



years to evolve by 1%. Many animal RNA viruses can evolve by more than 1% in a matter of days. It is not difficult to understand why we increasingly see the emergence of zoonotic viruses.

We have actually been watching such dramas play out in slow motion for more than a millennium in the case of pandemic influenza, which begins with viruses of wild waterfowl that host-switch to humans and then cause human-to-human transmission. A bird virus thereby becomes a human virus. Coronavirus emergence takes a different trajectory, but the principles are similar: SARS, the Middle Eastern respiratory syndrome (MERS), and Covid-19 all apparently have their origins in enzootic bat viruses. The parallels between the two SARS viruses are striking, including emergence from bats to infect animals sold in live-animal markets, allowing direct viral access to crowds of humans, which exponentially increases opportunities for host-switching. Such live markets have also led to avian epizootics with fatal human “spillover” cases caused by non-pandemic, poultry-adapted influenza viruses such as H5N1 and H7N9. One human cultural practice in one populous country has thus recently led to two coronavirus near-pandemics and thousands of severe and fatal international cases of “bird flu.”

But these are not the only examples of deadly viral emergences associated with human behaviors.<sup>2</sup> HIV emerged from primates and was spread across Africa by truck routes and sexual practices. The origin of Ebola remains uncertain, but in 2014–2016 the virus spread explosively in West Africa in association with fear and secrecy,

inadequate infrastructure and information systems, and unsafe nursing and burial practices. Emergences of arenaviruses causing Argentine and Bolivian hemorrhagic fever are associated with agricultural practices, and Bolivian hemorrhagic fever was spread across Bolivia by road building that fostered migration of reservoir rodents. In Southeast Asia, Nipah virus emerged from bats because of the intensification of pig farming in a bat-rich biodiversity hot spot. Human monkeypox emerged in the United States because of a booming international wildlife trade. In the 1980s, *Aedes albopictus* mosquitoes were being spread globally by humans; in 2014 and 2015, we had pandemics of aedes-borne chikungunya and Zika viruses.

Major epidemics associated with human crowding, movement, and sanitary inadequacy once occurred without spreading globally — for example, interregional plague pandemics of the 6th, 14th, and later centuries; influenza pandemics beginning in the 9th century; and cholera pandemics in the late 18th and early 19th centuries. When truly global pandemics did become common — for instance, influenza in 1889, 1918, and 1957 — they were spread internationally by rail and ship. Then, in 1968, influenza became the first pandemic spread by air travel, and it was soon followed by the emergence of acute enteroviral hemorrhagic conjunctivitis spread between international airports. These events ushered in our modern epidemic era, in which any disease occurring anywhere in the world can appear the next day in our neighbor's backyard. We have reached this point because of continuing increases in the human

population, crowding, human movement, environmental alteration, and ecosystemic complexity related to human activities and creations. Cartoonist Walt Kelly had it right decades ago: “We have met the enemy, and he is us.”

Preventing and controlling future pandemic occurrences remains a global priority.<sup>4</sup> With Covid-19, are we seeing a replay of 1918? Although we did not “witness” the beginning of the 1918 pandemic, evidence suggests that wherever it began, it silently spread around the world, causing mostly mild cases but also mortality of 0.5 to 1% or higher — a rate that was initially too low to be detected against a high background rate of death from unrelated respiratory illnesses. Then it suddenly exploded in urban centers almost everywhere at once, making a dramatic entrance after a long, stealthy approach. We are now recognizing early stages of Covid-19 emergence in the form of growing and geographically expanding case totals, and there are alarming similarities between the two respiratory disease emergences. Like pandemic influenza in 1918, Covid-19 is associated with respiratory spread, an undetermined percentage of infected people with presymptomatic or asymptomatic cases transmitting infection to others, and a high fatality rate.<sup>5</sup>

We are taking swift public health actions to prevent an emergence from becoming a pandemic, including isolation of patients and contacts to prevent secondary spread. But will these actions be adequate? Most experts agree that such measures could not have prevented the 1918 influenza pandemic. In fact, in the past century we have never been able to com-

pletely prevent influenza spread at the community level, even with vaccination and antiviral drugs. The problem is that most influenza cases are either asymptomatic, subsymptomatic, undiagnosed, or transmitted before the onset of symptoms. Can we do better with SARS-CoV-2, a virus with a presumably longer incubation period and serial generation time, but with an as-yet-undetermined ratio of inapparent cases to apparent cases and an unknown rate of asymptomatic spread? The answer to this question is critical, because without the ability to prevent such spread, we will cross a threshold where pandemic prevention becomes impossible. And we won't know that we have arrived there until it is too late.

With luck, public health control measures may be able to put

the demons back in the jar. If they do not, we face a daunting challenge equal to or perhaps greater than that posed by the influenza pandemic of a century ago. As the late Nobel laureate Joshua Lederberg famously lamented about emerging infectious diseases, "It's our wits versus their genes." Right now, their genes are outwitting us by adapting to infectivity in humans and to sometimes silent spread, without — so far — revealing all their secrets. But we are catching up. As we push ahead, we should take heart in the Hesiod version of the Pandora myth, in which Pandora managed to prevent a single escape: "Only Hope was left . . . , she remained under the lip of the jar, and did not fly away."

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