Emerging Infectious Diseases

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The concept of "Emerging Infectious Disease (EID)" was introduced to the scientific literature about 20 years ago and has been showed in daily language at a growing speed. Emerging infections account for at least 12% of all human pathogens. EIDs are caused by newly identified species or strains that may have evolved from a known pathogen or spread to a new population or to an area undergoing ecologic transformation. Though there is no standard and direct definition, emerging infectious disease could be defined as (1) a recognized infection spreading to new areas, species or populations, (2) the discovery that a known disease is caused by an infectious agent, (3) a new infection resulting from mutations in a known microorganism or (4) an "old" infection re-emerging because it has become resistant to treatment, as a result of a breakdown in public health initiatives or due to changes in the host population.

The predictable emergence of new infectious diseases has been documented for millennia, well before the discovery of causative infectious agents. They are considered a threat to public health that requires a collaborative effort to combat. This includes basic scientists, clinicians from medical and veterinary fields, public health experts and media forces. Today, despite the surprising advances in development of countermeasures (diagnostics, therapeutics, and vaccines), the easiness of world travel and increased global interdependence have added layers of density to controlling these infectious diseases that affect not only the wellbeing but the economic stability of societies. Physicians recognize a new disease entity but this might only be a first step for starting a massive scientific effort in microbiology, epidemiology and other health fields. This attempt might unlock new windows and may lead to revolutionary discoveries that could inform clinical practice. **Below, you will find some of the most significant modern examples of the emerging infectious diseases, in which most of them have caused global societal and financial impact related to sudden illnesses and deaths.**

Severe Fever with Thrombocytopenia Syndrome Associated with a Novel Bunyavirus (SFTS)

This syndrome was discovered in the year 2009 in Central China as a new emerged clinical syndrome with clinical and epidemiological likeness to human anaplasmosis. The causative agent is a novel phlebovirus (SFTSV). Presently, SFTS cases have been reported from China, Japan, and South Korea with case fatality rates ranging from 10 to 30%. Similar disease with a milder profile has been reported from the United States and was caused by Heartland virus, which is a recently related discovered phlebovirus. SFTSV is uncertainly classified as a novel member of the genus Phlebovirus, family Bunyaviridae. Since the detection in the year 2009, SFTS cases were only related to China, Japan, and South Korea until September 2013, where China has reported more than 600 laboratory confirmed cases, of which 10% were deadly. The greater part of these cases have been identified in rural, hilly areas of Central and Southern China. The primary transmission route of SFTSV is believed to be the exposure to or bite of an infected tick of the species Haemaphysalis longicornis which are widely distributed in China, Japan, and South Korea. Quite a few bunches of direct human-to-human transmission have been reported from China. SFTS patients commonly complain from fever, fatigue, nausea, vomiting, diarrhea, lymphadenopathy, and headache. Additional symptoms such as anorexia, abdominal pain, malaise, myalgia, arthralgia, cough, and chills have been described together with hemorrhagic (e.g., conjunctival congestion, gingival bleeding, and/or melena).

Bas-Congo Virus: A Novel Rhabdovirus Associated with Acute Hemorrhagic Fever

Bas-Congo virus is a recently discovered rhabdovirus originated in serum from a patient having acute hemorrhagic fever. A Rhabdovirus causing hemorrhagic fever in humans seems strange at first look for no member of this family has been associated with this kind of disease in humans earlier. Rhabdoviruses that were previously recognized to be pathogenic for humans have been associated with encephalitic syndromes or influenza-like syndromes. Rhabdoviruses are enveloped viruses with single-stranded negative-sense RNA genomes. BASV has only been found in the Bas-Congo province of Democratic Republic of Congo, Central Africa. The source of infection and the potential ways of transmission have not been well-known. Waterborne or airborne transmission appears unbelievable. Clinical symptoms include an abrupt onset of disease, with hemorrhagic manifestations not limited to gastrointestinal sites but also affecting mucosa: nose bleeding, ocular or conjunctival problems, oral hemorrhage, hemorrhagic vomiting and diarrhea.

Hantavirus Infections

Hantaviruses cause hemorrhagic fever with renal syndrome (HFRS) in Asia and Europe and can disseminate to cause Hantavirus Cardio Pulmonary Syndrome (HCPS) in the States, with mortality rates from 12% (HFRS) to 50% (HCPS). Hantavirus pulmonary syndrome (HPS) was first recognized in June 1993 as a result of the investigation of a cluster of fatal cases of adult respiratory distress syndrome (ARDS) in the southwestern United States. As part of the effort to locate the source of the virus, researchers located and examined stored samples of lung tissue from people who had died of mysterious lung disease. Some of these samples showed evidence of earlier infection with Sin Nombre virus - indicating that the disease had existed before the "first" known outbreak. Other early cases of HPS have been revealed by examining samples of tissue belonging to people who had died of unexplained adult respiratory distress syndrome. Hantaviruses (genus Hantavirus, family Bunyaviridae) are enveloped RNA viruses, spherical in shape and are single-stranded RNA viruses with a three segmented genome. The big bulk of HFRS cases, approximately 100,000 annually, are reported from Asia, where China represents 70-90% of all cases. In the environment, rodents act as reservoir host for pathogenic hantaviruses, with chronic and almost asymptomatic infection. The viruses are excreted in urine, feces, and saliva of infected reservoirs and it can remain infective in the atmosphere for more than 10 days, and even more if present in a cooler environment. The aerosol route of infection is the most common; however, infection after a rodent bite and person-to-person transmission has been reported. Symptoms include a sudden onset of high fever, chills, malaise, myalgia, headache, and other flu-like symptoms. Conjunctival hemorrhages, petechiae, and hypotension, which may progress to permanent shock, are frequent.

Lassa Fever (LF)

Lassa virus (LASV) is a leading cause of viral hemorrhagic fever, which is an acute systemic illness classically involving fever and may lead to bleeding and shock. Unlike many viral hemorrhagic fevers, LF is not a rare disease that emerges only in outbreak form. Lassa fever is an acute viral illness that occurs in West Africa (eastern Sierra Leone, northern Liberia, southeastern Guinea, and central and southern Nigeria). The illness was discovered in 1969 when two missionary nurses died in Nigeria. The virus is named after the town in Nigeria where the first cases occurred. The virus, a member of the virus family Arenaviridae, is a single-stranded RNA virus and is zoonotic, or animal-borne. Yearly infections may number in tens or even hundreds of thousands, with thousands of deaths. In some areas of Sierra Leone and Liberia, it is known that 10%-16% of people admitted to hospitals every year have Lassa fever, which indicates the serious impact of the disease on the population of this region. The risk of exposure to LASV varies significantly in a given country and often among regions within endemic areas. The reservoir, of Lassa virus is a rodent identified as the "multimammate rat" (Mastomys natalensis). Once infected, this rodent is able to excrete virus in urine for an extended period of time, maybe for the rest of its life. Human-human transmission of LASV occurs through direct contact with infected blood or bodily fluids, presumably from oral or mucous membrane exposure in the context of providing care to a sick family member in the public or to patient inside a hospital. Symptoms are almost non-specific and difficult to distinguish from a host of other febrile illnesses common in the tropics. Illness typically begins with the gradual onset of fever and constitutional symptoms, including general malaise anorexia, headache, chest or retrosternal pain, sore

throat, myalgia, arthralgia, lumbosacral pain, and dizziness. The most common complication of Lassa fever is deafness. Because the symptoms of Lassa fever are so varied and nonspecific, clinical diagnosis is often difficult. Lassa fever is also associated with occasional epidemics, during which the case-fatality rate can reach 50% in hospitalized patients.

Alkhurma Hemorrhagic Fever

Alkhurma hemorrhagic fever (AHF) is a viral infection lately described in Saudi Arabia, associated in severe forms of hemorrhagic and neurologic manifestations. Mortalities in hospitalized patients varied between 1 and 20%. Alkhurma hemorrhagic fever (AHF) is caused by Alkhurma hemorrhagic fever virus (AHFV), a tick-borne virus of the Flavivirus family (genus Flavivirus, enveloped, segmented, negative-strand RNA virus). The virus was initially isolated in 1995 from a patient in Saudi Arabia who presented a rapid, fatal hemorrhagic fever. The persistence of the virus within tick populations, and the role of livestock in the disease transmission process, is not well explained. AHFV is a variant of Kyasanur Forest disease virus (KFDV), which is endemic in the Karnataka State in India and a member of the tick-borne encephalitis group. Since the first case described in the Saudi Arabia, several hundred human cases have been reported in other western Governorates of Saudi Arabia: Jeddah, Jizan, and Najran. AHFV is a zoonotic virus, and has been isolated from adult soft ticks (Ornithodoros savignyi) and hard ticks (Hyalomma dromedari) sampled in western Saudi Arabia. Both ticks are widely distribute and people can be infected through tick-bite or when crushing infected ticks. The disease appears to be in two phases in some patients; starts as a non-specific flu-like syndrome with fever, anorexia, malaise, diarrhea, vomiting, then followed by either neurological or hemorrhagic manifestations. Thrombocytopenia, leukopenia, and elevated liver enzymes are almost observed in hospitalized patients.

Rift Valley Fever

Rift Valley fever (RVF) is an acute viral disease usually observed in domesticated animals (cattle, buffalo, sheep, and camels), with the ability to infect humans. The ability of Rift Valley fever virus (RVFV) to cause large outbreaks in animal and human populations and to cross geographic barriers, as demonstrated by the virus spread over the Indian Ocean and the Red Sea in the past three decades, is of great concern for health authorities worldwide. The disease is caused by RVF virus (RVFV), a member of the genus Phlebovirus in the family Bunyaviridae. It was first reported in livestock by veterinary officers in Kenya's Rift Valley in the early 1910s. Lately, considerable advancement has been discovered on various aspects of the disease and its etiological agent; however, unpredictability of virus emergence, gaps in knowing its ecology, and the mechanisms involved in inter-epizootic transmission stay a challenge for health scientists. Infections with RVFV in humans can happen from bites of infected mosquitoes and from other insects that have virus-contaminated mouthparts. What is well known is that humans are infected after the exposure to body fluids of RVF-positive animals. This exposure to infected animals can increase during slaughtering or butchering and/or from the disposal of carcasses or fetuses. Hence, certain workers such as herders, farmers, slaughterhouse, and veterinarians are at higher risk of acquiring the infection. Symptoms vary from moderate to severe; non-fatal, flu-like illness with headache, nausea, myalgia, joint pain, neck stiffness, ocular disease, loss of appetite, and vomiting. Less than 1% of human patients develop the hemorrhagic and/or encephalitic forms of the disease.

Ebola Virus Disease

Ebola is caused by infection with a virus of the family Filoviridae, genus Ebolavirus. There are five identified Ebola virus species, four of which are pathogenic and can infect humans. Ebolaviruses are enveloped, single-strand, negative-sense RNA. Ebola first appeared in 1976 in two simultaneous outbreaks, in Nzara, Sudan, and in Yambuku, Democratic Republic of Congo. Ebola was first discovered in 1976 near the Ebola River (Democratic Republic of the Congo). From 1976 to December 2012, Ebola viruses are found in several African countries and a total of 23 outbreaks have been reported; during these events a total of 2388 Ebola cases including 1590 reported mortalities. Since its discovery in 1976, Ebola virus disease (EVD) has mostly occurred in sub-Saharan Africa, however other countries like Sudan (1976, 1979, 2004), Democratic Republic of Congo (1976, 1977, 1995, 2007, 2008), Gabon (1994, 1996, 2001, 2002), Uganda (2000, 2007, 2011, 2012), and Republic of the Congo (2001, 2002, 2003, 2005) have reported several outbreaks. Scientists believe that the transmission occur through contact with an infected fruit bat or primate (apes and monkeys). Person-to-person transmission can also occur and may lead to large numbers of infected cases. In previous Ebola outbreaks, primates were also affected by Ebola, and several events occurred when people came in contact with infected primates. The virus spread is through direct contact (broken skin or mucous membranes), blood or body fluids, inanimate objects (like needles and syringes) and infected fruit bats or primates. Ebola is not spread through the air, by water or by food. The symptoms of acute viral illness are usually described by the sudden onset of fever followed by a 2/3 days period with non-specific symptoms; severe headache, muscle pain, intense weakness, and sometimes conjunctival disease. This is followed by a 2/4 day deteriorating period with sore throat, chest and abdominal pain, skin rash, diarrhea, vomiting, abnormal kidney and liver function, and in some instances internal and external bleeding. Recovery from this viral illness depends widely on the patient's immune response and people who recover may develop antibodies that last for at least 10 years.

Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) Infection

Middle East Respiratory Syndrome (MERS) is a respiratory illness and is caused by Middle East Respiratory Syndrome Coronavirus, or MERS-CoV. This virus was first reported in 2012 in Saudi Arabia and is different from any other coronaviruses that have been described in people before. It is a novel coronavirus that was initially designated HCoV-EMC. They can cause mild to moderate upper respiratory tract diseases in humans. The human coronaviruses, enveloped RNA viruses, are not new and were first identified in the mid-1960s. There are four virus clusters within the Coronavirinae subfamily. All known human coronaviruses belong to the genera Alphacoronavirus and Betacoronavirus. Between April 2012 and February 7, 2014 there were 182 documented cases of MERS-CoV infection worldwide. The majority of these occurred in Saudi Arabia where (148 cases). MERS-CoV is spread from an infected person's respiratory secretions such as coughing, however, the exact means in which the virus spreads are not well explained. MERS-CoV spreads through close contact, such as caring for or living with an infected person. The most common symptoms are fever (87%), cough (87%), and shortness of breath (48%) and serious respiratory disease, resulting in a high mortality rate of 60%. Most of the people who died had an underlying medical condition. About 35% of patients had accompanying gastrointestinal symptoms, including diarrhea and vomiting.

Norovirus Gastroenteritis

Norovirus gastroenteritis is a common acute non-bacterial gastroenteritis worldwide. The pathogen norovirus is a highly contagious agent and in some instances it can cause severe illness i.e. encephalopathy and chronic gastroenteritis in immune-suppressed patients. The disease is caused by norovirus, which belongs to the family Caliciviridae containing a single-stranded RNA genome and a relatively simple structure, containing one major (VP1) and one minor (VP2) capsid protein. Lately, it was described that norovirus strains can periodically emerge either globally or nationally, displace other strains, and increase disease incidence. In winter 2002, a new virus variant was attributed to a well-publicized surge of norovirus outbreaks on cruise ships and in nursing homes in the United States and in European hospitals. Cases of norovirus gastroenteritis are believed to increase in cold seasons. Norovirus transmission occurs mainly by ingesting contaminated food or water and the virus is also transmitted person to person or via contaminated environmental surfaces, and fomites, such as shared toilet facilities. The virus is extremely contagious with an estimated infectious dose as low as 18 viral particles. Shellfish, such as clams and oysters, are extremely common vehicles in outbreaks. Symptoms of the illness caused by each genogroup are indistinguishable. The incubation period for norovirus gastroenteritis is generally 24 to 48 hours, with a range from 18 to 72 hours. Symptoms include abdominal cramps or nausea, vomiting, diarrhea, myalgias, malaise, and headaches. Fever develops in about half of cases.

Enterohemorrhagic Escherichia coli (EHEC): Hemorrhagic Colitis and Hemolytic Uremic Syndrome (HUS)

Enterohemorrhagic Escherichia coli (EHEC) strains - mostly serotype O157:H7 - are a highly pathogenic subgroup of Shiga toxin–producing E. coli (STEC) that causes severe human diseases, including bloody diarrhea and hemolytic uremic syndrome (HUS). New strains emerge and adapt their virulence profile, for example, by lateral gene transfer between different potentially pathogenic E. coli bacteria colonizing a host's intestinal tract. The generation of new strains may in particular occur in settings where humans live in close contact with ruminants (asymptomatic carrier of EHEC) and where food contaminations occur frequently. The first outbreaks were described in Oregon and Michigan, USA, in 1982. In addition to E. coli O157, many other kinds (called serogroups) of STEC cause disease. Other E. coli serogroups in the STEC group, including E. coliO145, are sometimes called "non-O157 STECs." Currently, there are

limited public health surveillance data on the occurrence of non-O157 STECs, including STEC O145; many STEC O145 infections may go undiagnosed or unreported. Infections have mostly been linked with contaminated food or water. EHEC are Gram-negative, facultative anaerobic Enterobacteriaceae asymptomatically colonizing the intestinal tract of several ruminants with cattle being the main reservoir and source for direct or indirect human infections. More than 200 different serotypes are known. The most frequently reported serotype in North America, Japan, and Europe is the non-sorbitol-fermenting strain O157:H7. EHEC have been linked with hemorrhagic colitis around the world. For 2012, the Centers of Disease Control and Prevention (CDC) calculated an overall incidence rate of 2.28 cases per 100,000 population in the USA, while the incidence in Germany was officially published to be 1.9 cases per 100,000 population. The disease is a zoonosis and infections usually occur by food or waterborne as well as, infrequently, by person-to-person transmissions during outbreaks. The disease is characterized by watery diarrhea typically accompanied by abdominal cramps, bloody diarrhea in some other instances, fever, nausea and vomiting. Around 5–10% of those infected develop a potentially life-threatening complication as hemolytic uremic syndrome (HUS)

Emerging Clostridium difficile Infections

Clostridium difficile is a spore-forming, Gram-positive anaerobic bacillus that produces two exotoxins: toxin A and toxin B. It is a common cause of antibiotic-associated diarrhea (AAD). Clostridium difficile colitis remains the most common cause of nosocomial and antibiotic-associated diarrhea. Epidemic strain ribotype 027, not a conventional strain, had spread to Canada, the United States, England, parts of continental Europe, and Japan. In addition, hospital outbreaks of unusually severe and epidemic C. difficile infection were noted more than before. Epidemic strain was reported first in 2003 from Canada. A previous report revealed that disease severity is consistent with stool toxin level. It is thought that the toxin is related to cell retraction and apoptosis. The epidemic strain has the predisposition to produce larger quantities of toxins than other C. difficile strains. As a result, it is presumed to be associated with the development of perforation. About 2% healthy adult and 20% adult hospitalized patients are C. difficile carriers without diarrhea. C. difficile is the main contributor to gastroenteritis-associated deaths. Clostridium difficile is shed in feces. Any surface, device, or inanimate objects that become contaminated with feces may serve as a reservoir for the Clostridium difficile spores. The main clinical manifestations of CDI are watery diarrhea, fever, loss of appetite, nausea, abdominal pain/tenderness. The symptom typically begins after 5-10 days of antibiotic treatment. Surprisingly, it is present as late as 10 weeks after cessation of treatment.

Zika Virus

Zika virus is a mosquito borne Flavivirus that is the focus of an ongoing pandemic and public health crisis. Formerly limited to sporadic cases in Africa and Asia, the emergence of Zika virus in Brazil in 2015 heralded rapid spread throughout the United States. Although most Zika vi¬rus infections are characterized by subclinical or mild in¬fluenza-like illness, severe manifestations have been de¬scribed, including Guillain-Barre syndrome in adults. Neither an effective treatment nor a vaccine is available for Zika vi¬rus; therefore, the public health response primarily focus¬es on preventing infection, particularly in immune-suppressant. Zika virus is a positive-sense single-stranded RNA virus in the family Flaviviridae, which includes several other mosquitoborne viruses of clinical importance (e.g., DENV, WNV, and yellow fever virus). Zika virus transmission occurs through the bite of an infected Aedes species mosquito. This mosquito typically lays eggs in and near standing water in things like buckets, bowls, animal dishes, flower pots and vases. It prefers to bite people, and live indoors and outdoors near people. Mosquitoes that spread Zika are aggressive daytime biters, but they can also bite at night. Mosquitoes become infected when they feed on a person already infected with the virus. Infected mosquitoes can then spread the virus to other people through bites. Also, transmission can occur from mother to child, through sex, through blood transfusion and through laboratory exposure. In humans, the incubation period from mosquito bite to symptom onset is 3-12 days. Many people infected with Zika virus won't have symptoms or will only have mild symptoms. The most common symptoms of Zika are fever, rash, joint pain, conjunctivitis, muscle pain, headache and arthralgia. Rash is maculopapular and pruritic in most cas¬es; it begins proximally and spreads to the extremities with spontaneous resolution within 1–4 days of onset.

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