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## Chapter 9

# Antimicrobial Use and Ecotoxicological Risks from Pandemics and Epidemics

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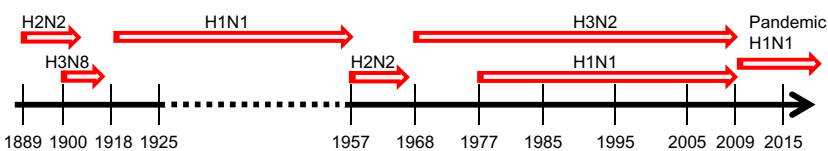
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### INTRODUCTION

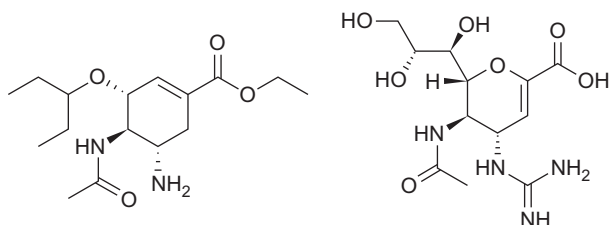
Influenza pandemics have been reported nearly every 40 years for the last 500 years. (Taubenberger and Morens, 2010) Modern influenza pandemics stand apart from those of the past because of the quantity and range of drugs available to treat primary and secondary infections, that is, antivirals and antibiotics. A new class of influenza antivirals, neuraminidase inhibitors (Alves Galvao et al., 2014), greatly improves on the largely ineffective antivirals developed in the mid-1960s (Davies et al., 1964). The large number of antibiotics in use today was not available during the last pandemic and was totally absent from the “toolbox” during the 1918 Spanish pandemic that caused the death of over 50 million people worldwide. This armory of drugs to fight infection has significant implications to not only human health but also the wider environment because of its inevitable release into the waste water through urine and feces and passage into sewage works and ultimately the rivers. The combination of huge volumes of drugs, the short span of time in which they are consumed, and the novelty of some of these drugs create a unique “downstream” risk to society, critical infrastructure, and the environment. This chapter aims to highlight rare but catastrophic events such as epidemics and pandemics and the threats they pose to the environment and human health from coordinated medical responses.

### CASE STUDY: INFLUENZA PANDEMIC 2009

Many nation states were exceptionally well prepared for the 2009 influenza A (H1N1) pandemic, but paradoxically, the pandemic came as a total surprise. The surprise came from the fact that the world had its eyes focused on the



**FIG. 1** Timeline of major influenza strains and the span of time they dominated the globe (Nicoll, 2010).

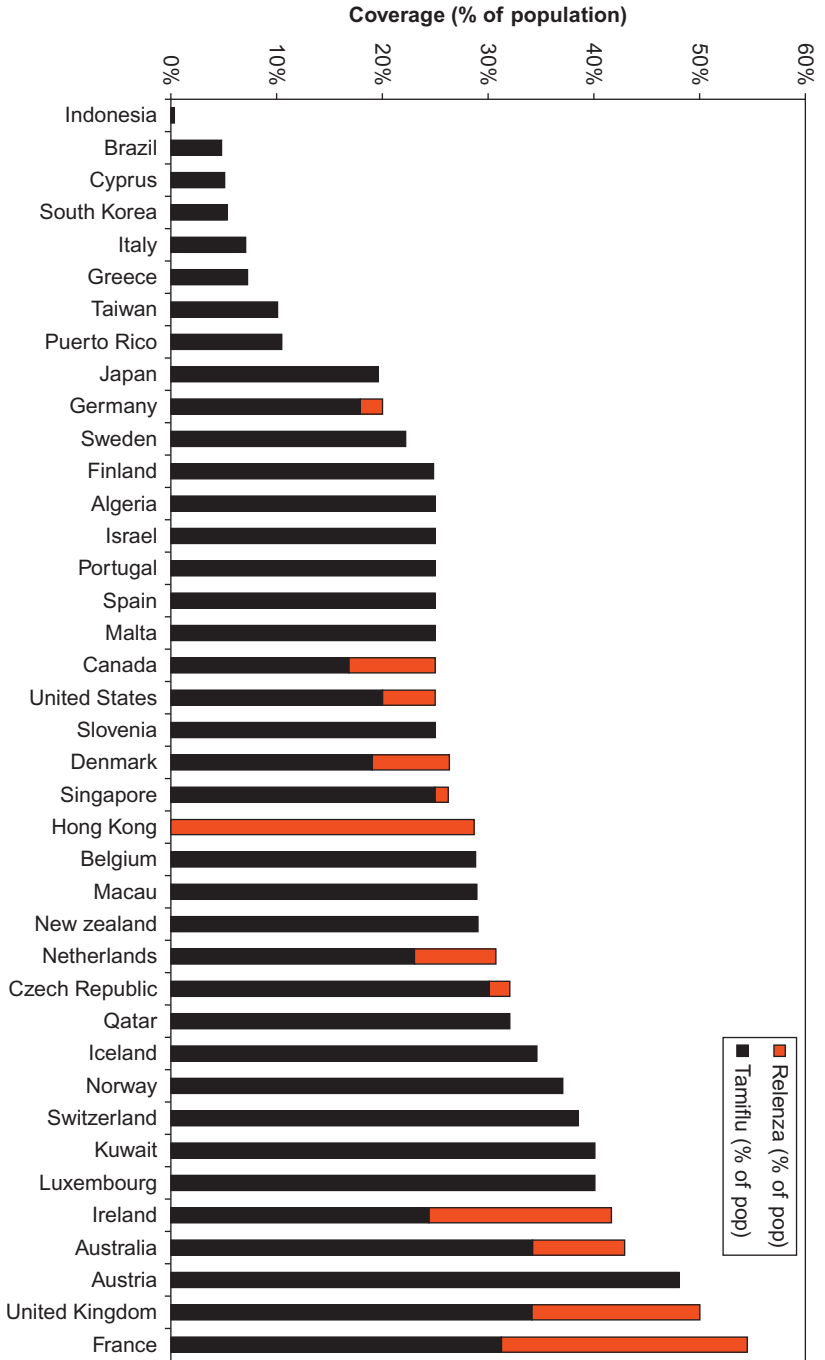


**FIG. 2** Left, oseltamivir (Tamiflu), and right, zanamivir (Relenza), the two neuraminidase inhibitors available at the time of the 2009 influenza pandemic.

highly pathogenic influenza A (H5N1) virus circulating for years in Southeast Asia since the end of the 1990s, not the influenza A (H1N1) virus that rapidly emerged out of Mexico in April of 2009 (Team PIP, 2011a). The mortality rate of the H5N1 in Southeast Asia back in 2005 was over 70%. It was this frightening mortality statistic that sparked the development and refinement of national pandemic preparedness plans (Health UDo, 2005), which included the stockpiling of antivirals. Hence, the degree to which society was prepared for the 2009 pandemic was a direct consequence of the looming threat from H5N1.

The growing problem of influenza resistance to amantadine and rimantadine, the only influenza antivirals available prior to the new millennium (De Clercq, 2006), helped spur the development of two novel antivirals, Relenza and Tamiflu (Fig. 2). Relenza (zanamivir; developed by Biota Holdings and manufactured and distributed by GlaxoSmithKline) was the first antiviral in a new influenza antiviral class called neuraminidase inhibitors (NAI). It was approved for the treatment of influenza A in the United States in 1999. The second drug in this class was Tamiflu (oseltamivir carboxylate; developed by Gilead and distributed by Hoffmann-La Roche; Fig. 2), which was also approved for therapeutic use in the United States in 1999. For those nations choosing to develop an influenza antiviral stockpile, most chose Tamiflu (Fig. 3).

A major contributing reason for the preference for Tamiflu over Relenza, speaking directly for the United Kingdom's decision to stockpile Tamiflu in lieu of Relenza, was the familiarity people had with consuming capsules (pills), as opposed to the disc inhaler used to administer Relenza (Scientific



**FIG. 3** Tamiflu (*black bar*) and Relenza (*grey bar*) stockpiles in national pandemic plans expressed in percent of population coverage (Singer and Schmitt, 2011; Singer et al., 2011).

[Pandemic Influenza Advisory Committee, 2008](#)). The risk of under- or mis-dosing using the disc inhaler was seen as a major barrier for Relenza, especially in those patients that find it hard to breathe and/or have asthma. However, Relenza was recognized as being more appropriate for children with renal insufficiency and pregnant women ([Scientific Pandemic Influenza Advisory Committee, 2008](#)). In addition, a stockpile of Relenza was seen as appropriate to prepare for the possible emergence of Tamiflu resistance. Relenza was also planned for use to prevent and treat influenza in frontline health workers at the earliest outset of Tamiflu resistance emergence ([Scientific Pandemic Influenza Advisory Committee, 2008](#)). On the balance of these factors, the United Kingdom acquired sufficient stockpiles of Tamiflu to treat 25% of the population, including prophylaxis and therapeutic prescription of the antiviral. This stockpile was further increased to cover up to 50% of the population at the outset of the pandemic ([Fig. 3](#)).

Antivirals were seen as a very important tool within pandemic preparedness plans for limiting morbidity and mortality. Preexposure prophylactic dosing was implemented to prevent infections before individuals were exposed to an infected contact, and postexposure prophylaxis dosing was implemented to prevent infections after an individual has been exposed to an infected contact. The clinical benefits acquired from antiviral treatment were maximal when given within 48h of symptom onset, most notably reducing the time to symptom alleviation by roughly half of 1 day, increasing to 1 day in cases where influenza has been confirmed by laboratory tests ([Team PIP, 2013](#)). Early treatment with NAIs compared with late treatment significantly reduced mortality in hospitalized patients by 62% ([Team PIP, 2013](#)). Antiviral prophylaxis was more than 80% effective in preventing laboratory-confirmed influenza when initiated within 48h of initial contact ([Team PIP, 2013](#)). The evidence clearly supported the widespread use of antivirals for as much of the population as could be afforded.

The benefits to society could be further enhanced during a severe pandemic with the combined use of postexposure prophylaxis, school closures, and the use of antibiotics, thereby reducing the clinical attack rate by 50% (i.e., the percentage of the whole population that becomes infected at some stage during the pandemic) and case fatality ratio by 80% (i.e., the percentage of those who become ill and subsequently die as a direct result of the illness). In the event that the influenza virus acquired reduced susceptibility to Tamiflu, it was expected that this challenge would be met by increasing the dose ([Scientific Pandemic Influenza Advisory Committee, 2008](#)). Hence, dosing would increase from the recommended dose for treatment (75 mg, twice daily, for 5 days) or prophylaxis (1 dose of 75 mg, once daily, for 10 days) to a dose to be determined empirically during the pandemic. In the event that antiviral resistance was seen to emerge, both NAIs may have been coadministered ([Scientific Pandemic Influenza Advisory Committee, 2008](#)); however, this did not occur, fortunately.

Considerable speculation in the academic community was raised about the efficacy of NAIs and whether they reflected sufficient value for money (Jefferson and Doshi, 2014). However, in the “evidence review,” the UK Department of Health writes “The research findings since the 2009-10 pandemic offer retrospective endorsement of the UK’s use of NAIs and increase the weight of evidence in favour of stockpiling for a future pandemic (Team PIP, 2013).” Hence, it should be expected that in the absence of any further innovation in influenza antivirals, that similar stockpiling will exist ahead of future influenza pandemics (assuming there is sufficient warning as we were fortunate enough to have this last pandemic).

## SECONDARY BACTERIAL INFECTIONS

An emerging point from the literature in the 2000s was the extent to which secondary bacterial infections (i.e., bacterial pneumonia) contributed to the overall death rate in the 1918 pandemic and the role it was likely to play in future pandemics (Brundage and Shanks, 2008; Gupta et al., 2008). Rates of secondary bacterial pneumonia among patients admitted to hospital with influenza have varied from 0.6% to 46% (Team PIP, 2011b). Influenza infection predisposes to secondary bacterial infection due to a combination of respiratory mucosal damage and a reduced capacity to mount an immune response to bacterial invasion (Team PIP, 2011b). Bacterial pneumonia can usually be easily treated with a course of antibiotics—a luxury that didn’t exist until the latter half of the 20th century.

The evidence prior to the 2009 pandemic strongly supported the use of NAI antivirals as it was apparent from the literature that the likelihood of requiring antibiotics was reduced by 60% if antivirals are given within 48h on the appearance of symptoms (Team PIP, 2013). Hence, an increased use of antivirals would lead to a potential reduction in bacterial pneumonia, which would translate into a reduction in antibiotic use as compared with a pandemic without the use of antivirals. The UK pandemic preparedness plans did not recommend stockpiling of antibiotics as it was felt that these drugs, which are already in high use, were already in plentiful supply (Singer et al., 2011; Lim, 2007).

## ENVIRONMENTAL RELEVANCE OF MEDICAL RESPONSE

Prior to the pandemic, influenza antivirals were not frequently prescribed; for most, influenza is a self-limiting disease. The decision to use these novel drugs during the pandemic presented a novel ecotoxicological challenge (Singer et al., 2007). Determining the quantity of antiviral to be used and developing scenarios for its potential effects within the waste water system and the wider environment became the focus of subsequent research in the late 2000s to the present day.

Unlike antivirals, antibiotics are in constant use throughout the world. One might conclude that given the widespread use of antibiotics, an increase in their prescription on the order of 1%–5% might pose a negligible increased ecotoxicological risk to sewage work operation and the ecosystem services of the wider river environment. On the other hand, given that the primary mode of action of antibiotics is the inhibition and death of bacteria, it would be reasonable to assume that there is a concentration of antibiotics, above which, one might witness the loss of microorganisms performing essential functions in sewage works and the wider environment (i.e., a tipping point). The loss of these key bacteria from increased antibiotic uses during a pandemic was (and remains) the main ecotoxicological concern from pandemic usage of antibiotics.

Most antibiotics are persistent, which is to say that most of the antibiotics that are consumed are excreted in their biologically active form (Table 1). The same is essentially true for antivirals (Table 1), with the only exception being that Tamiflu is a prodrug. Upon consumption, approximately 80% of Tamiflu is converted to the active antiviral (oseltamivir carboxylate), with the remaining 20% leaving in the feces unchanged. There is considerable uncertainty with regard to the removal rate of any one drug in any one sewage works at any one time. It is expected that both antibiotics and antivirals would reach sewage works and pass right through them with relatively minimal loss (Jain et al., 2013). Antivirals, in particular, are seen as highly resistant to biodegradation (Prasse et al., 2010) and photodegradation (Gonçalves et al., 2011; Fick et al., 2007). It is realistic to assume that antivirals could persist in the environment for sufficiently long enough to enter the drinking water system (Wang et al., 2016; Drinking Water Inspectorate, n.d.). For most modeling purposes and for predicting a realistic worst-case scenario, it is common practice to assume that sewage works and the wider environment do not result in significant loss in the drugs within the first 24 h.

Several questions arise when considering the use and fate of drugs used during a pandemic: Do the drugs persist in the sewage system? To what extent do they partition to the sludge or remain in the aqueous phase? Do these drugs have an impact on the operation of the sewage works? Do these drugs inhibit the growth and/or function of microorganisms within the receiving rivers that are important for its integrity and function? Are there acute or chronic toxicity issues relating to the exposure of aquatic organisms to environmentally relevant concentrations of these drugs? Do the drugs increase the prevalence of antiviral or antibiotic resistance in the environment with potential human health impacts? Do the drugs pose a threat to drinking water quality? Very few of these questions were addressed prior to the 2009 pandemic (Singer et al., 2008).

Evidence has emerged in the literature to suggest a mechanism by which microbial biofilms could indeed be disrupted by exposure to Tamiflu within sewage works (Singer et al., 2008; Parker et al., 2009; Gut et al., 2011;

**TABLE 1** Percentage of Parent Compound Excreted in the Feces and Urine (Singer and Schmitt, 2011)

Common Name	Total Excretion (%) <sup>a</sup>
<i>Tetracyclines</i>	
Tetracycline	91
Doxycycline	80
Oxytetracycline	35
Chlortetracycline	20
<i>β-Lactams</i>	
Floxacillin (flucloxacillin)	80
Amoxicillin	75
Clavulanic acid	38
Cephalexin	100
Cefuroxime	95
Cefaclor	85
Cefotaxime	61
Ceftriaxone	100
Imipenem	70
<i>Sulfonamide and trimethoprim</i>	
Trimethoprim	100
Sulfamethoxazole	100
<i>Imidazoles</i>	
Metronidazole	100
<i>Macrolides</i>	
Erythromycin	100
Roxithromycin	60
Azithromycin	85
Clarithromycin	55
Clindamycin	14
<i>Fluoroquinolones</i>	
Ciprofloxacin	100
Levofloxacin	96

Continued



**TABLE 1** Percentage of Parent Compound Excreted in the Feces and Urine (Singer and Schmitt, 2011)—Cont'd

Common Name	Total Excretion (%)
Norfloxacin	40
Ofloxacin	85
Moxifloxacin	100
<i>Influenza antivirals</i>	
Tamiflu-prodrug	20
Tamiflu-active <sup>2</sup>	80
Zanamivir	100
Amantadine	100
Rimantadine	100

<sup>a</sup>Total excretion includes the biologically active chemicals found in the urine and feces. In most cases, this is the same as the parent chemicals.  
<sup>2</sup>80% of oseltamivir phosphate is metabolised to the active antiviral. The remaining 20% of the parent chemical and all of the active antiviral oseltamivir carboxylate are excreted.

Slater et al., 2011). Hence, the risk of sewage work failure from exposure to elevated levels of Tamiflu during an influenza pandemic remains theoretically possible (Slater et al., 2011). The extent to which sewage works “fail” remains the next question. Total failure to treat raw sewage would mean the release of untreated sewage into the receiving rivers, some of which are the source of drinking water for major cities, such as the River Thames is for London. Such a release would result in the loss of fish and other sensitive aquatic lives downstream of any failing sewage works. It remains unclear as to the likelihood of pandemic quantities of drug resulting in incomplete treatment of sewage before discharge into the river.

Antibiotics are designed to have a biostatic or lethal effect on a wide range of microorganisms. They are thus capable of inhibiting the growth and function of microorganisms in sewage works (Singer and Schmitt, 2011; Singer et al., 2011). The degree to which this inhibition could and would be observed remains unclear as there are numerous complicating factors that make predicting inhibition of microorganisms in sewage works based on antibiotic concentrations extremely difficult to determine. All sewage works receive relatively high concentrations of a very broad mix of antibiotics all the time (Singer and Schmitt, 2011; Singer et al., 2014). This constant influx of these drugs and antibiotic-resistant microorganisms into sewage works contributes to the resilience of sewage works as much as it can contribute to the risk of its failure.

The release of the active antiviral of Tamiflu (oseltamivir carboxylate) into the receiving rivers of the world had the potential to select for antiviral resistance in wildfowl that cohabits sewage-impacted rivers (Singer et al., 2007; Fick et al., 2007). Wildfowl is attracted to the nutrient-rich, warm sewage outflows, exposing them to relatively high environmental concentrations of Tamiflu. The collocation of wildfowl and Tamiflu means that there is a risk of the avian influenza virus, naturally found in many wildfowl, to develop Tamiflu resistance. The concentration of Tamiflu predicted to be present in highly sewage-impacted rivers, such as in the United Kingdom, was expected to be sufficiently high to select for the Tamiflu-resistance gene in avian influenza, which would ultimately increase the risk of the next pandemic influenza strain containing the Tamiflu-resistance gene (Gillman et al., 2015; Orozovic et al., 2014). Application of ozonation to the sewage effluent would potentially reduce the load of antiviral released into the environment (Azuma et al., 2015); however, relatively few sewage treatment plants utilize such a treatment option, particularly in the United Kingdom, owing to the high cost and energy requirements. Few options for mitigation of the identified risks were available at the time, and little has changed since the pandemic.

In summary, the 2009 influenza A (H1N1)pdm09a virus, as it is officially called, generated a relatively small number of fatalities as compared with severe pandemics like the 1918 “Spanish flu,” which meant that the medical response was proportionately lower than would have been expected in a moderate or severe influenza pandemic (Singer et al., 2011). Hence, few negative effects to sewage work function and ecosystem services were apparent. The lack of evidence of an ecotoxicological effect might have as much to do with the fact that the research community were not looking/monitoring for such effects, as it has to do with the low pathogenicity of the pandemic influenza strain.

## PREPARING FOR THE NEXT PANDEMIC

The influenza pandemic of 2009–10 remains the only case study of a pandemic for which large quantities of pharmaceuticals were deployed worldwide within a very short time frame. One would be forgiven for thinking that pandemics are rare; however, at any one time, there is at least one ongoing. Depending on how one characterizes a pandemic, there are several right now! There are many well-known disease-causing pathogens that cause epidemics or pandemics, such as cholera, typhoid, tuberculosis, malaria, HIV, MERS, SARS, Ebola, chikungunya, and Zika virus.

Some pathogens are not prone to go pandemic for reasons that will be explained; others, despite being perfectly suited for a pandemic, have yet to go beyond an epidemic level. The following discussion is intended to raise awareness of the epidemic and pandemic risks of various high-profile human pathogens—speculate on how a pandemic might develop—and highlight some of the current treatment options.

**Cholera** is caused by a bacterium, *Vibrio cholerae*, and transmitted through unsafe water, most often contaminated with feces from others suffering or carrying the bacterium. There have been seven separate pandemics since 1816 and several notable outbreaks of cholera since 1991. Treatment for cholera can include antibiotics (doxycycline or azithromycin), but it is often not necessary if rehydration strategies are employed. It is unlikely that cholera will be anything more than an epidemic looking forward, as the availability of antibiotics is no longer limiting and suboptimal hygiene and water treatment standards can often be improved given adequate infrastructure. The biggest risk from cholera typically follows major losses in critical infrastructure, such as loss of water and sanitation following natural disasters, such as earthquakes, severe storms, or tsunamis.

**Typhoid** fever is caused by a bacterium *Salmonella typhi* and transmitted by consuming contaminated food or water and through person-to-person contact. Treatment includes doxycycline, ciprofloxacin, or a number of other antibiotics. Typhoid has a similar etiology as cholera and thus remains endemic and limited to areas of poor sanitation and water treatment (Karkey et al., 2016).

**Tuberculosis (Tb)** is currently found in every country in the world making it a global pandemic. It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis*, which represents the leading infectious cause of death worldwide (approximately 1.5 million per year). Tb is spread from person to person through tiny droplets released in coughs and sneezes, a mechanism similar to influenza. With tuberculosis, one must take antibiotics for at least 6–9 months. A sensitive strain may be treated with only one antibiotic, while a resistant strain will require several antibiotics all at once. These include isoniazid, rifampin, ethambutol, pyrazinamide, and fluoroquinolones. The emergence of multidrug-resistant tuberculosis is one of the highest priorities in international public health. With the continued loss of antibiotic efficacy as resistance spreads, there is a real threat of multidrug-resistant Tb becoming an even more severe public health threat.

**Malaria** is caused by *Plasmodium*, a parasite transmitted by the bite of an infected *Anopheles* mosquito. The World Health Organization estimates that there were approximately 198 million cases of malaria and 584,000 deaths, mostly among children under the age of five, just in 2013. Depending on the parasite, the antimalarial drugs include chloroquine, quinine sulfate, hydroxychloroquine, mefloquine, and a combination of atovaquone and proguanil (Malarone). Resistance to chloroquine has rendered the drug ineffective. The recommended treatment for malaria is currently a combination of antimalarial medications that include an artemisinin and either mefloquine, lumefantrine, or sulfadoxine/pyrimethamine. Quinine along with doxycycline may be used if an artemisinin is not available. Malaria is limited to areas where the *Anopheles* mosquito can live and reproduce, making the wider spread of this disease somewhat limited; however, the range of the mosquito

vector can expand in a changing climate, increasing the risk to regions that might have previously been free of malaria.

**Human immunodeficiency virus (HIV)** causes acquired immunodeficiency syndrome (AIDS) and is currently in a pandemic state. As of 2012, approximately 35.3 million people are living with HIV globally, with 1.8 million deaths from HIV/AIDS in 2010. HIV is transmitted from person to person through sexual contact, through blood, and during pregnancy to the child. There are several anti-HIV drugs: nonnucleoside reverse transcriptase inhibitors, which disable the protein needed by HIV to replicate (efavirenz, etravirine, and nevirapine); nucleoside or nucleotide reverse transcriptase inhibitor, which forces the HIV to make faulty copies of itself (abacavir and combinations: emtricitabine-tenofovir (Truvada) and lamivudine-zidovudine (Combivir)); protease inhibitors, which disable required protein production (atazanavir, darunavir, fosamprenavir, and indinavir); entry or fusion inhibitors that block the HIV's entry into the target CD4 cells (enfuvirtide and maraviroc); and integrase inhibitors, which prevent HIV from integrating its genome into CD4 cells (raltegravir, elvitegravir, and dolutegravir). The use of these drugs is sufficiently high that they are now among the most frequently recovered drugs in waste water of countries heavily impacted by HIV/AIDS and reach concentrations over 100 µg/L (K'Oreje et al., 2012, 2016). The implications of very high concentrations of antiviral in the environment and potentially drinking water have yet to be studied.

**Middle East respiratory syndrome coronavirus (MERS-CoV)** was first discovered in Saudi Arabia in 2012; MERS-CoV severely disrupts respiratory functions, leading to pneumonia, shortness of breath, coughing, and fever. As of July 2015, MERS-CoV cases have been reported in over 21 countries. Based on recent World Health Organization data, about 40% of reported cases have resulted in death. There is no curative treatment for MERS-CoV. Symptomatic treatment includes convalescent plasma-containing MERS-CoV antibodies (i.e., blood from patients that have raised antibodies to MERS-CoV) (Public Health England, 2015) and lopinavir (ABT-378), an antiretroviral of the protease inhibitor class that is nearly 100% bound to plasma proteins. Coadministering lopinavir with ritonavir is known as highly active antiretroviral therapy (HAART), which is also used to treat HIV/AIDS. The fact that MERS-CoV is easily transmissible and has limited treatment options makes it a serious pandemic risk.

**Severe acute respiratory syndrome (SARS)** is a viral respiratory disease caused by the SARS coronavirus that has symptoms nearly identical to influenza. SARS is a zoonosis and likely originated from infected bats that are sold as food in China, but it has since been found in several other mammals. SARS infection comes with a high risk of secondary infections such as pneumonia. SARS only emerged in 2002 and in 9 months infected 8273 people causing 775 deaths in 15 countries. Antibiotics are ineffective, as SARS is a viral disease, but much like in the treatment of influenza, antibiotics would be

employed to treat bacterial pneumonia. Much like MERS-CoV, SARS maintains a high pandemic risk.

**Ebola** is a filovirus that causes severe hemorrhagic fever with a fatality rate often near 90%. Transmission occurs through contact with infected body fluids such as blood. A massive epidemic of Ebola spread through three West African countries, Guinea, Liberia, and Sierra Leone, in early 2014 resulting in 28,602 cases and 11,301 deaths, as of early 2016. Recent research has indicated the potential for a broad-spectrum antiviral for such RNA viruses. An RNA polymerase-inhibiting molecule called BCX4430 (Immucillin-A), an adenosine analogue, is incorporated into growing viral RNA strands, preventing further RNA synthesis and therefore viral replication. The biocompatibility of this drug makes it potentially at risk of impacting environmental organisms if the drug was to be excreted intact. The ease by which Ebola is transmitted and the difficulty in treating infections make Ebola a serious pandemic threat.

**Chikungunya** is an RNA virus of the *Alphavirus* genus that causes an estimated 3 million infections each year. The disease causes sudden onset of fever with accompanying joint pains that can last weeks to years. Fewer than 1 in 1000 of infected individuals die from the disease, mostly the elderly and those with underlying chronic medical problems. The virus is most frequently transmitted from human to human within the blood carried by infected *Aedes albopictus* or *Aedes aegypti* mosquito. There are a number of animal reservoirs of the virus, including monkeys, birds, cattle, and rodents. This is in contrast to dengue, for which primates are the only hosts. There is no treatment for chikungunya other than for the fever and joint pain. There remains no vaccine for the disease. As the transmission of chikungunya requires a mosquito vector, it will remain constrained to the geographic range of the mosquito vector; however, it can still reach pandemic levels as the range of the vector is quite substantial (Kraemer et al., 2015).

**Dengue** is an RNA virus from the genus *Flavivirus*. It is transmitted via *A. aegypti* and *A. albopictus*, identical to chikungunya from human to human in the blood meal. Dengue can be found in other primates and was the original source of the dengue virus. The symptoms of dengue include high fever, headache, vomiting, muscle and joint pains, and a characteristic skin rash. The incidence of dengue has increased fourfold in the last 20 years. There are no licensed therapeutics available for treatment of dengue. Several antivirals have been investigated for their efficacy in treating dengue, including balapiravir, celgosivir, and chloroquine; however, none have shown beneficial effects on viremia or clinical outcome (Yacoub et al., 2016). The inability to control the day-biting anthropophilic mosquitoes is the main reason for the global spread of dengue (Yacoub et al., 2016). Promising avenues for breaking the transmission cycle of dengue have been to infect the mosquito with an intracellular bacterium, which reduces viral replication in the mosquitoes (Yacoub et al., 2016). The virus' reliance on a geographically restricted

mosquito vector limits infection to those who live and visit tropical environments (Kraemer et al., 2015). Despite that limitation on its range, dengue is common in more than 110 countries and infects 50–528 million people worldwide a year, leading to half a million hospitalizations.

**Zika** is an RNA virus of the genus *Flavivirus*, which first emerged from the Zika forest of Uganda in 1948. It more recently emerged in 2014 in French Polynesia to take center stage among the most serious emerging public health issues in the Americas after it was transmitted to South America. The virus is transmitted by the same mosquito as the chikungunya and dengue viruses, typically causing relatively minor ailments such as rash, fever, and headaches within a week of being bitten by the mosquito. The virus has spread to over 17 countries in the Americas by early 2016. The possible link to microcephaly in unborn fetuses has put this relatively minor viral infection on center stage. There are no vaccines for the virus. No antivirals have been reported to be effective for Zika, but one must assume that the experimental treatments used to treat dengue and chikungunya will be tested for their efficacy in this related virus. Zika virus is arguably at the cusp of being considered a global pandemic risk, with increasing cases of its transmission via sexual contact, thereby forgoing the otherwise geographically limited mosquito vector.

## THE SPECIAL CASES OF MOSQUITO TRANSMISSION

The fact that Zika, chikungunya, dengue, and malaria are spread by mosquitoes introduces another strategy for combating the disease, the use of insecticides. Unlike pharmaceuticals, which must be prescribed in controlled clinical settings, insecticides can be used in truly staggering quantities in very large areas. It remains to be seen what the implications to human health and the environment will be from the recent campaigns against the spread of Zika virus, particularly in the run up to the 2016 Summer Olympic Games. Lessons from history, that is, DDT, indicate that there will indeed be consequences to its widespread use, to both the virus, human health, and the environment.

Those living and traveling in the mosquito vector's range are urged to use the strongest mosquito repellent both day and night. Hence, it is to be expected that the amount of DEET and picaridin used in these areas will increase substantially. It remains largely unstudied as to the consequences of widespread use of repellent. Will the repellents select for insecticide-tolerant mosquitoes? What is known is that increased use of insect repellents, such as DEET, will greatly increase in concentration in the environment—as it is already a routinely measured pollutant in rivers around the globe (Costanzo et al., 2007). Further consideration is the routine exposure of air travelers in mosquito-infested areas to insecticides as part of aircraft disinfection (i.e., permethrin, phenothrin, and etofenprox) (World Health Organization, 2013).

## THE KNOWN AND UNKNOWN UNKNOWNNS

Currently, 1415 pathogens are reported to cause disease in humans, including 538 bacteria and rickettsia, 307 fungi, 66 protozoa, and 287 helminths (Taylor et al., 2001). The most abundant source of human emerging pathogens comes from the organisms classified as viruses (44%) followed by bacteria (30%) (Jones et al., 2008). The majority of pathogen species causing disease in humans are zoonotic (61% of the total) (Taylor et al., 2001). By contrast, 616 pathogens have been identified in livestock and 374 in domestic carnivores (Cleaveland et al., 2001). Although morbidity and mortality statistics are available for some human pathogens, it is more often the case that pathogens remain completely unquantified with regard to their impact on human health (Taylor et al., 2001). This reality stems from the fact that (1) most viral diseases are treated symptomatically owing to the challenge and cost of demonstrating the causative organism, (2) many illnesses are self-limiting and do not undergo analysis for the causative agent, and (3) the health-care profession will typically look for the “known knowns” and not seek to screen beyond what is expected. Without thorough unbiased surveillance, emerging pathogens will continue to surprise public health services.

## PANDEMICS OF CHRONIC DISEASES

It is also important to realize that pandemics do not have to be infectious or contagious diseases; they may take the form of chronic diseases, such as heart disease, diabetes, cancer, and obesity. The World Health Organization is monitoring the global pandemic of heart disease, which is being combated with the use of statins, among a wide range of other drugs. Statins are used for prevention of all the main cardiovascular events, reducing the risk of acute myocardial infarction, cardiovascular revascularization, stroke, cardiovascular mortality, and all-cause mortality. Statins are now the most prescribed drug in the world (Hobbs et al., 2016). Unlike episodic pathogen pandemics, non-communicable disease pandemics pose a constant (and increasing) pollution threat to the environment and human health.

## CONCLUSION

It is clear that society has much to gain from a well-coordinated medical response to a pandemic. It is likely that most will agree that a thorough and coordinated medical response to a pandemic is preferred over the application of a precautionary approach because of the potentially real effects of these chemicals on critical infrastructure and the wider environment. However, even if we are (nearly) all agreed that humans should be prioritized over the wider environment, this does not preclude society from having an understanding of what is *actually* at risk and determining whether anything can be done to mitigate these perceived threats.

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