

**MEDICAL EDUCATION: PEER-REVIEWED ARTICLE**

**Five Things Clinicians Need to Know About Zoonotic Viral Spillover and Spillback**

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**Abstract**

Since the 1990s, multiple infectious diseases have “spilled over” from nonhuman animals to infect humans and cause significant global morbidity and mortality. Despite efforts to detect and respond to such threats, surveillance and mitigation efforts have been criticized as ineffective. This article describes what “spillover” and “spillback” events are and canvasses 5 ways in which clinicians can improve emerging microbial pathogen, especially viral, detection and containment responses.

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**Viral Zoonoses**

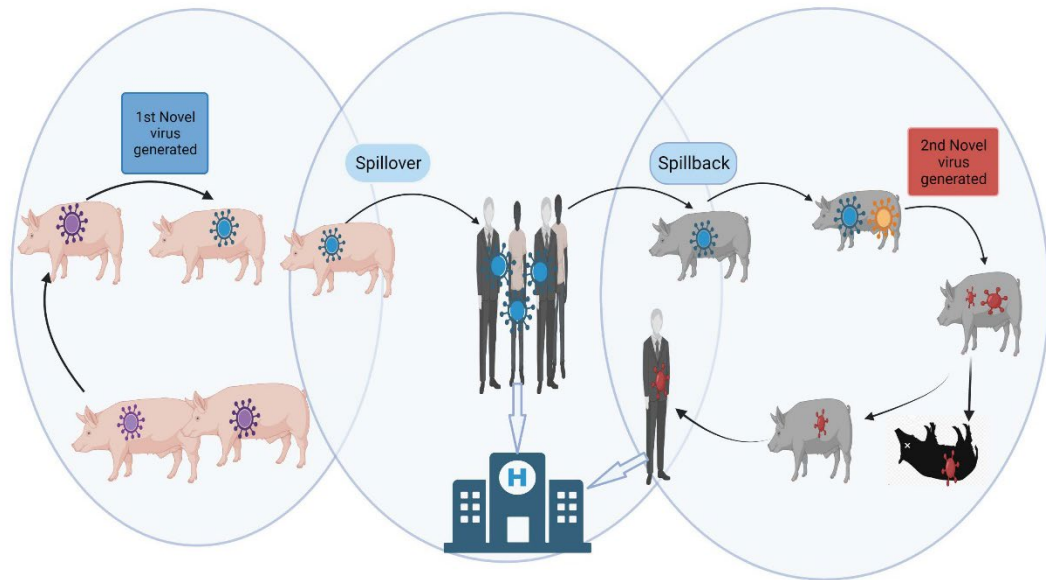
During the last 25 years, it has been painfully evident that modern medicine, despite all its remarkable advances, is woefully unprepared for epidemic threats, especially **viral zoonotic threats**.<sup>1,2</sup> One need only examine the recent human morbidity from epidemics of West Nile virus (2002-present),<sup>3</sup> SARS-CoV-1 (2002-2003),<sup>4</sup> Marburg virus (2004-2005),<sup>5</sup> H1N1 influenza A pandemic virus (2009-2010),<sup>6</sup> MERS-CoV (2012-2019),<sup>7</sup> H7N9 avian influenza virus (2017),<sup>8</sup> ebolavirus (2013-2016),<sup>9</sup> Zika virus (2013-17),<sup>10</sup> yellow fever virus (2016-2017),<sup>11</sup> Lassa virus (2018),<sup>12</sup> and SARS-CoV-2 (2019-present)<sup>13</sup> to affirm this position. Part of the difficulty in preventing such zoonotic viral epidemics is a lack of understanding of the nature of these threats. Here, we summarize observations on zoonotic viral spillover and spillback that we believe every clinician should know. Having this knowledge will aid clinicians in sounding a public health alarm should they be among the first to witness a new zoonotic emerging infectious disease problem.

**Definitions**

The following concepts are key to understanding the nature and scope of zoonotic threats.

- **Infection.** Porta et al define infection as “the entry and development or multiplication of an infectious agent in an organism, including the body of humans and animals.”<sup>14</sup> Infections do not always cause signs and symptoms of disease.
- **Zoonosis.** Any disease that can be transmitted from nonhuman animals to humans, or from humans to nonhuman animals (reverse zoonosis).<sup>15</sup>
- **Emerging infection disease.** An infectious disease that has newly appeared in a population or has existed previously but is rapidly spreading in terms of either the number of people infected or the geographical areas affected.<sup>16</sup>
- **Spillover.** Microbe transmission “from one species (usually the reservoir but potentially an amplifying or bridge host) to a novel, susceptible species, establishing infection in this individual new host”<sup>17</sup> (see Figure 1).
- **Spillback.** A specific case of spillover when a microbe spills from a new host back to the original host (see Figure 1).<sup>17</sup>
- **One Health.** The Association Veterinary Medical Association defines One Health as “The integrative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and the environment.”<sup>18</sup>

**Figure 1.** Virus Spillover and Spillback



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Abbreviation: H, human hospital.

A novel virus (blue virus) emerges in pigs and is transmitted to humans in a spillover event. This virus is amplified in humans and spills back to another group of pigs. In this second group of pigs, the virus mixes with other swine viruses and changes yet again (red virus). This new virus has the potential to cause new morbidity in both pigs and humans.

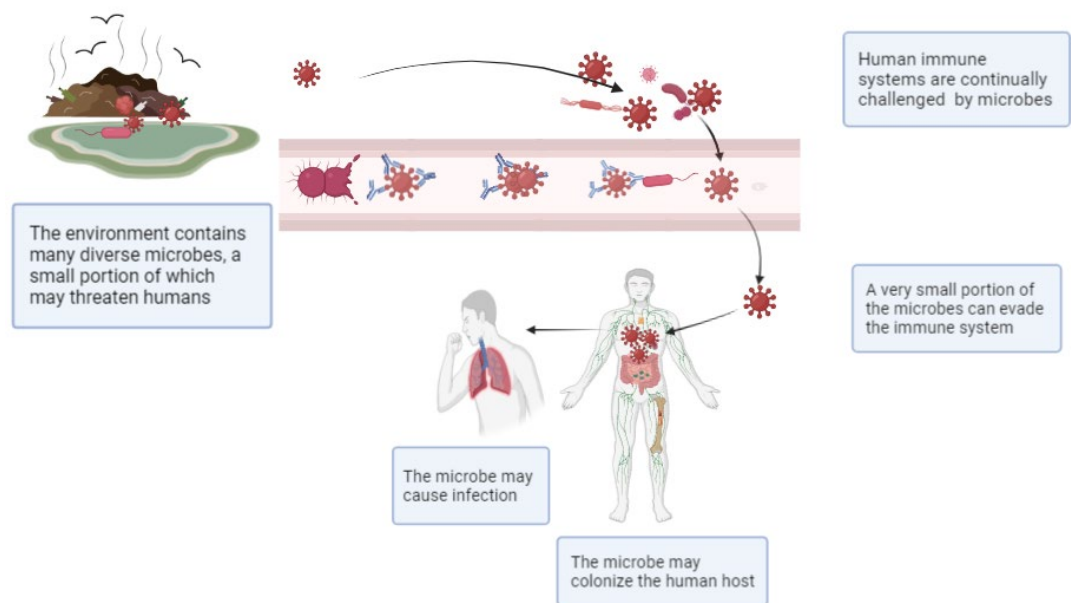
### Lesson 1: Viruses Are Everywhere

We are continually challenged by viruses from both outside and within our bodies.

Viruses of many kinds surround and threaten us, yet relatively few have the capacity to cause disease (see Figure 2). Exact counts of unique viruses or measurements of total viral mass are not available, but it is agreed that viruses greatly outnumber bacteria and that viruses can infect all forms of life, including bacteria and single cell organisms. It has been estimated that there are more than 10 nonillion ( $10^{30}$ ) individual virus particles on earth,<sup>19,20</sup> which is said to exceed the number of stars in the universe.<sup>21</sup>

Scientists have estimated that each of us harbors more than 380 trillion individual viruses living on or inside our bodies,<sup>22</sup> most of which do no harm. These difficult-to-comprehend figures are tempered somewhat when one recognizes that a high proportion of viruses in these estimates are copies of the same virus. Nevertheless, estimations of counts of unique viruses are also astounding. For instance, considering just mammals alone, it has been estimated that the earth currently has 5291 unique species of mammals, which in total harbor roughly 40 000 unique species of viruses.<sup>23</sup> Approximately 10 000 of these viral species are thought to have potential to cause illness in humans (ie, they are zoonotic).<sup>23</sup> Given the large number of diverse viral threats both outside and within a human host, one should marvel that our human immune systems are so effective in preventing viral disease.

**Figure 2.** The Human Immune System Prevents Most Microbial Assaults From Causing Infection



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Humans live in environments that contain trillions of microbes. Our bodies are extremely effective in preventing infections from the vast majority of these microbes. Nevertheless, a small percentage of these microbes can invade our body and cause disease.

## Lesson 2: Extant Medical Diagnostics Can Miss Clinically Important Viral Infections

Modern viral diagnostics are finely tuned to be both sensitive and specific with respect to previously recognized viral pathogens. When previously recognized viruses change or never-before-detected viruses emerge to cause disease, they are often missed by routine clinical diagnostics, as illustrated recently by delays incurred in developing and making widely available viral diagnostics for the A/(H1N1)pdm09 virus<sup>24</sup> and some novel emergent coronaviruses. Fortunately, modern laboratory diagnostic science is reducing these delays. For instance, in 2003, it took approximately 5 months for the newly emergent SARS-CoV-1 to be identified and sequenced, such that molecular diagnostics could be developed.<sup>25</sup> In contrast, in 2019, SARS-CoV-2 was sequenced approximately 3 weeks after visualization with electron microscopy.<sup>25</sup> Nevertheless, in January and February 2020, 6 European laboratories reported delays of up to 2 weeks in implementing molecular diagnostics for SARS-CoV-2 due to contaminated material,<sup>26</sup>

and by June 2020, these diagnostics were still not widely available in low- and middle-income countries in Africa and South Asia.<sup>27</sup> Hence, clinicians are wise to recognize that a negative clinical diagnostic assay—even a multiplex molecular assay—does not necessarily rule out infection from a targeted virus that has changed or a never-before-characterized virus.

### **Lesson 3: All Viral Spillovers Are Not the Same**

In a 2018 report, Carroll et al estimated that there were 1.67 million as-yet-undiscovered viruses in mammal and bird hosts.<sup>28</sup> As much of the microbial world is yet to be discovered, we need to develop tools to make those discoveries, especially for microbes that have just spilled over to infect humans but are not yet efficient in causing human-to-human transmission.<sup>29</sup> Detecting a pathogen in early spillover and mitigating transmission before it further adapts to humans could prevent human epidemics.<sup>29,30</sup> Special surveillance strategies and special broad diagnostic approaches are needed to pick up such viruses before they become problematic.

As there are many possible viral threats, it would be strategic to focus on viruses with the greatest spillover risk to humans. However, rates of virus spillover and spillback are largely unknowable because the vast majority of occurrences are dead-end events.<sup>31</sup> Moreover, many zoonotic virus infections might not cause signs or symptoms of disease. Nonetheless, scientific teams have conducted retrospective studies of the small proportion of detected spillover events and have attempted to establish spillover risk scores for specific viruses. One such modeling team has developed a rather compelling ranking system (SpillOver platform) for animal viruses; risk factors were identified on the basis of expert opinion as well as an examination of the limited scientific evidence.<sup>32</sup> In ranking the spillover potential of 887 wildlife viruses, Grange et al observed that their model identified 12 known zoonotic wildlife viruses, including SARS-CoV-2, but also ranked a number of other wildlife viruses as having high spillover risk that had not previously been observed to infect humans.<sup>32</sup> However, in their critique of this analysis, Wille et al recently argued: “we demonstrate that the virological data on which these analyses are conducted are incomplete, biased, and rapidly changing with ongoing virus discovery.”<sup>33</sup> Given these data deficiencies, other groups rely more on expert opinion in evaluating the limited available data and in ranking viruses for risk of either spillover or the generation of human epidemics. For instance, the World Health Organization is ambitiously assembling 20 to 25 groups of experts to review and prioritize viruses in numerous viral families for their epidemic and pandemic risk.<sup>34</sup>

Such data-centric and expert panel reviews have generated considerable debate on how best to conduct surveillance of spillover- and spillback-prone viruses. Some scientists have embraced a broad viral discovery approach with a central focus on studying the genetic characteristics of wildlife viruses.<sup>28</sup> Other scientists argue that surveillance would be better focused on performing **One Health-related studies** in geographical areas of previous emerging infectious disease risk where humans are in close contact with dense populations of animals.<sup>2,29,30,35,36,37</sup> For example, the first author (GCG) and colleagues were fortunate to partner with Chinese scholars in simultaneously studying Chinese pig workers, pigs, and pig farms for evidence of influenza A virus spillover from pigs to humans. We found that immunologically naïve swine workers had markedly increased risk of infection with swine influenza viruses.<sup>38</sup>

Whatever the logic, many experts agree that surveillance tools should focus on detecting novel viruses from families of viruses at risk of spilling over to humans and causing

disease and subsequent epidemics. Some argue, like the first author (GCG) and colleagues' research team, that respiratory viruses are the highest priority because they spread rapidly and are difficult to control.<sup>29,36,39</sup> A number of viral families have a history of causing respiratory disease epidemics: *Orthomyxoviridae* (contains influenza viruses), *Coronaviridae* (contains coronaviruses), and *Paramyxoviridae* (contains parainfluenza viruses).<sup>29,36,40</sup> To these we add *Adenoviridae* (contains adenoviruses), *Pneumoviridae* (contains respiratory syncytial virus and human metapneumovirus) and *Picornaviridae* (contains enteroviruses and rhinoviruses), as each of these viral families has been responsible for additional human respiratory virus epidemics.<sup>39</sup> Other short lists of important human-disease-causing viral families include *Bunyavirales* (contains hantavirus), *Filoviridae* (contains ebolavirus), *Flaviviridae* (contains dengue and yellow fever viruses), and *Togaviridae* (contains Sindbis virus).<sup>40,41</sup> Recently, Valero-Rello and Sanjuan studied a database of 12 888 virus-host associations (comprising 5149 viruses and 1599 host species) and concluded that enveloped viruses are more likely to spill over to new species.<sup>42</sup> No matter the specific viral families included in novel virus surveillance efforts, better viral discovery diagnostics are needed to detect specific viral spillover threats within these viral families such that future human epidemics could be averted.

With awareness that spillover events are not homogeneous, clinicians can help detect spillover events by being vigilant and considering novel zoonotic spillover as a possible cause of unusual signs and symptoms in their patients, especially those with intense occupational exposure to animals. Simply asking the question, "Could my patient be suffering a spillover or spillback novel virus infection?" could be the first step in novel virus discovery.

#### **Lesson 4: Viral Spillback Is a Global and Domestic Public Health Threat**

Zoonotic viruses that cause disease in humans can spill over to other animal populations, mutate or recombine, and spill back to humans, causing additional disease outbreaks. While the movement of the A/(H1N1)pdm09 virus from humans to various animal species, especially pigs, has caused considerable alarm,<sup>45,43</sup> it is the generation of novel variants of SARS-CoV-2 in these new animal hosts that is of most concern. As of August 23, 2023, human-adapted SARS-CoV-2 had infected at least 34 unique animal species in 39 countries.<sup>44,45</sup> Current evidence suggests that SARS-CoV-2 has adapted to new mink and white tail deer hosts and at least some mink-associated novel variants are capable of spilling back to humans.<sup>46</sup> Although current evidence suggests that pigs<sup>47,48,49,50,51,52,53</sup> and cattle<sup>54,55,56</sup> are not routinely susceptible to infection with circulating strains of SAR-CoV-2, were SARS-CoV-2 strains to adapt to infect livestock, other circulating strains of enzootic coronaviruses in livestock might increase the risk of novel virus generation through recombination. When confronted with a patient with unexplained illness and negative diagnostic tests, clinicians are wise to ask questions about a patient's exposure to animals and to consider animal pathogen involvement in the patient's signs and symptoms.

#### **Lesson 5: Clinicians Have Obligations to Be Knowledgeable, Vigilant Agents of Detection**

We currently only detect a small proportion of spillover events, and often, when we do, it is too late to take public health action. We need to adopt strategies to detect spillover events when and where they arise. Clinicians need to be vigilant and engage public health officials (locally, regionally, and, if necessary, through national or international reporting networks such as PROMED<sup>57</sup> and GOARN<sup>58</sup>) when they have suspicions that the populations they serve might be experiencing spillover or spillback events. While one

might argue that the A/(H1N1)pdm09 virus and SARS-CoV-2 spread so rapidly and efficiently that early warning would not have made much of a difference, other spillover events might be more amenable to public health intervention, as the majority of spillover viruses need considerable time to circumvent numerous immunologic barriers<sup>36</sup> to fully adapt to their new human host.<sup>29</sup> Recently, G.C.G. and colleagues<sup>49</sup> and other research teams<sup>59,60</sup> detected novel animal coronaviruses among humans with acute respiratory disease in several geographical areas.<sup>61</sup> It seems likely that these spillover viruses have not yet sufficiently adapted to their new human hosts to cause efficient human-to-human transmission. Such viral detections afford opportunity for the development of targeted molecular diagnostics to ascertain viral ecology and stop virus transmission. Given appropriate pan-species diagnostics,<sup>29,62</sup> a **vigilant health care professional** might sound an early alarm and engage public health authorities, who might then take measures to mitigate the threat before the virus has fully adapted to humans.

### Responding to International and National Vulnerability

Recent epidemics have demonstrated how novel zoonotic respiratory viruses can cause widespread human infections. We have reviewed the important concepts of zoonotic virus spillover and spillback, seeking to inform clinicians of the important roles they may play in detecting novel viruses and helping to reduce such viruses' spread.

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