Virologist discusses the vagaries of the flu

February 9 2018, by Ekaterina Pesheva

Credit: Harvard Medical School

The flu has been our viral companion for millennia, but its capricious behavior continues to confound scientists and public health experts.

A shapeshifting virus with virulence varying unpredictably from one season to the next, the flu kills thousands of people each year in the

United States alone, and many more worldwide.

Forecasting flu's severity from year to year invariably involves some degree of guesswork. So does predicting which strains will dominate the season, presenting challenges to designing a well-matched vaccine.

In the 40 or so years since the Centers for Disease Control and Prevention began publishing estimates of annual flu mortality in the United States, the virus's lethality has ranged from 3,300 deaths in 1986-1987 to 56,000 in 2013-2014.

This year's flu season is off to a strong start with a dominant strain that is particularly pernicious, H3N2, and a vaccine that has turned out to be a poor match.

According to the CDC, as of Jan. 27, 7 percent of Americans have seen a doctor for a flu-like illness, the agency's way of tracking the virus's weekly activity. The number represents a threefold jump from the typical national average of 2.2 percent.

But what are the tricks up the virus's sleeve that make it so elusive?

To find out, Harvard Medicine News sat down with virologist Daniel Kuritzkes, professor of medicine at Harvard Medical School. As a virologist, Kuritzkes studies HIV drug resistance and viral persistence. But as chief of the Division of Infectious Diseases at Brigham and Women's Hospital, it is the flu that has occupied Kuritzkes's attention more prominently over the last few months.

HMN: What are some of the lingering scientific challenges of the flu? What have we not "cracked" about the virus's behavior?

DK: The central challenge of influenza comes from its genetic make-up. Influenza is an RNA virus, which means it uses an RNA enzyme to replicate and propagate itself. RNA enzymes are inherently sloppy, without proofreading skills to guard against mutations during replication.

RNA viral replication charges ahead rapidly, regardless of what kinds of mistakes the enzyme makes. For the virus itself, this has advantages and disadvantages. On one hand, too many errors can cause the virus to die. The advantage for the virus is that some of those mistakes lead to variations in the surface proteins of the virus, the so-called antigens.

These surface proteins are like identity badges the virus carries. Our immune system spots viruses and other intruders by checking their identity badges. Sometimes, when these surface proteins—or viral IDs—change, the virus becomes unrecognizable to our immune system, sneaking past its defenses before it's had a chance to disarm it.

We see the same shapeshifting behavior in HIV and hepatitis C. What this means is that our immune systems are playing constant catchup with the rapidly changing flu virus. The antibodies we made last year may not work this year because the new flu virus is different.

The other trick up flu's sleeve is that the virus is made up of eight different segments of RNA, each coding for specific genes. When we get infected by more than one flu strain, the strains or viral types can swap segments with each other and come up with re-assorted versions of the virus. The high mutation rate and the ability to generate re-assorted versions by mixing and matching parts of its genome with other strains fuel the huge diversity that we see with the influenza virus. Figuring out how to counter this has been a formidable challenge.

HMN: What are some promising efforts on this

front?

DK: The biggest game changer on the prevention front would be a universal flu vaccine, an elusive goal that has tantalized scientists for decades.

Seasonal vaccines are premade every year based on expert predictions of what the most likely cocktail of viral strains for the looming season will be. The Achilles' heel of current vaccines is that they elicit response and protection to the most variable proteins on the virus's surface. So the very proteins targeted by the vaccine mutate the fastest and thus render vaccines less than perfect matches for the virus they are designed to combat.

A universal vaccine, by contrast, would target not these evasive surface proteins, but the virus's core proteins, which are far more stable and are common across a variety of strains and viral types. The hope is that a universal vaccine would not be given annually—perhaps several times over a person's life—and would induce long-lasting immunity. There have been several reports of advances on that front in animals, and a clinical trial in humans is currently under way in the United Kingdom based on research emanating from Oxford University.

HMN: These are the hurdles that scientists must overcome in the lab. What are some of the clinical challenges?

DK: The flip side of that coin is what happens once the virus infects a person—or how the pathogen interacts with the host. The flu virus doesn't kill you directly. Instead it causes a range of derangements that culminate in death. The most common causes of flu-related death are bacterial lung infections that develop following the flu, along with

complications from underlying cardiac or lung disorders in people with preexisting diseases.

But there is another group of seemingly healthy people who succumb to flu as a result of raging inflammation. Their immune systems respond too strongly. The response is worse than the disease. There is still a critical gap in our understanding of why some people are more vulnerable to this particular complication. It's not that the virus is more virulent because the same virus infected their neighbor or spouse and they did just fine. It must be something about the individual's own immune response that becomes overexuberant and causes the actual damage.

Once we identify the underlying causes for this aberrant response, we can begin to think about novel interventions to treat people who present with fulminant influenza. My own bias is that this is somehow genetically determined, perhaps not by a single gene but by a group of genes that govern responses to particular kinds of pathogens.

HMN: Until we cross that bridge, what are some more immediate solutions?

DK: The obvious things: Get vaccinated. The vaccine does work, albeit imperfectly, and even if you do get the flu, chances are it will be a much milder disease. If you do have symptoms, stay home because the flu is highly contagious. Just as importantly, we have to become more nimble in the way we treat infected patients with antiviral medications that stop the virus from multiplying. We know that with antiviral drugs, the earlier you intervene, the greater the benefit. But if you think about a typical person, they start to feel sick, decide to say home, feel worse later that day. Maybe the next morning they go to the doctor. The doctor tells them take some acetaminophen and drink plenty of fluids. And then

they're really lousy by the end of day. By that point, you've already missed much of the window because the antivirals are most effective when given within 48 hours of the onset of symptoms.

My daughter just had flu recently. She texted me early in the morning asking, "I think I have the flu. Should I go and be seen?" I said, "Yes, and ask for medication." They saw her and did a test. They said they would give her a prescription when the test came back. That's actually not what you're supposed to do. CDC guidance says in the setting of an influenza epidemic, if somebody presents with symptoms suggestive of the flu, then you should go ahead and treat presumptively without waiting for confirmatory results of diagnostic testing.

Provided by Harvard Medical School