Medical News & Perspectives

# Vulnerability to Pandemic Flu Could Be Greater Today Than a Century Ago

Rebecca Voelker, MSJ

Michael Osterholm, PhD, MPH, didn't mince words when he wrote a love letter to his children and grandchildren. His dispatch, a book entitled *Deadliest Enemy: Our War Against Killer Germs*, was published last year as a guide for surviving emerging infectious disease threats. "[F]ailure is not an option here," said Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota.

Concern for his loved ones' future prompted Osterholm to write the cautionary tale, but his intended audience is global. As the world observes the centennial of 1918's ruinous influenza pandemic, his message includes a societal call to arms for stepped-up flu vaccine research. "[I]t's not that we can't do this…it's will we do this?" he said.

Author Audio Interview

Prints and Photographs Division/Library of Congress

A global immunization program using a universal flu vaccine that might be needed only once every 10 to 20 years "could do more for the world's public health than we even did with the eradication of smallpox, and it would surely have a major impact economically in terms of taking off the table future pandemics," Osterholm said.

In a recent conversation with *JAMA*, Osterholm explained why the world is vulnerable to another 1918-like flu pandemic and what's needed to dodge the infectious bullet. An edited version of that discussion follows.

**JAMA:** Since the 1918 pandemic that killed millions of people we've had vaccine development, sanitation, and less crowded living conditions in some parts of the world. Do these improvements mean that we can avoid another pandemic like the one in 1918?

**DR OSTERHOLM:** Let's be clear that we don't understand why influenza pandemics do what they do—why are some much more severe than others? What is it that we can do about those pandemics in terms of both prevention and treatment? I would say that we are much more vulnerable today to a catastrophic influenza pandemic than we were in 1918. That may seem counterintuitive, but today there are about 7.6 billion people on Earth, more than 3 times the population in 1918. When we talk about less crowded living conditions today, that is true for part of the world. But for the vast majority of the world it's worse. In the slums of low- and middle-income countries today, the population far exceeds what it was in 1918.

We now have influenza vaccines that we didn't have in 1918, but the effectiveness is limited. In the 2009 influenza pandemic, which fortunately was mild, that vaccine was roughly 50% to 55% effective. More importantly, less than 1% of the world's population had access to the vaccine in the first 6 to 12 months of the pandemic because of our inability to quickly make a largely egg-based product. In the future, vaccines still are going to have only a limited impact.

Finally, we are extremely vulnerable today to any disruption in international trade in lifesaving medicines and medical devices.

Look no further than what happened last fall when a Category 5 hurricane hit Puerto Rico, an island where about 80% of IV (intravenous) bag manufacturing worldwide was concentrated. When that electrical grid system went down, we saw overnight a major shortage of IV bags around the world. Today the vast majority of drugs that we use in this country come from China. Even those that are not manufactured in China, the essential compounds that those drugs are based on come from China. Those are very fragile supply chains; there are no stockpiles anywhere. If China were plunged into an influenza pandemic and the fast freighters that bring those products around the world can't move because of the pandemic, the collateral damage from people dying of all kinds of medical conditions will far exceed even the first months' mortality associated with the flu itself. When you add that up, I'd have to say we're much more vulnerable today than they were in 1918.

**JAMA:** Are there substantial differences in how virulent the flu viruses are today compared with 1918?

**DR OSTERHOLM:** Virulence is how serious the disease is, so in this case we're talking about death or at least very serious health outcomes. One of the challenges we have is that in 1918 the mortality rates were highest in young adults, not in the elderly, and not in young children although they were elevated there. The second thing is most of these people ended up dying from what we call cytokine storms. These are immune system dysfunctions that occur when individuals are infected with the virus. Today we don't do any better with cytokine storm cases than we did in 1918. Why some viruses tend to cause these kinds of conditions, we're not sure. In 2009 with H1N1, we saw a higher proportion of cytokine storms in pregnant women and in indigenous populations in Canada. These individuals were at very high risk of fatal outcomes. So we have a lot left to understand about why certain influenza viruses tend to cause much more severe disease.

We're seeing that right now around the world with some avian influenza viruses. When H5N1 was of primary concern or H7N9, we saw case mortality rates in the 20% to 30% range and that was based on good surveillance. Many of these patients were dying of cytokine stormlike events, so the potential for another cytokine storm–based pandemic is surely very real, and we're very concerned. We kind of have 2 influenza pandemics that occur. One is the cytokine storm–based mortality that typically affects younger populations more severely, and then we have the seasonal-flu-on-steroids pandemics. In 1957 and '68, with both H2N2 and H3N2, we saw pandemics with the same age distribution and more older populations were impacted.

**JAMA:** A universal flu vaccine is currently in development to cover multiple flu strains and eliminate the need for a yearly flu shot. How close are we to having a universal flu vaccine?

**DR OSTERHOLM:** Unfortunately we're a long way away even though there's a lot of hype today that it's just around the corner. What I can report with a great deal of pleasure is that we finally recognize that we need a new type of flu vaccine. But we're talking about substantial research left to do. We're now in the eighth consecutive year of spending over a billion dollars globally on HIV vaccine research. I would not take a penny of that away, but last year as a world, we spent only about $80 million on new flu vaccine research. Even with the US government putting another $100 million into flu vaccine research, it is far short of what we need.

It used to be thought that the current vaccines don't work that well because the virus is constantly changing its hemagglutinin head, the part of a virus that we tend to target the antibody toward. Well, now we realize that isn't the major deterrent to an effective vaccine. Then we thought, well it's because we're growing it in chicken eggs and mutations occur in the virus to adapt to a chicken egg from its human source, that maybe that's the problem because we then use that adapted vaccine strain. And we realized that's a potential issue but it's not *the* issue.

We're looking very carefully now at what's referred to as original sin, or antigenic sin. When you're first infected as a child or you're vaccinated before you've been infected, this may set your immune system up with a permanent memory. Then the immune system may not be that effective when it encounters viruses that are not the same as the first strain or when you get a new vaccine. There's a great deal of research going on in this area right now. We think there's reasons to believe we can find a combination vaccine that would be much more effective. But I would say we're at least 5 to 8 years off before we're going to have really any convincing data that we're on to something different.

**JAMA:** So this is an issue of scientific complexity rather than complacency?

**DR OSTERHOLM:** It's a combination of both. We have known what we need to do to better understand this for the last 5 to 7 years, but very little was done. Now, globally, we're beginning to take that on and I think we have some real momentum. But it's going to take a substantial investment, and it's going to take a business model that works, too. We have a number of pharmaceutical companies around the world that have invested heavily in the current egg-based technology and to some degree a cell-culture technology using the same antigens. That will have to be in some ways eliminated and new technologies brought on, which is not going to be an easy business model to put forward. So it's a combination of we need much better science, but we also are going to have to figure out the business model. It will be worth it to do that work and make that kind of investment because just 1 flu pandemic will result in trillions of dollars of lost income and death and severe morbidity if we don't do it.

**JAMA:** Of all the microbes that could cause widespread harm, where does influenza rank?

**DR OSTERHOLM:** To put influenza into some perspective, there really are only 2 disease categories today that really have the ability to wreak havoc on the global society, both in terms of number of severe cases and deaths as well as economic disruption. That's influenza and pandemic influenza and its antimicrobial resistance, which is coming too. Those 2 have to be at the front and center of any major effort that we put forward on infectious diseases.

**JAMA:** Should pandemic flu strike the United States, how prepared is our health care system?

**DR OSTERHOLM:** When an influenza pandemic occurs, the whole world will be involved simultaneously. If anything causes a disruption in drugs and medical devices that come here from around the world, it doesn't matter how modern our health care system is if we don't have basic drugs or equipment like mechanical ventilators that have circuits that are almost all made outside the

United States. That's where we're going to have some real challenges. The second piece is that we're going to have a lot of health care workers that are going to be put at risk for influenza by going to work. We will run out of N95 respirators very quickly. We will not have vaccine available in a timely manner in our hospitals. We won't have anywhere near enough antiviral drugs. I think we've not really tested our system yet.

**JAMA:** How do we prepare for all of these issues? Is this a matter of stockpiling drugs or gathering more equipment now?

**DR OSTERHOLM:** This is the zillion dollar question. We're never going to be able to stockpile enough drugs for this country for any kind of crisis. One of the things we have to understand is our national vulnerability to this new global sourcing of some critical medical supplies and products. That kind of research has not been ongoing. If you can only do 10 things out of 1000, what are the 10 things that are going to have the most impact? Most of what we're going to have to understand is how to move civil society through day after day when we have a major pandemic. During the 2014-15 Ebola epidemic in West Africa, it only took 2 cases of Ebola in the United States to cause a crisis.

**JAMA:** You've mentioned so many things we need to combat a potential epidemic or pandemic. What barriers are currently standing in our way?

**DR OSTERHOLM:** I would like to say that these barriers are just short-lived challenges, but we have a science literacy issue today where so much antiscience has become the mainstay for how we make decisions. You can't do anything about improving your status and response to any of these issues if you don't have a population that is willing to support them. We used to talk about vaccine hesitancy where people were reluctant to get vaccines. Today it's much greater than that. It's a hesitancy to adopt any kind of science-based approach.

**JAMA:** Is there a top myth about flu or flu pandemics that you'd like to dispel?

**DR OSTERHOLM:** I think people believe that because you can go on the internet and order something from Amazon and it's here tomorrow, that anything we need in the medical care field will be available in equal speed. We don't have stockpiles of anything beyond a limited supply the US government has of some medical products, which would be quickly exhausted if we are in a real pandemic. We have to anticipate these things, and we have to have plans. Right now, anticipation is the word that probably applies to the next 12 hours. What we need to understand is that it has to apply to the next 10 to 15 years. ■

Listen to our podcast to hear Dr Osterholm speak about flu pandemic preparedness, flu vaccines, and much more.

**Note:** Source references are available through embedded hyperlinks in the article text online.

The JAMA Forum

# Extending the User Fee Approach to Pharmaceuticals

David M. Cutler, PhD

A central theme in economics is that people who benefit the most from a good or service should pay more for it. If a government decides to build a highway connecting 2 cities, charging a toll to users of the highway is preferred to financing the road through general taxation.

I think of the highway toll example in considering the pharmaceutical industry. The federal government provides many services that disproportionately benefit pharmaceutical firms. Most of these services are paid for by the public at large, through income and other taxes. In effect, we charge everyone for benefits realized by a few. Far more efficient would be to follow the highway example and charge pharmaceutical companies for the services they disproportionately receive. In this piece, I outline and propose user fees for 3 specific public policies.

## Precedent for the User Fee Approach

A precedent for the user-fee model is the Prescription Drug User Fee Act, or PDUFA. In the late 1980s, pharmaceutical firms and groups advocating on behalf of people with certain diseases (especially groups representing people with HIV/AIDS) were upset that review times for drug candidates at the US Food and Drug Administration (FDA) were so long—29 months on average. Such long review times meant lost sales for pharmaceutical companies and delayed access to potentially lifesaving medications for patients.

**Proposed User Fees for Pharmaceutical Companies**

| Area | Approximate Annual Fee, US $ Million |
|---|---|
| Current program | |
| US Food and Drug Administration approvals (Prescription Drug User Fee Act payments) | 916 |
| Potential new programs | |
| National Institutes of Health training fee | 125 |
| Academic detailing fee | 500 |
| Comparative effectiveness fee (Patient-Centered Outcomes Research Institute) | 500 |
| Total | 1 125 |

In response, the FDA and pharmaceutical companies agreed to create PDUFA. Under PDUFA, pharmaceutical companies pay money to the FDA, which allows the FDA to hire additional examiners. The FDA agreed to standards for review times, and the US Congress agreed that it would not reduce the federal contribution to the FDA. PDUFA is generally viewed as a success; review times have decreased to just more than 1 year, and pharmaceutical payments total nearly $1 billion annually.

## Extending PDUFA

The table outlines 3 additional areas to which the principles of benefit-related payment could be applied. I provide rough estimates of the amounts that might be collected, although the proper amount for each would clearly be a matter for discussion.

*Researcher Training Fee*. The National Institutes of Health (NIH) contributes about $350 million annually in support of the