INFLUENZA FAQ
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Influenza gets plenty of media attention. Every autumn there are stories about the upcoming “flu season” — will it be a bad year, will there be enough vaccine, will it be effective? Even when it’s not flu season, influenza shows up in the news when there are outbreaks of “bird” or “swine” flu, raising fears that the new strain will find its way into humans. What is it about the influenza virus that makes it such an ongoing concern? After all, it’s “just the flu.” In this report, you will learn how the virus comes back year after year, what the influenza vaccine can and cannot do, and why animal viruses can become a human public health concern. It all has to do with this tiny virus’s extraordinarily flexible set of evolutionary strategies.

Virus, bacteria, bug, germ..... what’s the difference?

The terms used to describe microbes — biological entities that are too small to see — can be confusing, especially since they’re often used inconsistently.

For the purposes of this report, all you need to know is that viruses are microscopic entities that have the same genetic material as all other life forms — that is, DNA and RNA — but cannot reproduce on their own. Instead, they invade other organisms and use those organisms’ cellular machinery to make more viruses.

All living organisms have viruses that infect them: bacteria (their viruses are called bacteriophage, which means “bacteria eater”), fungi, insects, plants, birds and mammals. Even dinosaurs must have had viruses. Recently, viruses have even been discovered that infect other viruses! Probably the very first cells on Earth also had something like viruses that infected them.

The take-home message is that viruses are a very ancient “life-form.” They are almost unimaginably diverse and have developed an impressive array of tricks to get from host to host and evade immune systems. They may be small, and they may appear simple, but they are in many ways extremely sophisticated — as befits a class of organisms that has been evolving for billions of years. It never pays to underestimate their ingenuity.
Influenza is both the name of a disease and the name of the virus that causes it. The influenza virus’s life strategy makes it a serious threat, both to individuals and to the community. Learning a little bit about how the virus works will help you understand how it makes you sick and why getting a flu shot is so important.

The influenza virus is extremely tiny. To an influenza virus, a human cell is the size of a small city. Hundreds of thousands of influenza viruses can fit in a single human cell (Figure 1). The surface of the virus is studded with proteins that recognize specific chemical compounds on the surface of the cells lining the inside of your nose. Once the virus binds to a host cell, it tricks the cell into letting it inside. Then it hijacks the cell’s own machinery to make more viruses and export them to the cell’s surface. Influenza virus stores its genome on eight short segments like miniscule chromosomes; each of these RNA segments is copied separately and complete sets are then packaged into new protein coats (Figure 2).

Once the new viruses have reached the cell surface, they use one of their own proteins to cut themselves free from the cell surface so that they can go off and infect the next cell, or be sneezed out to infect the next host (Figure 3). This whole process — from entering your nose to releasing thousands of new viruses — takes about six hours. Generally there is a gap of about two days between being exposed to the virus and showing symptoms; in other words, the virus can engage in several cycles of infecting cells and releasing progeny before you have any symptoms. By then, the virus may have spread to thousands of cells and infected many other people. Now you know why the influenza virus can cause such dramatic epidemics.
It is a brilliant strategy from the virus’s perspective. For humans, it is a disaster — both for the individual (who will soon experience chills, body aches, fever, coughing, sneezing, and severe fatigue as the virus spreads to more and more cells and the immune system launches battle against it) and for the community, as the virus spreads, invisibly at first, from victim to victim.

It is this stealthy strategy that makes the influenza virus such a serious public health threat. Unlike other viruses that are not very contagious, or cause symptoms that keep victims at home before they become contagious, influenza spreads quickly through a community and keeps spreading until it runs out of vulnerable hosts — in other words until so many people are home sick, or have already been sick, that there is no one left to infect. It generally takes a month or two for a wave of influenza infections to sweep through a community and once it gets started, there is almost nothing that can be done to stop it.

Influenza is not the same as the “stomach flu”!

“Stomach flu” is a misnomer and is not, in fact, caused by the influenza virus. Gastrointestinal symptoms are typically absent in flu infections, except in severe cases in children. What we call the “stomach flu” can be caused by several different (non-influenza) viruses, or sometimes by the bacterium Campylobacter.

Influenza is one of the only diseases that can shut down public services. Because the flu can spread so rapidly through populations, it can cause lots of people to miss work at the same time; staffing schools, hospitals, and police forces can become difficult.
2. Why does influenza come back year after year?

After an epidemic, shouldn’t everyone be immune to the virus? Why is influenza able to come back again and again? The answer lies in the virus’s genetic structure and high mutation rate. The truth of the matter is that an individual’s immune system rarely sees the same influenza virus twice and that means it cannot provide the permanent protection it offers against more stable infectious agents.

Whenever you are infected by a pathogen, your immune system generates compounds called antibodies that bind to the infectious agent and target it for destruction. After the infection is cured, a few of the white blood cells that make those specific antibodies continue to circulate in your blood. Called “memory cells,” these cells are quickly activated if the same infectious agent attacks you again, preventing the infectious agent from establishing itself and preventing you from getting sick. That is why vaccination works: a vaccine presents the immune system with a harmless form of an infectious agent so that if you are infected by the real thing, your immune system will be primed to destroy it quickly.

Unfortunately for humans, the influenza virus has evolved several strategies to outwit the immune system. Like all other organisms, the influenza virus changes every time it reproduces, generating progeny that are ever so slightly different from the parent. Influenza viruses practice an extreme form of this lifestyle — they can change in several ways, some of them gradual and subtle, and some of them rapid and dramatic, but all of them allowing influenza to appear like a brand-new virus to the immune system. As a result, influenza strains change enough from year to year to allow them to repeatedly cause new epidemics.

The situation is made more complicated because there are at least four different influenza viruses circulating at any one time in the human population. The influenza virus family includes three main groups, called influenza A, B, and C. Only influenza A and B cause epidemics. Of these two types, there are generally two distinct strains in circulation, and the strains are different enough that immunity to one of them does not confer immunity to the others. The variety of influenza viruses in circulation guarantees that there will be a “flu season” every year because last year’s flu victims will not have immunity if they encounter a different subtype or strain this year. It also greatly complicates the process of producing the annual influenza vaccine.

Influenza nomenclature

Influenza A strains are named according to which versions of two main proteins they carry on their surfaces, hemagglutinin and neuraminidase. So far, 16 varieties of hemagglutinin and 9 neuraminidases have been identified. So a strain called “H3N2” has hemagglutinin #3 and neuraminidase #2. Only strains carrying hemagglutinins #1, #2, and #3 and neuraminidases 1 and 2 have caused epidemics in humans. At present, both H3N2 and H1N1 viruses circulate widely in humans. All of the other varieties are found in wild birds, but some of those have caused serious zoonotics (outbreaks in an animal population) in domestic poultry.
3. How does the influenza virus change so fast?

Influenza has two ways to change — one slow and one fast. The slow change is called “drift” — the virus gradually accumulates individual mutations until its surface proteins are no longer recognized by our immune system. The fast change is called “shift” — different strains of influenza can exchange genetic material if they infect the same cell at the same time. A new “hybrid” strain can emerge with surface proteins that are completely different from the previous year’s epidemic strain.

To picture shift and drift, it helps to know a little bit about influenza virus genetics.

**DRIFT**

Influenza viruses are said to “drift” when their surface proteins change gradually. How do they change their surface proteins? All organisms use enzymes called polymerases to make the copies of their genetic material that are passed on to their offspring. These polymerases vary in accuracy and the influenza virus polymerase is especially sloppy. In fact, it is so inaccurate that every single progeny virus is likely to have at least one genetic difference from the parent and many of the new viruses will have so many errors that they will not even be functional. From an evolutionary standpoint, the influenza virus doesn’t mind if most of its offspring do not survive, as long as one of them is able to infect a new host. Mutations in the genes that code for the virus’s surface proteins — the parts of the virus that are exposed to the human immune system — may make one of the virus’s progeny unrecognizable to the antibodies generated by the previous infection (Figure 4). Changing even one letter in the genetic code can be enough to mask the virus.

Drift is both inevitable and unpredictable. Because the mutational changes are random, it is impossible to predict exactly what the virus will “look” like to the immune system from one year to the next. “Drift” is why influenza epidemics happen every year.

**Figure 4: Antigenic Drift**

Influenza A viruses are “typed” based on their HA and NA antigens, which can bind different types of sugar residues on cell surfaces. Over time, mutations in HA and NA genes accumulate resulting in **ANTIGENIC DRIFT** — gradual changes in the proteins so that our immune systems no longer recognize them.
The influenza virus has another even more dramatic strategy to evade the immune system. Instead of accumulating mutations that gradually change the appearance of its surface proteins, it can acquire entirely new surface proteins. This is called a genetic “shift.” “Shift” is made possible because of a process called reassortment (Figure 5).

Remember, the influenza genome is comprised of eight individual genetic segments each of which must be replicated and then packaged into a protein shell during the intracellular replication cycle. If two different influenza strains infect the same host cell, the genome segments can get shuffled and packaged in new combinations. Sometimes a hybrid virus can be formed that has acquired surface proteins that are completely unfamiliar to everyone’s immune system. Such hybrids are able to spread explosively, often breaking out over entire continents nearly simultaneously. These global outbreaks are called pandemics.

Influenza pandemics do not happen very often, but they cause such dramatic outbreaks that it is possible to look back at the historical record and see evidence of them going back hundreds of years. Some of the pandemics were extraordinarily destructive. In 1918 and 1919, an influenza pandemic killed at least twenty million, and perhaps as many as fifty million, people worldwide. In the United States, the 1918 influenza killed 675,000 people. Many of these deaths were actually caused by bacterial infections; lungs that had been weakened by influenza were easy prey for pathogenic bacteria. But even as recently as 1957, when antibiotics were available to treat victims of another pandemic strain, nearly 70,000 Americans died of influenza. There was simply nothing that could be done to slow down the spread of the virus or lessen the severity of the infection.

Shifts in the influenza virus are rare — “shift” strains generally emerge only about every thirty years. Like a ‘perfect storm’, it seems that several unusual events must all occur simultaneously for a shift virus to emerge. The historical record suggests, however, that even though these events are rare, they happen with enough regularity that we must assume that another pandemic will eventually happen. One of the important challenges facing influenza researchers is figuring out enough about the circumstances leading to shift that they can either be prevented from occurring or detected early enough to limit the huge outbreaks they have historically caused.
4. Where do new pandemic influenza strains come from?

The influenza virus family is very large. Almost all vertebrates, including birds, seals, pigs, horses and humans, can be infected by at least one influenza strain. Wild birds, especially waterfowl like ducks and geese, carry dozens of different influenza strains. These wild bird influenza viruses are highly adapted to their hosts.

Occasionally, and unpredictably, new influenza strains containing genes from wild bird viruses begin infecting humans. Exactly where and how these hybrid viruses form is not known. There are many obstacles to overcome for a bird virus to infect a human. That it ever succeeds is testimony to the tremendous genetic flexibility of the influenza virus family.

Viruses are highly specialized. Most of them only infect a single kind of cell in a specific host. Why is this? Host specificity is the result of millions of years of evolutionary battle in which the host evolves methods to avoid the virus and the virus evolves counterattacks to overcome host defenses. To survive, a virus must be able to infiltrate a host cell’s defenses and co-opt a variety of internal proteins, while preventing the cell from alerting the immune system to its intrusion for as long as possible. Like an undercover agent, a virus must, if you will, speak the language of its target cell fluently, fit in seamlessly to its culture, and be able to fool its watchdogs — in other words, the virus must be a specialist, not a generalist.

Influenza viruses are somewhat unusual in that very closely related viruses are found in a number of host species and some interspecies infection is possible. For example, humans can be infected by swine-adapted viruses and vice versa. Domestic birds, especially ducks, but also chickens and turkeys, can be infected by wild bird viruses. Generally, bird viruses do not infect mammals and mammalian viruses do not infect birds. There are a number of special adaptations that restrict bird and flu viruses to their particular hosts. For example, in wild birds, influenza is an intestinal virus that spreads via fecal matter. Bird influenza viruses also prefer to grow at the higher temperatures found in the bird gut. Human influenza viruses, by contrast, infect epithelial cells lining the nasal passage. So they spread through the air and prefer to grow at the cooler temperatures found in the upper respiratory tract. Also, as mentioned above, bird and human adapted influenza viruses bind to very specific chemical compounds on the surface of their target host cells. Mammalian adapted influenza viruses bind to compounds that are found more readily on mammalian cells, and less so on bird cells. Bird viruses bind to compounds found predominantly on bird cells. All of these specializations mean that bird viruses cannot spread directly to humans.

There are a few critical exceptions to this general rule, however. The H5N1 avian influenza can infect humans, although it does not spread easily between them. Also, swine respiratory cells display both kinds of chemical compounds on their surfaces, so they can be infected by both avian and mammalian viruses. Therefore, it has long been thought that pigs act as a ‘mixing bowl’ where reassortment between human and bird viruses can take place and create a “shift” pandemic strain.
5. Should I worry about bird flu?

Bird flu poses no immediate threat to the average person. The only people who have been infected with the highly pathogenic H5N1 bird flu that has periodically caused epidemics in poultry in the last decade are those who have come into close contact with sick poultry. There has never been an H5N1 outbreak in poultry in the United States, although a highly pathogenic H5N2 strain caused an outbreak in 1983-4 that was contained by destroying 17 million birds. No people were infected. Global surveillance is in place to detect and contain outbreaks in birds, and researchers are working to understand whether and how such strains could adapt to humans.

**What about H7N9?**

In March 2013, several people were found to be infected by an avian-adapted strain of the subtype H7N9. As of May 2nd, 128 cases had been verified, with 26 deaths. There was at that point no evidence that the virus could spread from human to human. An unusual feature of the H7N9 strain is that unlike the highly pathogenic H5N1, it does not cause severe disease in poultry, raising concerns that its presence in poultry flocks and live bird markets could take longer to detect.

An H5N1 strain that first emerged in domestic chickens and ducks in 1997 caused huge outbreaks with very high mortality in poultry flocks around the world over the past decade. It is also known to have infected at least several hundred people. In these cases, the H5N1 virus infected cells deep within the lung (where the temperature is several degrees warmer than in the nose), and spread very poorly, if at all, from human to human. However, when it did manage to establish an infection deep in the lung, it caused a severe pneumonia that was often fatal. Public health officials are concerned that if the H5N1 virus were to adapt so that it could spread more efficiently, it might cause an extensive pandemic with very high mortality. There are a great many unknowns about the adaptation process. For example, if the virus adapts so that it grows efficiently in the upper respiratory tract, it might no longer cause such severe disease. Nevertheless, since no influenza strain with hemagglutinin #5 has ever circulated in humans, no one would have any immunity and the pandemic could be very extensive. As a result, a global surveillance effort has been undertaken to ensure that outbreaks in poultry are contained promptly. Researchers are working to understand the process of adaptation in the hope of detecting early changes in the virus that might foretell an imminent jump to humans. Furthermore, H5N1 vaccine seed strains have been developed so that a vaccine could be developed quickly should the virus develop the capacity to spread from person to person.
6. Why is getting the flu shot every year so important?

Two simple reasons:

- It protects you
- It protects vulnerable people around you

And, remember, because the virus is constantly evolving to evade last year’s antibodies, you need to get the latest vaccine every year.

Many different viruses and bacteria can cause upper respiratory infections — like the rhinoviruses that cause the common cold. What distinguishes influenza from the diseases caused by other agents are the type and severity of the symptoms, as well as the range of symptoms experienced by different people. The vast majority of people who catch a cold will experience a few days of sore throat, congestion, and sneezing. Many people infected with influenza will have a similarly mild course of illness. But a significant percentage of people infected with influenza will have an experience unlike any common cold — an abrupt onset of high fever, head and muscle aches, fatigue, and coughing — all lasting from one to two weeks! A classical influenza infection can best be summed up by one word: misery. In a small percentage of cases, these symptoms will progress to pneumonia, respiratory failure, and even death.

Certain groups of people are more likely to experience the most severe symptoms, including infants, elderly people, those with compromised immune systems, and pregnant women. Indeed, vaccination of pregnant women not only protects mothers during pregnancy, but also ensures that protective antibodies are passed on to the babies who will then be protected from flu during the time when they are too young to be vaccinated themselves. Even if you do not belong to one of these vulnerable groups, however, you should bear in mind that it is impossible to predict how sick someone will get when he or she catches the flu, and even young, healthy people can become dangerously ill. If you get a flu shot, you are less likely to get the flu.

Perhaps even more importantly, if you get a flu shot, you will protect the people around you. Remember that if you are infected with influenza, you will be contagious for about two days before you experience any symptoms. By the time you start to feel ill, you may have already infected your elderly grandparent, your neighbors’ newborn baby, or the pregnant woman you gave your seat to on the bus. You may get lucky and have a mild case, but if you’d had your flu shot, you probably wouldn’t have passed the disease on to the vulnerable people around you.

The more people get their flu shots, the smaller the flu outbreak and the more quickly it burns out. Why? The answer is herd immunity. Influenza must have an unbroken chain of victims to survive. The more people are vaccinated, the less likely that an infected person will encounter and infect someone vulnerable to the virus. This is important because the ability of the traditional influenza vaccine to prevent illness decreases substantially in the very elderly. The likelihood of an explosive outbreak is greatly diminished when a significant percentage of the population is vaccinated.
The annual production of hundreds of millions of doses of a new influenza vaccine each year is a public health tour de force, made possible by extensive collaboration between public health authorities and private companies. The process has several steps, beginning during one flu season and culminating just before the next one begins (Figure 6).

**STEP 1: SURVEILLANCE**
A vast global surveillance network monitors the spread and evolution of influenza strains. As you now know, the influenza virus is constantly mutating to evade the immunity people have developed to the previously circulated strains. In doctor’s offices all over the world, samples are taken from patients suffering from “influenza-like-illness” (ILI). The samples are sent to public health laboratories that first verify that the illness was indeed caused by influenza virus (remember, its symptoms overlap with many other respiratory illnesses) and then test them to see if they are neutralized by antibodies to the current vaccine strain. Every few years, these surveillance networks begin to detect the emergence and spread of strains that are not sensitive to the antibodies stimulated by the current vaccine.

**STEP 2: PREDICTION**
Twice each year, public health officials from all over the world meet to review the surveillance results and decide whether it is time to replace any of the strains in the vaccine. For the past several decades, the standard vaccine has been trivalent, that is, it contains three different inactivated influenza strains matching those that circulated the previous year: influenza A H1N1 and H3N2 and the most commonly detected influenza B strain. Influenza B does not cause pandemics (there is no known animal host from which the virus could obtain entirely novel surface proteins) but it is often responsible for a large percentage of annual flu cases. In the 2012-2013 season, for example, about 1/3 of the flu-positive ILI cases tested by the CDC have been found to contain influenza B. Two strains of influenza B are in wide circulation so the trivalent vaccine often

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**How do anti-influenza antivirals work?**
If you don’t get a flu shot and come down with the flu, your doctor may prescribe an antiviral drug like Tamiflu® that works by binding to the virus’ neuraminidase (NA) protein. Normally, the NA protein snips newly emerging viruses from their host cells. By inhibiting NA activity, anti-neuraminidase antivirals ensure that new viruses can’t escape and infect new cells. They can’t “cure” the flu, but they can help limit the course of the disease, if you take them before the virus has spread to too many cells.
does not match the circulating strain. Therefore, in the next few years, the international recommendation will call for a quadrivalent vaccine containing inactivated viruses of both influenza B strains in addition to the H3N2 and H1N1 influenza A strains.

**STEP 3: DEVELOPMENT OF THE VACCINE SEED STOCK AND VACCINE PRODUCTION**

The first inactivated influenza vaccines were developed in the 1930’s and used for the first time during World War II. At that time, the only way to grow large quantities of influenza virus in the laboratory was by injecting the virus into chicken eggs. Most influenza vaccine is still produced in this way. But remember, influenza viruses are very strongly host-adapted, so the strains that circulate in humans do not grow well in eggs. As a result, each year scientists must generate a new reassortant virus to serve as the basis of the vaccine. The vaccine strain has the hemagglutinin from the human strain inserted into a strain that grows well in eggs. The hybrid viruses are then injected into eggs, where they grow to high numbers. The viruses are then isolated, inactivated, and used in the vaccine.

Changing the technique for producing vaccines requires regulatory approval that can only be obtained after extensive testing to demonstrate that the new technique is as safe and effective as the old one. New approaches that grow the viruses in mammalian cells have received regulatory approval and will probably soon replace the egg-grown vaccine. It will no longer be necessary to develop a hybrid vaccine strain so that it can grow in eggs and vaccine supply will no longer rely on an adequate supply of eggs if there is an unexpected surge in demand for vaccine. Cell-based vaccine production will shorten the time needed to produce the vaccine and allow the production of vaccine to be scaled up or down more easily.

Current vaccines do not provide perfect protection even when they are well-matched to the circulating virus and since the virus changes yearly, annual revaccination is necessary. Recent studies however have suggested new strategies to produce more broadly reactive influenza vaccines in the future. The ultimate goal of such work is a ‘universal’ vaccine that would provide robust protection from multiple strains and subtypes of flu. Much more research is needed before this dream can become a reality.
8. Can I get the flu from a flu vaccination?

In a word: no.

The flu ‘shot’ — the form of the vaccine that is injected, does not contain viable viruses. It contains viruses that have been inactivated so that they cannot invade cells and reproduce. They do, however, display the surface proteins of the currently circulating influenza strain. Exposure to those proteins stimulates the immune system to produce specific antibodies against them. Should you then be exposed to the live virus, your immune system will be able to react quickly and prevent the virus from establishing a full-blown infection.

In recent years, another kind of influenza vaccine has been developed that is sprayed into the nose instead of administered in a shot. The nasal spray vaccine does contain viable virus, but it has been chemically weakened — the technical term is “attenuated” — so that it reproduces very poorly. The immune system mounts a full attack on the localized infection caused by the weakened virus, generating a robust set of protective antibodies. The live attenuated vaccine is especially effective in children — indeed the immunity it stimulates lasts for two seasons, while the flu “shot” gives children immunity for only one year.
1. I’m young and healthy!
Even if you’re healthy, the flu can still cause serious complications. Further, you can pass the virus on to others who are more vulnerable.

2. I heard that flu shot isn’t 100% effective.
If there was a perfectly safe shot that had a 60% chance of preventing you from dying of cancer, would you get the shot? How about if it would also protect the people around you? Even if you still get the flu, it will likely be milder than if you hadn’t been vaccinated.

3. I was vaccinated last year.
That’s great! But you still need to get a new shot this year — flu viruses change from year to year and your immunity can wane, so go get your update.

4. I got the shot last year and felt sick afterwards.
There are two possible explanations for this. First, you might feel a little run down after getting vaccinated because your immune system is doing its job and building antibodies against the virus. The real flu would be far worse. Secondly, you might have been infected by another respiratory virus soon after getting your vaccination; the vaccination won’t protect you from other viruses, but those viruses are also unlikely to cause severe complications.

5. It’s already January and I haven’t gotten my vaccine yet.
It’s not too late to get vaccinated! Although it’s best to be vaccinated in the fall, even a January or February vaccine will help protect you against late-season flu.

6. I’m worried about vaccine safety.
Vaccine manufacturers conduct extensive safety screens, and health agencies around the world track adverse vaccine reactions, which are fortunately very rare.

7. What about Guillain-Barré syndrome?
Guillain-Barré syndrome (GBS) is a rare nervous system disorder that occasionally develops after infections. There was a potential link between the 1976 swine flu vaccine and GBS in 1976 (an excess of 1/100,000 GBS cases) but there has been no signal since then.

8. Don’t the shots contain thimerosal?
Although some people worry that thimerosal (an antiseptic and antifungal used as a vaccine preservative) causes autism, there is very good scientific evidence that there is NO ASSOCIATION between the two.