Chapter

Which Plagues are Coming Next?

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Abstract

Plagues and pandemics are no longer distant thoughts of the past. Previously referred as moments in history, infectious diseases have re-emerged as potential existential threats to mankind. International Health Security researchers have repeatedly warned society about impending pandemics and in 2020, the world experienced its first major pandemic in over a century. The SARS-CoV-2/COVID-19 pandemic came fast and hit hard, impacting the entire world within months of discovery. Although SARS-CoV-2 was a completely novel virus, there are an assortment of novel and timeworn pathogens fostering the potential to become the next pandemic. This chapter focuses on pathogens ranging from yeast to virus, capable of transmission through food, water, air, or animal, that could emerge as the next International Health Security threat.

Keywords: pandemic, vector-borne diseases, airborne diseases, waterborne diseases, foodborne diseases, public health, infectious diseases, International Health Security

1. Introduction

The current COVID-19 pandemic has given the world a new lesson that the war against human pathogens is not over. The next plagues are coming, that is for sure, we just do not know when and where they will emerge. The transcontinental global movement of human populations, animals, products, and food in unprecedented numbers and at immeasurable speeds has determined the emergence of new plagues. The International Health Security panorama is changing with the incorporation of vast geographical areas to the agroindustry; the displacement of large population groups either due to problems of floods, drought, wars, or people that search for better living conditions. In addition, the disposal of biological waste and the weaponization of pathogenic microorganisms are phenomena with serious consequences. International multinational cooperation is needed to improve the development and availability of drugs and vaccines at a global level, as well as, improving preventive health services, keeping safe all repositories of infectious agents, and the establishment of an International Health Security System focused on Infectious Disease Surveillance and Control.

2. Methods

An organized, systematic, four-step methodology for collecting key information was carried out to write this chapter. In a first step a search in websites such

as the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) was conducted to identify emerging infectious diseases pathogens. In a second step, the main emerging infectious diseases pathogens were classified in viruses, bacteria, parasites and fungi as well as by their mechanism of transmission. In a third step, all updated manuscripts related with each one the selected pathogens were extracted from scientific databases including Pubmed, MEDLINE, Google Scholar, and SCOPUS. Finally, all pathogens were classified using the WHO Pandemic Phase Descriptions and Main Actions by Phase [1].

3. Pathogens to study

3.1 Vector-borne

Vector-borne diseases are transmitted, either biologically or mechanically, via insect vectors or animal vectors. Vector-borne diseases were the cause of great plagues in the previous centuries and continue to take human lives every year. Although the invention of pesticides, better hygiene and sanitation, and improved physical barriers have contributed to the decreased incidence of these type of infections, globalization, deforestation, and global warming are causing Vector-borne diseases to experience a comeback [2]. With enough conditions in their favor, Vector-borne diseases are capable to expand from being endemic in some areas to becoming a pandemic. Vectors range from insects to mammals and are present in all parts of the world. The pathogens described in this section are transmitted by mosquitoes, ticks, rodents, lice, and fleas.

An important factor regarding Vector-borne diseases and their respective vectors compared to other mechanisms of infectious disease transmission (e.g., airborne, foodborne) is the emerging data indicating vectors are capable of hosting more than one pathogen at a time [3–7]. Co-transmission and co-infection are not well understood yet are raising questions regarding clinical manifestation, virulence, and possible future implications. Although the mechanisms of co-infections are not well comprehended, there are documented case reports with individuals presenting more than one Vector-borne disease at the same time [8–10]. Specifically, there is rising concern about mosquitoes and their capability to co-infect humans, with recent studies showing *Aedes aegypti* [4, 7] and *Ae. albopictus* [3] capable of transmitting Zika, Chikungunya, and Dengue viruses within one bite.

3.1.1 Viruses

3.1.1.1 Yellow fever virus

Yellow fever (YF), one of the deadliest infectious diseases less than a century ago [11], was historically a neglected infectious disease unit the 1902 creation of the Pan American Health Organization (PAHO) and International Sanitary Bureau of the American Republics [12]. Yellow fever is caused by the etiological agent yellow fever virus (YFV), belongs to the flavivirus genus and, is a part of the arboviruses group (i.e., a commonly used, yet unofficial, name for viruses transmitted by arthropods). [11]. YFV circulates between humans, non-human primates, and several species of mosquito vectors (*Aedes, Haemagogus, Saberges)*. Currently, YFV has not adapted as well to humans as Dengue virus, leaving YFV as a zoonotic disease but with a future capability to extend to an anthroponotic. In the past decade there is an increase in

concern of non-primate transmission which could go unnoticed and spillover to large human populations [13]. Due to the nature of the virus requiring epizootic transmission, unfortunately, YFV cannot be eradicated from the planet. *Aedes aegypti* and *Aedes albopictus* which are present in over 150 countries suggest nearly half of the global population is at risk of YFV transmission [14]. Traditionally, YF affects the Americas and the African continent with its warm temperatures and suitable habitat for the mosquito vectors of the virus. There are seven major genotypes of YFV, differentiating the American and African cases – with 5 circulating within Africa and 2 in the Americas. Depending on the location of cases and the type of mosquito species native to the area there are three main types of YF transmission – urban, sylvatic, and intermediate (only Africa). Urban transmission is caused mainly by *Aedes aegypti* or a similar urban mosquito as the transmitter in humans [11, 15]. Sylvatic transmission appears between non-human primates and sylvatic mosquitoes, typically apart of the *Haemagogus* or *Sabethes* genera. In Africa alone, YF is estimated to kill over 70 thousand individuals a year [16]. The case fatality rate (CFR) depends on the location of infection, with South America having a higher CFR (40–60%) compared to Africa (closer to 20%) [17]. However, most cases are mild and resolve with supportive care. Moreover, in areas with co-transmission of both Dengue and YF viruses, it is possible that previous Dengue infections may protect against severe YF infections [18]. Similarly, to how YFV is thought to have traveled from the African continent to the West Indies centuries ago on shipping routes, it is capable to continue expanding in the current age with increased globalization and construction within the vector habitat. As mentioned above, YF is endemic in mostly South American and Africa, with outbreaks consistently seen each year. Although not often heard about in North America and Asian countries, Yellow Fever was endemic hundreds of years ago in cities like New York, Philadelphia, Memphis, and New Orleans [19] and has the possibility to emerge in Asian countries [20, 21]. Although *Aedes* mosquitoes are also native in parts of Asia, the absence of YF cases has long been a scientific enigma [21, 22]. Common theories to the lack of YF cases in Asia are: the east African mountain range provides a natural barrier for Asia [21], competition with Dengue virus limits YF transmission [23], and vector competency [20] among others. However, in the recent years an increased number of imported YF cases into Asian countries have raised alarms to the potential introduction of YFV to the local environment [20]. The most important factor describing whether or not YFV will be transmitted in a specific area is the vector. Fortunately, YFV can only be transmitted via the bite of an infected mosquito, making mosquito control programs essential in YFV transmission reduction. However, the world currently is experiencing a re-emergence of YF due to increased globalization, deforestation, and climate change, with recent outbreaks occurring in Brazil [24, 25]. With globalization, both humans and mosquitos may hitch rides to different parts of the world where YF transmission is uncommon and becoming an International Health Security issue. Furthermore, the present deforestation occurring throughout the world, especially in the South American and African forests, is closing the distance between humans, infected non-human primates, and mosquitos. Lastly, the increasing temperatures seen due to climate change may have implications on YFV vectors and their global distribution [16] – increasing the risk for contracting YF. In a recent study, an increase in temperature is estimated to increase the chance of the annual amount of YF death by over 90% [16]. Currently, countries with endemic YFV transmission have mosquito control programs capable of decreasing/controlling mosquito populations. Furthermore, the use of Geographic Information Systems (GIS) in conjunction with mathematical models [11] assist in predicting future YF outbreaks and viral transmission [16].

Lastly, one of the most important tools available to fight infectious diseases exists against the Yellow Fever virus – a vaccine. The earliest version of a YF live-attenuated vaccine was created in 1936 and the same vaccine strain (17D) is still presently effective and used in areas with endemic transmission [11].

3.1.1.2 Dengue virus

Dengue virus (DENV) occurs in over 100 countries causing nearly 100 million acute infections and half a million deaths each year [26, 27]. The disease itself is characterized by an acute fever which is transmitted from mosquitos (*Ae. aegypti* and *Ae. albopictus*) to humans, however, most cases are asymptomatic. Anywhere from 5–20% of cases progress to severe dengue which includes bleeding, shock, organ failure, and death. Severe forms of Dengue are known as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue is described as early as 1600 and continues to be endemic to many parts of the world [27]. Similarly, to the Yellow Fever efforts initiated by PAHO, a major *Aedes aegypti* eradication program between 1947 and 1970 aimed to eliminate this mosquito species and therefore, eliminate Dengue. However, *Ae. aegypti* reinfestation occurred shortly after and has even increased in dispersion in the recent decades [27]. Like other infectious diseases, Dengue is thought as an exotic disease – perhaps many individuals have not even heard of Dengue before. It may surprise many individuals in developed countries that Dengue's main vector *Ae. aegypti* is capable of living in almost all continents except Antarctica [28]. Dengue was common in port cities in the Caribbean and all throughout the Americas and continues to cause outbreaks in developed areas such as the Florida (2020) and Hawaii (2015) [29]. A significant barrier in the diagnosis and reporting of Dengue is the commonality the disease shares with other Flaviviruses such as Yellow Fever virus and Zika and its cross-reactivity in serological testing. The aforementioned diseases share similar flu-like symptoms and serological misdiagnoses are believed to fuel the underreporting of DENV and other Flavivirus infections. As Dengue cases continue to increase it is essential to understand the current epidemiology and public health programs in place to reduce the outbreak risk and reinforce International Health Security. Dengue virus shares many similar characteristics with YFV - it is a part of the Flaviviridae family, and its main vectors are *Aedes aegypti* and *Ae. albopictus* mosquitoes. Typically, DENV is found in tropical and subtropical regions and unlike other viruses, individuals may be re-infected by different serotypes. This is especially important in public health prevention programs and epidemic mitigations. Unfortunately, individuals infected with one serotype only produce antibodies capable of neutralizing that specific serotype, leaving the individual unprotected against the other 3 serotypes. Moreover, through antibody-dependent enhancement, re-infection by a different serotype increases the risk of severe dengue disease [26]. In 2019 a vaccine against DENV was approved for individuals aged 9–45 years and who had experienced a prior DENV infection. However, providing this vaccine to individuals without prior DENV infection also increases the risk for the antibody-dependent enhancement and therefore greatly limiting who may be immunized [30]. In a pandemic scenario this limitation would be disastrous.

3.1.1.3 Zika virus

One of the most famous infectious diseases of recent decades, Zika came into the international spotlight during its 2015 epidemic. Although Zika virus (ZIKV) was discovered in a Ugandan forest over 50 years ago, in 2015 it emerged as a global epidemic affecting multiple countries and causing widespread panic [31]. In 2016,

the World Health Organization (WHO) declared the outbreak as a Public Health Emergency of International Concern, with ZIKV affecting throughout the Americas and Caribbean. One of the main reasons for the declaration and widespread worry is the increase in microcephaly cases and other neurological disorders that ZIKV brought with it. Interestingly, prior to the outbreaks in the recent decade, ZIKV infections were considered benign [32]. It was the increase in neurological disorders such as Guillain-Barré syndrome in older children and adults and microcephaly and other birth defects in newborns in the 2015 Brazil outbreak that forewarned the local and international community of the potential adverse effects from a ZIKV infection [32]. Although the incidence of Zika cases has decreased since the 2015–2016 epidemic, a substantial amount of Zika research continues to provide new data and information on this infectious disease. Current research suggest Zika will be around until the foreseeable future with research indicating ZIKV actually circulates in areas previously unknown. Moreover, in 2019 Europe's first autochthonous case [31] was identified and further confirmed the importance of vector control and public health programs. Like the flaviviruses mentioned above, ZIKV's main vectors are *Ae. aegypti* and *Ae. albopictus* placing a large proportion of the global population at risk of infection; therefore, threatening International Health Security [31, 33]. Although *Aedes* mosquitos are the confirmed vector for ZIKV, *Culex* genera mosquitoes, mostly *Culex quinquefasciatus*, are theorized to be capable to transmit Zika, further expanding its geographic reach [34]. However, recent studies did not support the ability for Culex mosquitoes to transmit ZIKV [35, 36]. In conjunction with its vectors wide global reach, a high proportion of Zika cases are asymptomatic and those who are symptomatic mirror symptoms to dengue and the flu (e.g., fever, rash, muscle and joint pain) compounding the barriers to diagnosis, treatment, and epidemic mitigation efforts.

3.1.1.4 West Nile Virus

An emerging zoonotic arbovirus, West Nile Virus (WNV), was first described in a sick woman located in the West Nile Uganda district in 1937 [37]. Sixteen years later WNV was detected in birds living in the Nile delta region, suggesting its transmission cycle involves mosquito vectors and birds – yet may infect humans [38]. It is now known WNV is capable of infecting both humans and other vertebrate species, with its sylvatic cycle infecting horses and humans as dead-end hosts and birds as the amplifying host. Unlike the previously mentioned viruses, WNV uses the *Culex* genus mosquitoes as its primary vector. Recently, additional mosquito genera, *Aedes* and *Ochlerotatus*, were identified as possible WNV vectors. Although this virus historically caused outbreaks in Africa, Asia, and the Middle East, cases of WNV are now common in Europe and the Americas. The first US case occurred in 1999 and within a decade cases were identified in Canada, Mexico, and South America – with cases as south as Argentina [37]. WNV has spread to all continents except Antarctica, increasing the risk of future and larger epidemics worldwide. WNV is now considered endemic in the US with as many as 47 US states reporting WNV cases each year [38]. Although the incidence of WNV has increased throughout the decades, most human WNV infection are asymptomatic [39]. About 1% of infected individuals experience severe neuroinvasive disease such as meningitis, encephalitis, and flaccid paralysis [39, 40]. The movement of migratory birds in addition to the local movement of sedentary birds are hypothesized to contribute to the global distribution of WNV [38]. Current public health programs aiming to reduce the spread of WNV rely on GIS and mosquito population control techniques. Furthermore, since WNV is able to infect horses and birds, many endemic areas have equine and sentinel programs focused on surveillance

and monitoring of WNV transmission. Moreover, recent mathematical and GIS models identified risk factors pushing WNV transmission such as populations living in poverty, environmental factors, and mosquito populations [41]. There are no current approved vaccines against WNV, leaving public health prevention programs and vector surveillance the main barrier between WNV causing larger human outbreaks.

3.1.1.5 Crimean-Congo hemorrhagic fever virus

A Nairovirus, Crimean-Congo hemorrhagic fever (CCHF), is an emerging infectious disease using *Hyalomma* genus ticks as its vector with distribution in Africa, Asia, and Europe [42]. CCHF was first described in the Crimean Peninsula less than a century ago, in 1944, during World War II when cases were brought on Soviet soldiers. Since then, the importance of CCHF has grown so much so that in the last 3 years the WHO considers it one of eight priority emergent pathogens [42]. Currently this zoonotic virus is endemic in approximately 50 countries throughout the world. Domesticated animals such as sheep, cattle, and goats as well as birds serve as the amplifying host, maintaining the transmission cycle alive in diverse regions. The Crimean-Congo hemorrhagic fever virus is transmitted to humans mainly through the bite of hard-bodied ticks yet can be transmitted with direct contract with blood and other infected bodily fluids. An infection typically comes directly from an infected tick or ticks on livestock that then bite humans. For those reasons many CCHF cases originate in individuals in agricultural jobs (direct) and nosocomial environments (direct bodily fluid contact). Most cases are asymptomatic or present mild symptoms such as fever, headaches, dizziness, and abdominal pain and myalgia [43]. In severe cases the course of infection includes an incubation period, pre-hemorrhagic, hemorrhagic, and convalescent phases [43, 44]. It is estimated approximately 10% of the cases will present severe disease with mortality rates ranging from 20- to over 30% in these severe cases [44]. Due to high mortality rates and global risk, the Centers for Disease Control and Prevention (CDC) considers CCHF virus a level 4 biosecurity risk pathogen [42]. There is currently no approved CCHF vaccine and treatment is usually supportive and symptomatic [42]. Fortunately, the current geographic distribution of the *Hyalomma* tick is limited to 50 degrees north latitude [45], preventing the disease to expand beyond this geographical limitation for now. Nonetheless, the climate change and increased environmental temperatures may provide the vector an opportunity to expand its traditional reach which may become an International Health Security threat. Consequently, CCHF prevention focuses on public health education, environmental programs, and physical barriers (e.g., thick clothing, long sleeve shirts, long sleeve bottoms) [43].

3.1.1.6 Mayaro virus

This emerging zoonotic pathogen is an enveloped +ssRNA virus belonging to the alphavirus genus of Togaviridae family [46]. Mayaro virus (MAYV) is part of the viruses of Semliki forest antigenic complex and causes Mayaro fever [46, 47]. Transmission of MAYV into humans occurs primarily through the bites of infected mosquitoes of the genus *Haemagogus* spp., especially *Haemagogus janthinomys*, with experimental studies showing the ability of MAYV to infect mosquitoes of another genus such as *Aedes aegypti*, *Culex*, *Mansonia*, *Psorophora*, and *Sabethes* [46, 48]. The sharing of common antigenic sites among viruses of Semliki complex causes serological misdiagnosis and underreporting of MAYV infection in endemic areas [46, 49]. MAYV infection produces self-limiting symptoms of fever, headache,

myalgia, arthralgias, maculopapular rash with more than 50% of them developing long-term incapacitating arthralgias. Sometimes Mayaro fever can result in complications resulting in hemorrhagic manifestations, neurological manifestations, myocarditis, intermittent fever, and death [46, 49]. Pharmaceutical countermeasures such as specific antiviral agent or licensed vaccine are not available against MAYV. Thus, prevention and control of MAYV infection is dependent on vector control techniques and barriers to prevent human-vector contact. This neglected tropical virus was first isolated from the sera of forest workers of Mayaro county, Trinidad and Tobago in August–September 1954 [50]. Even earlier evidence of transmission of MAYV in Panama and Colombia between 1904 and 1914 was provided by a retrospective study [51]. This was followed by reporting of MAYV infection in Brazil, Bolivia, Colombia, Surinam, Peru, Ecuador, French Guinea, Venezuela, and Haiti [46, 52]. Currently, the pathogen is endemic in regions of Central Brazil and the western coast of South America [52]. The import of MAYV cases in North America, Netherlands, France, and Germany in last decade shows the potential of travelling in introduction of agent in new areas [46, 52]. Infection with MAYV is detected in many vertebrate hosts such as nonhuman primates, rodents, sloths, small mammals, and birds with nonhuman primates (monkeys) being suspected of maintaining the enzootic cycle [46, 47]. The zoophagous nature of the *Heamagogus* spp. species results in the restriction of MAYV to rural areas with occasional outbreaks in humans [49]. However, the ability of MAYV to infect urban vectors like Aedes (*Ae. aegypti* and *Ae. albopictus*) suggest a potential future expansion and invasion of MAYV into urban areas of the world becoming an International Health Security threat [46, 52]. Anthropogenic changes, genomic mutations, insecticide resistance in vectors, globalization, climate change, and infection of urban mosquito vectors could result in epidemiological evolution of MAYV and MAYV fever becoming an International Health Security threat.

3.1.1.7 Chikungunya virus

First reported in 1952 in Tanzania, Chikungunya virus (CHIKV) is an alpha virus apart of the Togoviridae family and transmitted by Aedes mosquitoes [53]. The word Chikungunya translates as "the disease that bends up the joints", which is one of the severe symptoms of the disease (i.e., arthritis) [54]. The main transmission among humans occurs through epizootic cycles, where vertebrates are the viral reservoirs and the mosquito acts as the vector [55]. Since its discovery, there were CHIKV outbreaks throughout Europe, India, and Asia. CHIKV was a mostly a forgotten infectious disease until its 2006 resurgence and widened global reach. In 2007, Europe reported its first autochthonous CHIKV infection and by 2013 it had found the Americas, first landing in Saint Martin and then spreading throughout South America [53]. In spite of underreporting and misdiagnoses cases have occurred in more than 45 countries [55]. Active outbreaks allow humans to become the reservoirs and continue to fuel the outbreak. Like Zika, the first autochthonous cases in the Americas were fairly recent, with CHIKV's first outbreak in the Northern and Northeastern regions of Brazil [53]. The most serious outbreak was probably the Reunion Island outbreak between 2005 and 2006, where nearly a third of the island's population (255,000) was infected and over 250 individuals died [56]. A CHIKV infection typically causes symptoms such as fever, arthralgia, myalgias, and skin rashes [55]. In a subset of cases, joint inflammation and arthritis lasting up to 4 months may occur [55]. The increased incidence of CHIKV over the recent decades in areas previously unaffected, in addition to the wide geographical range of its vector (i.e., the Aedes genus) lead to heightened concern of future outbreaks and adverse health outcomes. Moreover, recently CHIKV infection is

associated with abortion during the first and last trimesters of pregnancy, further emphasizing the need for CHIKV research and therapeutics [55].

3.1.2 Bacteria

3.1.2.1 Rickettsia prowazekii

As one of oldest infectious diseases known to mankind, Typhus, caused by the bacteria *Rickettsia prowazekii* and *R. typhi*, continues to be an International Health Security threat. Due to the nature of the outbreaks caused by *R. prowaszekii*, having higher mortality rates [57] and a recently discovered animal reservoir (i.e., flying squirrel) [58, 59], only *R. prowazekii* will be covered in this section. *R. prowazekii*'s, the cause of epidemic typhus, history is unclear. Some scholars believe epidemic typhus to be have caused the 430 BC plague of Athens [57, 60, 61] where it killed 25% of the population [61]. While the origins of this pathogens may be unclear, it is certain it continues to be part of an International Health Security program today. Typhus is also referred to as a pestilential disease, or an infectious disease killing a large number of individuals, that is commonly used in old world diseases. Epidemic typhus is usually associated with cold months and poor sanitary conditions are conducive to lice proliferation [60]. Until the late 1900s, *Pediculus humanus corporis* (i.e., human body lice) was thought to be the only vector for *R. prowazekii* until the late 1970s when a US outbreak seemed to inculpate *Glaucomys Volans* (i.e., southern flying squirrel) [58, 59]. Infection occurs when an infected human body louse defecates on an individual and its feces, containing R. prowazekii, enters the bite site or wound [57, 60]. Transmission via flying squirrel is not yet completely understood [60], however it is thought to spread through aerosolized ectoparasite feces [57, 60]. Currently, epidemic typhus is endemic in South America, Africa, and Asia [57, 60]. Outbreaks propagate especially following famines, climate changes, wars, and social unrest all of which are currently present in the world [57, 60]. One of the most recent largest outbreaks was reported during the Burundi civil war in 1997, where approximately 100,000 individuals were infected and the case fatality rate was 15% [60]. Clinical manifestation of Typhus includes skin rashes (crucial for clinical diagnosis), fever, headaches, and cough [57, 60]. Without treatment, the case fatality rate could be as high as 60%, however, currently with treatment is closed to 4% [60]. Unlike the previously mentioned pathogens, once infected with *R. prowazekii* individuals may stay infected for life. This is even more alarming given a recrudescence may cause Brill-Zinsser disease [57, 60, 62]. Currently, epidemic typhus is treated using antibiotics (doxycycline) and there is no approved vaccine. Given infection by inhalation it is possible R. prowazekii may be used as a biological weapon and is warrants additional research and funding [60, 63, 64]. With the current International Health events including refugee camps, wars, and populations living in unsanitary condition, epidemic typhus may continue to produce outbreaks similar to the Burundi outbreak and therefore vaccine development should be encouraged.

3.1.2.2 Yersinia pestis

Perhaps the most infamous infectious disease, the Black Plague or Black Death, is caused by *Yersinia pestis*. *Y. pestis*, a bacterium, has caused multiple plagues throughout the history of mankind [60, 64]. The earliest epidemic caused by *Y. pestis* killed approximately 30 to 50 million people in the 541–542 AD Plague of Justinian [64]. Since then, there were four additional pandemics caused by this pathogen, the Black death (1347–1351), Italian plague (1629–1631), Great plague of

London (1664–1666), and the Third plague (1885) [64]. In total, the five pandemics caused by *Y. pestis* are estimated to have killed over 250 million people. Cases of the plague still exist, yet the discovery of antibiotics has greatly reduced the global burden of this disease [60]. There are five forms of plague, all affecting the human body differently and having different mortality rates, bubonic, septicemic, pneumonic, meningeal, and pharyngeal [64]. However, there are typically three types of plagues described in the literature and main causes of outbreaks: bubonic, septicemic, and pneumonic [64, 65]. Today most human cases of plague are of the bubonic or pneumonic form, caused by spillover of an infected flea (bubonic) or by the inhalation of infectious droplets (pneumonic) [66]. The transmission of *Y. pestis* relies on rats (*Rattus rattus*) and its ectoparasite the rat flea (*Xenopsylla pheopis*). Conversely, in 1941 body lice and human fleas were found to be infected with the plague, indicating other vectors may exist. Currently there are no documented cases of plague being transmitted by body lice or human fleas to humans [66], yet some scholars suggest previous epidemics were caused by plague infected lice based on genomic evidence and paleomicrobiology [60]. Buboes or swollen lymph nodes are classical characteristics for Bubonic plague and typically are transmitted from rodents [66]. Septicemic plague is a severe form of bubonic plague where the bacteria enter the blood stream. Pneumonic plague affects the lungs and is transmitted by aerosolized bacteria [66]. Due to the respiratory nature of pneumonic plague, pneumonic plague can be spread person to person yet usually the high case fatality rates end the outbreaks quickly [66]. The case fatality rate, in the absence of treatment, for pneumonic plague can near 100%, while bubonic plague being around 40–70%, and septicemic around 50% [65, 66]. As mentioned, the plague took millions of live throughout the history of mankind and continues to do so to this day. The largest (n = 2348 cases) latest outbreak occurred in Madagascar late in 2017, with 70% of the cases diagnosed as pneumonic plague and 202 deaths occurring [67]. While the probability of a pandemic caused by the plague has decreased, a recently discovered multidrug resistant strains of *Y. pestis* has raised alarms for potential future outbreaks becoming of International Health Security concern [65, 67]. The Madagascar strain (MDR *Y. pestis* plasmid pIP1202) was found to be resistant to eight common antibiotics (i.e., streptomycin, chloramphenicol, tetracycline, sulfonamides, ampicillin, kanamycin, spectinomycin, and minocycline) [68, 69]. Currently, there are still antibiotics (e.g., doxycycline) successful in treating MDR plague. Moreover, the high mortality rate in conjunction with the ability to be transmitted person-to-person leads *Y. pestis* to be classified as a Category A biothreat agent (i.e., high priority agent) [70, 71]. Without an approved vaccine available and the presence of a multidrug resistant plague, the Black Death may re-emerge from the history books.

3.1.2.3 Francisella tularensis

The causative agent of tularemia, *Francisella tularensis*, is transmitted to humans by different types of arthropods (e.g., ticks, flies, mosquitoes) or ingesting contaminated meat or water [65, 66]. First described in the 16th century, Tularemia affects mostly in the northern hemisphere [67]. It is now hypothesized Tularemia arrived from the Middle East to Central Anatolia since 14th century BC [67]. Due to its survival in water and its transmission, it may also be considered a waterborne pathogen [66]. The two main transmission cycles, terrestrial and aquatic, utilize different reservoirs and vectors and are differentiated by subspecies tularensis (also called Type A) and holarctica (also called Type B) [65]. Type A, being terrestrial and using mainly ticks, mosquitoes, and flies in its transmission cycle will be covered in this section. The most understood and established vector for *F. tularensis* is

the tick (e.g., *Dermacentor andersoni*, *D. variabilis*, and *A. americanum*). Mosquitoes and flies are thought to be mechanical vectors and their role in transmission is not fully understood [65]. The infectious dose for contradicting tularemia is extremely low, with only 10 *F. tularensis* bacteria needed to establish an infection subcutaneously and 25 when in aerosol form [65]. Disease typically is one of two forms either the ulceroglandular form (i.e., the most common) or the typhoidal form (i.e., the most severe form) [65]. There is currently no vaccine available against Tularemia and antibiotic treatments (doxycycline and ciprofloxacin) exist [68]. Due to its multiple forms of transmission in addition to mortality rate (30–60%) [65, 68], the pathogen is considered a Category A biothreat agent and requires a level 3 biocontainment [65, 68, 69]. This would not be the first time *F. tularensis* is considered a biological warfare agent, according to some scholars *F. tularensis* was used in the 1320–1318 BC Neshite-Arzawan conflict as a biological agent [67], warranting a need for further research and vaccine development as it constitutes an International Health Security threat.

3.1.2.4 Elizabethkingia anophelis

A newly uncovered bacterium, *Elizabethkingia anophelis* was discovered in 2011 in the midgut of an *Anopheles gambiae* mosquito [70–73]. Less than a decade since its discovery this pathogen has caused human disease in Asia [73–75], North America [76, 77], Europe [72, 78], and Africa [79]. The route of transmission remains unclear, although it is theorized mosquitoes transmit the bacteria to humans [80]. In Hong Kong there is evidence of perinatal vertical transmission [80] and both an outbreak in Singapore and Greece link *E. anophelis* cases to the water sources [78, 81]. The pathogen recently gained international attention by a large outbreak occurring in Wisconsin, USA, where over 60 cases were identified and 18 deaths occurred [71]. Clinical symptoms may include mostly sepsis, meningitis, fever, bacteremia, and pneumonia [71, 72, 76, 78], among others. Currently the case fatality rate is estimated between 23–70% [71–74, 80]. Disease was usually present in neonates, the elderly, chronic illness or immunocompromised individuals [80]. With increasing prevalence of people with co-morbidities this agent may see increased cases in the years to come. Since discovery, *E. anophelis* is found to be resistant to beta-lactam antibiotics and aminoglycosides [82], yet susceptible to minocycline, levofloxacin, among others, complicating treatment. With less than a decade since its discovery there are many knowledge gaps in all aspects of this pathogen from transmission cycle to disease manifestations. More research is warranted in addition to sustaining current mosquito control programs and surveillance.

3.2 Airborne

In the last century, some of the deadliest pandemics were spread through respiratory droplets or aerosols. Globalization and shortening of travel time have further increased the speed of spread of airborne diseases. Scientific advances in vaccine development and antimicrobials has helped to counter these outbreaks however risk of massive outbreaks due to emerging and re-emerging pathogens remain and is an International Health Security issue. The 2019 coronavirus disease (COVID-19) pandemic has shown the susceptibility of human population to novel emerging or re-emerging pathogens and its significant effect on economic, social, and human health. It has also shown the ability of a pathogen to rapidly disseminate through airborne or respiratory route and the difficulties associated with prevention and control measures. The majority of pathogens require isolation, quarantine and

respiratory precautions (surgical masks, personal protective equipment in hospitals, cleaning of surfaces, disinfection of surfaces, and hand hygiene) as prevention and control measures. Dangerous pathogens such as viruses, bacteria, or fungi transmitted from environment, animals or humans through respiratory route and having potential to cause epidemics and/or global pandemics are listed below along with the available medical countermeasures.

3.2.1 Viruses

3.2.1.1 Variola virus

Variola virus, a member of the *Orthopoxvirus* genus is the causative agent of smallpox. Before the 15th century, the disease was limited only to the continents of Europe and Asia. The smallpox was introduced into the Americas, Africa, and Australia between 15th and 18th century due to European colonialism and resulted in massive outbreaks with high case-fatality rates due to immunological naïve populations [83]. The variola virus was transmitted in humans predominantly through respiratory droplet nuclei. It can also transmit the infection through contact with body fluids, skin lesions, and scab fluids of infected person. The smallpox virus is limited to the human population with no animal reservoir [83, 84]. The global health campaign for smallpox eradication resulted in the eradication of smallpox in 1980 with the last natural case of smallpox in Somalia in 1977 [83]. In 1978, the accidental laboratory release of variola virus in Birmingham, United Kingdom and the resulting infection and death of a photographer due to smallpox is the last known death due to smallpox in the world with her mother being the last known case of smallpox. The eradication of smallpox was followed by cessation of smallpox vaccination programs and that has resulted in the mankind losing immunity to smallpox and other orthopoxviruses [84].

The variola virus is recognized as a huge threat to human health if used as bioweapon. This was based on the ability of Soviet Union to weaponize smallpox in the 1980s [83]. In 1994, the WHO Committee on orthopoxviruses decided, the stocks of variola virus DNA should be kept at only two international laboratories in world, namely Centers for Disease Control and Prevention (United States) and State Research Center of Virology and Biotechnology -VECTOR institute (Russia) [84]. However, fear remains that secret variola virus stocks could be kept illegally somewhere and be used in bioterrorist attacks; therefore, it is a threat for the International Health Security [83]. Genomic studies on orthopoxviruses has suggested the deletion of genes as an important concept for the reductive evolution of orthopoxviruses in adapting to new host species or emergence of new virus species [83, 85]. The existence of zoonotic orthopoxviruses with the ability to cause sporadic human cases raises the possibility of reemergence of variola virus as part of these natural evolution of orthopoxviruses [84]. Like the introduction of the smallpox in the Americas, either the release of variola virus intentionally or its reemergence as part of natural evolution can result in public health emergency of global concern with high fatality. This concern is mainly due to a huge proportion of the world being immunologically naïve, increased percentage of immunologically suppressed population, and globalization resulting in rapid spread of virus [83]. The effective vaccine and two antiviral drugs (brincidofovir and tecovirimat) are available pharmaceutical measures to fight any future outbreak due to either natural evolution or bioterrorist attack [83]. However, the lack of practical knowledge among healthcare professionals related to smallpox clinical characteristics may further delay early diagnosis, treatment and control of the outbreak.

3.2.1.2 Monkeypox virus

Monkeypox virus, has emerged as the most common pathogenic Orthopoxvirus and causes a zoonotic disease Monkeypox [86]. Similar to the variola virus, transmission is through respiratory droplets/secretions or contact with the lesion material [86]. Monkeypox is endemic in Central and West Africa with similar clinical manifestations as smallpox and a case-fatality rate of 10% [83, 84]. The clinical manifestations include fever, myalgia, exhaustion followed by appearance of rash and lymphadenopathy in 1–3 days [86, 87]. Monkeypox virus can infect a wide range of mammalian species with various species of African rodents acting as natural reservoir [88]. Monkeypox virus usually results in sporadic cases due to low efficiency of person-to-person transmission and occurs mainly from primary human cases but never from secondary cases [83, 84, 86]. However, during the recent outbreaks in Nigeria and Democratic republic of Congo (DRC), increased person-to-person transmission was observed along with associated imported cases in UK, US, Israel and Singapore [83, 89]. Additionally, in the US Midwest outbreak, the virus showed the ability to infect intermediate hosts (prairie dogs) from natural reservoirs and subsequently infect humans [90]. Infection with a Orthopoxvirus or smallpox vaccination provided protection against monkeypox virus and thus smallpox eradication and cessation of vaccination has resulted in decreasing number of vaccinated individuals [90]. Currently the monkeypox virus is in stage-3 of pathogen evolution to cause disease and phase-3 of WHO pandemic security alert level. The risk factors of absence of population-scale immunity, increasing efficiency of person-to-person transmission, and the presence of animal reservoir along with potential intermediate host suggests that monkeypox is no longer a rare disease and has potential to cause widespread epidemics becoming a threat for International Health Security. There is currently no approved antiviral or detailed case management for monkeypox however, selective agents developed for smallpox virus could be tested for treatment efficacy in case of outbreaks [89].

3.2.1.3 Nipah virus

Nipah virus is an emerging zoonotic -ssRNA virus belonging to the Henipavirus genus and Paramyxoviridae family. The natural reservoirs of Nipah virus are the Pteropid bats (fruit bats) with pigs acting as intermediate hosts [91, 92]. The fruits bats are limited to farms and orchards in the tropical and subtropical regions of Asia, East Africa, and Australian continents [91, 92]. The consumption of fruits by pigs which are contaminated or partially eaten by the Nipah virus infected Pteropod bats results in the spillover of the virus to intermediate hosts [93]. The transmission of the virus from intermediate hosts to humans is through direct contact with the excretions and secretions of infected pigs such as urine, saliva and respiratory secretions [92, 93]. The animal to human route is the primary mode of transmission with limited person-to-person transmission through direct contact with respiratory droplets or fomites. The major clinical manifestation of Nipah virus infection is acute encephalitis with headache, fever, vomiting, and dyspnea [92].

The Nipah virus outbreaks are limited to Asian continent with Malaysia (43%), Bangladesh (42%), and India (15%) reporting the incident cases worldwide [92]. The first outbreak of Nipah virus was identified in Malaysia in 1998 which spread to Singapore in 1999. This was mainly due to the importation of infected pigs from Malaysia to Singapore and the spillover of infection among pig farmers and abattoir workers [94]. This was followed by outbreak in Bangladesh in 2001 and neighboring India. In Bangladesh cases are identified nearly every year while India has reported outbreaks in 2001, 2007, and 2018 [92, 93]. All the Nipah virus outbreaks reported

till now had limited person-to-person transmission with R0 < 1 [93]. However, due to the high rate of mutations in the RNA virus, it has the potential of generating a strain with R0 > 1 [93]. Currently the disease is in the stage-3 of pathogenic evolution with phase-3 on pandemic alert scale. There is currently no medical countermeasure (antiviral or vaccine) approved or available against Nipah virus [92]. The genomic heterogeneity combined with the known susceptibility in humans and ability to cause person-to-person transmission suggests a future pandemic risk of Nipah virus and thus the listing of Nipah virus diseases as one of the WHO priority diseases with greatest danger for International Health Security [93, 95].

3.2.1.4 Hendra virus

Similar to the Nipah virus, Hendra virus is an emerging zoonotic pathogen belonging to the genus Henipavirus and family Paramyxoviridae. The Pteropid bats (Australian flying foxes) are the natural host with horses acting as amplifying hosts [91, 96]. Human disease follows transmission through contact with respiratory secretions of infected hosts while no person-to-person has been documented until now [96]. The clinical feature of Hendra virus disease in humans is acute encephalitis with or without influenza-like illness [96]. The first outbreak was identified in 1994 in Australia and the disease has been limited to Australia. There have been 7 human cases until now with a high case-fatality rate of 57% [96]. Currently, the disease is limited to stage-2 of evolution with phase-2 of pandemic alert level. There is currently no medical countermeasure (antiviral or human vaccine) approved against Hendra virus; however. an equine subunit vaccine is approved in Australia [92, 96]. The identification of virus in horses and presence in Pteropid bats underpins the potential of virus to cause large outbreaks in future becoming a threat for International Health Security.

3.2.1.5 Influenza viruses

These are a group of four types of enveloped -ssRNA Influenza viruses (A, B, C and D) belonging to the Orthomyxoviridae family of virus and are the common etiologic agent of respiratory infections in humans [97]. The virus is transmitted from person-to-person through respiratory droplets or contact with fomites [68]. Of the four types of influenza viruses, Influenza A and B cause disease in humans with influenza A having the ability to infect hosts of multiple species (pigs, horses, aquatic birds and poultry) in addition to humans [68, 98]. Influenza A undergoes antigenic drift and antigenic shift and thus causes seasonal epidemics and global pandemics while Influenza B undergoes only antigenic drift and is responsible for only seasonal epidemics [68, 99]. Antigenic drift is due to point mutation and results in minor genomic changes while antigenic shift is due to genetic reassortment and results in major genomic changes [68]. The antigenically different 18 hemagglutinin and 11 neuraminidase proteins further divides influenza A viruses into various subtypes i.e. H1N1, H3N2, H5N1, H7N9, H5N8.

Influenza A viruses have caused the highest number of known global pandemics in human history with Spanish flu (H1N1) in 1918, Asian influenza (H2N2) in 1957, Hong Kong influenza (H3N2) in 1968, and Swine flu (H1N1) in 2009 [100]. The seasonal influenza is responsible for annual epidemics in the human population with approximately 5–15% of the total world population being affected annually [68]. The clinical features of influenza infection include myalgia, headache, fever, sore throat, and non-productive cough with nearly 50% of infections asymptomatic [98]. The worldwide dissemination of avian influenza A viruses in domestic poultry flocks and birds and the demonstrated ability to infect humans has raised

the potential of future pandemic due to avian influenza A viruses which is of main International Health Security concern [101]. In 1997, an outbreak of H5N1 in Hong Kong resulted in 18 human cases and resulted in six deaths [102]. This was followed by continuous circulation of H5N1 strain in China with the widespread geographical distribution of this epizootic strain. Between 2003 and 2009, H5N1 resulted in 4o3 human cases with a high case fatality rate of 63%. Despite the high fatality, biological barriers prevent efficient binging of influenza virus to human receptors and thus the virus continues to have inefficient person-to-person transmission [102]. Similar human infections resulting in small outbreaks have been seen in H5N8 and H7N9 strains of avian influenza A viruses [101, 102]. However, the high propensity of influenza virus to undergo mutational changes may result in a complete species switch and lead to a pandemic which becomes an International Health Security threat.

M2 proton channel inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) are the traditional antiviral drugs approved for influenza prevention and treatment [103]. All the influenza A viruses are resistant to M2 proton channel inhibitors making the neuraminidase inhibitors the drugs of choice against influenza viruses. Balovir Marboxil, a viral replication inhibitor was approved by FDA in 2018 but rapid emergence of resistance has prevented its routine use [103]. The seasonal influenza inactivated vaccine requires yearly evaluation due to genomic heterogeneity and is effective mainly against the vaccine strains [68]. Thus, the antigenic shift that results in emergence of pandemic strain would make seasonal vaccines ineffective. Currently, the influenza A virus are in different stages of pathogenic evolution ranging from stage-2, stage-3 or stage-5 and have a phase-3 or phase-5 pandemic alert level depending on serotype [68, 101]. The ability of influenza virus to infect multiple species, cross species barrier, and high genomic variability resulting in novel viruses with low immunity among the population are the reasons behind the constant threat of pandemic by influenza A viruses.

3.2.1.6 SARS-CoV-2

In 2019, a novel zoonotic beta-coronavirus (+ssRNA) emerged as the cause of viral pneumonia in Wuhan, China and was later named as *Severe Acute Respiratory Syndrome-related coronavirus-2* (SARS-CoV-2). SARS-CoV-2, the etiologic agent of COVID-19 is transmitted from person-to-person predominantly through respiratory droplets and secretions [68, 104]. The SARS-CoV-2 causes an influenza like illness with severe cases presenting with dyspnea, septic shock, and acute respiratory distress. The mammalian reservoir for the virus is believed to be bats and contact with contaminated live animals is believed to be the cause of spillage of virus into humans [68, 104]. The virus rapidly spread globally affecting 218 countries in 6 continents with the outbreak being declared a global pandemic by WHO on March 11th, 2020 [104, 105]. According to WHO, a total of 83,910,386 cases of COVID-19 has been reported till January 4, 2021 with 1,839,660 of them having fatal outcome. A new variant of SARS-CoV-2 known as B.1.1.7 emerged in the United Kingdom in late September, 2020 due to N501Y mutation and has nearly 71% (95% CI: 67%–75%) higher rate of transmission than previous variant [106]. As of January 4th, 2021, three types of vaccines have been approved in United States and United Kingdom for emergency use for prevention of COVID-19 [107, 108]. This includes the mRNA vaccine by Pfizer/BioNTech, Moderna and non-replicating vector vaccine by AstraZeneca/University of Oxford [107, 108]. Additionally, the Russian Sputnik (vector) and Chinese Sinopharm (inactivated) vaccines have been approved in other parts of world to fight the COVID-19 pandemic [109, 110].

Antiviral remdesivir is the only therapeutic agent approved by FDA against SARS-CoV-2 with baricitinib currently under emergency use authorization for therapy in combination with remdesivir [111]. Currently, the SARS-CoV-2 pathogen is in the stage-5 of pathogenic evolution with ongoing global pandemic and becoming a menace for International Health Security. Despite the authorization of vaccine, the challenges associated with logistics of vaccination and emergence of new variants of SARS-CoV-2 suggests that SARS-CoV-2 will continue to be an agent of public health concern for years to come.

3.2.1.7 SARS-CoV-1

The first of the beta-coronavirus (+ssRNA) to emerge in Guangdong Province, China by zoonotic transmission was called Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV) and was responsible for the 2002/2003 Severe Acute Respiratory Syndrome (SARS) outbreak [68, 104]. The SARS-CoV-1 causes symptoms similar to SARS-CoV-2. The main mammalian reservoir host of this virus were bats with Asian civet cat believed be to the source of initial human infection [104]. The person-to-person transmission occurred due to contact with respiratory droplets or fomites. The epidemic started in November 2002 and spread rapidly to 29 countries in 5 continents resulting in 8437 cases and 813 deaths [68]. The outbreak was contained in July 2003 and since 2004 no cases of SARS has been reported [104]. Currently, there is no known transmission of SARS-CoV-1 to humans (stage-1) and it has a phase-1 pandemic alert level.

3.2.1.8 MERS-CoV

In 2012, a novel beta-coronavirus was identified to be the causative agent for acute respiratory disease in humans in Saudi Arabia and was named Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) [104, 112]. Bats are the main mammalian reservoir for MERS-CoV with dromedary camels as the source of human infection [104, 112]. This enveloped +ssRNA virus is transmitted from animals to human through close contact with infected dromedary camels and/or person-to-person through respiratory droplets [104, 112]. The majority of cases of MERS-CoV are limited to Middle East with the lack of rapid global spread due to poor efficiency of person-to-person transmission [104]. MERS-CoV infection results in symptoms similar to other beta-coronaviruses and range from mild influenza like illness to severe disease with respiratory distress, septic shock, and multi-organ failure [112]. The initial case in 2012 was followed by an outbreak in Middle East in 2014 impacting 27 countries in Europe, Asia, Middle East, and North America with cases related to Middle East travel history [104]. The associated Korean outbreak in 2015 was precipitated due to a super spreader event with the individual having travel history to Middle Eastern countries [104, 112]. Till December 2019, a total of 2499 confirmed cases and 858 deaths have been reported due to MERS-CoV [68]. Research studies have shown the natural susceptibility among Alpacas and Llamas camelids to MERS-CoV [113, 114]. This raises the potential of widening of the geographic distribution of MERS-CoV to the South American region with high new world camelids population (Peru, Argentina, Chile, Bolivia) if the virus is introduced to these regions, becoming a threat for International Health Security in the Americas. Currently, the virus in stage-3 of pathogenic evolution and phase-3 of pandemic alert level. The lack of vaccine or treatment along with the potential for viral mutation that could increase zoonotic and/or person-to-person transmission may increase the epidemic potential of MERS-CoV and cause an International Health Security threat.

3.2.1.9 Hantavirus

Different than any previously mentioned pathogens, Hantaviruses are an entire genus capable of causing human diseases. In 1981, this group of -ssRNA viruses were introduced into the Bunyaviridae family [115]. Before 1993, Hantaviruses were thought to be solely responsible to cause hemorrhagic fever with renal syndrome (HRFS) in old world [115]. The main reservoirs for this type of viruses are rodents such as Cricetidae and Muridae. In 1993, the first new world Hantavirus was found in the Southwestern region of the US. This virus would later be named Sin Nombre virus (SNV) and be known to cause hantavirus cardiopulmonary syndrome (HPS) [115]. Since the discovery of SNV, the hantavirus genus includes more than 20 species and 30 genotypes [115]. Scientists have identified the deer mouse as the major host of SNV with cases confirmed in at least 30 US states [116]. The transmission of virus in humans is predominantly through inhalation of aerosolized rodent urine or salivary droppings. The pulmonary syndrome presents flu-like symptom lasting 3 to 5 days and after 7 days the cardiopulmonary phase may begin [115, 116]. Unfortunately, diagnosis of HPS has proved difficult and leads to misdiagnosis and underreporting [116]. Currently, the SNV has a high case fatality rate of 35% with no licensed antivirals or vaccine. Since close contact with or among rodents account for majority of exposures, rodent prevention and population surveillance is essential for transmission control. In 1996, a study found evidence of person-to-person transmission of another hantavirus in Argentine, raising concern of larger outbreaks in future [117]. Luckily person-to-person transmission is rare, if non-existent suggesting pathogen is in stage-2 of pathogenic evolution and thus, phase-2 of pandemic alert level. Yet, recent outbreaks of other Hantaviruses (e.g., Andes virus) are an alarm for International Health Security surveillance systems who worry about future local outbreaks or global pandemics due to potential for person-to-person transmission.

3.2.2 Bacteria

3.2.2.1 Burkholderia pseudomallei

This gram-negative bacillus is commonly found in environment and is the etiologic agent of a serious disease "Melioidosis" in humans and animals [118]. The agent was first identified in 1911 in Burma but was named *Burkholderia pseudomallei* in 1992 [119]. Melioidosis, also known as "Whitmore disease" mimics various other diseases such as community-acquired pneumonia, tuberculosis and sepsis and has a case fatality rate of 10–40% in humans [120–122]. Infection with *B. psuedomallei* is seen in numerous wild and domestic animal species with most cases seen in pigs, sheep, and goats [123]. The disease was first identified in Australia in 1950 and is currently endemic in Northern Australia and South East Asia [119, 120, 122]. In addition to the endemic areas, sporadic cases of *B. pseudomallei* occur in non-endemic areas of Central America, South America, and Africa and result in an estimated 165,000 cases per year worldwide with 89,000 of these cases having fatal outcomes [119, 122]. The predominant method of transmission is percutaneous inoculation, inhalation of aerosols, or ingestion of contaminated water with rare incidence of placental transmission [118–120]. *B. pseudomallei* infects both humans and animals but very rarely there is person-to-person, animal-to-animal or zoonotic transmission [120, 123]. The infectious form of *B. pseudomallei* can persist for prolonged periods in the environmental with soil or water acting as reservoir [123]. Improvement in diagnostic facilities and risk factors such as increased diabetes prevalence, anthropogenic changes, and globalization of humans and animals

may result in increase in infections by *B. pseudomallei* [123]. The lack of animal to humans or person-to-person transmission suggest the gram-negative bacteria is in stage-1 of pathogenic evolution. In the US, melioidosis is not a nationally notifiable disease but *B. pseudomallei* is a tier-1 select agent with a potential for use as a bioweapon due to its ability to infect humans and animals [123]. *B. pseudomallei* is resistant to penicillin, ampicillin, 1st and 2nd generation cephalosporins, and aminoglycosides like gentamycin, tobramycin and streptomycin. The therapeutic management consists of an 10–15 days intensive therapy with ceftazidime or carbapenems (meropenem/imipenem) followed by eradication therapy with trimethoprim-sulfamethoxazole [124]. The increase in areas with endemicity and susceptibility to infections in large number of species suggests a future risk in increase in reported cases and thus warrants increased awareness and attention from International Health Security experts. The lack of vaccine and long-term pharmaceutical therapy would further complicate the response in case of an outbreak.

3.2.2.2 Coxiella burnetti

Coxiella burnetti, the causative agent of Q fever in humans is an intracellular gram-negative coccobacilli that occurs in all geographic regions of the world except New Zealand [125–127]. The main reservoir of *C. burnetti* are cattle, sheep, and goats with marine mammals, birds, and arthropods reported to harbor the bacterium [127, 128]. Ticks are the main source of transmission of the bacterium in domestic animals but are not the source of transmission in humans [125]. Human Q fever is a worldwide zoonosis transmitted due to the inhalation of aerosolized bacteria from the environment. The bacterium is mostly spread in the environment due to shedding of bacteria in mammalian birth products, milk, feces, and urine with the bacterium surviving in the environment for long period [125, 128]. There have been only anecdotal reports of person-to-person transmission [127, 128] suggesting the pathogen is currently in stage 2 of evolution. The epidemiological profile of *C. burnetti* differs by countries and ranges from sporadic cases such as in US marines in Iraq, an epidemic in Cayenne, French Guiana, a major outbreak in Netherlands from 2007–2010, and a hyperendemic situation in Africa [127–129]. The widespread geographical distribution of *C. burnetti*, the recent outbreaks and description of disease in South-East Asia, India, and Brazil suggest the disease is very common cause of fever in the inter-tropical areas [127, 128]. The strains of *C. burnetti* resistant to doxycycline and erythromycin has been reported in many endemic areas of the world however most isolates still remain susceptible to doxycycline, fluoroquinolones, and trimethoprim-sulfamethoxazole [128]. The CDC has recently classified *C. burnetti* as select agent with potential to be used as in bioweapon [128]. Currently, *C. burnetti* causes zoonotic diseases but has not resulted in human-to-human transmission and thus is at the phase-3 of WHO pandemic alert level. The ability of *C. burnetti* to infect wide range of vertebrate and invertebrate hosts, persist in environment for long time, and cause massive outbreaks such as in Netherlands suggest that *C. burnetti* could become a major International Health Security threat in future with potential to cause pandemics.

3.2.2.3 Bacillus anthracis

This gram-positive spore forming bacilli is the causative agent of anthrax, a zoonotic disease which is rare in humans and common in animals. Human anthrax is a highly contagious disease and can be transmitted from animals to human through contact with infected animal or animal products or ingestion of animal meat. However, this highly virulent disease has no documented person-to-person

transmission [68, 130]. Herbivores animals are the primary reservoir of anthrax with all warm blood animals susceptible to *B. anthracis* infection [130]. Depending on the method of entry of the pathogenic endospores (inhalation, ingestion, skin), the disease can have respiratory (5%), cutaneous (94%), and gastrointestinal (1%) forms [130].

Worldwide approximately 20,000–100,000 cases of anthrax are reported annually, with the disease a major threat in arid regions of Central Asia, Africa, Middle East, Haiti, and South America [68, 131]. In the US, a total of 18 cases of inhalational anthrax and no case of gastrointestinal anthrax has been reported in the 20th century [132]. The largest outbreak of human anthrax was reported in Soviet Union in 1979, due to ingestion or contact with contaminated meat. The spores of the bacilli are resistant to environmental conditions such as drying, heating, ultraviolet (UV) rays, and gamma radiation and can survive for decades [68, 130]. This makes *B. anthracis* a major biological risk with a potential to be used in bioterrorist attack. In October–November 2001, intentional release of anthrax resulted in 22 cases of inhalational or cutaneous anthrax in US [133]. The drug of choice for treatment is oral or intravenous doxycycline or ciprofloxacin with the vaccine having no efficacy in post-exposure prophylaxis [130]. The causative agent is sensitive to most antibiotics with the exception of 3rd generation cephalosporins and trimethoprim-sulfamethoxazole but requires long duration of treatment due to endospores [130]. Currently, the disease in in stage-2 of evolution of pathogenic microbe resulting in limited animal to human outbreaks and phase-2 pandemic security level. This combination of factors such as high virulence, persistence in environment, and the fact that it has already been weaponized makes *B. anthracis* a major concern for International Health Security.

3.2.2.4 Mycobacterium tuberculosis

Tuberculosis (TB) is a chronic inflammatory disease caused by an acid-fast bacilli *Mycobacterium tuberculosis*. In addition to *M. tuberculosis*, *M. bovis* a member of the *Mycobacteriaceae* genus also can cause TB infection [134]. With the advent of antibiotics, public health experts believed they had achieved control over TB however, the emergence of HIV pandemic in 1980s resulted in the re-emergence of TB [135]. In 2019, TB was the infectious disease responsible for the largest number of deaths due to communicable diseases worldwide [136]. The *M. tuberculosis* bacilli is transmitted from person-to-person through small droplet nuclei while *M. bovis* is a zoonotic disease transmitted from cow to humans through ingestion of unpasteurized milk [134, 137]. *M. tuberculosis* has also shown to have bidirectional transmission between elephants and humans i.e. reverse zoonosis and zoonosis [138, 139]. The zoonosis- reverse zoonosis transmission is mainly possible due to close contact between humans and elephants during training of elephants, living in close proximity, and cleaning of barn [138, 139]. The inappropriate usage of antimycobacterial agents and antibiotics associated selective pressure led to the emergence of drug resistance strains of *M. tuberculosis*. Multi-drug resistant TB (MDR-TB) is defined as resistance to isoniazid and rifampicin, two of the first line antimycobacterial agents. Additionally, selective strains of bacteria have emerged with resistance to even second line antimycobacterial agents causing extensively drug-resistant tuberculosis (XDR-TB) and some with total lack of susceptibility to antimycobacterial agents causing total drug-resistant tuberculosis (TB) [140]. MDR-TB chemotherapy consists of drugs with severe toxicity to be given for 18–24 months and thus MDR-TB is associated with significant morbidity and mortality.

TB affects all regions of the world with nearly a quarter of the world's population infected with *M. tuberculosis* [136]. In 2017, worldwide TB incidence was 10 million

with 1.57 million fatal outcomes [136]. Approximately 5.6% of the total TB cases and 3.6% of the incident cases were MDR-TB [136]. Nearly 70% of the global burden of TB was found in South-East Asia and Africa with India, China, and Russia having more than 50% of the global burden of MDR-TB [140]. Only 57% of all MDR-TB cases receives and completes treatment [140]. Tuberculosis is primarily a disease transmitted airborne from person-to-person and thus is in stage-5 of pathogenic evolution. MDR-TB continues to be a threat to public health and international security due to the concerns related to long duration of chemotherapy, lack of safe and effective antimycobacterial agents, morbidity, mortality, socioeconomic impact, airborne transmission and recent zoonotic-reverse zoonosis transmission. Many International Health Security experts believe MDR-TB could be the plague of century 21st.

3.2.3 Fungi

3.2.3.1 Candida auris

Candida auris is an emerging pathogenic yeast belonging to the genus Candida and is responsible for multidrug-resistant invasive infections in nosocomial settings [141–143]. The species has been mainly isolated from nosocomial environment, where it survives for a long time and can form biofilms resulting in inter and intra-nosocomial transmissions [141, 142, 144]. *Candida auris* was first identified in 2009 in Japan and has rapidly spread to five continents (North America, South America, Europe, Asia and Africa) becoming an International Health Security threat [143, 145]. *C. auris* infections has been identified in Australia, Bangladesh, Kuwait, India, Japan, Pakistan, Oman, Singapore, Iran, Panama, Venezuela, Colombia, Brazil, Chile, United States, United Kingdom, Spain, Germany, Israel, France, and the Netherlands [141–143]. The emergence of *C. auris* has been attributed to widespread usage of antimicrobial (antibiotics and antifungal) agents and rising ambient temperatures [141]. *C. auris* results in skin or mucosal colonization in patients with the organisms being recovered from physical surfaces such as furniture, medical equipment or sinks [141, 142]. No animal or environmental reservoir for *C. auris* has yet been identified. Previous [141] studies done in the United Kingdom, India and United States suggest community transmission and community reservoir are unlikely [141]. However, *C. auris* has a very efficient person-to-person transmission that allows it to spread rapidly among patients [141, 142, 144]. The person-to-person transmission and presence of yeast on surfaces suggest a potential respiratory droplet mode of transmission but no specific mode of transmission has been established yet [141, 142].

One unique feature that differentiates *C. auris* from other *Candida* spp. is its ability to cause invasive infections in individuals with normal neutrophil counts [144]. This is due to the reduced activity of human neutrophils against *C. auris* leading to poor outcomes [144]. Individuals requiring multiple medical procedures that results in prolonged hospital stay such as surgical procedures, cardiac catherization, endoscopic gastrotomy tube insertion and mechanical ventilation are at higher risk of *C. auris* infections [146, 147]. Infection or colonization with *C. auris* is also found frequently in patients with co-morbidities such as chronic/acute renal failure, immunosuppressive conditions/diseases, cardiovascular diseases, liver disease, diabetes mellitus and benign/malignant solid tumors [148]. The *C. auris* yeast exhibits a high range of antifungal resistance with resistance to fluconazole as high as 93% [141, 142]. Amphotericin B has a wider range of MIC and thus are less likely to be used as empirical therapy. Echinocandins has a more favorable susceptibility making it the drug of choice for *C. auris* infections [141, 142].

The lack of knowledge related to any animal reservoir makes the *C. auris* pathogen currently in stage-5 (exclusive human agent) of pathogen evolvement. The combination of drug resistance, persistence on environmental surfaces, reduced neutrophil effectiveness, and rapid person-to-person transmission has resulted in increased nosocomial outbreaks around the world with significant mortality and morbidity [141, 142, 144]. Currently, these outbreaks are limited to nosocomial settings and thus are in Phase-3 of WHO Pandemic alerts. These factors of rapid transmission, outbreaks in widespread geographical regions and reduced human neutrophil activity makes *C. auris* a huge potential International Health Security threat in case of sustained community outbreaks.

4. Conclusions

Since ancient times, large number of pathogens (viruses, bacteria, parasites, fungi) found in the environment are responsible for causing severe morbidity and mortality. These pathogenic organisms mainly infect humans through respiratory droplets, aerosols, dust, vector bite, contaminated food or water, or direct contact with animal hosts. The emergence of SARS-CoV-2 in 2019 and its global spread resulted in the announcement of the sixth public health emergency of international concern in last 10 years after Influenza A (H1N1) in 2009, Ebola virus in 2014, Polio in 2014, Zika virus in 2016, and Ebola in 2019 [68]. Moreover, in the last 20 years the emergence of novel pathogens such as SARS-CoV-1, MERS-CoV, Candida auris, and drug resistant bacteria in addition to the ongoing epidemics/local outbreaks of vector-borne diseases such as Crimean-Congo Hemorrhagic fever and Zika has raised International Health Security alarms. This chapter mainly concentrates on the epidemiology, pharmaceutical tools, prevention, and control of pathogens having respiratory or vector mediated transmission. Infectious diseases continue to be major causes of fatality worldwide despite the significant advances in civilization, scientific technology, and medicine. On the contrary, these same advances may contribute to the emergence, re-emergence, and rapid spread of diseases due to climate change, deforestation, globalization, and over usage of pharmaceutical tools. In the last few decades, the rapid emergence/re-emergence of novel and resistant pathogens make it essential to establish surveillance and research programs into potential pandemic causing pathogens. It is important to take cognizance of the hazards posted by these vector-borne and airborne pathogens, already circulating among the animal or human population to prevent the risk of epidemics and global pandemics. Majority of the viruses with potential to cause pandemics lack antivirals and vaccines while fungi and bacteria have developed resistance to antimicrobials. Thus, special attention needs to be paid in the research and identification of effective drugs against these pathogens to have the medical countermeasures available to fight future pandemics and protect our International Health Security.

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