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Major article

Emerging infectious diseases: Focus on infection control issues for novel coronaviruses (Severe Acute Respiratory Syndrome-CoV and Middle East Respiratory Syndrome-CoV), hemorrhagic fever viruses (Lassa and Ebola), and highly pathogenic avian influenza viruses, A(H5N1) and A(H7N9)

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Over the past several decades, we have witnessed the emergence of many new infectious agents, some of which are major public threats. New and emerging infectious diseases which are both transmissible from patient-to-patient and virulent with a high mortality include novel coronaviruses (SARS-CoV, MERS-CV), hemorrhagic fever viruses (Lassa, Ebola), and highly pathogenic avian influenza A viruses, A(H5N1) and A(H7N9). All healthcare facilities need to have policies and plans in place for early identification of patients with a highly communicable diseases which are highly virulent, ability to immediately isolate such patients, and provide proper management (e.g., training and availability of personal protective equipment) to prevent transmission to healthcare personnel, other patients and visitors to the healthcare facility.

Dr William Stewart, U.S. Surgeon General, is alleged to have said in the late 1960s, "it is time to close the book on infectious diseases, and declare the war against pestilence won."[1] This widely repeated statement turned out to be an urban legend and never to have been said.[2] However, the "belief that infectious diseases had been successfully overcome was pervasive in the biomedical circles—including among a Nobel Laureate, medical Dean, and other thought leaders—from as early as 1948, and extending into the mid-1980s."[2] The discovery that the 1976 outbreak of pneumonia (Legionnaires' disease) was caused by a newly described bacteria, *Legionella* spp, was an awakening call for public health and infection control professionals.[3,4] The first reports of the disease later known as AIDS in 1978[5,6] and the discovery of the virus that causes AIDS,[7] now known as HIV, in 1983 further demonstrated that infectious diseases would continue to be a major source of morbidity and mortality for patients. Importantly, although *Legionella* spp turned out not to be a new human pathogen but one that had caused human diseases for centuries, HIV was a new pathogen to humans, and its origin was traced to simian immunodeficiency viruses in primates.[8]

The public health threats posed by emerging diseases have been well described in 2 reports from the Institute of Medicine, one in 1992 and one in 2001.[9,10] Since the discovery of *Legionella* and HIV, many emerging infectious diseases have had important infection control implications. This review will focus on several of the most important threats, including novel coronaviruses (severe acute respiratory disease [SARS] and Middle East respiratory syndrome [MERS]), hemorrhagic viruses (Lassa, Ebola), and novel influenza viruses, and the infection control strategies required to mitigate the associated public health threat posed by these viruses.

EMERGING INFECTIOUS DISEASES

Definitions

The World Health Organization defines an emerging infectious disease as "one that has appeared in the population for the first time,

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or that may have existed previously but is rapidly increasing incidence or geographic range."[11] The Centers for Disease Control and Prevention (CDC) define emerging infectious diseases as follows[12]:

- New infections resulting from changes in or evolution of existing organisms.
- Known infections spreading to new geographic areas or populations.
- Previously unrecognized infections appearing in areas undergoing ecologic transformation.
- Old infections re-emerging as a result of antibiotic resistance in known agents or breakdowns in public health measures.

Factors in the emergence of infectious diseases

In 1985, Wilson described the basic concepts in infectious disease emergence as follows[13]:

- Emergence of infectious diseases is complex.
- Infectious diseases are dynamic.
- Most new infections are not caused by genuinely new pathogens.
- Agents involved in new and re-emergent infections cross taxonomic lines to include viruses, bacteria, fungi, protozoa, and helminths.
- The concept of the microbe as the cause of disease is inadequate and incomplete.
- Human activities are the most potent factors driving disease emergence.
- Social, economic, political, climactic, technologic, and environmental factors shape disease patterns and influence emergence.
- Understanding and responding to disease emergence require a global perspective, conceptually and geographically.
- The current global situation favors disease emergence.

An important concept listed by Wilson is that most new and emerging infections are zoonotic diseases that have jumped taxonomic lines to infect humans. Of the approximately 1,400 known human pathogens, 58% are zoonotic, including 73% of the 117 that meet the definition for emerging or re-emerging infectious pathogens.[14] Importantly, all of the pathogens that are the focus of this article are zoonotic. A more complete list of pathogens considered to have emerged via a species jump have been published.[15] Karesh et al have reviewed how zoonotic diseases result from natural pathogen ecology and how other circumstances, such as animal production, extraction of natural resources, and antimicrobial application, change the dynamics of disease exposure to human beings.[16] The stages in emergence of pandemic zoonotic diseases have also been reviewed.[17-19] Morse et al described 3 stages in emergence of zoonotic diseases: (1) pre-emergence (encroachment into wildlife habitat and change in land use); (2) localized emergence (expansion of the wildlife–human being interface, for example Ebola virus); and (3) pandemic emergence (international travel, for example SARS, HIV and AIDS).[18] Pike et al described 5 stages in zoonotic disease emergence: (1) exclusive to animals; (2) primary human infections only; (3) limited human-to-human transmission; (4) sustained human-to-human transmission; and (5) exclusive to humans.[17]

The 1992 Institute of Medicine report on microbial threats listed the factors in infectious disease emergence as follows: (1) ecological changes, including those caused by economic development and land use (agriculture: dams, changes in water ecosystems; deforestation/reforestation; flood-drought; famine; climate changes); (2) human demographics and behavior (societal events: population growth and migration; war or civil conflicts; urban decay; sexual behavior; intravenous drug use; use of high-density facilities); (3) international travel and commerce (worldwide movement of goods and people; air travel); (4) technology and industry (globalization of food supplies; changes in food processing and packaging; organ or tissue transplantation; drugs causing immunosuppression; widespread use of antibiotics); (5) microbial adaptation and change (microbial evolution, response to selection in the environment); and (6) breakdown in public health measures (curtailment or reduction in prevention programs; inadequate sanitation and vector control measures).[9,20] A more recent article listed the following factors as influencing new and re-emerging infections: exotic pets, exotic foods (eg, bush meat), companion animals, alterations in livestock management, acquisition of new virulence factors, pathogen adaptation to new host species, changes in land use, tourism, translocation of infected animals or persons, and climate changes influencing arthropods.[21]

EMERGING INFECTIOUS DISEASES OF INFECTION CONTROL IMPORTANCE

Overview

In the last 35 years, many emerging infectious diseases of infection control importance have been described (Table 1).[22-24]

Table 1
Selected emerging diseases of infection control importance

Disease (initial location)	Cases (United States)	Outcome	Person-to-person transmission	Patient-to-HCP transmission	Infection control risk	Year
Legionnaires' disease	Unknown (thousands)	Endemic and epidemic	No	No	High	1976-present
HIV (Africa)	Millions (thousands)	Ongoing epidemic	Yes (blood exposure, organ transplantation, vertical, sexual)	Yes (blood exposure)	Moderate	1978-present
vCJD	Hundreds	Controlled	Yes (blood, theoretically via contaminated medical instruments)	No	Low	1996
West Nile fever	(Thousands)	Endemic	Yes (blood transfusions, vertical, organ transplantation)	No*	Low	1999
SARS (China)	~8,000 (8)	Controlled	Yes (droplet, contact, airborne?)	Yes	High	2003-2004
Monkeypox (Africa)	(37 confirmed, 10 probable)	Eliminated in United States	Yes (droplet, contact)	Yes†	High	2003
MERS (Middle East)	Thousands (2)	Controlled	Yes (droplet, contact)	Yes	High	2014-present
Ebola (West Africa)	Thousands (4)	Controlled United States, reduced Africa	Yes (contact, sexual)	Yes	High	2014-present

HCP, health care personnel; *MERS*, Middle East respiratory syndrome; *SARS*, severe acute respiratory syndrome; *vCJD*, variant Creutzfeldt-Jakob disease.
*Infection via a needlestick theoretically possible.
†No HCP developed infection during the U.S. outbreak but patient-to-HCP transmission described in Africa.

Diseases of infection importance included *Legionella*,[25] HIV, variant Creutzfeldt-Jakob disease,[26] West Nile virus disease,[27] SARS, monkeypox,[28] MERS, and Ebola virus disease (EVD). These diseases are of infection control importance because they are spread person-to-person (HIV, SARS, monkeypox, MERS, and EVD), health care personnel (HCP) may be at substantial risk of acquiring infection during patient care (HIV, SARS, monkeypox, MERS, and Ebola), they may be transmitted by blood transfusions (HIV, variant Creutzfeldt-Jakob disease, and West Nile virus), or they have the potential to cause outbreaks in health care facilities (*Legionella*, SARS, MERS, and EVD). Screening of donated blood has largely eliminated transmission of HIV and West Nile via blood transfusions. Interestingly, although most of the emerging diseases are endemic in lesser developed countries, 5 developed countries (United States, United Kingdom, Australia, Japan, and Germany) accounted for the most reports of emerging disease events.[29]

The emergence of anti-infective resistance among microbes has also been an emerging threat in U.S. health care facilities. The most important microorganisms have included methicillin-resistant *Staphylococcus aureus*,[30] vancomycin-resistance enterococci,[31] extended-spectrum β-lactamase–producing enteric gram-negative bacilli (especially *Escherichia coli*, *Klebsiella*, and *Enterobacter*),[32] and carbapenem-resistance *Enterobacteriaceae*.[33] Pathogens with enhanced virulence in recent years have included *Clostridium difficile* (BI/NAP1/027)[34] and norovirus (GII.4 strains).[35] Also of concern are continued outbreaks of vaccine-preventable diseases, mumps[36] and measles,[37] and the resurgence of pertussis.[38]

Key considerations in assessing and managing the threat of emerging infectious diseases in health care facilities

Assessing and managing the threat of an emerging infectious disease requires an understanding of the biology of the pathogen, its epidemiology, the clinical manifestations of infection, the methods of diagnosis, and therapies (if available). In addition, there are a number of issues more specific to infection control (Table 2). Key information on the infectious diseases discussed in detail in this article is provided in Table 3.

Table 2
Key considerations in assessing and managing the threat of an emerging infectious disease in health care facilities

Pathogen
• Taxonomy (provides clues regarding transmission routes, environmental stability, germicide susceptibility)
• Hosts
Epidemiology
• Locations of endemicity (ie, locations in the world where sources or reservoirs reside)
• Incubation period
• Transmission routes
• Infectivity (ie, communicability)
• Duration of infectivity
Clinical
• Symptoms
• Signs
• Risk factors for acquisition of infection
• Morbidity
• Mortality
• Risk factors for morbidity and mortality
• Diagnostic methods (sensitivity, specificity, biosafety)
• Therapy (availability, efficacy, safety)
Infection control
• Environmental survival
• Germicide susceptibility
• Isolation recommendations
• Recommended personal protective equipment
• Pre-exposure prophylaxis (availability, efficacy, safety)
• Postexposure prophylaxis (availability, efficacy, safety)
• Recommended biosafety level in the laboratory
• Recommended waste disposal (liquids and solids)

All health care facilities should have a highly communicable disease management plan (Table 4). A detailed discussion of each of these components is beyond the scope of this article. Detailed information is best found, especially early in an epidemic, on the Web pages of local and state health departments, the Centers of Disease Control and Prevention, and the World Health Organization. General recommendations have been provided by infection control experts.[39-44] There are 2 areas that place a health care facility and the personnel at substantial risk for disease acquisition and transmission. First, inadequate screening procedures when patients enter a health care facility can potentially allow transmission from an ill patient to HCP, other patients, or visitors. Second, inadequate supplies of personal protective equipment (PPE) or inadequate training of HCP in proper donning and doffing procedures can increase the risk of exposure for HCP.

Another important issue is the use of an appropriate antiseptic for hand hygiene and an appropriate surface disinfectant. However, once the nature of the emerging disease is known (ie, bacteria, nonenveloped virus, enveloped virus), it is possible to determine the proper antiseptic and disinfectant, even in the absence of studies of the exact infectious agent.[45] For example, an enveloped virus (eg, Lassa, EVD, MERS-CoV, SARS-CoV, influenza A) would be inactivated by any agent active against vegetative bacteria, nonenveloped viruses, or mycobacteria. Any vegetative bacteria would be inactivated by an agent active against a nonenveloped virus or mycobacteria. It is important to remember that alcohol has reduced activity against nonenveloped viruses (eg, norovirus) and no activity against spores (eg, *C difficile*).

EMERGING INFECTIOUS DISEASES OF SPECIAL INTEREST

Lassa fever

Microbiology

Lassa fever is a single-strand negative RNA virus belonging to the *Arenaviridae* family.[46,47] The family is serologically divided into 2 major complexes: the Old World complex (eg, Lassa virus, Mobala virus) and the New World complex (eg, Junin virus, Machupo virus, Sabia virus). With the exception of the lymphocytic choriomeningitis virus, all virus species show a restricted geographic occurrence. The host for Lassa fever is the multimammate rat (*Mastomys natalensis*).

Epidemiology

Lassa fever is endemic in Sub-Saharan West Africa, including Sierra Leone, Liberia, Guinea, and Nigeria. It is estimated that the number of Lassa virus infections per year is West Africa is 100,000-300,000, with approximately 5,000 deaths. Transmission of Lassa virus to humans occurs most commonly through ingestion or inhalation of the virus. *Mastomys* rodents shed the virus in urine and droppings, and direct contact with these materials through touching soiled objects, eating contaminated food, or exposure to nonintact skin can lead to infection. Person-to-person transmission may occur after exposure to virus in the blood, tissue, secretions, or excretions of a Lassa virus–infected individual. Nosocomial transmission has been common in health care settings where proper PPE or training in the correct use of PPE was not available.

The incubation period ranges from 6-21 days.

Outbreaks

In 1969, 3 American missionary nurses became ill in Lassa, Nigeria. Two Yale University laboratory workers studying the disease also became sick. Two of the nurses and one laboratory worker died

Table 3
Key infection control information for selected highly communicable emerging infectious diseases

Characteristic	Lassa fever	Ebola virus disease	MERS	SARS	Novel influenza A
Virus					
Year identified	1969	1976	2012	2003	
Family	*Arenaviridae*	*Filoviridae*	*Coronaviridae*	*Coronaviridae*	*Orthomyxoviridae*
Genome	RNA	RNA	RNA	RNA	RNA
Coat	Enveloped	Enveloped	Enveloped	Enveloped	Enveloped
Epidemiology					
Endemic location	West Africa	West and Central Africa	Middle East	China	Worldwide (location varies with strain)
Prevalence	100,000-300,000 cases per year			No recent human cases	Varies by strain
Reservoir	Rodent (rat)	Bats (fruit)	Bats, camels (intermediate host)	Bats, palm civet	Migratory birds, pigs
Transmission	Inhalation, ingestion, contact (nonintact skin)	Contact (nonintact skin, mucous membranes, sexual)		Droplet, contact, airborne	Inhalation, contact
Incubation period (d)	10 (range, 6-21)	6-12 (range, 2-21)	2-15	2-14 (range, 2-21)	Varies by strain
Infectivity, Rho	Not determined	1.5-2.0	0.3-1.3	2.2-3.7 (range, 0.3-4.1)	Varies by strain
Duration, maximum (d)	28	21			
Case fatality rate	15%-20%, hospitalized patients	~50% (range, 25%-90%)	>35%	~10%	
Biologic safety					
Biothreat level	A	A	Not specified	C	C (some strains)
Biosafety level	4	4	3	3	2-3
Clinical					
Therapy	Ribavirin	Supportive	Supportive	Supportive	Neuraminidase inhibitors
Infection control					
Isolation	Contact, droplet, airborne for aerosol-generating procedures	Contact, droplet, airborne for aerosol-generating procedures	Contact, airborne	Contact, airborne	Droplet, airborne for aerosol-generating procedures
Pre-exposure prophylaxis, vaccine	No	No	No	No	Yes (some strains)
Postexposure prophylaxis	No	No	No	No	Yes (antivirals)

from what was later identified as Lassa fever.[48] Since then, multiple cases of imported Lassa fever have been reported in Europe.[49] In addition, multiple imported cases have been reported in the United States.[50-53] The most recent imported case in the United States, which occurred in May 2015, died from his infection.

Since the first description of Lassa fever in 1969, nosocomial transmission has emerged as a prevalent mode of acquisition of infection.[49] The largest nosocomial series occurred in Nigeria in 1989, involving 34 cases, including 9 HCP, with a 55% attack rate among patients and a 65% overall fatality rate.[54]

Clinical manifestations

The clinical manifestations of Lassa fever include the gradual onset of fever, nausea, abdominal pain, severe sore throat, cough, conjunctivitis, ulceration of the buccal mucosa, exudative pharyngitis, and cervical adenopathy.[40] Late complications include severe swelling of the head and neck and pleural and pericardial effusions. Hemorrhagic complications are less common. Most infections are subclinical or mild, but up to 20% of cases are severe. Importantly, it may be difficult to differentiate Lassa fever from other hemorrhagic fevers in the first 3-7 days of illness because they all present with a similar, influenza-like illness and lack pathognomonic features.[55]

The overall case fatality rate is approximately 1%, but the observed case fatality rate among hospitalized patients is 15%-20%. The disease is especially severe late in pregnancy, with maternal death or fetal loss occurring in >80% of cases during the third trimester. Deafness occurs in 25% of patients who survive the disease but may return within 1-3 months in half of those affected.

Lassa fever is most often diagnosed using an enzyme-linked immunosorbent assay. Real-time polymerase chain reaction (PCR) can be used in the early stage of the disease. Intravenous ribavirin has been used successfully to treat patients with Lassa fever. It is most effective when used early in the course of illness. Convalescent plasma has also been used as therapy.

Infection control issues

Patients with Lassa fever should be placed in a single room on special isolation precautions similar to that used for patients with EVD (Table 4). HCP should wear appropriate PPE similar to that used when caring for patients with EVD, including a full body protective suit with hood, cover gown, 2 sets of gloves, N95 respirator, and face shield or goggles. No published data on environmental survival or germicide susceptibility are available. However, as an enveloped virus, it is likely susceptible to quaternary ammonium compounds, phenolics, and alcohol.[45] Lassa virus is considered a class IV biosafety agent; patient samples should only be handled by trained staff and processed in suitably equipped laboratories.

There is currently no vaccine that protects against Lassa fever. There is no evidence to support the role of ribavirin as postexposure prophylaxis for Lassa fever.[56]

EVD

Microbiology

Ebola is caused by a nonsegmented, single-strand negative RNA virus of the family *Filoviridae*.[40,57,58] There are 5 identified Ebola virus species, 4 of which are known to cause disease in humans: Zaire, Sudan, Tai Forest (formerly Cote d'Ivoire), and Bundibugyo. The fifth, Reston virus, has caused disease in nonhuman primates, but not in humans.

The natural reservoir host of Ebola virus remains unknown. However, the detection of antibodies against Ebola and Ebola virus

Table 4
Preparedness for managing a highly communicable emerging infectious disease

General
• Have a comprehensive facility plan for managing a highly communicable emerging infectious disease.
• Nestle the plan for emerging infectious diseases within the general disaster plan.
• Base the plan on the route(s) of transmission for the infectious agent.
• Incorporate the incident command structure in the plan.
• Periodically train key personnel on the plan.
• The plan should include care of single patients (eg, Ebola) and managing large number of patients in an epidemic (eg, novel influenza).
• Incorporate communications with local and state health department officials.
Screening and signage (when appropriate based on the threat of a highly communicable disease)
• Place signs at every entrance to the hospital and clinics that includes the following: epidemiologic clues to possible disease exposure (ie, travel locations), signs and symptoms of infection, and who to notify if the patient or visitor has both exposure and appropriate signs or symptoms.
• Include messaging about the signs and symptoms of the concerning disease in all telephone contacts with the patient (eg, reminders about appointments) and who to contact prior to arrival at the health care facility.
• Screen all patients immediately at the time of all health care visits.
• Include screening in the electronic medical record (also have alerts in the medical record that require screening).
• Place an appropriate isolation sign on the door of all patients being isolated because of the possibility of a highly communicate disease.
• For diseases transmitted via the droplet or airborne routes emphasize respiratory hygiene (ie, immediate use of a mask and proper disposal of tissues).
• Emphasize the need for proper hand hygiene.
• All messaging should be in appropriate languages for the region.
Triage
• Train frontline person in all clinics and the emergency department in appropriate use of personal protective equipment.
• Have appropriate personal protective equipment available.
• Have a designated location in the emergency department and all clinics in which to immediately place the patient (a private room; ideally with access to a sink and toilet, and if possible, one that meets standards for a disease transmitted by the airborne route (ie, negative pressure, out-exhausted air, >12 air exchanges per hour) if applicable.
• For diseases transmitted by the airborne route and when an airborne isolation room is not available, ideally place a portable high-efficiency particulate air purifier in the room.
• Have a well-defined process for alerting key health care facility officials about the presence of a patient with a possible highly communicative disease (eg, disaster manager, infection preventionist).
• Avoid blood tests or other procedures that may place the laboratory staff or other health care personnel at risk.
• Have a well-defined and safe method for transporting a patient either to a properly equipped emergency department or hospital facility able to safely care for a patient.
Inpatient care
• Have a well-defined plan for the inpatient location that will provide care to a patient with a highly communicative disease (or a plan for transporting such a patient to facility that can provide such care).
• In the inpatient care unit designate areas that are hot (ie, potentially contaminated) and cold (ie, areas that are not contaminated).
• Have a well-trained medical care team. For highly communicable diseases (eg, Lassa, Ebola), ideally provide 3-step training: (1) basic individual training on personal protective equipment donning and doffing (and including how to manage contamination of the environment from a spill and breach of the personal protective equipment. Such training should be individualized to the specialty of the health care providers [ie, physician, nurse, respiratory therapist]); (2) team training using mannequins; and (3) team training in the designated containment unit.
• Train team personnel on donning and doffing using an explicit written list of all donning and doffing steps.
• Screen and exclude health care personnel unable to wear the proper personal protective equipment. Consider excluding from the care team personnel at high risk for disease acquisition or more severe illness, such as persons with nonintact skin, pregnancy, and immunocompromised persons. Consider excluding trainees from providing care.
• Store an adequate supply of personal protective equipment.
• If needed, have dedicated point of care laboratory equipment.
• Develop a method to safely dispose of solid and liquid wastes.
• Restrict visitors (if indicated) and maintain a log of all visitors.
• Maintain a log of all health care personnel providing care.
• Develop a plan for managing health care personnel with unprotected exposure to the infectious agent (eg, needlestick).
• Assure that care team members receive proper rest.

fragments in fruit and insectivore bats are highly suggestive that these animals serve as a reservoir.

Epidemiology

Past Ebola outbreaks have occurred in West and Central Africa, including the Democratic Republic of the Congo, Uganda, Sudan, and Gabon.[59-61] Single cases caused by laboratory accidents have also been reported from Russia and England.

Once the virus enters the human population, transmission is sustained via person-to-person spread, which is enhanced by the lack of active case finding with isolation or quarantine. The incubation period of Ebola is generally 8-10 days (range, 2-21 days). Infection has been transmitted only from symptomatic persons.[58]

Ebola is transmitted person-to-person through direct contact (ie, nonintact skin, via mucous membrane contact) with blood, body fluids (eg, urine, saliva, sweat, feces, vomit, breast milk, semen) of an ill person, objects (eg, needles, syringes) that have been contaminated with body fluids from an ill person, or infected fruit bats or primates. More recently, the sexual transmission of this virus has been recognized in Liberia. Recently, cases have been reported in which persons who had recovered from EVD developed recrudescent infection with Ebola virus being recovered from protected body locations, such as eyes and central nervous systems. Ebola is not transmitted through the air or by water. However, in Africa, it may be acquired by handling bushmeat and contact with infected bats. HCP have been a substantial risk for acquiring Ebola through patient care.[59] The World Health Organization reported (September 23, 2015 http://www.who.int/csr/disease/ebola/situation-reports/archive/en/) that since the start of the epidemic in 2014 a total of 881 confirmed cases have occurred in health care providers (from Guinea, Liberia, and Sierra Leone), with 513 reported deaths (58%). HCP in the United States have acquired Ebola during the current outbreak.

Outbreaks

The first recognized outbreaks of Ebola occurred in West Africa in 1976. In the 40 years since the initial outbreaks in Zaire and Sudan,

approximately 24 outbreaks have occurred.[59] The current outbreak, which began in 2014 in West Africa, has involved Guinea, Sierra Leone, and Liberia. Cases were also reported in Nigeria, Senegal, Spain, Mali, United Kingdom, Italy, and the United States. As of September 24, 2015, there have been 28,355 total cases (15,235 laboratory-confirmed cases) and 11,311 deaths (case fatality rate, approximately 40%). Moreover, for the first time, Ebola has crossed international boundaries, involving Nigeria and Mali, and crossed continents into Europe and North America. Four cases have been acquired in the United States.

Clinical manifestations

EVD is characterized by the sudden onset of fever, headache, myalgias, arthralgias of the large joints, and back pain.[57,62] Typically, 2-3 days after the initial symptoms, gastrointestinal symptoms occur, including abdominal pain, nausea, vomiting, and diarrhea. A macular or maculopapular skin rash may appear on days 5-7 of the disease. Hemorrhage is less common, occurring in only 15%-20% of patients. Terminal cases develop disseminated intravascular coagulation, septic shock, and multiorgan system failure.

Mortality ranges from 40%-90% and depends in part on the infecting species. The Zaire species has the highest mortality (up to 90%) followed by the Sudan species (approximately 50%); Bundibugyo species (approximately 40%), the Tai Forest species has a low mortality (although only a single infected person has been reported) and the Reston species causes subclinical infection in humans. Pregnant women have a higher mortality.

Diagnostic testing is achieved with the use of real-time PCR on blood. Viral RNA is usually detectable by PCR between 3 and 10 days after the onset of symptoms. Therefore, early in the course of illness, diagnostic tests may be falsely negative. There are currently no approved therapies for Ebola; however, there are investigational therapies, including immunoglobulins from recovered patients, humanized monoclonal antibodies produced transgenically by using the *Nicotiana benthamiana* plant, and a number of antiviral agents, including adenosine analogues, viral RNA-dependent RNA polymerase inhibitors, and short interfering RNA.[63,64] Additionally, multiple vaccine platforms have been developed with some in clinical trials.

Infection control issues

The high mortality of Ebola coupled with the low inoculated dose required to initiate infection has led to a massive public health response in the United States, including screening by public health personnel of persons returned from epidemic countries in West Africa, development of specialized Ebola treatment centers, and training of thousands of HCP in the use of specialized PPE to minimize the risk of Ebola acquisition during patient care. Detailed recommendations on screening for Ebola among potentially infected returned travelers and management of patients with EVD are available on the CDC Web pages and in published articles.[65-67]

Given the high volume of diarrhea and vomiting and the potential for fomite transmission, environmental control is a critical issue in the care of an Ebola-infected patient. Ebola virus may persist on steel and plastic surfaces for >7 days.[68,69] It may also persist in liquid media for prolonged periods. Sodium hypochlorite (0.5% and 1%) sterilized surfaces within 5 minutes, and 67% ethanol sterilized carriers at 5 minutes.[68] A >4 $\log_{10}$ reduction of an Ebola strain was achieved in 15 seconds using the following povidone iodine solutions: 4%, 7.5%, 10%, and 3.2% iodine with 78% alcohol.[70]

Consistent use of appropriate PPE with strict adherence to donning and doffing protocols is crucial to preventing acquisition of EVD during patient care.[65-67] A key component of reducing HCP risk is proper training in PPE donning and doffing with ongoing training to maintain competency.

SARS

Microbiology

SARS was caused by a novel coronavirus, SARS-CoV, that was phylogenetically distinct from all previously known human and animal coronaviruses.[71] As with other coronaviruses, SARS-CoV is a positive-strand RNA virus belonging to the family *Coronaviridae*.[72] It is classified as lineage 2B β CoV.

SARS-CoV–like viruses were detected in Himalayan palm civets and a raccoon dog in a market in Southern China. The ultimate reservoir is felt to be the Chinese horseshoe bat (*Rhinolophus sinicus*).

Epidemiology

The incubation period for SARS was 4.6 days, whereas the mean time from symptom onset to hospitalization was 2-8 days.[73] Human-to-human transmission occurred most commonly via the droplet route. SARS was also transmitted via contact (direct and indirect). Airborne transmission may have occurred during aerosol generating procedures.

The attack rate for SARS-CoV ranged from 10%-60% or 2.4-31.3 cases per 1,000 exposure hours.[74] Importantly, some patients appeared to be superspreaders, with some cases transmitting SARS to >100 contacts.

Outbreaks

SARS first appeared in Southern China in November 2002 and was recognized as a global threat in March 2003 when it spread to 33 countries or regions on 5 continents and was contained by July 2013.[75] SARS re-emerged in late 2003 and early 2004 in South China after resumption of wild animal trading activities in markets. There have been no reported cases since 2004. Overall, 8,098 people worldwide became ill with SARS, of which 774 died (case fatality rate = 9.6%). In the United States, only 8 persons had laboratory evidence of SARS-CoV infection.

Independent risk factors of superspreading nosocomial outbreaks included minimum distance between beds <1 m (odds ratio [OR], 6.98); washing or changing facilities for staff (OR, 0.12); performance of resuscitation (OR, 3.81); staff working while experiencing symptoms (OR, 4.30); SARS patients requiring oxygen therapy (OR, 4.30); and SARS patients requiring noninvasive positive pressure ventilation (OR, 11.82).[73]

Clinical manifestations

SARS generally began with a high fever (temperature >38.8°C) and included headache and myalgias. Some people had mild respiratory symptoms at the onset of illness. After 2-7 days, most patients developed a dry cough. Diarrhea was present in 10%-20% of cases. Laboratory abnormalities included lymphopenia, slightly decreased platelet counts, prolonged coagulation profiles, and mildly elevated serum hepatic enzymes.[71]

Overall mortality was 9.6%. Risk factors for death included age >60 years, diabetes mellitus, hepatitis B infection, and higher viral load.[74,76]

Infection control issues

The SARS epidemic exposed global weakness in infection control practices. Overall, approximately 21% of infected persons were HCP, but some areas, such as Hong Kong and Hanoi, experienced higher rates of HCP infection (46% and 63%, respectively).[75] The infection control lessons learned from SARS have been reviewed.[76-80] The risk of developing SARS was 12.6 times higher for those that did not wear a mask during patient care activities.[76] Other risk factors for acquisition of infection by health care providers included contact with respiratory tract secretions; exposure to body fluids of health care providers' eyes and mucous membranes; inconsistent use of goggles,

gowns, and caps; and performing aerosol-generating procedures (intubation, manual ventilation, chest physiotherapy, and suctioning).[76] Inadequate patient placement in proper isolation rooms was also a risk for nosocomial transmission. Handwashing was shown to be protective in multiple studies.[81]

SARS-CoV was shown to survive in diarrheal stool samples for 4 days and in respiratory tract secretions for >7 days at room temperature.[82] Human coronavirus (HCoV 229E) was inactivated within 1 minute by 2% glutaraldehyde, multiple quaternary ammonium compounds, and multiple phenolics.[83] Using human coronavirus (HCoV229E), Sizun et al demonstrated survival of the viruses on aluminum, sterile sponges, or latex surgical gloves for >6 hours.[84] Using transmissible gastroenteritis virus as a surrogate for SARS, survival on isolation gowns was documented up to 24 hours postinoculation.[85]

Data on inactivation of coronaviruses come primarily from work with HCoV 229E, in which this virus is inactivated within 1 minute by 2% glutaraldehyde, multiple quaternary ammonium compounds, and multiple phenolics.[83] It can also be inactivated within 1 minute by 10% povidone-iodine, 0.05% chlorhexidine gluconate, and 70% alcohol.[83] SARS-CoV was inactivated using a 5-minute exposure time by 1:100 hypochlorite.[82]

MERS

Microbiology

The MERS is a new viral respiratory disease of humans first described in 2012 and caused by a novel coronavirus (lineage 2C β CoV).[86-89] The microbiology, epidemiology, and clinical manifestations of SARS and MERS have been compared.[72,90-92]

Epidemiology

As of September 25, 2015, the following countries in the Middle East have reported cases: Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen. Countries with travel-associated cases have included Algeria, Austria, China, Egypt, France, Germany, Greece, Italy, Malaysia, Netherlands, Philippines, Republic of Korea, Thailand, Turkey, United Kingdom, and the United States. The United States has had only 2 travel-associated cases, both of whom were health care providers who lived and worked in Saudi Arabia.[87] No person-to-person transmission has been documented in the United States.

MERS-CoV is a zoonotic disease that it transmitted from animals to humans. The origins of the virus are not fully understood, but it is believed to have originated in bats and then transmitted to camels. Currently, it is believed that dromedary (single-humped) camels are a major reservoir host for MERS-CoV and an animal source for humans.

MERS may be transmitted from person to person. This occurs most commonly when there is close contact, such as providing unprotected care to an infected patient. Thus far, no sustained community transmission has been documented. The R_0 for MERS-CoV is generally estimated to be <0.7, making sustained transmission unlikely unless it mutates.[91] Studies of family clusters and HCP contacts of patients have reported low frequencies of transmission (ie, 1%-3%).[93] However, increased transmission has occurred in health care settings with limited infection control procedures.

The incubation period of MERS is approximately 5 days (range, 2-15 days).

Outbreaks

MERS has been epidemic in the Middle East in recent years. As of September 11, 2015, the World Health Organization has reported a total of 1,583 confirmed cases of MERS, with 566 deaths.

In the summer of 2015, a large outbreak of MERS was reported in the Republic of Korea and China. As of September 11, 2015, the World Health Organization reported that this outbreak involved 186 total confirmed cases (Republic of Korea: n = 185; China: n = 1), with 36 deaths. The last case of MERS infection in the Republic of Korea that was reported to the World Health Organization was on July 4, 2015.

Clusters of cases have been reported in households and in health care facilities, especially when infection prevention and control practices have been inadequate.[94]

Clinical manifestations

The clinical spectrum of MERS infection ranges from asymptomatic or mild respiratory symptoms to severe acute respiratory disease and death. Typical symptoms of MERS include fever, cough, and shortness of breath. Pneumonia is common but not always present. Gastrointestinal symptoms (vomiting and diarrhea) frequently occur.

Risk factors for more severe disease include older age, comorbidities (eg, chronic lung diseases, diabetes), and immunosuppression. The reported mortality is approximately 36%.

Currently, there are no specific therapies or vaccines available.

Infection control issues

Multiple outbreaks of MERS have involved health care facilities.[91,93,95-97] One outbreak involved 23 patients receiving hemodialysis in an intensive care unit; the case fatality rate was 65%. In the recent outbreak in South Korea, substantial transmission was reported in health care facilities.[98,99] For example, a hospital reported a single primary case, 25 secondary cases, and 11 tertiary cases.[98]

HCP have been at high risk of acquiring MERS. Al-Tawfiq and Perl reported that of 952 cases reported in Saudi Arabia (June 2012-September 2014), approximately 27% were HCP. Factors contributing to intrahospital transmission include: (1) initial symptoms of MERS are nonspecific leading to a failure to isolate the patient; (2) inadequate compliance with infection control practices; (3) inadequate health care facilities (eg, overcrowding, close proximity of patients to cases); (4) use of aerosol-generating procedures; and (5) prolonged viral shedding.[93]

Per the CDC, key methods for preventing transmission of MERS in health care facilities include notifying patients to call before arrival at a health care facility if they have had travel to the Middle East plus signs and symptoms of MERS; strict adherence to respiratory hygiene in clinics and the emergency department; early identification of possible patients; and prompt institution of contact and airborne isolation for possible cases.[100]

Similarities and differences between SARS and MERS

Similarities include the following: caused by coronaviruses of animal origin; severe respiratory disease; global spread through infected travelers; no effective therapies or vaccines; disease transmission to family and HCP; and infection control in health care facilities plays a critical role in limiting transmission.[87] Differences include the following: no evidence of sustained human-to-human transmission of MERS-CoV; limited evidence of superspreaders of MERS; slower global spread of MERS, likely because of lower infectivity; and higher mortality of MERS compared with SARS (may be an artifact of ascertainment).[87]

MERS-CoV has been shown to be recoverable after 48 hours on steel or plastic washers (20°C and 40% relative humidity).[101] Further, no decrease in stability was observed during aerosolization experiments. This study, studies on SARS-CoV (discussed previously), and studies on other coronaviruses suggest that they survive on

environmental surfaces for a sufficient time to allow fomite transmission.[102]

Studies on inactivation of SARS-CoV (previously discussed) and other coronaviruses are inactivated within 1 minute by phenolics (1.3-2.0 $\log_{10}$ reduction) and 70% ethanol (3.2-3.9 $\log_{10}$ reduction).[103] Hypochlorite with a 1:00 dilution, had a 1 minute decrease of <1 $\log_{10}$.

Novel influenza A viruses

Background

Influenza A viruses are negative-sense RNA-enveloped viruses which belong to the *Orthomyxoviridae* family and are the causative agents of influenza, a contagious respiratory viral disease of birds and humans.[104,105] Influenza A viruses are subdivided into distinct serotypes based on the genetic and antigenic properties of their hemagglutinin and neuraminidase, the envelope glycoproteins expressed on the surface of virus particles which are responsible for virus binding to relevant hosts and releasing newly formed infectious virions, respectively.[105] Sixteen hemagglutinin and 9 neuraminidase subtypes have been detected in wild aquatic birds and poultry throughout the world, whereas new strains (H17-18 and N10-11) have been identified in bat species.[105] Influenza A viruses exhibit drift each year (minor changes) and occasional shifts (major changes) which lead to pandemics. Influenza pandemics are relatively rare; there have been only 4 in the last 100 years. Multiple influenza A pandemics are likely to have occurred in the last 4 centuries, including 3 in the 18th century, 4 in the 19th century, 3 in 20th century, and 1 in the 21st century.[106] The first pandemic of the 20th century occurred in 1918 because of the novel A(H1N1) influenza virus, followed by pandemics in 1957 because of A(H2N20), 1968 because of A(H3N2), and 2009 because of novel A(H1N1).[107] In addition, influenza A(H1N1) was reintroduced in 1977, which may have been caused by a laboratory release. In the era before 1977, there was only a single circulating strain of influenza causing seasonal influenza in humans. Since 1977, both A(H1N1) and A(H3N2) have circulated.

Avian influenza (bird flu) is an infectious disease of birds caused by influenza A strains. The infection may cause disease in birds ranging from mild illness, which may pass unnoticed, to a rapidly fatal disease that can cause severe epidemics. Multiple subtypes of influenza A of avian origin have been reported to cause human disease in recent years, including H5N1, H6N1, H7N2, H7N3, H7N7, H7N9, H9N2, H10N7, and H10N8.[105,108-111] Of these, H5N1, H7N2, and H7N3 have been responsible for human infections in North America.

Influenza pandemics (outbreaks that affect a large proportion of the world because of a novel virus) are unpredictable but recurring events that can have health, economic, and social consequences worldwide. An influenza pandemic occurs when key factors converge: an influenza virus emerges with the ability to cause sustained human-to-human transmission, and the human population has little to no immunity against the virus. With the growth of global trade and travel, a localized epidemic can transform into a pandemic rapidly, with little time to prepare a public health response.[112]

Avian influenza A subtypes with pandemic potential

Based on the number of cases reported and duration over which these subtypes have been isolated, H5N1[113-115] and H7N9[113,114,116-118] are the most likely viruses to cause a new worldwide pandemic. Most human cases of A(H5N1) and A(H7N9) infection have been associated with direct or indirect contact with infected live or dead poultry.

The A(H5N1) virus subtype, a highly pathogenic influenza A virus, first infected humans in 1997 during a poultry outbreak in Hong Kong. Since its widespread emergence in 2003 and 2004, A(H5N1) has spread from Asia to Europe and Africa and has become entrenched in poultry in some countries. To date it has been reported in 16 countries, infected >500 persons with a reported mortality of approximately 60%. The incubation period for A(H5N1) is generally 2-8 days (maximum, 17 days), which is much longer than the 2- to 3-day incubation period for normal seasonal influenza. Other known H5 subtypes include H5N2, H5N3, H5N4, H5N5, H5N6, H5N7, H5N8, and H5N9.

The A(H7N9) virus subtype, is a low pathogenic influenza virus, which first infected a few residents of Shanghai in March 2013. No cases of A(H7N9) have been reported outside of China. Other known H7 subtypes include H7N1, H7N2, H7N3, H7N5, H7N6, H7N7, and H7N8. In humans, H7N2, H7N3, and H7N7 have caused mild to moderate illness. H7H3 and H7N7 have caused mild to severe and fatal illness. To date, >100 human cases of infection have been reported with a high mortality. The incubation period for A(H7N9) is approximately 5 days (range, 2-8 days).

Initial symptoms of A(H5N1) and A(H7N9) include high fever, usually with a temperature >38°C, and other influenza-like symptoms (cough or sore throat). Early symptoms may include diarrhea, vomiting, abdominal pain, chest pain, and bleeding from nose or gums. Characteristically, patients will develop lower respiratory tract symptoms early, including respiratory distress and a hoarse voice. Complications include hypoxemia, multiple organ dysfunction, and secondary bacterial infections. The case fatality rate is much higher than that of seasonal influenza.

Infection control

Avian influenza viruses are transmitted by close contact with infected poultry. All hospitals should have plans in place to deal with epidemic or pandemic influenza, especially if the influenza strain is both highly pathogenic for humans and easily spread from person to person.[119-121] Influenza is transmitted by contact and droplet routes. It is recommended to place patients with highly pathogenic influenza viruses in hospital rooms meeting airborne isolation requirements. HCP should wear gloves, an isolation gown, an N95 respirator (or powered air purifying respirator), and eye goggles or face shield while providing care.

A(H5N1) placed on galvanized metal or glass persisted <1 day at room temperature and with low or high humidity.[122] However, at low temperatures (<10°C), A(H5N1) persisted for up to 13 days. A(H5N1) was susceptible to hypochlorite solutions with 15 seconds.[123,124]

Currently, circulating influenza A strains are susceptible to the neuraminidase inhibitors, including A(H5N1).[125] However, because circulating strains of A(H1N1) in 2008 exhibited resistance, one must be concerned that in the future, circulating influenza strains may develop resistance to neuraminidase inhibitors. Vaccines are available for A(H5N1) but not for A(H7N9).

CONCLUSIONS

Over the last several decades, we have witnessed the emergence of many new infectious agents, some of which are major public threats. All health care facilities need to have policies and plans in place for early identification of patients with a highly communicable disease, immediate isolation, and proper management to prevent transmission to HCP, other patients, and visitors to the health care facility.

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