1 Communicable Diseases and Emerging Pathogens: The Past, Present, and Future of High-Level Containment Care

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Introduction

The past few decades have witnessed a number of outbreaks of communicable disease caused by novel or emerging pathogens with the potential to produce significant morbidity and mortality in humans. Although highly hazardous communicable diseases (HHCDs) such as smallpox and plague date to antiquity, the year 1969 saw a convergence of events that brought such diseases, and the pathogens that cause them, into the forefront of public consciousness. The publication, that year, of Michael Crichton's fictional work, *The Andromeda Strain*, magnified concerns initially raised by media coverage surrounding the decision to shutter the US offensive biological weapons program. The success of the Apollo 11 mission later that year and the possibility that returning astronauts might bring extraterrestrial pathogens back to earth upon their return further heightened these concerns and was partly responsible for the decision to build the first specialized units dedicated to the isolation of patients potentially harboring highly hazardous communicable pathogens [1]. These units, the Lunar Receiving Laboratory at the Johnson Manned Spaceflight Center in Houston and the "Slammer" at the US Army's Medical Research institute of Infectious Diseases (USAMRIID) at Fort Detrick MD, would usher in a new era of "high-level containment care" (HLCC) and foster a reexamination of institutional

The views expressed herein are those of the authors and do not necessarily reflect the position of the University of Nebraska or its component entities.

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infection control procedures. Nearly simultaneously, an emphasis on improved laboratory safety would be prompted by the 1969 discovery of the contagious and deadly viral hemorrhagic fever virus, Lassa, by researchers at Yale [2]. After a Yale technician died of laboratory-acquired Lassa fever, research activities were relocated to a new maximum-security laboratory (the predecessor of today's Biosafety-Level-4 [BSL-4] laboratories) at the Communicable Disease Center (now the Centers of Disease Control and Prevention [CDC]) in Atlanta.

USAMRIID's "Slammer" was a two-bed unit that employed engineering controls analogous to those seen in BSL-4 laboratories. Designed with the ability to isolate (care for patients infected with HHCDs) and quarantine (observation of individuals potentially exposed to these diseases), the unit was utilized for the latter role 21 times over its 40-year existence [3], but was never required to isolate a symptomatic patient, a fact which likely factored into its decommissioning in 2012.

In the meantime, partly in response to bioterrorism concerns raised by the 2001 anthrax attacks, as well as to the subsequent outbreaks of severe acute respiratory syndrome (SARS) and monkeypox, civilian HLCC units were constructed at Emory University and at the University of Nebraska. These two facilities cared for seven Ebola virus disease (EVD) patients during the 2014–2016 outbreak, while another two were cared for at the National Institutes of Health's Special Clinical Studies Unit, which had also developed HLCC capability. A tenth EVD patient was successfully managed under improvised HLCC conditions at New York's Bellevue Hospital.

While US ETCs have, as of this writing, cared for a handful of EVD victims and a single patient with Lassa fever [4], it is expected that such facilities will be ready to manage patients with a number of additional HHCDs. In this regard, we envision that four broad categories of patients might be viewed as candidates for admission to a HLCC unit (Table 1.1). We briefly discuss each of these categories, as well as the pathogens contained therein, allowing that the list of such pathogens is designed to be neither under- nor over-inclusive. In this regard, we acknowledge that some institutions may elect to care for patients in a HLCC setting even though the disease they harbor may not be included on this list, and the same patient might not necessarily be managed under HLCC conditions at another institution. Similarly, we realize that new diseases may emerge and be cared for under HLCC conditions until a certain level of confidence with their management is gained. Finally, we acknowledge that future developments in vaccinology and therapeutics may well lead to the removal of some diseases from the current list.

Patients Who Might Warrant Care in a High-Level Containment Care Unit

First, patients harboring diseases caused by pathogens that require handling under BSL-4 conditions in the laboratory would seem to be obvious candidates for clinical management under HLCC conditions. Several taxonomic families contain such highly hazardous viruses:

The orthopoxvirus, Variola (the causative agent of smallpox)
The henipaviruses, Hendra and Nipah
The filoviruses, Ebola and Marburg
The arenaviruses, which can be divided into Old World (Lassa, Lujo) and New World (Guanarito, Junin, Machupo, Sabia) agents, the latter causing Venezuelan, Argentinian, Bolivian, and Brazilian hemorrhagic fevers, respectively
The bunyavirus, Crimean-Congo hemorrhagic fever (CCHF)
The flaviviruses, Kyasanur Forest (and the closely related Alkhumra virus), Omsk hemorrhagic fever, Russian spring-summer encephalitis (as well as closely related viruses), and viruses of the tick-borne encephalitis complex (such as Absettarov, Hanzalova, Hypr, and Kumlinge)

Table 1.1 Potential candidates for management under HLCC conditions

1. Persons with diseases having the potential for person-to-person transmission whose causative agents require handling under biosafety-Level-4 conditions
Arenaviral hemorrhagic fevers
Lassa fever
Lujo hemorrhagic fever
Argentinian, Bolivian, Brazilian, Venezuelan hemorrhagic fevers
Bunyaviral hemorrhagic fevers
Crimean-Congo hemorrhagic fever
Filoviral hemorrhagic fevers
Ebola, Marburg
Henipavirus infections
Hendra
Nipah
Smallpox
2. Persons with other diseases caused by highly hazardous pathogens with the potential for person-to-person transmission
Coronavirus infections
Severe acute respiratory syndrome (SARS)
Middle East respiratory syndrome (MERS)
Influenza
Highly pathogenic avian influenza (HPAI)
Other novel and highly pathogenic influenza virus infections
Orthopoxvirus infections
Monkeypox
Pneumonic plague
Extensively drug-resistant tuberculosis (XDR-TB)
3. Persons with apparently severe diseases of unknown etiology for which optimal therapy and infection control measures are unknown
4. Persons with apparently severe diseases for which public assurance concerns might warrant management under high-level containment conditions

Of these, we advocate that patients infected with any except the flaviviruses be considered for movement to a HLCC facility. The latter do not require containment because they lack person-to-person (PTP) transmission, with naturally occurring disease being acquired solely through the bite of an arthropod vector. With the exception of variola and the henipaviruses, the remaining BSL-4 pathogens produce a clinical syndrome of viral hemorrhagic fever (VHF) in humans, and all are transmissible, to varying degrees, from PTP.

In addition to the BSL-4 pathogens, there are several other diseases that cause high morbidity and mortality, which are potentially communicable and thus might prompt management in a HLCC unit. While a lower risk to laboratorians permits the causative agents of these diseases to be handled utilizing BSL-3 or even BSL-2 precautions, in many cases, the precise nature of PTP transmission risk is unknown. We thus propose that the optimal management of patients harboring these agents take place under HLCC conditions. Included in this category are persons infected with a number of viral pathogens: the SARS or MERS coronaviruses, highly pathogenic avian influenza (HPAI) and other seemingly morbid novel influenza strains, and the orthopoxvirus, monkeypox.

In addition, while pneumonic plague, caused by the bacterium *Yersinia pestis*, is treatable with antibiotics, its high degree of contagion, almost universal lethality in the absence of prompt intervention, and narrow window of opportunity for successful postexposure treatment or prophylaxis make its management in a conventional hospital setting dangerous. Moreover, its history as a cause of frightening global pandemics and its past association with biological warfare make it a public perceptual and surety risk (see below). Finally, while most patients with pulmonary tuberculosis caused by conventional strains of *Mycobacterium tuberculosis* are readily cared for in a negative-pressure isolation room within a conventional medical facility, the recent emergence of strains of extensively drug-resistant tuberculosis (XDR-TB) provides justification of the need for high-level containment.

We allow for the certainty that new diseases will continue to emerge and that these new diseases may initially be severe yet insidious, their causative agents unidentified, and optimal means of their control unknown (*The Andromeda Strain* problem). In such circumstances, it may, on occasion, be prudent to manage and study victims in a HLCC environment. In this regard, SARS, MERS, Nipah, Hendra, and most of the VHFs could have been considered “Andromeda strains” at the time of their initial appearance.

Finally, we acknowledge that newly emerging and highly lethal diseases raise security and surety issues and that these are compounded by fears of biological warfare and terrorism. There may be circumstances, then, when it would be reasonable to manage patients in a HLCC unit in response to political, public assurance, and risk management concerns.

The Pathogens

Ebola

The 2014–2016 outbreak of Ebola virus disease (EVD) in West Africa involved at least 28,616 cases with 11,310 deaths [5]. The 25th such outbreak, larger than the previous 24 combined [6], resulted in the infection of several Western aid workers, led to their repatriation to the United States and Europe [7], and prompted the current ongoing expansion of HLCC facilities and capabilities. EVD is caused by viruses of the genus *Ebolavirus* in the family Filoviridae; the viruses derive their name from the Ebola River in the Democratic Republic of the Congo (DRC, then called Zaire), from whence the first cases were described in 1976. While the 2014–2016 outbreak was caused by the same Ebola virus (the type species, previously known as Ebola Zaire), EVD is also caused by at least three additional members of the *Ebolavirus* genus, Bundibugyo, Sudan, and Tai Forest viruses. A fifth species, Reston virus, produces fatal disease in nonhuman primates and has resulted in seroconversions among laboratory workers, but is not known to cause overt disease in humans. To date, all outbreaks of EVD have arisen in a small handful of African nations; Guinea, Liberia, and Sierra Leone accounted for the vast majority of cases during the 2014–2016 outbreak, while previous outbreaks occurred in the DRC, Congo, Gabon, Uganda, and South Sudan. While the ecology of EVD remains unclear, fruit bats likely serve as a reservoir host for the viruses [8]; outbreaks may begin when humans acquire the disease through contact with these bats or with duikers and nonhuman primates (who are also susceptible to EVD) consumed as bush meat. EVD is then transmitted from PTP through infected blood and body fluids. Given the profuse amount of vomitus and diarrhea often seen among victims, along with the high concentration of virus in those fluids, the risk of such transmission is quite high, especially among family caregivers and those involved in funeral preparations. Similarly, patients with EVD pose an extraordinary risk of nosocomial transmission through exposure to blood and other bodily fluids during medical procedures. Finally, Ebola virus persists in semen for many months after recovery, raising the possibility of sexual transmission.

Ebola has an incubation period of 2–21 days (mean 8–10 days), after which patients develop fever, headache, myalgia, and gastrointestinal symptoms. Hemorrhagic manifestations may be mild or profound, with hematemesis and hematochezia, purpura, and ecchymosis sometimes seen. Death typically occurs as a result of multi-organ failure rather than hemorrhage per se, and the mortality rate has ranged from 25% to 90%, depending on the species. Supportive care is the cornerstone of EVD management, and meticulous attention needs to be paid to hemodynamics, respiratory status, fluid balance, and electrolyte abnormalities. While no licensed antiviral therapy exists, monoclonal antibodies [9] and other experimental treatments have demonstrated great promise, and a vaccine candidate has been shown to be 100% efficacious in a postexposure vaccination trial [10]. Ebola viruses should be handled in the laboratory using BSL-4 safety measures, and the processing of clinical specimens potentially harboring these viruses should involve at least

BSL-3 precautions, as would be the case with all of the pathogens discussed in this chapter. The corpses of EVD victims are teeming with virus and pose an extreme risk to handlers and family members; they should only be handled by trained persons wearing appropriate PPE. Patients infected with Ebola were managed under HLCC conditions in multiple countries that evacuated infected expatriate healthcare and aid workers from West Africa, including Germany, Switzerland, Britain, France, Norway, Italy, Netherlands, Spain, as well as the United States. The infection of two nurses who cared for an EVD patient in a conventional hospital setting in Dallas, Texas, and the more favorable mortality rates of patients treated in HLCC conditions (18.5% compared to 37–74% in West Africa) [12] underscore the value of HLCC units in EVD management.

Marburg

Marburg virus was first described as the cause of a lethal outbreak of viral hemorrhagic fever among laboratory workers in Marburg, Germany, in 1967. The prototype member of the newly described family Filoviridae, Marburg, caused 7 deaths among the 32 victims (22% mortality rate) managed in modern German medical facilities, 6 of whom represented secondary cases attributable to PTP transmission. Only rare sporadic cases of Marburg were seen subsequently until 1998, when an outbreak occurred in Congo in which 128 of 154 known cases died (mortality rate 83%). A second large and very lethal outbreak occurred in Angola in 2004 (227 deaths among 252 victims, mortality 90%). Marburg disease typically begins, following a 3–9-day incubation period, with the onset of fever, headache, myalgia, and gastrointestinal symptoms (vomiting and diarrhea). Rash, hemorrhage, and thrombocytopenia are common, and uveitis often occurs; death results from multi-organ failure. Nosocomial transmission is well documented. Management is supportive; there are no licensed therapeutic agents available to treat Marburg hemorrhagic fever, although immune plasma has been used [11], and experimental therapies have proven efficacious in nonhuman primates [12]. Laboratories should handle Marburg virus under BSL-4 conditions. The management of patients with Marburg infection in HLCC settings has occurred in both the Netherlands [13] and Germany [14].

Lassa

Lassa virus is a member of the family *Arenaviridae* and is an important cause of viral hemorrhagic fever in West Africa. Endemic in the same region affected by the 2014–2016 EVD outbreak, Lassa causes as many as 300,000–500,000 human infections annually in Nigeria, Guinea, Liberia, Sierra Leone, and other nations in the region, where it accounts for 10–16% of all hospitalizations [15]. Seroprevalence rates in these countries range as high as 20%, attesting to the fact that many infections are mild or silent. Among patients ill enough to require hospitalization, mortality typically ranges from 15% to 20%. While most Lassa infections result from

exposure (via ingestion or inhalation) to the urine and feces of *Mastomys* rats, PTP transmission is well documented, and the risk of nosocomial spread via exposure to blood and body fluids is high. Like Ebola, Lassa virus can persist in semen for several months, thus promoting sexual transmission. Symptomatic Lassa fever begins, following a 7–10-day incubation period, as a non-specific flu-like illness. Fever, myalgia, sore throat, and cough are followed by gastrointestinal symptoms and, often, by a maculopapular rash. In severe cases, manifestations of vascular leak (edema, ascites, pleural effusion) occur during the second week, as do neurologic symptoms such as seizures and coma. Overt hemorrhage occurs in only about 17% of patients [16], and death results from shock and organ failure. An elevated serum aspartate aminotransferase portends a poor prognosis, and levels above 150 IU/liter have been associated with a 55% mortality rate. It is in this group, however, that ribavirin was initially studied [17]. When administered intravenously within the first 6 days of illness, it reduced mortality to 5%. The use of ribavirin is also advocated for postexposure prophylaxis. Lassa is a BSL-4 pathogen and should be handled accordingly in the laboratory. Until the West Africa EVD outbreak, Lassa fever had been the most common VHF treated in an HLCC setting. Multiple HLCC units in Germany, Sweden, and the United Kingdom have experience managing Lassa fever patients, as does Emory University Hospital's Serious Communicable Diseases Unit, which treated a patient with Lassa in 2016. While three Lassa fever patients treated in the European facilities were medically evacuated from endemic countries, most were imported cases that were locally hospitalized and later transported to an HLCC facility [18, 19].

Lujo

Lujo virus, an Old World arenavirus closely related to Lassa, was first described in 2008 as the cause of a single outbreak of viral hemorrhagic fever involving five patients in Lusaka, Zambia, and Johannesburg, South Africa (the name, Lujo, derives from the two cities) [20]. Four of these patients died (mortality rate 80%), and there was evidence of spread to medical caregivers. Of note, the lone survivor was the only patient to receive ribavirin. No other cases have been reported as of this writing. Laboratories should handle specimens containing Lujo virus as they would those containing Lassa.

New World Arenaviruses

Guanarito, Junin, Machupo, and Sabia are members of the family *Arenaviridae* and the causative agents of Venezuelan, Argentinian, Bolivian, and Brazilian hemorrhagic fevers, respectively. The New World arenaviruses all have rodent hosts, and humans are incidentally infected, likely through exposure to aerosolized rodent excreta. Only a single case of naturally occurring (and two cases of laboratory-acquired) Sabia has been reported, and its potential for PTP and nosocomial

transmission is thus unknown. Data supporting PTP transmission of Guanarito is likewise sparse. The close relationship of these agents to Junin and Machupo, however, both of which are known to be transmitted from PTP in nosocomial and other settings, prompts us to advocate for the management of patients infected with any of the four viruses under HLCC conditions. The incubation periods of these diseases are generally thought to range from 5 to 19 days (shorter in the case of parenteral exposure such as via needle stick injury), after which time patients develop fever and malaise, accompanied by headache, myalgia, vomiting, and diarrhea. Neurologic manifestations may differentiate New World arenaviral infections from other VHFs, where they are far less common. These manifestations may include hyporeflexia, tremor of the tongue and upper extremities, gait abnormalities, seizures, and coma. Leukopenia and thrombocytopenia can be profound, and signs of vascular leak, such as proteinuria and large ecchymoses, are often prominent. Mortality is approximately 15–30% in the case of Junin or Machupo [21]. As with Lassa, however, ribavirin appears quite beneficial in the treatment of New World Arenaviral infections, as does convalescent plasma [22]. Although not licensed in the United States, a Junin virus vaccine has been widely employed in Argentina and is thought to be more than 95% efficacious [23]. Limited animal data supports the possibility that it may protect against Machupo infection as well. All four of these viruses warrant the use of BSL-4 precautions in the laboratory.

Chapare, another virus closely related to the abovementioned four, was isolated from a single fatal case of hemorrhagic fever in Bolivia [24], and three fatal hemorrhagic fever cases in California were attributed to another closely related arenavirus, the Whitewater Arroyo virus [25], which is widely distributed among woodrats in the American Southwest. Whether these two viruses can be transmitted from PTP is unknown, and while many additional arenaviruses have been discovered in rodents, their role in human disease likewise remains unknown. It would seem prudent to manage patients potentially harboring such diseases under HLCC conditions when feasible and to handle their causative viruses in a BSL-4 laboratory.

Crimean-Congo Hemorrhagic Fever

Although reports of a disease consistent with Crimean-Congo hemorrhagic fever (CCHF) date to the twelfth century, the illness derives its name from a large outbreak of hemorrhagic fever in 1944–1945 among Soviet troops serving in the Crimea and a subsequent outbreak in the Belgian Congo [26]. The causative agent of CCHF is a *Nairovirus* in the family *Bunyaviridae*, the only member of this taxon requiring BSL-4 handling. Spread largely via the bite of *Hyalomma* ticks, it is endemic throughout much of this vector's range in Africa, Central Asia, the Middle East, and the Balkans [27]. Nonetheless, it also poses a significant risk of PTP transmission (the only bunyavirus apparently capable of this), with over 80 cases having occurred among healthcare personnel. On a global scale, CCHF is the most important tick-borne infection of humans, responsible for over 140 separate outbreaks

since isolation of the virus in 1967. While 80% of human infections are thought to be subclinical, symptomatic CCHF presents in similar fashion to most other VHFs—following an incubation period of 1–3 days after a tick bite (or 5–6 days after exposure to the fluids of an infected person), patients typically experience the abrupt onset of fever, myalgia, and headache, often accompanied by neck stiffness and photophobia. Gastrointestinal symptoms (nausea, vomiting, diarrhea) are frequently seen, and thrombocytopenia with hemorrhagic manifestations (petechiae, ecchymoses) is often prominent. Although CCHF has a mortality rate of 10–40% in the absence of therapy, ribavirin may be beneficial in reducing mortality and in the prophylaxis of exposed contacts [28]. Despite a relatively wide geographic distribution, confirmed cases of CCHF in Western Europe are relatively rare. In 2004 and 2012, imported cases of CCHF were treated in HLCC units in France and the United Kingdom, respectively [29, 30]. Two autochthonous cases of CCHF occurred in Spain in 2016: the first patient was initially admitted to an ICU before being transported to an HLCC facility, and the second patient was a nurse who had cared for the first patient in the conventional ICU [31].

Another bunyavirus, Rift Valley fever (RVF) virus, is a relatively common cause of disease outbreaks throughout Africa and the Arabian Peninsula. Although it can cause a hemorrhagic fever syndrome in a small minority of cases, there is no evidence for PTP transmission of RVF and HLCC management is thus unnecessary.

Nipah

Nipah virus infection is caused by a paramyxovirus in the genus *Henipavirus*. It was first described in 1999 as the cause of an outbreak of respiratory illness and encephalitis in Malaysia and Singapore; during the initial Malaysian outbreak, at least 100 of 257 cases resulted in death [32], for a mortality rate of 39%. Subsequent outbreaks have been limited to Bangladesh and neighboring areas of India. While virtually all cases of Nipah infection in Malaysia and Singapore are thought to have resulted from close contact with infected pigs, PTP transmission appears to be a factor in the spread of disease during Bangladeshi outbreaks [33]. The Malaysian pigs presumably acquire the disease from *Pteropus* bats which roost in the orchards where pigs are permitted to feed on fallen fruit. In Bangladesh, a Muslim-majority nation in which pigs are seldom raised, disease appears instead to be spread via the consumption of raw date palm sap contaminated with bat excrement. Nipah has an incubation period of 5–14 days, after which time patients develop fever and headache, followed by drowsiness, confusion, and, in some cases, respiratory distress. Permanent neurologic sequelae, including personality changes and seizures, occur frequently. Treatment of Nipah is generally supportive, although ribavirin appears efficacious in vitro. Laboratories should handle Nipah virus under BSL-4 conditions.

Hendra

Like Nipah, Hendra virus infection is caused by a *Henipavirus* in the family *Paramyxoviridae*. The virus was discovered in 1994 as the cause of fatal infections among horses in Hendra, a suburb of Brisbane, Australia. Similar to the situation with Nipah, the horses appear to have contracted the disease through exposure to the secretions of infected *Pteropus* bats. Although human infection has been exceedingly rare (only seven cases have been reported as of this writing), mortality is high (4/7, 57%). Hendra appears to have an incubation period of 9–16 days, and clinical disease involves a severe respiratory illness accompanied by encephalitis. Ribavirin has in vitro activity against the virus but has not been studied in vivo. While PTP transmission of Hendra has not been documented, we feel that the similarities between this virus and Nipah, coupled with scant clinical experience, warrant extreme prudence. We thus advocate for the management of human Hendra virus infection in a HLCC setting: laboratory handling should be done under BSL-4 conditions.

The SARS Coronavirus

The severe acute respiratory syndrome (SARS) first appeared as a distinct clinical entity in the Guangdong province of China in 2002. The disease was ultimately attributed to a newly described coronavirus, a taxonomic family previously associated with the common cold. While 85% of the 8–10,000 cases associated with the 2003 epidemic occurred in China, global travel resulted in infections in 37 nations, with a mortality rate of approximately 10%. Toronto, Canada, experienced roughly 250 cases, with evidence of local PTP transmission. The disease then disappeared, and there have been no reported cases anywhere in the world since 2004. Bats appear to be the reservoir for the SARS coronavirus (SARS-CoV) and are thought to have spread the pathogen to civet cats; early human infections resulted from contact with these cats [34]. Although animal hosts may be asymptomatic, human infection with SARS-CoV results, after a 2–7-day incubation period, in an initial flu-like illness with fever, cough, sore throat, myalgia, and lethargy. This typically progresses to a severe viral pneumonia, sometimes with secondary bacterial involvement. Diarrhea and other gastrointestinal symptoms occur in a significant minority of patients. Laboratory findings often include lymphopenia, as well as elevated transaminases, lactate dehydrogenase, and creatine phosphokinase. The treatment of SARS is supportive, and BSL-3 precautions should be employed by laboratories.

During the SARS outbreak, 33 cases were imported into Western Europe, and most were treated in HLCC settings in Germany, France, Italy, Sweden, and the United Kingdom [35]. At the epicenter of the outbreak, isolation capabilities in Beijing and Singapore were exhausted quickly, and hospital complexes with HLCC capability were built for increasing numbers of SARS patients [36, 37]. In Singapore and Taiwan, insufficient space led to the temporary designation of SARS hospitals,

where engineering controls were installed, contamination zones established, and PPE donning and doffing areas designated [38].

The MERS Coronavirus

The Middle East respiratory syndrome is caused by another coronavirus (MERS-CoV) closely related to SARS-CoV and was first described as the cause of an outbreak of severe and often fatal respiratory disease on the Arabian Peninsula in 2012. While autochthonous cases have been reported only in the Middle East, travel-associated cases have occurred in the United States, Western Europe, and East Asia. As of this writing, the outbreak is still ongoing, with well over 1500 cases reported; although asymptomatic infection does occur, the mortality rate of MERS is 35–40% among symptomatic patients. Person-to-person transmission occurs frequently. Following an incubation period of 2–14 days, MERS begins with non-specific flu-like symptoms and progresses, much like SARS, to a severe viral pneumonia, acute respiratory distress syndrome, and respiratory failure. Laboratory findings are similar to those seen in patients with SARS, and clinical management is likewise supportive. The World Health Organization has published comprehensive guidance for the provision of supportive care to patients with MERS [39]. MERS-CoV isolates, as well as specimens from patients suspected of having MERS, should be handled in the laboratory using BSL-3 precautions.

Highly Pathogenic Influenza Strains

Influenza is caused by a number of viruses in the family *Orthomyxoviridae*. Human infections are attributed to three genera, *influenza viruses* A, B, and C. While influenza B and C are known to cause seasonal disease in humans, only influenza A has the potential for causing devastating pandemics. This potential results from the virus's ability to exchange genes among strains, a process resulting in "antigenic shift." The most important of these genes are those coding for two viral proteins, hemagglutinin (H) and neuraminidase (N). Viral strains are characterized by these proteins, with H1N1 and H3N2 currently circulating as causes of seasonal influenza among humans. While most viruses are somewhat species specific, both human and avian strains have the ability to infect pigs; simultaneous infection of pigs risks the exchange of genetic material between human and avian strains within the porcine host. Such an exchange caused the 2009 H1N1 swine variant outbreak and, while this outbreak was milder than some feared initially, the devastating potential of novel influenza strains is best highlighted by the global 1918 Spanish flu pandemic, which is estimated to have caused 50–100 million deaths worldwide (3–5% of the world's population) [40]. Even in the absence of a pandemic, seasonal influenza causes a mean of 36,000 excess deaths annually in the United States alone, largely among the elderly. Although most patients recover from seasonal human influenza, disease caused by avian strains among poultry and aquatic birds can be devastating.

Highly pathogenic avian influenza (HPAI) H5 or H7 strains can have mortality rates of 90–100% in chickens, turkeys, and ducks. While most avian influenza viruses are not particularly infectious for humans, there is fear that a novel emerging influenza strain might combine the infectivity for humans with mortality rates seen in birds.

Seasonal influenza has an incubation period of 1–4 days, and patients may be contagious 24 h prior to the onset of symptoms, which poses a challenge to infection control efforts. Initial symptoms include fever and respiratory complaints (cough, sore throat, rhinitis), accompanied by myalgia, headache, and malaise. Primary viral and secondary bacterial pneumonias occur frequently and are often the cause of death in fatal cases. Avian influenza strains, when they do produce symptomatic disease in humans, often result in rapid progression to severe respiratory distress and respiratory (as well as other organ) failure. While supportive care is a mainstay of treatment for all forms of influenza, adamantanes (amantadine, rimantidine) and neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) have been beneficial in some cases. Susceptibility to these drugs varies greatly among strains, however, and their use should be considered in view of guidelines put forth annually by the CDC and World Health Organization. Annual influenza vaccination will not protect against novel and avian strains but is useful in lowering the prevalence of seasonal influenza in the community, thereby potentially providing diminished opportunities for viral reassortment events. The sporadic occurrence of a case of influenza caused by a novel, seemingly highly pathogenic strain might merit isolation and care under HLCC conditions. In the face of a pandemic, however, HLCC bed capacity would quickly be overwhelmed, and alternative management strategies would need to be employed. Seasonal influenza virus strains, and clinical specimens harboring such strains, can be handled under BSL-2 conditions. Non-contemporary and HPAI strains warrant BSL-3 handling.

Variola (Smallpox)

Smallpox ranks as, perhaps, humanity's greatest killer. Responsible for the deaths of several hundred million people over the course of history, its eradication, the result of an intense and coordinated global effort, similarly ranks among public health's greatest achievements. Naturally occurring smallpox was last seen in Somalia in 1977, and worldwide vaccination against the disease was halted in the early 1980s. A case today would likely be the result of a laboratory accident, a bio-terror attack, or a reawakening of dormant virus (e.g., from a corpse preserved in permafrost). Smallpox is caused by variola virus, a member of the *Orthopoxvirus* genus in the family *Poxviridae*. Its control was enabled by the use of a vaccine derived from vaccinia, a related, but far less pathogenic virus in the same genus. Unusual among viruses, variola is quite stable ex vivo and can survive (e.g., in crusted scab material) for decades. Smallpox is transmissible via both contact (e.g., with scabs) and droplet nuclei. Following an incubation period of 7–17 days, initial symptoms include fever, malaise, prostration, headache, and myalgia [41]. These symptoms are followed very closely by a characteristic exanthem and enanthem

(lesions can be seen in the mouth and other mucosal surfaces and are present on internal organs). The rash progresses in synchronous fashion from macules to papules to vesicles to pustules to tense painful lesions said to mimic pellets embedded in the skin. The lesions are centrifugal in distribution and involve the palms and soles, differentiating them from those of chickenpox. When the disease was endemic, smallpox had a 30% mortality rate (from multisystem organ failure), and survivors were left with deep scars from these lesions.

Historically, supportive care served as the primary means of treatment for smallpox patients, although recently cidofovir [42], licensed for the treatment of cytomegalovirus retinitis, has shown promise in treating other orthopoxviruses in animal models and in immunocompromised humans. Similarly, tecovirimat has been used under an investigational new drug protocol to treat persons with complications arising from receipt of live vaccinia virus and has also demonstrated efficacy in animal *Orthopoxvirus* models [43]. As evidenced by its past success, vaccination is quite effective in preventing smallpox, and the US Strategic National Stockpile contains robust quantities of vaccinia vaccine. Administering vaccine promptly postexposure (within 4 days) may prevent or ameliorate disease, an unusual attribute among vaccines. Despite these countermeasures, an outbreak of smallpox today, occurring in an immunologically naïve population, would likely pose a significant risk of mortality, and a single case would constitute a grave public health emergency. Smallpox stores are held in only two authorized laboratories at the Centers for Disease Control and Prevention (CDC) and at the State Research Center of Virology and Technology in Koltsovo, Russia. Any handling of clinical materials potentially containing virus should only be done under tight security and BSL-4 conditions.

Monkeypox

Monkeypox is caused by an *Orthopoxvirus* closely related to variola and was only differentiated from smallpox in 1970 during efforts to eradicate the latter [44]. While its primary host appears to be macaque monkeys, it can infect humans and a number of other animals, notably rodent species. While monkeypox is endemic in the Democratic Republic of the Congo, contact with infected rodents has resulted in cases elsewhere. In 2003, an outbreak of monkeypox in the upper Midwestern United States was traced to the importation of infected Gambian giant rats. The rats transmitted the disease to prairie dogs; exposure to these rodents resulted in the infection of over 70 people [45]. In fact, fear among clinicians and refusal to care for infected patients during this outbreak [46] was one factor leading to the University of Nebraska's decision to build its HLCC unit. Human monkeypox presents a clinical picture very similar to that of smallpox, albeit with a milder course and lower mortality rate (<10%). In addition, monkeypox produces significant generalized lymphadenopathy whereas smallpox does not, perhaps indicative of more effective immune recognition [47]. It is principally for this reason—the need to rule out smallpox—that we advocate for the management of suspected monkeypox patients under HLCC conditions. Monkeypox is transmissible from PTP, and

special caution is warranted until such time as smallpox is ruled out. Vaccinia vaccine administration appears protective against other orthopoxviruses, including monkeypox, and HLCC unit personnel can thus be protected through immunization. Monkeypox should be handled in the laboratory using BSL-3 precautions.

Pneumonic Plague

Few diseases conjure up images of fear and destruction as vividly as plague. The disease was first described as the cause of a great pandemic that began in Egypt in 541 AD. Known as the "Plague of Justinian," it led to the death of 50–60% of the population of Europe and is said to have sealed the fate of the Eastern Roman Empire. A second pandemic, known as the "Black Death," struck Europe in 1346 and wiped out one-third of the existing population. A third pandemic began in China in 1855 and killed at least 12 million. Plague, caused by the Gram-negative bacillus, *Yersinia pestis*, presents clinically in multiple forms, with bubonic, septicemic, and pneumonic being the most common. Bubonic plague is most often contracted by the bite of an infected flea, particularly *Xenopsylla cheopis*, the Oriental rat flea; in the United States, prairie dogs often serve as a reservoir. Pneumonic plague can be acquired primarily through exposure to infectious droplets (as might be generated by coughing or sneezing) or secondarily following the seeding of the lungs of a septicemic patient. It is this form of the disease that is readily transmissible from PTP. Pneumonic plague typically begins following an incubation period of just 2–3 days, when patients experience the abrupt onset of high fever, chills, and rapidly developing tachypnea and dyspnea. Hemoptysis, a hallmark finding in pneumonic plague, occurs within 18–24 h of symptom onset and heralds an almost universal and rapidly impending death. As a bacterial disease, plague is amenable to treatment with antibiotics; aminoglycosides (streptomycin, gentamicin), fluoroquinolones, doxycycline, and chloramphenicol are typically effective but must be started very early in the course of disease. We advocate for the management of patients with pneumonic plague under HLCC conditions due to plague's extreme infectivity, short incubation period, very rapid progression from the onset of symptoms to death, and futility of treatment once patients have become symptomatic. Preexposure and postexposure prophylaxis with oral doxycycline or ciprofloxacin may be useful in protecting healthcare workers caring for a plague victim. A licensed vaccine is currently out of production; while it provided some efficacy against bubonic plague, it was ineffective at protecting against disease acquired via inhalation. BSL-3 controls should be employed by clinical laboratories handling *Yersinia pestis* or specimens potentially containing the organism.

XDR-TB

Tuberculosis (TB) is caused by infection with the bacterium *Mycobacterium tuberculosis* (and occasionally by *M. bovis*) and has been a scourge of mankind since

antiquity. Responsible for the deaths of 25% of adults in eighteenth-century Europe, the disease was brought under control with the discovery of streptomycin in 1946 and isoniazid in 1952. Most isolates of *M. tuberculosis* remain susceptible to these drugs today and to others such as rifampin, ethambutol, and pyrazinamide. Nonetheless, the recent emergence of multi-drug-resistant TB (MDR-TB) strains, defined as having resistance to both isoniazid and rifampin, is a cause for concern given the limited number of effective tuberculocidal drugs available. Even more ominous are strains of extensively drug-resistant TB (XDR-TB), defined as having resistance to isoniazid, rifampin, and fluoroquinolones, plus at least one of three "second-line" drugs (kanamycin, amikacin, and capreomycin, all of which are only effective when administered parenterally). Patients harboring such strains pose significant treatment challenges and only 30–50% achieve cure. Even in cases where treatment is ultimately successful, the period of contagion may be prolonged, and patients may require airborne isolation for many months.

One-third of the world's population has TB, although the vast majority of these persons have latent infection and are asymptomatic (and noninfectious). While tuberculous disease may involve lymph nodes, kidneys, spine, bone, and other organs, it is the pulmonary form of TB which is most common among symptomatic patients, however, and the form which poses the greatest risk of PTP transmission. Patients with symptomatic pulmonary TB typically present with chronic cough, night sweats, low-grade fever, and weight loss. Radiographic findings vary considerably, but often include hilar and paratracheal lymphadenopathy, as well as pulmonary cavitary lesions and upper lobe atelectasis or infiltrates. Most patients with pulmonary tuberculosis caused by susceptible strains are readily managed in a negative-pressure isolation room using airborne precautions. We believe, however, that disease due to MDR-TB should prompt consultation with an expert in TB management. We further advocate that disease due to XDR-TB should be considered for management in a HLCC unit; the agent, and clinical specimens potentially containing it, should be handled under BSL-3 conditions.

Discussion

The list of pathogens that might warrant care under HLCC conditions is short, and the incidence of disease caused by the majority of these pathogens, at least in developed settings, is low. This is fortunate given the very limited capacity to provide such care. While we foresee that this capacity will increase in the coming years, driven in large part by the collaborative efforts of the National Ebola Training and Education Center (NETEC), we expect that their principal benefit will derive from a reexamination and a strengthening of "conventional" infection control practices throughout the healthcare system. While some might call for a more dramatic expansion in HLCC capacity, further additions to the list of diseases managed in HLCC units, or even a return to BSL-4-like care, there is reason to proceed cautiously. HLCC, and especially BSL-4-like care, is not without disadvantages. The most obvious of these are economic. It is estimated that the average cost incurred by

US Ebola Treatment Centers in acquiring HLCC capabilities during the 2014–2016 EVD outbreak exceeded $1.19 million per hospital [48]. While some of these are one-time investments (e.g., unit construction and planning), others are ongoing operational costs, such as staff training and the maintenance of supply stocks. Moreover, the provision of care under HLCC or BSL-4-like conditions creates numerous challenges for caregivers: PPE ensembles can be awkward and clumsy and can lead to claustrophobia. They also limit the time that caregivers can spend performing direct patient care activities, and they decrement auditory and tactile sense. All of these factors risk decreasing, rather than improving, patient and provider safety. While intense training and frequent exercising assist in mitigating against these risks in existing HLCC units, they may be impractical on a larger scale.

Conversely, the management of these HHCDs outside the HLCC environment is fraught with hazard. Cases have been successfully treated in conventional hospitals when an HLCC setting was unavailable or there was a delay in diagnosis; a woman with undiagnosed Marburg virus infection was successfully managed at a community hospital in Colorado [49]. Institutional responses to such exigencies have involved modifying policies, adapting infrastructure, and relying on universal standard precautions. Such approaches, however, heighten the exposure risk to healthcare workers and can cause critical delays in treatment and laboratory testing. Documented nosocomial transmission of many of the aforementioned diseases and high infection rates among healthcare workers during the SARS and EVD outbreaks reinforce the importance of engineering controls and highly trained staff to provide safe, quality care to patients harboring highly hazardous contagious pathogens. Therefore, while these diseases may be managed safely in a conventional facility if absolutely necessary, in most cases transfer to an HLCC unit is warranted to ensure the safety of healthcare workers, other patients, and the general public.

In summary, the HLCC unit incorporates a broad range of infection control measures, engineering modifications, and personnel considerations (detailed in another chapter in this text) that differentiate it from the "conventional" negative-pressure hospital isolation ward. These serve to:

1. Protect patients by providing care in a self-contained unit staffed by selected individuals with expertise in critical care and infectious diseases
2. Protect families by removing difficult decisions about visitation
3. Protect other patients from the threat of contagion
4. Protect laboratory personnel handling specimens containing highly hazardous communicable pathogens
5. Protect the community by offering an additional level of safety, surety, and confidence
6. Protect the healthcare worker against nosocomial transmission

This latter protection is especially vital given that at least 815 cases of nosocomial Ebola occurred during the 2014–2016 West African outbreak [50], a risk to clinical personnel 21–32 times that of the general population [51].

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