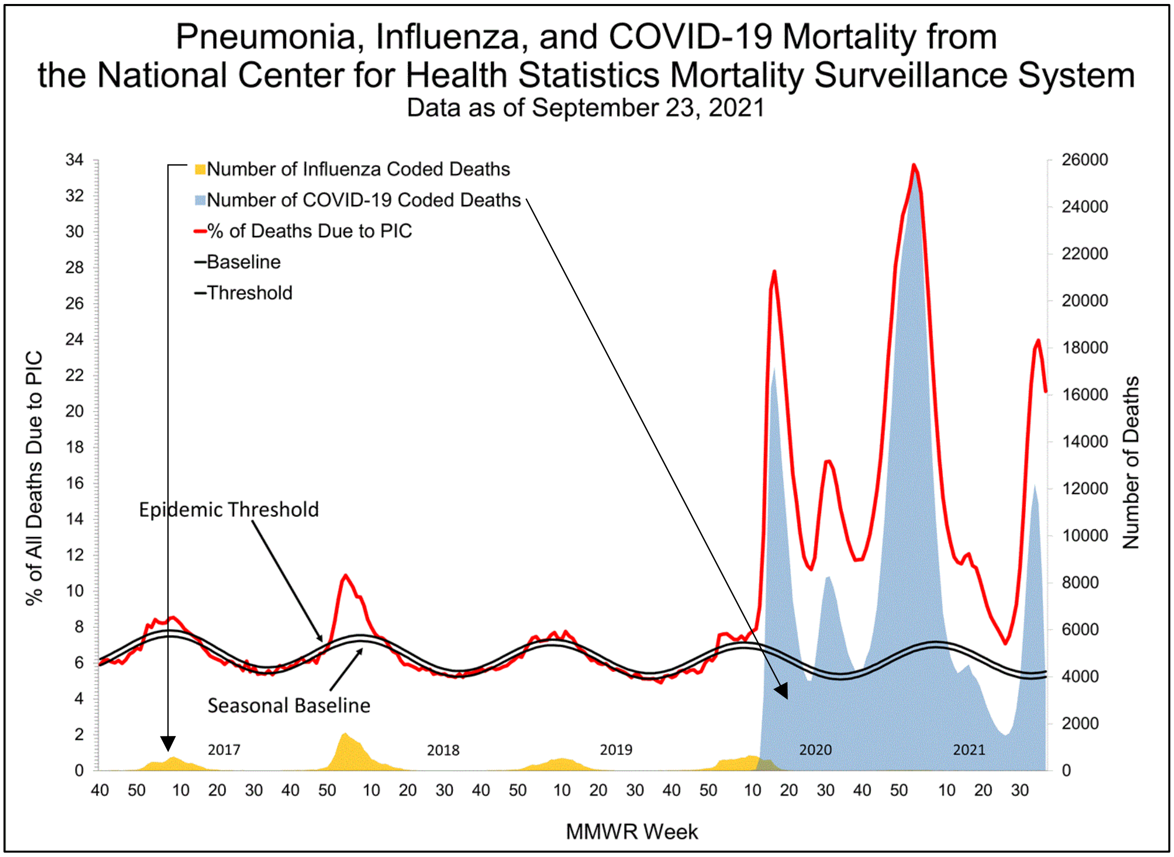


**Analyzing a Graph: What Do These Terms Mean?**

| | |
|---|---|
| Number of Influenza Coded Deaths | Number of deaths that listed influenza as underlying or contributing cause of death (use right axis for numbers) |
| Number of COVID-19 Coded Deaths | Number of deaths that listed COVID-19 as underlying or contributing cause of death (use right axis for numbers) |
| — % Deaths Due to PIC | Percentage of all deaths that listed PIC (pneumonia, influenza, or COVID-19) as underlying or contributing cause of death (use left axis for numbers) |
| — Baseline<br>— Threshold | Baseline number is calculated using statistics from previous flu seasons; an increase of 1.645 standard deviations above the seasonal baseline is considered the **epidemic** threshold, indicating viral spread that is far above expected values |
| *MMWR* Week | Weeks of the year are numbered 1-53 based on *MMWR* number; ensures consistent and timely reporting of cases by local and state health departments |

Flu season is reported from *MMWR* week 40 of one year to week 39 of the next (labelled on the x-axis). You can make this easier to visualize by drawing a vertical line at each 40 on the x-axis to separate the seasons from each other.

How would you describe each of these flu seasons based on the information in the graph above?

2016-17: ______________________________

2017-18: ______________________________

2018-19: ______________________________

2019-20: ______________________________

2020-21: ______________________________

You often hear people dismiss COVID-19's severity by describing it as "just a flu." Although both illnesses affect the lungs and share some common symptoms, the two illnesses are unrelated. The influenza **virus** causes the flu while the SARS-CoV-2 **virus** causes COVID-19. Let's ignore the differences and just compare the numbers.

Looking at the data from 2016-2021, how do the numbers of deaths from influenza compare to the deaths from COVID-19?

______________________________________________________________________

______________________________________________________________________

Based on what you know about flu, why should people take it seriously?

______________________________________________________________________

______________________________________________________________________

______________________________________________________________________

The graph at right shows the 10 leading causes of death in 2019, which account for 73.4% of all deaths. What does this tell you about the flu? Is this surprising to you? Explain your answer.

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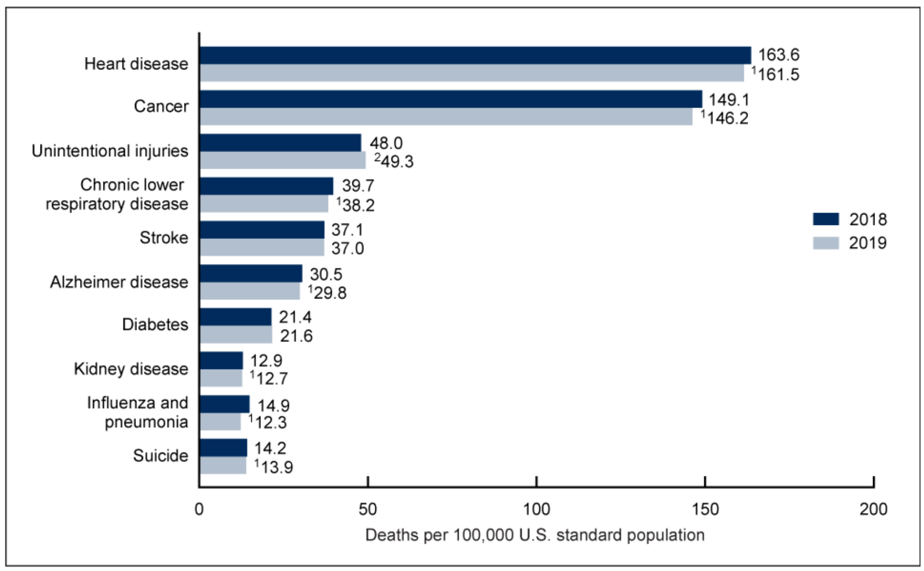
Figure 4. Age-adjusted death rates for the 10 leading causes of death in 2019: United States, 2018 and 2019




[1]Statistically significant decrease in age-adjusted death rate from 2018 to 2019 ($p < 0.05$).
[2]Statistically significant increase in age-adjusted death rate from 2018 to 2019 ($p < 0.05$).
NOTES: A total of 2,854,838 resident deaths were registered in the United States in 2019. The 10 leading causes of death accounted for 73.4% of all deaths in the United States in 2019. Causes of death are ranked according to number of deaths. Rankings for 2018 data are not shown. Data table for Figure 4 includes the number of deaths for leading causes. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db395-tables-508.pdf#4.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

### Just for Fun: Take it Further!

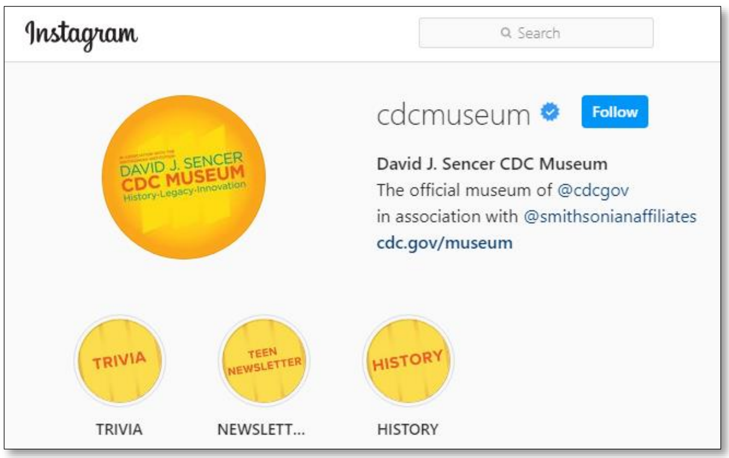
The graph above is updated weekly at https://gis.cdc.gov/grasp/fluview/mortality.html by the National Center for Health Statistics (NCHS). You can find current mortality **surveillance** information for the United States plus more information about current influenza rates.

For an in-depth exploration of respiratory illnesses based on the information above, read the article "Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic — United States, 2020-2021." https://www.cdc.gov/mmwr/volumes/70/wr/mm7029a1.htm

## Share Your Findings

The David J. Sencer CDC Museum uses award-winning exhibits and innovative programming to educate visitors about the value of **public health** and presents the rich heritage and vast accomplishments of CDC. Your work could be a valuable contribution! Share your findings with the CDC Museum on Instagram using **@CDCmuseum**.

The Influenza Division of the National Center for Immunization and Respiratory Diseases (NCIRD) improves global control and prevention of seasonal and novel influenza and improves influenza pandemic preparedness and response. In collaboration with domestic and global partners, the influenza division builds **surveillance** and response capacity, monitors and assesses influenza **viruses** and illness, improves **vaccines** and other interventions, and applies research to provide science-based enhancement of prevention and control policies and programs. Connect with them on Twitter using **@CDCFlu**.




**Name:** ______________________

## Reflections

**Now that you have completed this investigation, think about what you learned from your research. Answer the questions below.**

1. Who is most at risk for hospitalization or death from influenza? What are some ways they can they protect themselves from getting the flu?

2. What are some similarities and differences between H3N2 and H2N2 **viruses**?

3. A researcher is conducting a single-blind vaccination trial. What are some ways that the researcher might accidentally introduce bias because they know who will get placebos?

4. Free flu **vaccines** are widely available to people in the United States. Why do you think health insurance companies and other organizations are willing to fund these shots?

5. A healthy 30-year-old man tells you he doesn't need a flu shot. How do you convince him?

6. After the success of the new mRNA **vaccines** for COVID-19, research is underway to produce mRNA **vaccines** for influenza that use the sequences for influenza surface proteins. What challenges might be involved with this process?