Zika: The Unexpected Pandemic

World remains unprepared as novel pathogens just keep coming 

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No one really saw Zika virus coming or cared much if it did.

In general, it has been regarded "clinically inconsequential," Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, told *MedPage Today* -- so much so that it wasn't even on a recent World Health Organization list of pathogensthat need urgent research to prevent epidemics.

And -- absent its apparent association with a spike in cases of microcephaly in Brazil -- it probably still would be thought of as a minor nuisance, experts told *MedPage Today*.

But Zika virus illustrates a worrisome fact -- the pace of emerging infectious diseases is both increasing and unpredictable.

Mild Illness

Zika is a flavivirus, discovered in 1947, that is carried mainly by the mosquito *Aedes aegypti*. It causes a mild, self-limiting febrile illness in 20% to 25% of the people it infects; most people would never know they had it.

Until recently, it was pretty much confined to its ancestral home in Africa. Then in 2007 it was found in Micronesia and in 2013 ongoing transmission was documented in French Polynesia.

Early last year, it made its appearance in Brazil and it now appears to be established in 20 countries or territories in the Americas, including Puerto Rico.

Given that much of the region also has endemic dengue fever and chikungunya -- with similar but more serious symptoms and also carried by *A. aegypti* -- the appearance of Zika virus was originally just recorded with the notation that it would be nice to know more about these concurrent infections.

Then in September 2015, reports emerged of a spike in cases of microcephaly in the region of Brazil where the outbreak of Zika had been noted. It was an alarm bell, even though there's still no definitive proof that Zika infection causes microcephaly.

"Microcephaly is obviously where the significant global public health concern is," according to Michael Diamond, MD, PhD, of the Washington University School of Medicine in St. Louis.

But, he told *MedPage Today*, there have also been reports of a spike in Guillain-Barré syndrome during the Polynesian outbreak. Again, it's an association with nothing to prove that Zika was responsible.

Still, there are now two clinical syndromes that have appeared at the same time as a Zika outbreak. It might be coincidence but health officials are urging precautions anyway.

And it's yet another instance of a pathogen emerging from the shadows.

'Emerging' Pathogens?

The term "emerging diseases" is widely used but it's often bit of a misnomer. Many such pathogens are bugs that have moved into new places, while a few are actually novel. In the latter group, put HIV, SARS and MERS. But Zika -- like dengue, chikungunya, and West Nile virus -- is a traveller.

Previously known or not, the list of such pathogens has grown in recent years. Consider a partial list: West Nile in 1999, SARS in 2002, the H1N1 pandemic influenza in 2009, MERS in 2012, Ebola in 2013, chikungunya in 2013.

And now Zika.

Is the apparent increase real? If so, what's causing it? And what can we do?

The answers, experts told *MedPage Today*, are:

- Yes, it's probably a real phenomenon
- It has multiple causes
- And while there are steps we can take to minimize the effects -- if we have the will and the cash -- emerging diseases are going to be a continuing problem

"We're definitely seeing more, there's no question about it," according to James LeDuc, PhD, director of the Galveston National Laboratory.

And it really shouldn't be a surprise, he told *MedPage Today*: The National Academy of Sciences warned in 1992 that infectious disease had not been conquered and that -- as a consequence of human activities -- we were likely to see more and more pathogens spreading beyond their ancestral ranges.

The causes, that 1992 report said, include:

- Increasing human populations, often pushing into new places and coming in contact with new pathogens
- More and faster travel
- Growing urbanization
- Erosion of some traditional public health infrastructure, such as mosquito control programs

To those, we might have to add climate change, LeDuc said. For some of the mosquito-borne diseases especially, climate change might expand or move their ranges, as temperate regions become semi-tropical.

What propels Zika into the headlines is the link with birth defects. And however nuanced health officials try to be -- it's only an association, we still need more research, there might be other causes -- just making the link creates fear.

"We're still trying to figure out what's going on with Zika and microcephaly," commented Heidi Brown, PhD, of the University of Arizona in Tucson. That's going to take a lot of study and some time.

Put simply, an outbreak of disease needs three pro-conditions, Brown told *MedPage Today*: "You need the vector, you need the virus, and you need a human population that is susceptible."

In the case of Zika, as well as dengue fever and chikungunya, the vector is *A. aegypti*, a mosquito that historically was implicated in the spread of yellow fever. In the early part of the last century, huge public health programs aimed to eradicate *A. aegypti*, with some success at reducing yellow fever.

But it's the fate of successful public health programs to wither once they've achieved success and *A. aegypti* has made a comeback.

And, Brown said, *A. aegypti* is an "urban mosquito" -- it likes to feed on people and to breed in the pools of standing water we all-too-often leave around our dwellings. The increasingly large cities of South and Central

America, usually with slums where people can't afford window screens or other protection against mosquito bites, offer a huge pool of targets.

Then an outbreak is just one plane ride away. "It's very easy now for an infected person or an infected mosquito to move from one area to another," Diamond said.

Of course, local conditions play an important role. Fauci told *MedPage Today* that it's unlikely Zika will make huge inroads into the U.S. for two reasons. In the first place, most of the country has a severe enough winter to cause the mosquitoes to die off. And second, he said, "we can do vector control if we want to do vector control" -- a capability that some other countries in the Americas don't have.

Other experts noted that our cities are less densely populated than those in South and Central America and conditions are better -- there's air conditioning and household screens.

The same applies to other pathogens carried by *A. aegypti,* like dengue. But not every pathogen needs a mosquito. It's still not clear what is the animal reservoir for Ebola, for instance, but in the recent epidemic, the vector was good old *Homo sapiens*. And other pathogens have intermediate hosts that don't necessarily die off in the winter.

If the pathogens are likely to keep coming, what can we do? Slowing the pace and speed of travel is a nonstarter, we're not going to stop living in cities, and our numbers, while growth is slowing, continue to rise.

In other words, the third of Brown's triad -- the pool of susceptible people -- is going to remain.

That leaves the vector or the pathogen.

Mosquito Control

"Mosquitoes, in the end, don't contribute much to society," Diamond said, so *A. aegypti*is an obvious target if we want to prevent Zika, dengue, chikungunya, or yellow fever. And it's something we know how to do, noted LeDuc, citing the mass eradication campaigns of the 20th century.

But that effort used "armies of people," LeDuc noted. "That kind of commitment is just not economically feasible today," he said.

On the other hand, the modern age has brought new tools. For instance, Australian researchers, focusing on dengue, think they can use *Wolbachia*, bacteria found in many insects, as a way to reduce the ability of *A. aegypti* to transmit viruses.

And the Brazilian city of Piracicaba is working with a British company, Oxitec, to release male mosquitoes genetically modified so their offspring don't survive. The males don't bite, so they can't transmit disease, but if they outcompete normal males for mates, the net result would be a reduction in adult mosquitoes.

A similar program to prevent screwworm among livestock has been working in the U.S. since the 1950s, Brown said, so it's not a pipe dream. But neither approach is a "silver bullet," she said, and will need to be used in combination with other approaches.

Some approaches are decidedly low-tech. Eliminate sources of standing water. Wear insect repellent if you're somewhere with mosquitoes. Ditto long sleeves and long pants. Put up bednets.

Those have the advantage that they work against all mosquito species, Diamond said, and therefore lots of pathogens.

No Help

A recurring theme in the story of emerging diseases is that there are no specific treatments and no vaccines. And if you think about it, that makes perfect sense -- if we don't know something is coming (because it's emerging, after all), how can we have a vaccine or a therapy?

So consider the current Zika outbreak. Most people working in the field would not have predicted it for the next viral epidemic in the Americas and if they had would not have been especially worried.

"It took a lot of people by surprise and they were perhaps a little bit dismissive," Brown said.

Other pathogens -- Lassa fever, Rift Valley fever, Marburg, and MERS among them -- might well have been higher on the priority list. Indeed, they are higher on the WHO's blueprint for future research into epidemic prevention.

And who pays for the research? It's not as if there is a huge commercial market for a vaccine or treatment for Zika, which in most cases causes mild or no illness. There might be a better market for other pathogens but how do you know where to focus?

The problem with vaccinology in this field, LeDuc said, is that vaccines generally have to be pathogen-specific and they are costly to develop. They're also technically challenging; work on a dengue vaccine has been going on for years, he noted. That said, Fauci commented, researchers on West Nile virus have developed a "platform" for a flavivirus vaccine that might be quickly adaptable to Zika. The issue then would be getting it through the regulatory hurdles and into the field -- a long expensive process.

Even if a vaccine were available, how would it be used?

Writing with a colleague recently in the *New England Journal of Medicine*, Fauci noted that outbreaks are unpredictable, so vaccinating a population against a given pathogen would not be cost-effective, while stockpiling a vaccine for later deployment might be too slow to stop an epidemic. And, of course, both approaches depend on knowing the pathogen is there or on its way.

The Ebola epidemic, which left thousands dead in West Africa, was missed for months because health officials in the region weren't expecting it and didn't recognize it when it arrived. In the case of Zika, the silent circulation of the virus in asymptomatic people makes it hard for surveillance systems to pick it up. Then there's treatment.

Broad-Spectrum Antivirals?

There is a specific therapy for just a handful of viruses, Diamond noted: hepatitis C, HIV, herpes simplex, and influenza. Such drugs are not easy to develop, especially in the throes of reacting to a crisis. But LeDuc, for one, is "quite optimistic" that broad-spectrum antivirals can be developed. "The more we understand how pathogens cause disease," he said, "the more we see common pathways" that might be avenues for intervention.

Once again, though, we run into the issue of getting drugs to people when they need it. Even if a Zika treatment were available, the vast majority of infected people would not take it because they would never know they were infected. "One of the biggest challenges is diagnosis -- and early diagnosis -- so that we have a chance to intervene," LeDuc said.

Mug's Game

So what's next?

Predicting the next outbreak is a mug's game, as the case of Zika illustrates. "There are many viruses that could emerge," Diamond said, but whether they do or not depends on a host of variables, such things as the presence or absence of a vector and the titer needed to cause infection.

But the world could do better at being prepared, he said. "You can be reactionary or you can be proactive," Diamond said. The reactionary approach is to wait until something happens and then wheel out the fire trucks to put out the blaze. But we'd be better off, Diamond said, investing in "ways to make your house fireproof."

Those investments would certainly include better surveillance, drugs, and vaccines, he said. But first on the list, Diamond said, should be basic research on the nature of viruses so that we are "prepared to deal not just with the pandemic du jour but to really respond to any virus that comes up."