Human-Animal Infections: A Primer for Clinicians

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MERS-CoV Leaves the Belfry

In September 2012, a 49-year-old man from Qatar was diagnosed with a case of acute respiratory syndrome with renal failure in a United Kingdom hospital. Initially seen in his home country after traveling to Saudi Arabia, he was transferred to the United Kingdom by air ambulance after 8 days in the hospital. Upon arrival in the United Kingdom, laboratory testing was done, and the presence of a novel coronavirus was confirmed.

Later testing showed that this virus was almost identical to one that had been isolated from a case reported earlier in 2012: a 60-year-old Saudi national who had died of a lung infection. More cases appeared in November 2012 after enhanced surveillance in the Middle East. As of November 2013, a total of 157 laboratory-confirmed cases of this novel virus, dubbed "Middle Eastern respiratory syndrome coronavirus" (MERS-CoV), have been reported, 66 (42%) of which were fatal.

Like the last emergent human coronavirus, severe acute respiratory syndrome (SARS), evidence suggests that MERS-CoV has a nonhuman reservoir: bats.[1] Although bats appear to be the ultimate reservoir for both of these coronaviruses, other intermediate hosts may play a role in transmitting these viruses to humans. In the case of SARS, this may be civet cats,[2] and for MERS-CoV, camels have been implicated as a possible intermediary between bats and people.

New Influenza Viruses

As MERS-CoV has been capturing attention in the Middle East, another emergent zoonotic virus has been evoking concern in China. The world has been tracking an avian influenza virus called H5N1 for the past 10 years across Asia, Europe, and Africa, in the fear that this bird strain may adapt to humans and cause a pandemic. Instead, it has caused only sporadic human cases over the past decade, almost exclusively in people who have had close contact with domestic poultry or wild waterfowl.

In February 2013, another avian influenza virus -- called H7N9 -- was found in humans in China. Since that time, this virus has been detected in 10 of China's eastern provinces, causing 137 infections and 45 deaths to date.

Meanwhile, as we were watching H5N1 and other avian viruses, a swine influenza virus adapted to humans and quickly spread around the world, causing the 2009 H1N1 pandemic.

Zoonotic Disease

All of these infections are termed "zoonotic" diseases, which means that they can be transmitted between humans and animals. More than one half of all known infections are zoonotic, as are approximately 75% of "emerging" infections (those that have been newly discovered, are found in new geographic areas, or are increasing in numbers).[3]

There are several reasons for this emergence. Sometimes, it is the result of increased surveillance for infections in particular geographic areas or high-risk populations, as was probably the case with H5N1, H7N9, and MERS-CoV. It may be a localized outbreak that spreads widely, leading to the recognition of a new pathogen, as with SARS-CoV. It could be a pathogen that has spread relatively silently in the human population, and is not recognized until it affects a group unique enough to draw the attention of physicians. This is what happened with HIV/AIDS in the early 1980s, when the then-unknown virus caused unusual infections in a specific group: homosexual men. Or, it could be a pathogen whose clinical symptoms are so extreme that they are impossible to ignore, such as outbreaks of the Ebola virus.

Global changes over the past 3 decades have allowed new infectious diseases, and particularly zoonotic illnesses, to emerge from their animal reservoirs. Changes in land use -- for example, clearance of forests or farmland, or human encroachment into areas that were previously inhabited mainly by wildlife -- are key drivers of emergence. As humans come into contact with native animal species, they also are exposed to the microbes carried by these animals, some of which can cause disease in humans.

These animals don't even have to be exotic. Change in land use in Connecticut was one of the drivers of Lyme disease emergence, when previously cleared farmland was reforested, deer populations boomed, and residences were built among these woody tick habitats.[4,5] Humans were consequently more likely to be bitten by deer ticks that had been infected by their first hosts: the white-footed mouse, which carries *Borrelia burgdorferi*, the bacterium that causes Lyme disease.

What Causes Zoonotic Emergence?

Climate change may also play a role in disease emergence, particularly in the establishment of recognized pathogens in new areas. Increasing temperatures have allowed mosquitoes to move into areas that were previously inhospitable to these insects, bringing with them their associated microbes: viruses, including dengue, yellow fever, and West Nile, or parasites, such as malaria. Ticks and their pathogens also are moving into new territories, potentially exposing expanding human populations to disease.

The globalization and intensification of our food production may also contribute to disease emergence. For any given meal, the products may come not only from several different states, but even different countries. This may make tracing the origins of foodborne disease difficult, because the origin of the ingredients or whole products implicated in an outbreak may be unknown. Farming intensification, particularly with livestock, can also amplify the exposure of animals (and their meat products) to emergent microbes, including antibiotic-resistant bacteria.

Approximately 80% of antibiotics used in the United States are given to animals[6]; as a result, bacteria that are resistant to several classes of drugs have arisen in the farming setting and can be transmitted to humans. Other types of organisms can also be generated in an agriculture setting, including reassortant influenza viruses (which can result from swine and poultry species being raised in close proximity), or animal-origin pathogens with novel virulence genes, such as *Escherichia coli* O157:H7.

Globalization also increases human travel and the movement of products. It is possible to travel to any location worldwide in approximately 24 hours -- well within the incubation period of many infectious diseases. As such, even an asymptomatic individual could transport a pathogen around the world in just 1 day. Indeed, international transportation certainly facilitated the spread of SARS from China to Europe, Australia, and Canada and throughout Asia.

In addition to humans, live animals and animal products can also be quickly transported between countries. Between 2000 and 2006, approximately 1.5 billion live animals were imported into the United States,[7] and 25 million kilograms of meat from wildlife enter through various ports. A recent study examined several shipments of imported bush meat (hunted from wild African mammals) and found several zoonotic viruses in the meat products.[8] Imported products, including live animals, are rarely inspected upon arrival, allowing for the potential introduction of zoonotic pathogens into the destination country.

Novel technology can also lead to the introduction or spread of new pathogens. In the early days of the HIV epidemic, the virus was spread through blood transfusions, and it continues to be spread by the sharing of needles (especially by persons using intravenous drugs). Early outbreaks of Ebola were likewise exacerbated by needle reuse in impoverished hospitals.

In other cases, novel technologies are in place that can detect organisms that were previously undiagnosed.[9] Researchers suggest that there may be as many as 320,000 undiscovered mammalian viruses.

Emerging and Reemerging Microbes

Microbes are also constantly evolving, which leads to an ever-expanding reservoir of pathogens. Bacteria are frequently acquiring novel genes from other isolates or species, including genes that encode resistance to antibiotics. In recent decades, we have seen the emergence and spread of novel strains of methicillin-resistant *Staphylococcus aureus*, some of which are zoonotic.[10]

Although many of these examples may seem to be rare events, or to occur internationally but not domestically, zoonotic disease can occur anywhere. Recent studies have shown that many urinary tract infections (approximately 8 million per year)[11] and cases of bacterial sepsis caused by *E coli* [12] are, in fact, caused by zoonotic *E coli* strains that evolved in poultry and pigs.

Viruses, such as influenza, are also constantly "reemerging" through the accumulation of mutations and reassortment between different strains of virus. A recent multistate outbreak of influenza was caused by a novel swine influenza virus (called H3N2v) that was transmitted between pigs and people attending agricultural fairs.[13]

Other viruses can stealthily invade through healthy intermediates. The importation of Gambian giant rats and dormice (originating in Ghana) led to a multistate outbreak of monkeypox in the midwestern United States in 2003. The African rodents, already infected subclinically with the virus, were housed in close proximity to prairie dogs, which contracted the virus and were subsequently sold as pets at flea markets or from other distributors. At least 71 human cases of monkeypox resulted from this chain of events.[14]

Other pets, including reptiles and small turtles, can harbor *Salmonella* strains that young children in particular can pick up and then become ill. *Salmonella* has also caused infections in both humans and animals as a result of handling or consumption of contaminated pet food or treats.

Adorable baby chicks from a mail-order hatchery have caused outbreaks of *Salmonella* at Easter, particularly among children.[15] An act as common as sharing a bed with your pet can spread disease between species.[16]

What Can Busy Clinicians Do?

It is safe to say that zoonotic diseases will continue to emerge. Some, such as SARS-CoV, may be explosive but then retreat into the wild. Others, such as hantavirus, may cause a slow, consistent burn, rarely causing outbreaks but sporadically infecting at-risk individuals.

Still others may steadily increase over time. West Nile virus was initially recognized in New York City in 1999, thanks to the combined work of public health practitioners, basic researchers, and veterinarians.[17] This zoonotic disease now has spread across the United States, causing human disease in 46 states in 2013.

What should a healthcare clinician do about zoonotic diseases? Acknowledging that time with each individual patient is short, obtaining information about a patient's occupation, hobbies, or other factors that could put them at an increased risk of acquiring a zoonotic infection should be considered in some cases to make a correct diagnosis, prescribe effective treatment, or adequately counsel a patient about prevention of reinfection.

Remaining up to date on zoonotic diseases enables healthcare providers to learn about what is emerging around the world, or on their doorstep. Finally, developing and maintaining relationships with local professionals in both public health and veterinary medicine allows clinicians to become familiar with common zoonotic infections in their region, and encourages a "One Health" perspective on disease diagnosis and treatment.

Although the odds are slim that you will uncover the newest SARS or "bird flu," this knowledge could result in more appropriate antibiotic treatment in patients presenting with an *E coli* urinary tract infection, or in clearing up a recurrent methicillin-resistant *Staphylococcus aureus* infection in a patient by an act as simple as treating the family cat.[3]

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