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FEATURE

INFECTIOUS DISEASES

Convicting Zika

Scientists are racing to prove that Zika virus has caused the recent spike in cases of microcephaly in Latin America. But, asks **Peter Doshi**, what might be being overlooked?

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When the director general of the World Health Organization, Margaret Chan, declared a public health emergency of international concern in February, she did so without any definitive knowledge that Zika virus was causing the spike in microcephaly cases in Brazil. The link, she said, while strongly suspected, was not yet scientifically proved.[1] The committee advising Chan recommended increased research "to determine whether there is a causative link to Zika virus, other factors, and cofactors."[2] Two months later, over 20 new studies have been published on the neurological complications of Zika infections, and while the cause of the Brazilian microcephaly cases may technically be unsolved, Zika virus remains the prime suspect.

A recent review coauthored by scientists from WHO seems to have strengthened the agency's conviction.[3] Highlighting a case-control study[4] of Guillain-Barré syndrome and a cohort study[5] describing fetal abnormalities among 88 women with rash during pregnancy, the review said the studies "provide evidence for a causal link." But the authors cautioned: "Most of the data summarized here derive from studies whose designs are typically classified as weak, and the data are not entirely consistent."[3] Nevertheless, WHO's actions seem to remain focused on Zika, as they were in mid-February when Bruce Aylward, WHO's executive director of outbreaks and health emergencies, declared the virus's status bluntly: "guilty until proven innocent."[6]

The stream of new studies has even convinced some scientists who had been critical of the rush to judgment. In February, Glen Armstrong, professor of microbiology, immunology, and infectious diseases at the University of Calgary, cautioned against rushing to blame Zika, noting the link was based entirely on "circumstantial evidence."[7] But in an interview with *The BMJ*, he explained that while Zika's link to microcephaly and other neurological disorders was still only a correlation, "I think the evidence is getting stronger and stronger in favour of the conclusion that the Zika virus is, if not the only major player, the major player."

Acting in the face of uncertainty

As the WHO emergency declaration makes clear, establishing the aetiological agent is an important step, but public health responses are not waiting for proof. Acts in the face of limited evidence are as old as epidemiology itself. More than a century ago in 1854, John Snow, the "father" of modern epidemiology, had the Broad Street pump handle removed to protect citizens from cholera, long before *Vibrio cholerae* became widely accepted as the causal agent.

Nevertheless, much rides on the accuracy of WHO's running assumption. Should non-infectious factors prove to be the root cause of the epidemic, or a contributory cause, the spike in microcephaly could rapidly fade from the public spotlight as richer nations begin to rationalise the tragic events of Brazil as unrelated to themselves.

Still, clarifying Zika's role may be the only way to reliably calculate the effect that reducing Zika infections should have on the incidence of neurological disorders. Microcephaly, it must be remembered, has many causes, of which Zika is potentially just one. According to WHO, these include infection (eg, toxoplasmosis, rubella, herpes, syphilis, cytomegalovirus, and HIV), exposure to toxic agents, alcohol, genetic abnormalities, and severe malnutrition during pregnancy.[8]

Further complicating the picture, established surveillance systems may be unreliable for gauging microcephaly's true epidemiology. The WHO emergency committee has noted that there is no standard surveillance case definition for microcephaly,[2] and when a Brazilian team recently reanalysed four years of perinatal data covering 16 000 births in north eastern Brazil between 2012 and 2015, they found a far higher than expected incidence of microcephaly that not only had been previously missed but also preceded the apparent entry of Zika virus into Brazil in mid-2014.[9]

"The first question to be addressed is the real incidence of microcephaly in Northeast Brazil," the researchers wrote. In addition, the authors urged the research community to consider other potential aetiological factors such as malnutrition, viral coinfections, and teratogen exposure, including drugs and

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vaccines. They noted that "most of the reported cases have occurred in low income families," a finding compatible with the recent cohort study of 88 pregnant women with rash. Karin Saines, coauthor of that study, tells *The BMJ* that although the sample size is small, seven of the 12 women with adverse fetal outcomes were classified in the study's lowest income bracket.

When does evidence turn to proof?

Whatever their suspicions, officials at WHO and the US Centers for Disease Control and Prevention (CDC)[10] have indicated a desire to withhold final judgment on Zika at least until early summer, when the neurological effects of the current Zika outbreak in neighbouring Colombia can be seen. There, WHO has reported over 2000 confirmed cases of Zika and more than 50 000 suspected cases,[11] and the CDC has announced it is conducting two case-control studies.[10]

In forming a final judgment on Zika's role, WHO has indicated it intends to follow some version of the Bradford Hill framework for establishing causality.[3] This framework, primarily concerned with epidemiological rather than laboratory data, gives nine considerations for helping judge causation, including specificity and temporality.[12] Some argue that these considerations are less rigorous than Koch's postulates, four laboratory based criteria that have served as a key reference point for over a century, although the WHO emergency committee did put these forth as an aspirational goal.[2]

New questions of an old virus

For a virus first documented in 1947, there is surprisingly far more unknown about Zika than known. Only this year did scientists confirm Zika to be neurotropic and transmitted not only through mosquito bites but also by human sexual contact.[13] Changes in the viral genome have also been confirmed, but the significance of the changes to the current outbreak remains unclear.

"Zika virus has been forgotten for many years. I have to say rightfully so. It hasn't been an issue, why make it an issue? There are so many viruses like it," says virologist Leslie Lobel of the Uganda Virus Research Institute, which owns the Zika forest where the virus was first detected in 1947. Lobel, who studies Ebola virus, says that Zika is a relatively benign virus–even given the recent outbreak in the Americas. Pointing to a recent study[14] that estimated the risk of microcephaly at around one in 100 women infected with Zika during their first trimester of pregnancy, Lobel says the risk is "quite low." He says people have forgotten about German measles: "If you got infected [with rubella] you'd have a very high risk of birth defects."

He is not the first to make the comparison. Alfonso Rodriguez-Morales, chair of the Colombian Collaborative Network on Zika (RECOLZIKA) now studying the outbreak in Colombia, told *Nature* that the risk imposed by Zika may be less than other causes of microcephaly, such as rubella and toxoplasmosis.[15] Yet in a population with no immunity, even relatively small risks can have a notable population impact, if the situation in Brazil is predictive.

There, however, lie the basic uncertainties of the medical mystery. How can one predict the future path of the epidemic without a firm understanding of Zika's role? As Armstrong puts it, "Zika virus could be the trigger, but it may be that there have to be other factors that line up with the Zika virus in order to get the microcephaly."

Whatever the case, the risks associated with Zika can be expected to decrease over time. Referring to the situation as "classic virology," and drawing a parallel with the emergence of other viruses in immunologically naive populations, Lobel said that what we are seeing with Zika is an epidemic wave in a population lacking immunity. As soon as the population gains substantial herd immunity through infection, the virus should become endemic. When this occurs, "most women will be infected when they are young," when the virus causes mild or (more commonly) no symptoms, "so they are immune by childbearing age." And even if not infected when young, substantial herd immunity among the population protects the others.

Again, Lobel mentions rubella. "German measles was not a major problem before the vaccine. It was only a problem because there were a few women who did not get it as children."

Opportunities amid tragedy

On 31 March, WHO further strengthened its suspicions, announcing "there is strong scientific consensus" that Zika virus is a cause of Guillain-Barré syndrome, microcephaly, and other neurological disorders but stopped short of saying it had reached an official conclusion.[16] Yet whether or not the virus is ultimately convicted, the world is now witnessing a new generation of children born with serious birth defects and disabilities that will last a lifetime, straining families and healthcare systems to care for their needs. Amid the tragedy may lie a rare opportunity for public health, contends Nancy Krieger, professor of social epidemiology at Harvard University. "It can't be overemphasised how fractious the relationships are [between the different specialists] that do infectious disease." Noting Zika's status as both vector borne and sexually transmitted, Krieger contends that the virus may force the "proverbial silos of public health" to learn how to work together.

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