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## The art of medicine Disease X and other unknowns

On Feb 26, 2003, Carlo Urbani, an infectious diseases specialist in WHO's country office in Vietnam, was called to the French Hospital in Hanoi to examine a grievously ill Chinese-American businessman. Johnny Chen had been admitted with severe breathing difficulties shortly after stepping off a flight from Hong Kong and was being nursed in intensive care, where x-rays revealed ominous shadows on his lungs. Fearing Chen had a virulent form of avian influenza, Urbani convinced the Vietnamese authorities to quarantine the hospital and made staff wear high-filter masks and double gowns. But the tests for avian influenza were negative and by the end of the week, 14 doctors and nurses were ill with the same respiratory symptoms as Chen. Urbani did not realise it, but he was dealing with a virus that was entirely new to medical science. Within days, the disease had spread to five other countries and WHO had given it a name: severe acute respiratory syndrome (SARS). A few weeks later, WHO would identify SARS as a new type of coronavirus, but by then both Chen and Urbani were dead and many other health workers across the globe had also been infected.

In 2018, recognising that a "serious international epidemic could be caused by a pathogen currently unknown to cause human disease", WHO added a new category to its emergency priority list: Disease X. In the taxonomy of knowledge, Disease X corresponds to what the former US Secretary of State Donald Rumsfeld infamously termed an "unknown unknown". A classic example is HIV, the virus now known to be the cause of AIDS but which, in 1980, when doctors began treating the first patients with AIDS, had never been seen to cause disease in humans.

However, AIDS was not the first time a previously unknown pathogen had caught scientists unaware. In 1976,

the US Centers for Disease Control and Prevention (CDC) had been baffled by an outbreak of atypical pneumonia at an American Legion convention in Philadelphia, PA, USA. At first, the CDC was convinced the outbreak at the Bellevue-Stratford Hotel was caused by a new swine influenza virus and convinced the Ford administration to vaccinate millions of Americans. Then, when swine influenza was ruled out, they wondered whether the Legionnaires had been poisoned with phosgene gas or a toxic metal. In fact, the culprit was a tiny bacterium, *Legionella pneumophila*, that thrives in aquatic environments, including the cooling towers of hotels. In the case of the Bellevue-Stratford, the organism had most likely been aerosolised by the hotel's antiquated air conditioning system. Later, it was realised the bacterium had been the cause of earlier outbreaks at other institutions, but because scientists lacked an appropriate stain for the organism, the outbreaks had never been solved.

Given the history of microbiology and that the past century has been littered with similar missed alarms, the only wonder is that WHO did not think to coin the term Disease X sooner. From the 1918 "Spanish" influenza pandemic—initially blamed on a bacterium rather than a virus—to the 1930 "parrot fever" pandemic, which was initially thought to be typhoid until it was discovered that parrots and parakeets harboured a tiny bacterium, *Chlamydia psittaci*, which when inhaled could cause a deadly pneumonia, to the epidemics of Ebola virus disease and Zika virus infection in the 21st century, medical confidence has been repeatedly rocked by unexpected outbreaks of infectious disease.

This is not simply because, as is sometimes argued, microbes are constantly mutating and evolving, outstripping our ability to keep pace with their shifting genetics and transmission patterns. It is also because of the tendency of medical researchers to become prisoners of particular scientific models and theories of disease causation, blinding them to the threats posed by pathogens both known and unknown. Thus, in the case of SARS, scientists' delay in realising they were dealing with a new respiratory pathogen was due in no small part to their conviction that the world was on the brink of an epidemic of H5N1 avian influenza—a view that seemed to be confirmed when ducks, geese, and swans suddenly began dying in two Hong Kong parks. In other words, the known threat of H5N1 blinded researchers to the unknown threat of SARS.

But on other occasions, it is incomplete knowledge that can confound health experts and breed false confidence. Take Zika virus infection, the mosquito-borne illness responsible for a major epidemic in Brazil and other Latin American countries in 2015–16. Scientists had known about Zika since 1947, when the virus was first isolated in Uganda. However,



Goran Tomasevic/Reuters

because Zika was thought to cause a self-limiting human illness, it was largely overlooked by medical researchers until 2015, when Brazilian women who had been infected with the virus during pregnancy began giving birth to children with microcephaly and other neurological disorders.

Similarly, in the spring of 2014, most infectious disease experts could not envision that Ebola, a virus previously confined to remote forested regions of Central Africa, might spark an epidemic in a major city in Sierra Leone or Liberia, much less across the Atlantic to threaten citizens of Europe and the USA. But that is precisely what happened when Ebola emerged from an unknown animal reservoir to infect a 2-year-old boy in southeastern Guinea, from where the virus travelled by road to Conakry, Freetown, and Monrovia, and by air to Brussels, London, Madrid, New York, and Dallas. In each case, what was known before the outbreak—that Ebola is unlikely to reach a major urban area or that Zika is a disease that causes a mild rash-like illness and is not a threat to unborn babies—was shown to be wrong.

Another lesson of these recent epidemics is that by focusing on specific microbial pathogens—whether Ebola, SARS, or Disease X—we risk missing the bigger ecological picture. Thus, it is only when tropical rain forests are degraded by clear-cutting, dislodging from their roosts the bats in which the Ebola virus is presumed to reside between epidemics, or when people hunt chimpanzees infected with the virus and butcher them for the table, that Ebola risks spilling over into humans. And it is only when the blood-borne infection is amplified by fragile health systems and poor hospital hygiene practices that it is likely to spread to the wider community and have a chance of reaching urban areas. Similarly, the 2014–15 Zika epidemic might have been averted, or its impact reduced, if municipal authorities in Recife and other Brazilian cities had provided regular water services to women living in favelas where the *Aedes* mosquito that transmits the virus breeds in uncovered water containers and other sources of standing water. Such measures would also help reduce the risk of epidemics caused by other viruses transmitted by *Aedes*, such as dengue and yellow fever.

In such circumstances, it is worth keeping in mind the view expressed by George Bernard Shaw in his play *The Doctor's Dilemma*, namely, that “the characteristic microbe of a disease might be a symptom instead of a cause”. Indeed, updating Shaw's axiom for the 21st century, we might say that infectious diseases nearly always have wider environmental and social causes, and unless and until we take account of the ecological, immunological, and behavioural factors that govern the emergence and spread of novel pathogens, our knowledge of such microbes and their connection to disease will always be partial.

In fairness, there have always been medical researchers prepared to take a more nuanced view of our complex interactions with microbes. For instance, writing at the height of the so-called conquest of infectious disease, the

Rockefeller researcher René Dubos (1901–82) cautioned against the prevailing medical hubris. “Modern man believes that he has achieved almost complete mastery over the natural forces which molded his evolution in the past and that he can now control his own biological and cultural destiny”, Dubos warned in his 1959 book *Mirage of Health*. “But this may be an illusion. Like all other living things, he is part of an immensely complex ecological system and is bound to all its components by innumerable links.” Instead, Dubos argued that complete freedom from disease was a “mirage” and that “at some unpredictable time and in some unforeseeable manner nature will strike back”. Yet for all that Dubos's writings were hugely popular with the American public in the 1960s, his warnings of a coming disease Armageddon were largely ignored by his scientific colleagues. The result was that when, shortly after his death in 1982, the CDC coined the acronym AIDS to describe an unusual autoimmune condition that had suddenly appeared in the gay community in Los Angeles and New York and was now spreading to other segments of the population, it took the medical world by surprise and sparked hysterical media coverage.

Thankfully, the lessons of AIDS were not lost on Dubos's colleague Joshua Lederberg (1925–2008), the head of Rockefeller University, who in an influential 1992 report for the US Institute of Medicine called for medical researchers to pay attention to other emerging infectious diseases. Lederberg argued that air travel and the mass movements of goods and people from one part of the globe to another had tilted the balance in favour of microbes, altering what Stephen Morse, another Rockefeller researcher, called “the rules of viral traffic”. The insight was taken up by the writer Laurie Garrett, who as a science reporter had witnessed the ravages of AIDS first-hand. Thanks to globalisation, “few habitats on the globe remain truly isolated or untouched”, she argued in her 1994 book, *The Coming Plague*. AIDS “does not stand alone”, she concluded but was a harbinger of epidemics and pandemics to come. Two decades later, the world has yet to witness a pandemic comparable to AIDS. However, with WHO and governments currently battling outbreaks of Lassa fever in Nigeria, measles in Madagascar, hantavirus pulmonary syndrome in Argentina, Ebola virus disease in the Democratic Republic of the Congo, and rising numbers of vaccine-preventable diseases in Europe this is no time for complacency. Instead, medical researchers would do well to cultivate what Dubos termed “an alertness to the unexpected” and keep in mind that too much knowledge can be as much of a trap as too little.

#### Mark Honigsbaum

[www.markhonigsbaum.com](http://www.markhonigsbaum.com)

Mark Honigsbaum is a medical historian and the author of *The Pandemic Century: One Hundred Years of Panic, Hysteria and Hubris* (2019), is published by WW Norton & Company in New York and Hurst in London.

#### Further reading

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