The Mother of All Pandemics

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

[Sarah Gregory] Hi, I'm Sarah Gregory, and today I'm talking to Dr. David Morens in Washington, D.C. Dr. Morens works at the National Institute of Allergy and Infectious Diseases, and we'll be discussing the 1918 influenza pandemic. Welcome, Dr. Morens.

[David Morens] Good to talk to you.

[Sarah Gregory] So, in 2006 you wrote a Perspective for the EID journal called, "1918 Influenza: The Mother of All Pandemics." I worked on communications here at CDC for the swine flu and the H1N1 outbreaks. This is what we were all afraid of, right—a flu, bacteria, fungus, whatever, that wipes out all of us?

[David Morens] Well, it's the, it's the Andromeda Strain idea, that infectious diseases are appearing all the time, including influenza, and one of them, someday, might be as deadly as the Black Death in the fourteenth century or the 1918 influenza, which killed so many millions of people.

[Sarah Gregory] I also have to add that, at the moment, your article is our number one AltMetric article. It's a, it's having its, a resurgence of its heyday here. I guess it's 'cause it's the centennial.

So, in the 2018 centennial, as I said, of the 1918 pandemic, let's talk about that flu. What happened in 1918?

[David Morens] Well, we wish we knew what happened, but a brand new type of influenza that hadn't been around before, appeared suddenly around the world. And it was far more deadly than we had thought influenzas could be, in that era. And that pandemic killed an estimated 50 to 100 million people in a matter of two years, which makes it the deadliest single event in all of human history. Why it happened, where that virus came from, and why it was more deadly than influenza viruses before and since, we don't really know.

[Sarah Gregory] So, a zoonotic host was never identified?

[David Morens] Well, we do know that the ultimate source of all influenza viruses—influenza A viruses are the type we're talking about—they come in flavors of A, B, C, and D, but the big pandemic ones are all influenza A—we know that all of those viruses ultimately come from wild water fowl, mostly ducks and geese and some shore birds and other birds. That's the reservoir. They exist in this reservoir, they have for centuries, if not millennia, they probably will for centuries into the future. They don't change much in the bird population because they're adapted to it, but every once in a while, one of these viruses, through some trick that we haven't figured out, is able to jump out of its host species, the water bird, and get into mammals, like human beings. When that happens, there can be a pandemic. And, we presume, because of the genetics of the virus, that is, the gene sequence—genes…viruses have genes, just like people do—that that virus in 1918 came from a bird, probably in 1918 or very shortly before.

[Sarah Gregory] So, it started in 1918, it wasn't eeping up before that. And geographically, where did it come from? In 2006, the basis of its pathogenicity was unknown. In the intervening 12 years since your article was published, have we learned more about it?

[David Morens] We've learned a lot more about it now and one of the things we've learned is that the influenza virus has eight genes that code for 11 or more proteins, and one of those proteins is called hemagglutinin, or HA. It's the protein that sticks out on the outside of the virus. And in the bird world—in bird viruses, that is—there are 16 different varieties of HA. We call them HA1, 2, 3, 4, all the way up to 16. We now know that that HA in 1918, which we call, nowadays we call that H1, we now know that, when you put that into a virus, experimentally, and then infect mammals, rodents, for example, it's much more deadly. It causes more damage to the tissue and a bigger inflammatory response. So, that implies that, whatever happened in 1918, something, a component of a virus that came right out of the bird world, and a brand new virus, was deadly from the get-go. It was just naturally deadly—probably by accident. You know, viruses don't think, they don't try to be deadly, they don't want to kill their host. That's not a good survival mechanism to kill your host, because you need to be spread…the virus needs to be spread on from one host to the other. So, it's probably just a freak accident that this virus contained a gene segment that was completely harmless to birds but was deadly to people.

[Sarah Gregory] And was there an original hotspot for this?

[David Morens] Well, probably not. There's a lot of creation myths that have evolved about the 1918 pandemic beginning in one place or the other. And every historian and amateur historian has their own favorite place, all the way from a little city in Kansas, to the front lines in the war in Europe, to various other places—the country of Spain, for example. But, in fact, the pandemic started almost simultaneously in large cities all over the world, in the summer and fall of 1918. So it couldn't have gone from place to place. The idea that it started in place A and went to B, and from B to C, and C to D, and so on, in 1918, can't be correct because it appeared simultaneously in many places all around the world. And that means that the virus had to have been seeded, meaning that it spread slowly from one case to two cases to four cases to eight cases, all around the world, before we ever recognized it. When a pandemic appeared, that virus had already traveled, been traveling around the world for a long time, probably for many months. So, obviously, to answer your question, obviously it began somewhere, and we have no real…we can only guess. Most pandemics begin somewhere in Asia, that would be a good guess. But there's no proof and we'll probably never know.

[Sarah Gregory] Okay, alright, that helps me understand. I was getting a little bit confused about it spreading all at once, all over the world. Were certain regions of the world affected more than others?

[David Morens] Yes, they were. And the death rate tended to be the worst in the developing countries, the poor countries, with crowded populations. And, in fact, probably, historians believe that the largest number of deaths came from India. And it's speculated that a similarly large number of deaths came from China. But the record keeping in China wasn't so good at the time and we don't really know that. But, clearly, the vast majority of deaths occurred in the developing world, not in the developed world. Also, there were certain remote locales with native peoples—small islands in the Pacific or remote villages in Alaska—where the death rates

were very high, for reasons that aren't entirely clear. Those were small populations, but in some villages as many as 80 percent of everybody died.

[Sarah Gregory] Without getting too technical, can you explain how this virus was discovered?

[David Morens] Yes, so, the 1918 pandemic occurred in the very early era of virology, and it wasn't really possible, with the techniques of the time, to isolate that virus. A descendant of that virus was isolated when virology advanced in the 1930s, 15 years later, but not the virus itself that was around in 1918, just a descendant. And people imagined, throughout those intervening decades, over the last hundred years, people imagined that maybe someday we could find a frozen corpse, up in Alaska or someplace far north, somebody who'd been buried in the ice. And that, if the corpse was preserved, it could be dug up and the virus isolated in the way we, in those days, isolated viruses, by putting them in animals or in tissue culture. And, in fact, that was attempted in 1951.

An American pathologist went up to Alaska and dug up a grave that was in the permafrost, and found a corpse that was relatively well preserved, and got some tissue to try to isolate virus, but nothing was isolated. So, that was the end of that story until 1995, when a team of virologists and molecular biologists at the Armed Forces Institute of Pathology—now here at NIH, it's our biggest flu group at NIH—that group had access to pathology specimens that were put in paraffin, it's like wax that you might use in canning, which is what pathologists do. But the Armed Forces Institute of Pathology, in those little chunks of tissue, stuck in wax for, then 85 years, or 80 years, proved to reveal that they had genes, RNA genes, that could be recovered by, or identified rather, by a then rather new technique called "PCR," polymerase chain reaction. It's a complicated term for a mechanism to identify individual bases that compose genes of DNA or RNA, the building blocks…DNA being the master plan for all life, including viruses, which are not really alive, but they carry DNA or RNA, and in this case, it was RNA.

And so sequences of something that looked like an influenza virus were identified. Once they got underway, the team that had been up to Alaska in 1951 went back. The leader of that team, Dr. Johan Hultin, went back 50 years later, to try to dig up those bodies again, and this time used the new genetics technique, the PCR technique, to identify the sequence of the gene, that he couldn't grow…'cause he couldn't grow the virus decades earlier. And that's in fact what happened. The virus, with painstaking techniques, was reconstructed, its blueprint was reconstructed, base by base, for the RNA that comprised it, until we have the whole sequence. And that sequence is not a virus, not a live virus, it's like a, it's like a code that tells you how the virus is made. And once we had that code, the virus was made and turned into a real virus, and studied under high containment security procedures, in high containment laboratories.

[Sarah Gregory] That's actually a truly amazing story.

[David Morens] Well, it is amazing. And it would have been, if you would, if Dr. Hultin had heard that predicted in 1951, I'm sure he would… he's a physician…I'm sure he would have disbelieved it. I'm sure he would have said, "That's impossible, it can never happen." But, you know, science moves along, and things that were impossible 10 years ago are possible today.

[Sarah Gregory] But that he was even still alive and able to go back and do that, is something…

[David Morens] Yeah, then in his 80s.

[Sarah Gregory] The pandemic also apparently came in waves. What was that about?

[David Morens] Well, it's hard to know because it came in waves in some places, but not in others. And the waves were, in some cases…some places had no pandemic at all, some had only one wave and no more, some had two, some had three; at least one place had six waves. And it's hard to know what that is. It's probably a complicated thing that relates to the geography of the place, the humidity and the temperature, the elevation above sea level, the timing, the population size.

Influenza viruses are much more likely to spread when the temperature is low and the humidity is low—in other words, in the winter—and not so likely to spread in the summer, when the temperature is high and the humidity is high. And that's particularly true in temperate climates, you know, climates away from the equator, north or south of the equator. And it's…for a lot of reasons…it's, it seems reasonable to think that this funny behavior of waves, or multiple waves in some cases, is just a function of peculiar circumstances, variables that are individual to a particular place, that allowed the virus to peter out when the weather doesn't… when the weather's not so good, then come back when the weather is more favorable. And also, the winter, you know, the winter is a time when it gets colder, rather, in the fall and the winter. It's a time when people, in those days, in particular, were more likely to be indoors, where there's more likely to be crowded air, that's not…you know, in those days, there was no air conditioning, and so, when you stayed indoors with a lot of people, a big family, or in a train station or something, you breathed a lot of air that you wouldn't be breathing in the summer when the windows were open.

[Sarah Gregory] How is this flu different from others? Why were so many young adults affected?

[David Morens] Well, you're right. The mystery of the young adults is a, is a complicated one that nobody has answered satisfactorily yet. And just to say what it was: Most influenza, virtually all influenza, is most deadly in the age groups of the very young—infants and small children, toddlers, and the very old. And the mortality is very low in every age in between, and the mortality is usually extremely low in healthy young adults. That was not true in 1918. In, in that age group, roughly 20 to 40 year olds, and otherwise healthy adults, the death rate was extraordinarily high—not as high as in the elderly and in infants, but still, extraordinarily high—something that's never been seen before or since. And it's a mystery that people have speculated on for a hundred years now, and…and there are just no good answers.

[Sarah Gregory] So, speaking of speculation, what would happen if the world was struck with a pandemic of this severity now?

[David Morens] Well, I think it would be a good news story and a bad news story, but mostly a bad news story. The good news part of it is we now have antibiotics and, remember that most people who died in 1918 did not die of the influenza virus, they died of the bacteria that they carried in their nose and throat, which went down into their lungs to cause pneumonia after the virus came. So we now, in theory at least, we can treat that with antibiotics. And we have, you know, we have good public health knowledge and we have a more educated public, in the developed world, at least. And that's all to the good. And we've had, of course, a hundred years of experience with influenza of different varieties.

But, here's, here's the problem. The population of the world is much bigger now. And if you, if the death rate…if the virus that came tomorrow was as deadly as 1918, we now have a world population of seven and a half billion, as opposed to one and a half billion, I believe it was in 1918. And so, instead of 50 to 100 million deaths, we'd probably have about 400 million deaths, unless we were able to save people with our modern armamentarium of antibiotics and ICUs, and things like that. The problem with that, though, is that, when, if you, if…what happened in 1918 would happen again, which is that, wherever you lived, that virus would come to your town and come through it and infect everybody, and they'd either live or die, in a very short period of time, a matter of weeks. So, that means that it's not like the cases are spread out over a whole year, they're…all the people that are going to get sick get sick within a very narrow window of time. Well, so imagine in the United States. We would have…in 1918, 675,000 people died in the United States—most of them within a matter of weeks. In our current population of 328 million, that would translated into well over two million people dying or, you know, getting…you know, four or five, six million people getting deathly ill and needing to be in the hospital, and two million of those people dying. Well, there aren't enough hospital ICU beds and enough ventilators, because they pretty much all die of pneumonia. There's just not the capacity to be able to medically handle that many deadly emergencies that happen all at once. So, you know, it would be better than it was in 1918, of course, but it would still be very deadly.

[Sarah Gregory] Sort of a tangential question…People who've had pneumonia vaccines—would they be better off?

[David Morens] They would be better off. We have, we have two pneumonia vaccines that are recommended…that have different recommendations. And the particular target group for these vaccines, with respect to flu, would be the elderly. And yes, one of, of the bacteria that killed people in 1918, and we would expect would kill people in a future pandemic, the three most common ones were the pneumococcus, and the other two were the streptococcus, *Streptococcus pyogenes*, or group A beta-hemolytic strep, and *Staphylococcus aureus*. We don't have a vaccine, we don't have vaccines to the latter two of those, but we do have the vaccines for the pneumococcus types. And it's recommended that older people get those vaccines, and there's a recommendation for children, as well, but particularly talking about older people who…of which there are many more older people than younger people, and they're more likely to die. It's almost certain that having those, having had those pneumococcal vaccines would have, would be a good thing if an epidemic of influenza came through, because it would have to have an impact on severity of illness and the chance that you'd get a pneumococcal pneumonia that could be fatal.

[Sarah Gregory] What are the predictions for future pandemics? Are there any or are we just sort of flying blind here?

[David Morens] Well, we really are flying blind. We can say that there's been a, you know, there's been regular pandemics over at least the past 1,200 years. In the last century, when we have viral evidence, we know there've been four pandemics. That's four pandemics in 100 years or about one every 25 years. And so, we're virtually certain they will come again, but what they'll be and how deadly they'll be, we don't know. If history is a lesson, some pandemics are very deadly, like 1918, and others are not so deadly at all, like the one we had in 2009. And the same is true historically, going back, you know, to the 800s. But, you know, every pandemic is a law unto itself, every pandemic is a new virus, and what it does is not predictable based on what happened before.

I should say also that these hemagglutinins that I mentioned earlier, that come in 16 different varieties, numbered 1 through 16, H1 through H16, those 16 different hemagglutinins exist in nature, and five of them appear to be very deadly when you put them into a virus and test them in animals nowadays. And one of them, of course, was H1, which caused, which was the HA in the 1918 virus. But there are some other ones, as well, H6, H7, H10, and H15. And if those hemagglutinins, which exist in nature now and will never be eradicated—they'll be here hundreds of years from now—if and when any of those gets into a virus and if that virus infects people and becomes pandemic, the evidence suggests there's a likelihood that something just as deadly as 1918 would occur.

[Sarah Gregory] Well, on that happy note, can you suggest any ways a person might survive a true pandemic like the 1918 one, other than, I guess, getting your flu shot and your pneumonia shot, if you're elderly?

[David Morens] That's true. Get all the shots that the doctors recommend—the flu shot and the pneumococcus shot, the pneumonia shot, of course. I think that, the other thing, too, the other thing I would say is that, you know, when a pandemic occurs, there are some things that, you know, we can't prevent. But there are things that we can do personally to reduce our chances of getting infected and having a severe or fatal illness. And before I say what those are, I just want to say that, here's the way it works with influenza. It takes…when we have a new virus that appears, it takes, with our best efforts, it takes about six months to make a new vaccine; and so, that's a long time. But, if you, if when the pandemic occurs, you can find a way to not get infected for six months, then you can get vaccinated and then you may be okay. The other thing that happens is pandemics can appear at any time of year. And if they appear in the late spring—for example, that's what happened in 1957—they're likely to go away in the summer, or almost go away, and then come back in the fall. And so, that buys more time to get a vaccine because the pandemic won't rip through the country right away, it'll slow down for a few months in the summer and then pick up again. So, the point is, you can expect that in an influenza, in a new influenza pandemic, there will be a period of time, that will be six months or, hopefully, less, a little less, in which you can think about what to do to avoid getting infected.

So, you know, there are obvious personal things that one can do, which is try to avoid traveling and going into crowded places—you know, don't sit around in a bus station, don't sit around in an airport, if you can avoid it. I would, you know, I think that in, there are simple sanitary things, like, you know, always washing your hands properly, just like grandma told us, and use…nowadays, in the modern era, using hand sanitizers. There is some controversy about these masks you see people wearing. In parts of Asia, like Japan, people wear masks every time they get a cold, and they've been doing that since 1918. And some doctors argue, "Well, the virus will get right through the mask anyway, so it's useless." I don't think that's true because, you know, the virus can be in large particles that don't get through the mask. And, in any event, wearing a mask prevents you from touching your face, which is another, you know, if it gets on your hands, they get contaminated with flu, you can touch your face and inoculate yourself with it. So, having a mask there prevents you from touching your, touching your nose and mouth. You know, you know, also, paying attention to the, what the health department says, you know, where is the virus spreading in your area, and what are the recommendations they have, which might include things like shutting down schools or liberal work leave policies. There's a lot of

public health things we can do that won't make a pandemic go away, but they will potentially slow it down.

And in fact, even in 1918, people survived, you know, by isolating themselves. People did what they did in the, in the, in the 14th century, when the Black Death occurred, they went off to their country house and hid themselves away, for example. Not everybody can do that because not everybody has a country house, but, and many people have a job, they have to work. But for those who can find a way to isolate themselves, they can reduce their chances. There's really a lot that can be done.

[Sarah Gregory] People should take that little bit of information and paste it to their bathroom walls. So, what's your position at NIH and do you still look into flu or have you moved on to other pathogens?

[David Morens] Well, I do. I'm, I'm…my position is senior advisor to the director of our institute, National Institute of Allergy and Infectious Diseases. And in that role, I do a lot of different things, but yes, I'm involved in flu work every day. I'm, you know, more of a senior person, I'm not in the lab doing the research myself. But I'm working with our folks here to do a lot of things to understand influenza, not only the 1918 virus, but modern viruses and bird viruses. And we're doing, we're doing work that we hope will lead one day to better influenza vaccines. And we're doing work to understand the pathogenesis, that, which is to say, you know, what is the mechanism by which a lowly influenza virus can make you very sick and even kill you.

[Sarah Gregory] In 2015, you did a podcast with me about your very moving article on historical deaths from measles and lack of vaccination. So, we already talked about vaccination a little bit—is that a priority with you, also?

[David Morens] Well, it always is. You know, I'm not only a pediatrician, but I'm an infectious disease physician, a virologist, and an epidemiologist, who used to work at CDC and learned all about this stuff when I was at CDC. So yes, vaccination, for anybody, for any physician or scientist in infectious diseases, vaccination is always one of those things that is at the very top of the list in importance. Because, with a good vaccine, like the measles vaccine, which, the one you and I talked about several years ago, with a really good vaccine, you can stop a disease dead in its, dead in its tracks. And you can even, as we know with smallpox, eradicate it. And we will one day eradicate measles. It doesn't look like we are gonna be able, in the foreseeable future, to eradicate influenza, because it's always going to be out there in birds, but we can make better vaccines, I think, and that's what we're trying to do.

[Sarah Gregory] Well, thank you so much for taking the time to talk with me today. It's such a pleasure. Listeners can read the January 2006 article, "1918 Influenza: the Mother of All Pandemics," online at cdc.gov/eid.

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

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