

Susceptibility of Influenza Viruses to Baloxavir

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hi everyone, I'm Sarah Gregory, and today I'm talking with Dr. Larisa Gubareva of the Influenza Division at CDC. We'll be discussing the susceptibility of different types of flu viruses to a drug called baloxavir. Welcome, Dr. Gubareva.

[Larisa Gubareva] Thank you very much.

[Sarah Gregory] So, right now there are four main types of influenza viruses—A, B, C, and D. Would you describe the differences to us?

[Larisa Gubareva] What is known is influenza is a large and diverse group of related viruses. They're divided in four types: A, B, C, and D. Genetically, type A and type B are closely related to each other, and are distant from type C and D. Among influenza viruses, type A is considered the most dangerous to human health. Flu A viruses circulate widely in nature and cause infections of humans, pigs, horses, bats, and other animals. They can also infect cats and dogs. However, the largest natural reservoir of influenza A viruses is wild aquatic birds, such as ducks. These nonhuman flu viruses occasionally infect humans who were in direct contact with sick or infected animals—at the market place, the county fair, or somewhere else. This is dangerous because animal flu viruses can learn to spread from human to human and cause a pandemic.

Influenza A viruses have two important proteins—hemagglutinin and neuraminidase—that add this antigen on the virus surface. So far, scientists identified 16 subtypes of hemagglutinin and nine subtypes of neuraminidase among bird flu viruses. So, for example, when you hear about H7N9 bird flu, this virus has one antigen of H7 subtype and another antigen of N9 subtype. Since 2013, when these viruses first emerged, they have infected over 1,500 people in China and caused more than hundred deaths.

The infamous Spanish flu that occurred in 1918 and led to millions of deaths, was caused by an avian H1N1 virus. In 2009, a different H1N1 virus, which originated from swine, caused the first pandemic of the 21st century. This pandemic was relatively mild, but this new virus continues to circulate and cause seasonal disease in humans. Type A viruses demand special attention when vaccines and new antiviral medications are being developed because of the pandemic threat and the severity of illnesses that they can cause.

Unlike type A viruses, type B viruses circulate mostly in humans. Two distant lineages of type B viruses are currently in circulation. Type C viruses also circulate in humans, generally causing mild respiratory disease. They're widely distributed throughout the world, but mainly affect children. These viruses have been found in pigs, dogs, and camels. Type D viruses were only recently discovered, in 2011. These viruses infect cattle and pigs. Flu D viruses have not been isolated from people, although there is some evidence suggesting that people may get infected.

[Sarah Gregory] So, when we talk about the flu season each year, which type of virus is most commonly circulating?

[Larisa Gubareva] Well, influenza A and B viruses cause seasonal epidemics. In recent years, flu A viruses have been represented by two groups: H1N1 and H3N2. Of the two, H3N2 viruses typically cause more severe disease. Overall, type B viruses cause less severe disease, but occasionally can be also very harmful.

[Sarah Gregory] What kinds of drugs are used to treat the flu? And how are they different—do they attack different parts of the virus?

[Larisa Gubareva] Antiviral medications provide invaluable addition to vaccines. Anti-flu medications that are marketed in the United States act by bonding to specific parts of the virus. The two oldest drugs are known as anti-blockers and are active against type A viruses, but they do not work against type B viruses. Unfortunately, seasonal flu A viruses have become resistant to these two drugs, and CDC does not recommend their use. Another class of anti-flu drugs target a different viral protein, the neuraminidase, and are called neuraminidase inhibitors. They work against both type A and type B viruses. And the most commonly prescribed neuraminidase inhibitor is Tamiflu, and the generic name is oseltamivir phosphate. The flu virus is known for its ability to mutate, change its structure, and can become resistant to antiviral medications. A decade ago, the group of seasonal viruses became resistant to Tamiflu and rapidly spread globally. If not for pandemic of 2009, this virus is likely to be in circulation. However, they were displaced by the new virus which emerged in 2009. However, this event of widespread resistance to Tamiflu, highlighted the ability of influenza viruses to change rapidly and unpredictably. Neither anti-blockers nor neuraminidase inhibitors are active against types C and D viruses.

[Sarah Gregory] Your study focuses on the impact of the drug baloxavir on different types of flu. What is baloxavir? And is that the generic name or the company name? And it's a fairly new drug, right? And, also, how is it different from Tamiflu?

[Larisa Gubareva] One year ago, a new anti-influenza drug, baloxavir marboxil, or baloxavir for short, was approved in the United States. This medication targets yet a different viral protein. It has a novel antiviral mechanism. It was approved for treatment of type A and B virus infections. It's trade name is Xofluza and it is prescribed as a one-dose oral medication. Tamiflu is also an oral medication, but it needs to be taken twice a day for five days. Also, one published study suggests that the new drug may be more effective than Tamiflu in treating influenza B infections.

[Sarah Gregory] Okay, I just want to be clear here. So, the baloxavir is one time only, not once a day?

[Larisa Gubareva] Just one dose, one pill, and...is all it requires for the whole treatment course.

[Sarah Gregory] And how does baloxavir work?

[Larisa Gubareva] Baloxavir targets a vital viral protein which is needed for virus multiplication in infected cells. The name of this protein is polymerase acidic endonuclease. And...but it's only interesting for virologists to know how exactly it works.

[Sarah Gregory] I was reading the literature about baloxavir and it says that it will reduce the flu symptoms by about a day. Is it worth the possible side effects to feel better by a single day? Or does it also lessen symptoms for the whole period?

[Larisa Gubareva] This is interesting question and it's not easy to answer. While it is important to remember that flu can cause mild but also severe infection, even death in some people. At this time, baloxavir is the only medication that is approved by FDA to treat patients who are at a high risk of developing influenza-related complications. The studies have shown that side effects related with the baloxavir treatment are very few and are less than those for antiviral drug Tamiflu. So, this and other properties makes baloxavir an attractive option for treatment of influenza infections.

[Sarah Gregory] Do the flu viruses ever develop resistance against these drugs?

[Larisa Gubareva] Well, unfortunately, influenza viruses can change or mutate to become resistant to any of the available drugs. In clinical studies, emergence of baloxavir-resistant viruses was detected in one out of 10 baloxavir-treated patients. Clinical studies are underway to learn more about drug resistance to baloxavir and its public health impact.

[Sarah Gregory] It's only been available for a year and it's already forming resistance? That doesn't sound like a good scenario.

[Larisa Gubareva] There are sort of two types of resistance to be concerned. One is emergence of resistance when patient is treated and they...and after this treatment you see emergence of drug-resistant viruses, but they may not be transmitted to other people. So, basically, patient gets well and there is no major consequences of drug resistance. However, if the resistant virus can spread and compete with other viruses, so, that is the more concerning, because that virus can spread widely and now drugs will not work for other people.

[Sarah Gregory] Why did you do this study? What were you looking for?

[Larisa Gubareva] Well, it was quite exciting to study baloxavir since this drug has a novel mechanism to fight flu. We wanted to know if this drug works against a wide variety of influenza viruses, especially those that pose a high threat to human health.

[Sarah Gregory] Okay, well now go ahead and tell us about your study.

[Larisa Gubareva] In our study, we tested baloxavir against viruses from all four types of influenza—A, B, C, and D. Most of the viruses tested were from type A. This included numerous birds- and pig-origin viruses that have the potential to cause pandemics. Because these viruses are dangerous, we had to test them in the secure laboratory. In our study, we used an array of new assays and analyzed the virus genomes by next-generation sequencing. It was quite interesting to show that baloxavir is active against flu C viruses because there are new antiviral drugs that can be used to treat people infected with these type of viruses. And why it's significant, because flu C viruses can cause severe infections in children.

[Sarah Gregory] What were the results of your study?

[Larisa Gubareva] We showed that baloxavir has broad anti-influenza activity. In our experiments, it was active against all the viruses tested. Based on sequence data analysis, we showed that baloxavir-resistant influenza A viruses are very rare in natural reservoirs. And this is important because we don't know which virus could cause the next pandemic.

[Sarah Gregory] Why do you think baloxavir worked so well against all four types of flu? And on the flip side, why was it most effective against type A?

[Larisa Gubareva] Baloxavir targets a viral protein that is found not only in type A and B, but also in type C and D viruses. And what is more important, the part of the protein where this drug binds is similar in all four types. This gave us the idea to test all four types under the same experimental conditions. We had to learn new techniques ourselves since we never worked with influenza C and D viruses in our lab before. We showed that type A viruses are the most sensitive, while flu D viruses are less sensitive to baloxavir. Well, baloxavir was designed to be effective against type A viruses, so it was not surprising that this virus has been most sensitive to this drug. But what we also showed that the drug's strength can be reduced by small differences in the target viral protein, and it's important for predicting its efficacy in the future.

[Sarah Gregory] What are the next steps in this research

[Larisa Gubareva] First of all, we will continue testing flu A and B viruses every season. This way we will know if baloxavir-resistant viruses emerge and spread, and that is the type of resistance we're most concerned about, when resistant virus can spread. We will also test that all new, nonhuman flu viruses that pose a threat to public health. Because there are no medications against type C viruses, we plan to expand the study by testing more type C strains and using additional techniques. We hope that this will provide additional evidence that baloxavir can be useful in controlling flu C infections, especially in children. Some of these next experiments will be conducted in cooperation with our colleagues from Japan, where the drug is also approved and used for treatment.

[Sarah Gregory] Will my doctor give me a prescription for baloxavir or do doctors still want to prescribe more traditional antivirals?

[Larisa Gubareva] Baloxavir is one of several options for antiviral treatment that a doctor can prescribe. Baloxavir is approved by FDA for early treatment of uncomplicated flu in outpatients 12 years and older. That way, baloxavir is given as a single dose versus five days compared to some other anti-influenza drugs.

[Sarah Gregory] Can you treat patients whose flu infections are resistant to these drugs?

[Larisa Gubareva] Fortunately, anti-flu medications have different targets. So, infections caused by baloxavir-resistant viruses can be treated with any of the three approved neuraminidase inhibitors: Tamiflu, Relenza, or Rapivab.

[Sarah Gregory] Since there are so many types of flu, does the flu shot protect us from just one type or multiple types? And how is it decided each year what goes into this year's vaccine?

[Larisa Gubareva] Seasonal flu vaccines contain components of three to four flu strains. This includes two flu A viruses, one H1N1 and one H3N2, and type B viruses from one or both lineages. Because flu viruses evolve fast, it is challenging to decide which strains to include in the vaccine. CDC and other centers participate in global flu surveillance. They collect and categorize flu viruses circulating year 'round. Flu experts gather twice a year with the stakeholders to make recommendations on the composition of the vaccines for the Northern and Southern Hemispheres.

[Sarah Gregory] And, of course, the all-important question: Why do people continue to think you can get the flu from flu shots, but the same people don't believe you can get measles from the measles vaccine?

[Larisa Gubareva] I believe there are several reasons for that perception. It is impossible to get a flu infection from the vaccine shot because flu shots do not contain live virus. But it's still possible to get the flu shortly after you get the shot because it takes two, three weeks for the vaccine to provide protection. So, during that time you're not protected against influenza. Or a person may get infected with another respiratory virus that causes a flu-like illness, so you feel like you got influenza, but in reality, you could be sick with a different infection. Additionally, the vaccine does not protect against all flu strains, and so you can still get sick from a virus that is different from that in the vaccine. And that is a challenge and scientists continue to improve influenza vaccines.

[Sarah Gregory] So, basically, what's happening is people get a flu shot, and then they get sick because they were going to get sick anyway in that timeframe, and then they blame it on the flu shot.

[Larisa Gubareva] Well, this is how human brain works sometimes. We see two events and we feel that one is a consequence of another.

[Sarah Gregory] Even if you do get sick after you've gotten the flu shot, what are the benefits of getting one?

[Larisa Gubareva] There are several benefits from a flu shot. The shot can reduce severity of illness in people who get vaccinated but were not completely protected. It also can reduce the risk of flu-associated hospitalization, helps prevent serious medical events associated with some chronic conditions, will it help protect women during and after pregnancy, and it can be lifesaving in children. Getting vaccinated yourself may also protect people around you, because there are people who are more vulnerable to serious flu illness: young children, older people, people with chronic health conditions.

[Sarah Gregory] And this is actually kind of a personal question: Is there such a thing as a flu booster? I got my flu shot in mid-August because I was taking an international trip the first week of September and was going to be on a lot of public transport. I understand there is some question about continued efficacy. Can I get another one to see me through?

[Larisa Gubareva] Well, it's excellent question and, actually, I had a similar question when I started working in influenza at CDC. And our medical officer explained to me that there is no evidence that the booster would work, and the best way is to get vaccinated once a year, but every year.

[Sarah Gregory] Okay. So, tell us about your job at CDC. What do you do and what do you like best about it?

[Larisa Gubareva] Well, being a flu researcher, I'm quite excited working at CDC. I joined the influenza division in 2006 and this was quite thrilling time. My colleagues and I work hard to learn as much as we can about flu viruses. It makes me happy to know that our efforts contribute to the fight against flu. We actually call ourselves "flu fighters."

[Sarah Gregory] Oh!

[Larisa Gubareva] This work is challenging, as this virus is fast-moving target. It continuously evolves and finds ways to escape our defenses, so we have to work quite hard. At CDC, we have highly secure facility, and that allow us to study the most dangerous flu strains, and again, for flu researchers it's quite exciting. And it also makes work quite rewarding. My very favorite part of the job is working with researchers and public health specialists around the world, as we tackle these challenging tasks together. That's a truly pleasure to work at CDC as a virologist.

[Sarah Gregory] Thank you for joining us today.

[Larisa Gubareva] Thank you.

[Sarah Gregory] And thank you listeners, for joining us. You can read the full October 2019 article, "Susceptibility of Influenza A, B, C, and D Viruses to Baloxavir," online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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