Viral Interference between Respiratory Viruses

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

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Guy Boivin, an infectious disease specialist and the head of the virology laboratory at the Research Center in Infectious Diseases at Laval University in Quebec, Canada. We'll be discussing viral interference between respiratory viruses.

Welcome, Dr. Boivin.

[Guy Boivin] Hi, Sarah. How are you?

[Sarah Gregory] Doing well, thank you. So glad to have you here.

In your article, you talk about viral interference. Tell us what that is.

[Guy Boivin] Well, there is viral interference when there's an infection by a first virus—let's say, rhinovirus causing common cold—and the first virus reduces or prevents the infection by a second virus—for example, the flu virus (the influenza virus). So this is a negative interaction (also called viral interference). One needs to remember though that there are plenty of respiratory viruses in addition to the rhinoviruses and influenza we just mentioned. There's also the common coronaviruses as well as SARS-CoV-2 (responsible for COVID-19), and there's parainfluenza virus, human metapneumovirus, adenovirus, RSV, and so on. And coinfection with more than one respiratory virus is not that rare, especially in young children. So there's a lot of interaction that could occur in the respiratory tract, and these can have a positive or a negative outcome.

[Sarah Gregory] I see, okay. So your article says that viral interference has been demonstrated at the cellular, host, and population levels. What are the differences between those?

[Guy Boivin] Well, let's start with the population level. You should suspect viral interference when an epidemic or a pandemic virus (like SARS-CoV-2) affects the normal circulation or the spread of another virus. And then you just have, again, to think about SARS-CoV-2 pandemic virus that completely or almost completely shut down most other respiratory viruses over the pandemic. So when you suspect this phenomenon to occur in the population, you want to confirm that in either a cell culture or animal models. And in these animal models, you can control the condition of the infection, control the time between each infection (for example, 24, 48, or 72 hours apart), and the outcome is controlled also. You look at the viral load, if it is reduced or increased.

[Sarah Gregory] How and when was this concept first discovered?

[Guy Boivin] Believe it or not, Sarah, this concept was developed in the late 50s, early 60s, by Russian investigators. In particular, there's a lady, Dr. Voroshilova—she developed a live attenuated enterovirus vaccine. Enteroviruses are viruses that can infect the central nervous system and replicate in the gastrointestinal tract. So these investigators attenuated enterovirus vaccine strains, they immunized the patients, and they showed that they can protect with their vaccine against pathogenic enteroviruses (such as polio). But what was unexpected, they also reduced a number of respiratory viral infection in those children. So that was amazing. And this concept got a little bit forgotten for a couple of decades, and then there was renewed interest into viral interference with the pandemic.

[Sarah Gregory] Does viral interference affect only certain respiratory viruses? You mentioned so many.

[Guy Boivin] Yeah, I would say yes. Not all respiratory viruses induce interference, at least not to the same extent. And furthermore, there might be interference in one direction but not necessarily in the other direction. Let me explain that...if you start with an infection that was influenza virus, and then come up with an infection by SARS-CoV-2 a few days later, you will see that influenza reduced the replication of SARS-CoV-2 compared to a single infection. But when you start with SARS-CoV-2 followed by influenza, you don't have necessarily this viral interference phenomenon. And because there are plenty of respiratory viruses, not all viral combinations have been tested and they have not been tested certainly in both ways. So there's still a lot to learn about this concept in respiratory viruses.

[Sarah Gregory] What about other viruses? You mentioned polio and gastrointestinal viruses. So how does that work? Can interference occur with those as well? In what way?

[Guy Boivin] Like we mentioned, the concept of viral interference was discovered by testing enteroviruses, which replicate in the gastrointestinal tract. But this being said, there have been much less study devoted to gastrointestinal viruses such as noroviruses or rotaviruses. But I do not see why it could not exist in the gastrointestinal viruses as well, why this concept of viral interference exists only in respiratory and not in gastrointestinal viruses. I think this is a concept that is a general concept that would apply to both respiratory and gastrointestinal viruses, although there is less research regarding the latter viruses.

[Sarah Gregory] How does viral interference affect the spread of respiratory viruses?

[Guy Boivin] Yeah, here we come to the mechanism of viral interference. And the main mechanism underlying this concept is the production of certain types of molecules (that we call interferon) by our cells in response to a viral infection. In fact, there are many types of interferon, and they can be seen as a non-specific, broadly reactive, natural antiviral. And the interferon is induced, again, when our cells recognize a threat, and by a threat, it could be a virus, or it could be cancer cells. So the infected cells and the cells in the liver would start secretion of interferon. But that doesn't last forever. That lasts for a certain period of time, and then it's waning.

[Sarah Gregory] So virus–virus interactions can either be negative or positive. What exactly does this mean?

[Guy Boivin] Compared to a single virus infection, coinfection with two viruses can be seen as negative (which is antagonistic interaction of viral interference), or positive (either additive or synergistic). So a positive interaction—and by the way, that's not the focus of our article—but a positive interaction would mean that a greater viral replication for potentially the two viruses resulting in a potentially more severe clinical outcome.

[Sarah Gregory] What triggers a negative virus interaction compared to a positive one?

[Guy Boivin] Well, it depends probably on several factors. We still do not know the right answer to this important question, Sarah. But among the reported factors that could play a role in these interactions, there is first the capacity for a virus to induce production of interferon (some viruses induce greater production for more rapid production of interferon than others), the time interval between the two viral infections (is it simultaneously or sequentially, how many days apart), and also the facility of certain viruses to evade or neutralize the interferon response. In particular,

there are viruses such as influenza and SARS-CoV-2 that have developed more mechanisms to neutralize interferon response.

[Sarah Gregory] I think you mentioned earlier that flu reduces COVID, but COVID does not reduce flu symptoms.

[Guy Boivin] Not necessarily. A couple of studies that have shown that the interference between influenza and SARS-CoV-2 was bilateral. There are other studies that have not reported the same, that there was unilateral viral interference between influenza and SARS-CoV-2. So I will say that the jury is still out.

[Sarah Gregory] Okay, alright.

Do positive interactions make treating the virus more difficult?

[Guy Boivin] Well, I would say in a sense, yes, because viral load will be increased probably for the two viruses with potentially more secretion of inflammatory molecules that we call cytokines or chemokines. And furthermore, there are animal studies that show the positive interaction between flu and SARS-CoV when the two viruses are inoculated in the animal simultaneously. But there is viral interference when flu precedes SARS-CoV in a sequential infection. So the positive or negative interaction depends highly on the timing of the infection by the two viruses.

[Sarah Gregory] Is testing for two concurrent respiratory viruses more difficult than testing for just one?

[Guy Boivin] Well, I will say this day, not really, because most hospitals have been using (since the pandemic) upfront and multiplex PCR tests, and these tests can rapidly detect more than 15 or 20 viral pathogens at a time in less than one hour and a half. And these multiplex assays reveal that coinfections were more frequent than we thought previously. In up to 10% of adults we can see a coinfection in the respiratory tract, and up to 30% coinfection in young children have been reported.

[Sarah Gregory] Oh, that's actually very interesting.

You talk about a “refractory period”, where a person is less likely to be infected by another respiratory virus. How long does this refractory period usually last, and does it vary with viruses or, say, environmental conditions?

[Guy Boivin] Yeah, you're right. It depends on the model you look at. If you start with in vitro cell culture experiments, you infect the human cells with one virus, and then after a few days, with another virus. This refractory or interference period could last for a few days. If you are using the ferret (a small animal model) to look at viral interference, we see that this refractory period could last up to a week. But when you come up to population (human population), it's far more complex to estimate because in that situation, the infections are not synchronized like we do in animals or in cell cultures. And there are also some confounders effects by the environmental condition, such as the temperature and the humidity, that you need to take into account. This being said, a few researchers have tried to look at this refractory period in epidemiologic studies, and they reported that the interference could last a couple of weeks in human population. But I would say that certainly more studies are needed to define this refractory period.

[Sarah Gregory] What factors can contribute to there being an interference between respiratory viruses?

[Guy Boivin] Well, probably we don't know all the factors, again, but the one that we mentioned a bit earlier is the propensity of a virus to trigger the induction of interferon and the rapidity of induction of interferon different depending on the viruses. And certainly, secondly, the susceptibility of a virus to the effect of interferon (I mentioned that some viruses have developed means of neutralizing interferon response). And thirdly, I would say the time interval between the two infections.

This being said, besides interferon response, there are also other less well-studied factors that may play a role in viral interference. I would give an example here, like reduction of cellular receptors. The first virus occupied all the cellular receptors, the second virus cannot enter the cells. There could be also competition for cellular resources by the two viruses, and so on.

[Sarah Gregory] COVID-19 and flu infections, as we've talked about, can occur in a person at the same time. How does viral interference come into play in this situation?

[Guy Boivin] Well, viral interference may explain partially why there has been no real influenza epidemic during the COVID-19 pandemic, so that means for the past two years. I think that there are more than sanitary or mitigation measures to explain this absence of the influenza epidemics. So that's why I think that virus interference may play a role and may explain in part what's going on right now, which is really unusual. In my 25-year career as a virologist, I've never seen skipping in an influenza epidemic in the winter season, and that happened twice during the past two years.

[Sarah Gregory] That's really fascinating about no flu. That's been something of a lot of interest. I was sort of thinking that it was because of social distancing and masking and all the other strategies that were in place for COVID, but do you think something else might be going on biologically?

[Guy Boivin] Yeah, I think so because other respiratory viruses were delayed by SARS-CoV-2 but were not eliminated. For instance, the respiratory syncytial virus activity was delayed by a few months with the SARS-CoV-2 pandemic virus. But in influenza, there was no delay. There was absence of an epidemic. I would like to add also the fact that the interference could be in the other way around. So those who had flu as they entered the pandemic had 58% less chances to test positive for COVID-19 in the few months, subsequently. This being said, I think it's too early to fight COVID-19 with flu, but maybe—and that's what we discuss in our article—maybe a defective influenza particle (an attenuated influenza particle) could be of potential benefit to fight against a pandemic virus before we get a good vaccine.

[Sarah Gregory] What's unique about HRV and SARS-CoV-2?

[Guy Boivin] So HRV (or human rhinoviruses) in contrast to most other respiratory viruses, they continued to circulate despite the mitigation or sanitary measures put in place during the pandemic. And one biological reason for that is that rhinoviruses are nonenveloped viruses, in contrast to most other respiratory viruses. That means that they are more resistant to disinfectants such as ethanol. And masks do not protect as well against rhinoviruses than against the other respiratory viruses. And when we do experiments in cell culture (human cell culture), rhinovirus impairs the replication of SARS-CoV-2, but the opposite is not true.

[Sarah Gregory] What prompted you to write this article?

[Guy Boivin] Well, I was most interested in the observation we discussed that there was virtually no flu activity during the pandemic so far (almost two years now), and this is something that I've

never seen before in my career as a virologist. So I thought that there was something else playing a role in that absence of flu activity. And that's why I've become interested in the concept of viral interference.

[Sarah Gregory] How did you go about collecting the information for your paper?

[Guy Boivin] Well, my research associate, Dr. Jocelyne Piret, and I started to look at all articles dealing with the new pandemic virus (SARS-CoV-2) and influenza first. And then we increased our search to interactions between all respiratory viruses. My biggest surprise, I have to say, came when I found that the concept of interference dated back to the 60s. That was very amazing to me.

[Sarah Gregory] What are the major public health implications of your findings?

[Guy Boivin] Well, one implication is that good knowledge about this phenomenon of viral interference may improve the mathematical models that we use to predict the timing and the magnitude of an epidemic peak or a pandemic wave. Also, we discussed that a bit in the paper...the interfering but still immunostimulatory activities of defective viral particles make them attractive antiviral candidates. So a new class of broad spectrum antiviral agents that we are discussing—for example, a genetically modified attenuated flu virus could interfere with replication of seasonal flu viruses, but also with that of other unrelated viruses (such as SARS-CoV-2)—so that we can do something about this phenomenon of viral interference that could result in improving our development and design of antiviral...broad antiviral agents.

[Sarah Gregory] Okay. So kind of along those same lines, that's how you'd like to see this information used moving forward? Do you have anything specific in mind?

[Guy Boivin] Yeah, I think when we talk about coinfections, most people and most scientists will think about positive interactions in more viruses and greater viral loads and will be a negative viral outcome. So I would like that people think that it's not because there's coinfection that there will be a positive interaction, but you can see also a negative interaction.

[Sarah Gregory] Which is probably at least as important, if not more important.

So tell us about your job, where you work, and what you like most about it.

[Guy Boivin] Well, I'm an infectious disease specialist and a researcher in virology. I work with respiratory viruses, but also other viruses such as herpes viruses, which are DNA viruses. And what I like is that I do my clinical and research work in the same place (in the same hospital), and I like switching jobs or switching hats many times during the day. So starting with a meeting with my graduate students and then going in the clinic and seeing a patient and then going back in the lab, this is very challenging but very interesting. And being an MD, I always look at clinical application for my research. And working with respiratory viruses, I will say is both stimulating but also very challenging.

[Sarah Gregory] And you live in Quebec. What’s your favorite thing about living there?

[Guy Boivin] Well, everybody knows that it can be cold during the winter in Quebec, but I like living in Quebec simply because I think there are four real different seasons, and there's a lot to do in each season. For example, during the fall, there's this nice festival of colors from the maple trees. And during the winter, we always have a lot of snow. So for cross-country skiing, the sport I like a lot, it's the perfect place to practice this sport. During the spring, there's a tasting of maple syrup. Do you know that Quebec is producing 70% of maple syrup in the world? And I will

finish by saying that in the summer, we have nice, not too hot, not too humid temperatures where we can practice a lot of outdoor activities.

[Sarah Gregory] I know it's supposed to be incredible....I've been there a few times, but incredibly beautiful in the winter. Lots of beautiful lights.

[Guy Boivin] Yes, we have the winter carnival. But with the sanitary measures, we didn't have parades and things like that this year. It's a shame, but anyway.

[Sarah Gregory] And I love your maple syrup. In fact, I just gave a little bottle of it to my son-in-law for Valentine's Day.
Thank you so much for taking the time to talk with me today, Dr. Boivin.

[Guy Boivin] It was my pleasure.

[Sarah Gregory] And thanks for joining me out there. You can read the February 2022 article, Viral Interference between Respiratory Viruses, online at cdc.gov/eid.

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

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