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Emerging and re-emerging infectious diseases in Japan: epidemiology and infection prevention measures

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Abstract: In recent years, emerging and re-emerging infectious diseases, such as the Ebola virus disease and Middle East Respiratory Syndrome (MERS), have been frequently reported. In this review, we summarize the representative outbreaks of emerging and re-emerging infectious diseases since 2000 and outbreaks of various infectious diseases that have occurred around the world and in Japan. Moreover, the emerging and re-emerging infectious diseases that could develop in Japan are also summarized. Especially, for mosquito-borne infectious diseases, viral hemorrhagic fever and severe fever with thrombocytopenia syndrome, and avian Influenza and MERS, the disease features, routes of infection, and infection prevention measures are reviewed in this article. Healthcare workers are at high risk of infection, and therefore, a sufficient understanding of disease features and routes of infection and the appropriate infection prevention measures are needed to increase self-protection.

***Keywords*:** Emerging and re-emerging infectious diseases, standard protective equipment, standard preventive measures

Introduction

In recent years, emerging and re-emerging infectious diseases have been frequently reported, causing concern. Table 1 shows representative outbreaks of emerging and re-emerging infectious diseases since 2000 and outbreaks of various infectious diseases that have occurred around the world and in Japan.

As factors that cause these emerging and re-emerging infectious diseases increase in a population, such as ecosystem changes, weather/climate changes, economic development and land use, development in scientific technology and industry, and increases in travelers, the susceptibility of individuals, especially those who are poor or not vaccinated, to infectious diseases increases. In particular, the number of travelers has been increasing since World War II; and today, as many as 1.1 billion people travel between countries per year. The trend is similar in Japan, wherein approximately 17 million Japanese citizens travel abroad and 28 million foreigners visit each year. Due to this background, Japan cannot do anything regarding the emerging and re-emerging infectious diseases and is in a situation where emerging and re-emerging infectious disease could occur at any time within the country. The development of dengue fever in Japan in 2014 (*1*) is one such incidence.

Emerging and re-emerging infectious diseases that could develop in Japan include those shown in Table 2. Based on the routes of infection, major emerging and re-emerging infectious diseases are divided into mosquito-borne infectious diseases, tick-borne infectious diseases, respiratory infectious diseases caused by droplet transmission, and viral hemorrhagic fever transmitted by contact with blood/body fluids.

Mosquito-borne infectious diseases

Mosquito-borne infectious diseases include dengue fever, chikungunya fever, Zika virus infection, and yellow fever. All are infectious diseases that are prevalent in tropical/subtropical regions and are transmitted by *Aedes* mosquitoes, such as *Aedes aegypti* and *Aedes albopictus*. In Japan, *Aedes albopictus* mosquitoes are distributed across wide areas, excluding Hokkaido, and an outbreak that originates from an individual with an imported infectious disease can occur within the country.

Dengue fever is an infectious disease that is caused by the dengue virus, which belongs to the genus *Flavivirus*. An estimated 390 million people are infected with dengue fever worldwide every year (*2*). Among Japan's imported infectious diseases, most individuals are infected in Southeast Asia and South Asia. The incubation period is 3-7 days, and the fever has a typical course of 5-7 days. In addition to fever, headache and

Table 1. Outbreaks of major emerging and re-emerging infectious diseases since 2000

Emerging and Re-emerging Infectious Disease	Year of Outbreak	Country/Area
SARS	2004	China, Taiwan, Singapore, *etc*.
H1N1 influenza	2009	From Mexico spread worldwide
MERS	2012	Middle East
H7N9 influenza	2012	China
Ebola virus disease	2013	Guinea, Sierra Leone, Liberia, *etc*.
Chikungunya fever	2013	Central and South America
Dengue fever	2014	Japan
MERS	2015	South Korea
Zika virus infection	2015	Central and South America
Pest	2017	Madagascar

MERS, Middle East respiratory syndrome.

Table 2. Emerging and re-emerging infectious diseases that can develop or have developed in Japan

Major Route of Infection	osquitoes	Ticks	Droplets	Blood/Body Fluids
Disease	Dengue fever Chikungunya fever Zika fever	SFTS Emerging relapsing fever Anaplasmosis	MERS Avian influenza (H5N1, H7N9)	Viral hemorrhagic fever (Ebola hemorrhagic fever)
Route of invasion into Japan	Imported infections	Community-acquired infections	Imported infections	Imported infections
Transmission within Japan	Humans→Mosquitoes →Humans	Ticks→Humans	Humans→ Humans Birds→Humans	Humans→ Humans
High-risk individuals	Individuals living in cities	Individuals exposed to wooded areas	Healthcare workers Poultry-rearing individuals	Healthcare workers
Medical treatment institution	Medical institutions across the country	Medical institutions across the country	Medical institutions designated for specific/type 1/type 2 infectious diseases	Medical institutions designated for specific/type 1/type 2 infectious diseases

joint pain are common, and symptoms of muscle pain, diarrhea, and nausea/vomiting may occur.

Chikungunya fever is an infectious disease caused by the chikungunya virus, which belongs to the *Togaviridae* family. There are approximately 10 cases of imported infections per year in Japan, which is less compared to dengue fever. However, the disease is rampant: an outbreak also occurred in Central and South America in 2013, and chikungunya virus infections have also been reported in the U.S. (*3*). The incubation period is 3-12 days (commonly 3-7 days), and the clinical features include fever, headache, muscle pain, joint pain, and rash. Although the symptoms are similar to those of dengue fever, chikungunya fever is characterized by more painful joint aches in the acute phase than dengue fever and possible long-term joint pain/arthritis.

Zika virus infection is an infectious disease caused by the Zika virus, which belongs to the genus *Flavivirus*, as does the dengue virus. In recent years, after outbreaks in French Polynesia in 2013 (*4*) and in Brazil in 2015, the disease became a pandemic in Central and South America in 2016 (*5*). In addition to mosquito bites, Zika virus can be transmitted through sex and blood transfusion. The incubation period of Zika virus infection is 2-7 days, and infected persons exhibit fever, headache, joint pain, muscle pain, bulbar conjunctival injection, and rash (*6*). There have been many individuals who have developed Guillain-Barré syndrome following Zika virus infections (*7*), which is considered a rare complication. Zika virus infection in pregnant women is associated with a high risk of fetal microcephaly (*8*), and this has become a social issue.

In the diagnosis of these mosquito-borne infectious diseases, the detection of viral genes by virus isolation from blood/urine or RT-PCR, of IgM antibodies or neutralizing antibodies with paired serum, or of significant increases in antibody titers are used as diagnostic methods. There are no effective antiviral drugs or vaccines for any infectious diseases. Therefore, it is important to take the following precautionary measures to protect one self against mosquitoes.

In order to eliminate skin exposure, wear long-sleeve shirts and long pants, and avoid sandals without socks. DEET is widely used as an effective ingredient in repellents; and in Japan, aerosols, wet sheets, and lotions or gels that contain up to 30% DEET are commercially available. Repellents can be appropriately used in accordance with required drugs or quasi-drugs following directions/dosages in accordance with age and precautions. Re-apply repellents often when sweating or getting wet by rain or stationary water. *Aedes aegypti* mosquitoes and *Aedes albopictus* mosquitoes, which

transmit dengue fever, Zika virus infection, *etc*., also inhabit cities and resorts overseas, and their numbers increase during the rainy season. These mosquitoes have a habit of actively sucking blood, particularly in the early morning/daytime/evening (especially before and after sunset); and thus, mosquito protection needs to be performed mainly during these periods. In Japan, *Aedes albopictus* mosquitoes transmit disease and suck blood from the morning through the evening (highly active in the early morning/daytime/evening, before and after sunset). Although *Aedes albopictus* mosquitoes suck blood indoors and outdoors, blood-sucking is more common outdoors.

Viral hemorrhagic fever and severe fever with thrombocytopenia syndrome

In Japan, viral hemorrhagic fever, which is transmitted by contact with blood/body fluids, is designated as a category I infectious disease, and the treatment is supposed to be provided by four institutions that are designated for specific infectious diseases and 54 institutions that are designated for type 1 specific infectious diseases across the country.

Viral hemorrhagic fever is designated as a category I infectious disease, and this category includes five diseases in Japan: Ebola virus disease (Ebola hemorrhagic fever), Marburg virus disease, Crimean-Congo hemorrhagic fever, Lassa fever, and South American hemorrhagic fever. In particular, Ebola virus disease has repeatedly caused outbreaks in Africa, and the 2014 outbreak in West Africa infected 28,652 people and caused 11,325 deaths (the mortality rate: 39.5%), which is the largest outbreak to date (*9*). Since then, Ebola virus disease has repeatedly increased in prevalence in the Democratic Republic of the Congo; and most recently, an outbreak has been reported in May 2018.

Although the life cycles of pathogens that cause viral hemorrhagic fever have not been fully elucidated for some diseases; for example, the natural host of Lassa virus is considered to be *Mastomys*, whereas that of Ebola virus is considered to be bats. Ebola virus disease has been known to occur not only in humans, but also in gorillas and chimpanzees. Thus, the disease can be transmitted by the consumption of bats, gorillas, and chimpanzees infected with Ebola virus. It can also be transmitted by direct contact with the body fluids of humans with Ebola virus disease (including dead bodies), and human-to-human transmission was the main route of transmission in the Western African epidemic. Therefore, healthcare workers who frequently come into direct contact with the blood and vomit of patients with Ebola virus disease are at high risk of infection and should wear appropriate personal protective equipment (PPE) during the medical care of patients with Ebola virus disease. After an incubation period of less than three weeks, viral hemorrhagic fever develops with nonspecific symptoms, such as fever, headache, and joint pain. Gastrointestinal symptoms such as nausea/diarrhea start to occur three days after onset, and impaired consciousness and shock occur seven days after onset, in a typical course (*9*). Bleeding symptoms such as blood in the stool and petechiae occur in approximately 20% of patients. Blood tests show decreased white blood cell counts, decreased platelet counts, increased AST/ALT, prolonged PT/APTT, renal dysfunction, and electrolyte abnormalities (hyponatremia and hypokalemia). Since viral hemorrhagic fever is transmitted by direct contact with blood/body fluids, preventing direct contact with body fluids is the main measure for infection prevention. However, "preventing direct contact with body fluids" measures are the exact idea of standard preventive measures, and special measures for infection prevention are never needed. Nevertheless, since becoming infected is directly linked to life or death for healthcare workers, strict infection prevention measures are needed in addition to ordinary standard preventive measures. In Japan, there are no rules regarding PPE use against viral hemorrhagic fever; and thus, specific rules need to be made in accordance with the actual situation, such as the arrangement and space of the rooms at each institution. The standard protective equipment that is used in the care for patients with viral hemorrhagic fever (including suspected patients) at our hospital is shown in Figure 1. Double gowns, double gloves, an N95 mask, goggles, a face shield, boots, and shoe covers are worn. The center for disease control has prepared guidelines for PPE that should be used in the examination of patients with Ebola virus disease (including suspected patients), and these guidelines are expected to be used as the PPE reference at each institution (*10*). PPE may be contaminated when it is taken off, and one should properly put on and take off PPE. Therefore, continued training to ensure the proper application and removal of PPE is essential.

In Japan, specifically in western Japan, patients with severe fever with thrombocytopenia syndrome (SFTS) have been also reported. SFTS is viral hemorrhagic fever in the broad sense, and a case of transmission by direct contact with body fluids in a healthcare worker is reported (*11*). Although there are no regular measures for infection prevention in the care for patients with SFTS, Disease Control and Prevention Center, Center Hospital of the National Center for Global Health and Medicine prepared "The 2019 revision of the guidance for the care for patients with severe fever with thrombocytopenia syndrome (SFTS)" (*http://dcc.ncgm.go.jp/information/pdf/SFTS_2019.pdf*), in which an example of measures for infection prevention is introduced.

Avian Influenza and Middle East Respiratory Syndrome (MERS)

Figure 1. The standard protective equipment in the care for patients with viral hemorrhagic fever (including suspected patients) at Center Hospital of the National Center for Global Health and Medicine.

Avian influenza and MERS are designated as category II infectious diseases, and treatment can be conducted in 346 institutions across Japan that are designated for type 2 specific infectious diseases. The clinical features of both diseases include fever, respiratory symptoms, such as cough and breathing difficulty, and general symptoms, such as headache, joint pain, and muscle pain. The mortality rates are very high (40-50% (avian influenza), 35% (MERS)); as the name suggests, birds are reservoirs for avian influenza, whereas bats and dromedary camels are reservoirs for MERS. Although both diseases are transmitted through droplets, H5N1 avian influenza is prevalent in Southeast Asia and Egypt and H7N9 avian influenza is prevalent in China and are both rarely transmitted through human-to-human contact. However, MERS is commonly transmitted through human-to-human contact and easily spreads within hospitals (*12*). Healthcare workers were found to be at high risk of infection during the outbreak in South Korea. Therefore, appropriate infection prevention measures are required for patient care.

For infection prevention, when a suspected or confirmed patient requires admission, the patient should be placed in a well-ventilated private room or a negative-pressure room, as recommended by the World Health Organization (*13*). Healthcare workers rigidly enforce standard preventive measures (hand hygiene, wearing PPE that avoids contact with patient blood/body fluids/discharge) and take contact and droplet precautions (medical mask, goggles or face shield, gown, and gloves). When performing a procedure that generates aerosol, such as endotracheal intubation, BAL, and manual ventilation, airborne precautions are recommended. The CDC recommends wearing an N95 mask regardless of the presence/absence of aerosol generation (*14*).

Conclusions

As seen from the above stated measures for prevention of the transmission of emerging and re-emerging infectious diseases, ultimately, standard preventive measures are the most important. Even if, by chance, a patient with Ebola virus disease unexpectedly visits your hospital, the risk of infection can be minimized if standard preventive measures are properly taken. Because it may be impossible to know when a patient with an emerging or re-emerging infectious disease visits your hospital, regular standard preventive measure enforcement is crucial.

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