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Viral Infections, an Overview with a Focus on Prevention of Transmission

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Introduction

Traditionally, the epidemiological control of most viral infections depends on the isolation of cases, quarantine of contacts, personal protection by infection control measures, and mass vaccination, because specific antiviral treatment is generally not available for most viral infections (Table 1). This scenario is rapidly changing with the increasing availability of rapid diagnostic tests that use nucleic acid amplification and the development of increasing number of effective antiviral agents. Common acute viral diseases such as respiratory, diarrheal, exanthematous, or neurological infections can overlap with each other and appear as seasonal epidemics that peak in incidence every few years and coincide with the accumulation of sufficient number of nonimmune hosts in the young population. Arboviral disease activity often coincides with arthropod vector activity such as mosquito breeding in hot rainy seasons that are associated with increased incidence of hemorrhagic fever or neurological diseases such as dengue hemorrhagic fever, West Nile virus, or Japanese encephalitis in Southeast Asia. Many chronic blood-borne viral illnesses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) are still taking a major toll in certain geographic regions due to specific human behaviors or vertical transmission. Some of these chronic viral infections such as HBV, HCV, HIV, polyomaviruses, and papillomaviruses are also linked to the genesis of cancers. Over 70% of emerging viral infections such as the Ebola virus, severe acute respiratory syndrome (SARS) coronavirus, and Middle East respiratory syndrome (MERS) coronavirus are associated with acute explosive outbreaks after the virus jumps the species barrier from bats or other animals to human (Table 2). This chapter will focus on the prevention and control of viral infections, while other article in this book will cover information on specific viruses.

Diagnostic Approaches for Viral Illness

Unlike bacteria, fungi, and parasites, viruses are too small to be visible under light microscopy. Moreover, viruses are obligate intracellular pathogens and do not grow in artificial culture medium. Collecting the correct clinical specimens during the peak of viral shedding in appropriate viral transport medium is crucial for accurate diagnosis. Electron microscopy is not sensitive and has a limited role in the examination of feces from viral gastroenteritis and vesicular fluid from skin lesions caused by herpesviruses and poxviruses. Virus isolation in cell lines or chick embryo is the gold standard for virological diagnosis but seldom alters clinical management due to its long turnaround time. Viral antigen detection by immunofluorescence, enzyme immunoassay, and point-of-care rapid lateral flow immunochromatographic assays has significant impact on therapeutic and infection control strategies.

The most important rapid virological tests are nucleic acid amplification tests such as real-time or multiplex reverse transcription-polymerase chain reaction (RT-PCR) assays that are useful for accurate diagnosis and subsequent viral load monitoring during antiviral treatment. Genotyping by nucleic acid amplification and sequencing for detection of mutations associated with antiviral resistance directly from clinical specimens is now available for many antiviral agents and is routine for antiretroviral drugs used to treat HIV infection. Though nucleic acid amplification tests still have practical limitations in the field settings of developing areas, such tests are now routine in most hospitals in developed countries. Antibody testing by enzyme immunoassay for IgM in acute infection, IgG for immune status of exposed individuals, and retrospective diagnosis by the presence of rising antibody titers in paired acute and convalescent sera of symptomatic patients is useful for making clinical and epidemiological

Table 1 Common human viral infections

Major viral families	*Viruses within the family*	*Modes of transmission*	*Major clinical syndrome*	*Diagnostic methods*	*Antiviral treatment*	*Vaccine prevention*
Herpesviridae	HSV-1, HSV-2 VZV EBV CMV HHV-6, HHV-7 HHV-8	Contact/droplets Airborne (VZV)	Oral/genital herpes Chickenpox/shingles Infectious mononucleosis Roseola infantum Kaposi's sarcoma Encephalitis (HSV, VSV)	Viral culture/PCR/serology CMVpp65	Acyclovir, valacyclovir (HSV, VZV, HHV-8) Ganciclovir, valganciclovir, foscarnet, cidofovir (CMV, HHV-8) Imiquimod (HHV-8)	Varicella (VZV) vaccine
Orthomyxoviridae	Influenza A Influenza B Influenza C	Contact/droplets	Upper respiratory tract infection Pneumonia Pneumonitis Encephalitis Pericarditis/myocarditis	Viral culture/PCR/serology Immunofluorescent staining	Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) for influenza A or B M2 inhibitors (amantadine, rimantadine) Favipiravir	Seasonal trivalent or quadrivalent influenza vaccine (e.g., H1N1, H3N2, B) Monovalent influenza vaccine (H5N1, H7N9)
Filoviridae	Ebolavirus Marburgvirus	Contact	Viral hemorrhagic fever	Viral culture/PCR/serology	None	Ebola vaccine (phase II/III trial)
Picornaviridae	Enterovirus	Droplets	Hand, foot, and mouth disease, respiratory illness, aseptic meningitis, and myocarditis	Viral culture/PCR/serology	None	None
	Hepatovirus		Hepatitis A infection			Hepatitis A vaccine
	Poliovirus		Poliomyelitis			Oral polio vaccine
	Rhinovirus		Upper respiratory tract infection			None
Rhabdoviridae	Rabies virus	Contact	Rabies	Viral culture/PCR/serology	Human rabies immunoglobulin	Rabies vaccine
Flaviviridae	Dengue virus Japanese encephalitis virus St. Louis encephalitis virus Tick-borne encephalitis virus West Nile virus Yellow fever virus Hepatitis C virus	Arthropod Blood-to-blood contact (hepatitis C)	Hemorrhagic fever Acute and chronic hepatitis (HCV)	Viral culture/PCR/serology	None Polymerase/protease inhibitors/ribavirin/pegylated interferon (HCV)	Dengue vaccine (phase III) Yellow fever vaccine
Paramyxoviridae	Measles virus Mumps virus Human parainfluenza virus Human metapneumovirus	Droplets	Measles Mumps Upper respiratory tract infection Pneumonia	Viral culture/PCR/serology	None	MMR vaccine (measles, mumps)

Togaviridae	Rubella virus Chikungunya virus Equine encephalitis virus	Droplets Arthropod (Chikungunya virus/ equine encephalitis virus)	Rubella Chikungunya disease	Viral culture/PCR/ serology	None	MMR vaccine (rubella)
Retroviridae	HIV-1, HIV-2	Body fluid/blood contact	Acquired immune deficiency syndrome	Viral culture/PCR/ serology	HAART	None
Hepadnaviridae	Hepatitis B virus	Body fluid/blood contact	Acute and chronic hepatitis B	Viral culture/PCR/ serology	Nucleoside and nucleotide analog Hepatitis B immunoglobulin	Hepatitis B vaccine
Hepeviridae	Hepatitis E virus	Fecal–oral route	Acute hepatitis E	Viral culture/PCR/ serology	None	None
Reoviridae	Rotavirus	Fecal–oral route	Gastroenteritis	Viral culture/PCR	None	Rotavirus vaccine
Coronaviridae	Human coronavirus	Droplets	Upper respiratory tract infection, pneumonia	Viral culture/PCR	None	None
Papillomaviridae	Human papillomavirus	Contact	Warts	Viral culture/PCR	Imiquimod	HPV vaccine

Table 2 Examples of outbreaks of emerging viral infections with bats as the most likely natural reservoir

Viral agent	*Intermediate or amplification hosts*	*At-risk population*	*Epicenter for animal to human transmission*	*Reference*
SARS-CoV	Palm civets	Wet market workers	Wet markets (healthcare facilities and household)	Guan et al. (2003) and Lau et al. (2005)
MERS-CoV	Dromedary camels	Close contact with camel	Camel farm (healthcare facilities and household)	(Woo et al., 2014)
Ebola virus	Nonhuman primates	Bush meat hunters, healthcare workers, and family/community members with exposure	Forests (healthcare facilities and household)	Feldmann et al. (2003)
Nipah virus	Pigs	Pig farmers and abattoir workers	Pig farms and abattoirs (healthcare facilities)	Goh et al. (2000)
Hendra virus	Horses	Close contact with horses	Horse farms	Halpin et al. (2000) and Hooper et al. (2000)
Rabies virus	Nil (direct bat to human transmission)	Scientists and personnel handling bats	Rural residents with contact with bats (organ transplantation)	Dietzschold and Koprowski (2004) and Kusne and Smilack (2005)

decisions. Antibody screening is especially important in antenatal visits of expectant mothers, blood donors, and organ donor and recipients before transplantation. Next-generation sequencing performed directly on clinical specimens may revolutionize virological diagnosis in the coming decade. The timely and accurate diagnosis of viral infections has important implications for effective epidemiological control in the community and infection control for hospital outbreaks.

Viral Transmission and Infection Control Prevention for Blood-Borne Viruses Including HIV, HBV, and HCV

Transmission of blood-borne viruses can result from sexual intercourse and maternal–fetal transmission in the community setting and needlestick injury and other exposure-prone procedures in the healthcare setting. In a study from the United States, the annual death rate of healthcare workers from occupational events was estimated to be 17–57 per 1 million workers, and most of these deaths resulted from infection-related complications of blood-borne viruses (Sepkowitz and Eisenberg, 2005). The overall risk of transmission of blood-borne viruses by hollow needlestick injury is 33%, 3%, and 0.3% if the source is a hepatitis carrier with positive HBe antigen or high viral load, hepatitis C carrier with RNAaemia, and HIV, respectively. Compliance with standard precautions including wearing gloves when handling blood during patient care practice, disposing sharp and needles into puncture-resistant box, and avoidance of recapping needles remains the most important way to prevent nosocomial acquisition of blood-borne viruses (Garner, 1996).

Active immunization for HBV can protect healthcare workers from HBV infection with an efficacy of 80–95% (Dienstag et al., 1984; Sabido et al., 2007; Shim et al., 2011). Postimmunization anti-HBs antibody level should be measured at 4–8 weeks after completion of the 3-dose immunization regimen given at baseline, 1 month, and 6 months. A good responder is defined as a person whose anti-HBs antibody level is >100 IU l^{-1}. If the hepatitis B antibody level is between 10 and 100 IU l^{-1}, a booster dose of vaccine should be given. For nonresponders whose anti-HBs antibody is <10 IU l^{-1}, another course of HBV vaccine should be given. The response rate is about 61% in repeated HBV vaccination by the same route as the initial vaccination (Struve et al., 1994). Alternatively, immunization with high-dose intradermal recombinant HBV vaccine, given in up to four doses, can achieve immunity in 88% of healthcare workers who failed to respond to intramuscular vaccination and boosters (Levitz et al., 1995). The anti-HBs titer was persistently higher than the protective level for at least 10 years after primary HBV vaccination (Floreani et al., 2004).

When a healthcare worker sustains a needlestick injury, he or she should be advised to rinse the wound with tap water and allow natural bleeding. The source patient's blood is collected to check for the presence of HIV, HBV, and HCV. If the status of blood-borne viruses of the source patient is positive or unknown, postexposure prophylaxis (PEP) should be offered according to current guidelines (Kuhar et al., 2013). The exposed healthcare worker will be closely followed up for counseling, baseline, and HIV testing and monitored for drug toxicity. If a newer fourth-generation combination HIV p24 antigen–HIV antibody test is utilized for follow-up HIV testing, HIV testing may be concluded 4 months after exposure. Otherwise, follow-up HIV testing is performed 6 months after the exposure (Kuhar et al., 2013). For HBV, PEP with hepatitis B immune globulin (HBIG) and/or HBV vaccination should be considered for occupational exposures after evaluation of the HBsAg status of the source and the vaccination and vaccine-response status of the exposed person (2001). For HCV, PEP is not currently recommended. However, an open-label pilot trial was conducted to determine the safety, tolerability, and acceptance of peginterferon alfa-2b as PEP. Among 213 healthcare workers exposed to an HCV antibody-positive source, 51 HCWs enrolled in the study and 44 (86%) elected to undergo peginterferon alfa-2b as the study group. Seven subjects elected not to undergo PEP were treated as the control group. In this pilot study, peginterferon alfa-2b was proved to be safe without serious adverse side effects. However, the lack of HCV transmission

in both the study and control groups did not support the routine use of PEP in healthcare workers after HCV exposure (Corey et al., 2009). It is likely that the new polymerase and protease inhibitors used in the treatment of HCV infection will result in new strategies for PEP of HCV exposures.

Blood-borne viruses can also be transmitted from healthcare workers to patients, especially during exposure-prone procedures in dental and cardiothoracic operations. The most well-known example involved an HIV-positive dentist working in Florida, the United States, who infected five of his patients after performing invasive dental procedures on them (Ciesielski et al., 1992). Sequencing of the HIV proviral envelope gene showed that the viruses infecting the dentist and the five patients were closely related (Ou et al., 1992). However, the overall risk for transmission of HIV from a healthcare worker to a patient is very small. In a study conducted by the Centers for Disease Control and Prevention (CDC) of 22 171 patients being cared by 51 HIV-positive healthcare workers, 113 (0.5%) patients became HIV-positive. Epidemiological investigation did not implicate healthcare workers as the source of infection in any of these patients (Robert et al., 1995). In contrast, transmission of HBV and HCV from healthcare workers to patients was more frequently documented. Between August 1991 and July 1992, 19 of 144 (13%) patients who were operated on by a thoracic surgeon with acute HBV infection became HBV-infected. Sequencing of 160 bases in the core region of HBV showed an indistinguishable pattern among the strains of the surgeon and nine infected patients (Harpaz et al., 1996). Subsequently, numerous healthcare worker-to-patient transmissions of HBV and HCV were reported. Among all these reported cases, the viral loads of the index healthcare workers were more than 10^6 genome copies per milliliter (Buster et al., 2003; Gunson et al., 2003). In this connection, the Society for Healthcare Epidemiology of America (SHEA) issued a guideline for the management of healthcare workers who are infected with HIV, HBV, and HCV to impose restriction on different categories of exposure-prone procedures according to the viral load (Henderson et al., 2010).

Viral Transmission and Infection Control Prevention for Droplet and Airborne Agents Including All Respiratory Viruses, Chickenpox, and Measles

Epidemiologically important respiratory viruses such as influenza A virus are predominantly transmitted by the droplet route. By definition, the virus can spread within 1 m from the index case. However, individuals infected with influenza A virus may produce as many as 40 000 droplets of 0.5–12 μm in size and expel them at a velocity of 100 m s^{-1} upon sneezing (Tang et al., 2006). Droplet nuclei of <3 μm may suspend in air and do not settle onto the ground (Knight, 1980). Therefore, an explosive outbreak with high clinical attack rate as a result of aerosol transmission may occur under special conditions. In a jet airliner with nonfunctioning ventilation system, 72% of 54 passengers developed influenza-like illness within 72 h after being kept on ground for 3 h due to delay in flight time (Moser et al., 1979). As the virus may survive on inanimate surfaces for 12–48 h and on the surface of hands for 10–15 min (Kampf and Kramer, 2004; Kramer et al., 2006), influenza virus can be transmitted indirectly by contact with hands from the contaminated environment to the pharyngeal mucosa. Symptomatic influenza may develop after intranasal inoculation of one $TCID_{50}$ of influenza A virus (Tellier, 2006). Hand hygiene is always the core component of infection control measures in both community and hospitals to prevent the transmission of influenza A virus. Wearing face masks by either the index case as source control or the healthcare workers as contacts has shown to be equally effective in the control of nosocomial transmission of pandemic influenza A H1N1 (Cheng et al., 2010). Hand hygiene and face masks have been shown to prevent household transmission of influenza virus when implemented within 36 h of the index patient's symptom onset (Cowling et al., 2009). Oseltamivir PEP halted an outbreak of pandemic influenza A H1N1 in a secondary school (Asiedu-Bekoe et al., 2012), but not in nursing homes (van der Sande et al., 2014).

Prevention of nosocomial transmission of influenza A virus requires multiple actions. Early identification of symptomatic cases by direct antigen detection from nasopharyngeal specimens and initiation of droplet precautions by wearing surgical masks, along with staff education, could achieve reductions in nosocomial pandemic influenza to near zero (Cheng et al., 2010), while a similar protocol was also effective in minimizing the risk of nosocomial transmission of avian influenza A/H7N9 virus (Cheng et al., 2014). To ensure hand hygiene compliance, directly observed hand hygiene was adopted to control the spread of respiratory viruses in hospitals (Cheng et al., 2007b, 2010). Alcohol-based hand rub is delivered to every healthcare worker and conscious patient once every 2–3 h in the clinical areas, which may further reduce the spread of respiratory viruses.

Varicella zoster virus (VZV) and measles are predominantly transmitted by aerosols and deposited in distal airways (Roy and Milton, 2004). The exact mechanism of airborne transmission remains to be elucidated. However, an early study demonstrated that nosocomial outbreak of VZV occurred even when the index case was strictly isolated in a single room (Gustafson et al., 1982). There was a lack of nosocomial spread of VZV when all index cases were placed in negative-pressure airborne infection isolation rooms (Anderson et al., 1985). Measles virus can survive in the air for at least 1 h, as shown in an outbreak where three susceptible children who contracted measles were never in the same room with the source patient and one of the three arrived at the office 1 h after the source patient had left (Bloch et al., 1985). A massive community outbreak of measles occurred in a modern suburban elementary school in New York in spring, 1974, when the index case produced 28 secondary cases in 14 different classrooms. The epidemic subsided after two subsequent generations when 60 children had been infected. From estimates of major physical and biological factors, it was possible to calculate that the index case produced $\sim$93 units of airborne infection (quanta) per minute, which was higher than that of patients with laryngeal tuberculosis (Riley et al., 1962, 1978). Early recognition and placement in airborne infection isolation room of index case of VZV and measles may reduce the risk of nosocomial outbreaks.

Viral Transmission and Infection Control Prevention for Viral Agents Spread by Contact

Standard and transmission-based precautions are important to prevent the spread of respiratory and gastrointestinal viral infection (Table 3). Some of the respiratory viruses such as respiratory syncytial virus (RSV), parainfluenza virus, and the gastrointestinal viruses, norovirus, and rotavirus are predominantly spread by direct contact. As an illustrative example, RSV is the most frequent cause of nosocomial infection in pediatric wards and causes lower respiratory tract disease in 40% of young children. Prolonged shedding of RSV for 3–11 days has been observed in immunocompetent children (Hall, 2000), and the virus can survive on inanimate surfaces for 6 h (Kramer et al., 2006). All these factors contribute to fomite-mediated transmission of RSV in the hospital. The risk of nosocomial RSV transmission was not related to age or underlying disease, but to length of hospitalization (Hall et al., 1975). Contact precautions with cohort nursing and wearing gloves and gowns during patient care resulted in a significant reduction in nosocomial transmission of RSV in three consecutive winters (Madge et al., 1992). In another study, the incidence of nosocomial acquisition of RSV was significantly decreased after implementation of wearing gloves and gowns and isolation of case events though the duration of RSV shedding remained unchanged before and after the intervention (Leclair et al., 1987).

For the gastrointestinal viruses, norovirus is the most famous agent to cause outbreaks in the community and hospital. Transmission is predominantly by the fecal–oral route. Numerous community outbreaks of norovirus have been reported in restaurants, resorts, cruise ships, schools, and nursing homes (Arvelo et al., 2012; Britton et al., 2014; Kuo et al., 2009; Lai et al., 2013; Wikswo et al., 2011). The emergence of new variant of norovirus, genogroup II, type 4 (GII.4), in Australia, Europe, and North America associated with increased acute gastroenteritis activity has been reported since 2006 (Bruggink and Marshall, 2010; Hasing et al., 2013; Kanerva et al., 2009; Yen et al., 2011).

Norovirus is a nonenveloped RNA virus that is relevantly resistant to common disinfectants. As norovirus is unculturable, feline calicivirus has been used as a surrogate for *in vitro* and *in vivo* testing for different preparations of disinfectants (Gehrke et al., 2004; Lages et al., 2008). In the WHO formulation alcohol-based hand rub (AHR), formula I preparation contains ethanol (80% v/v) that, based on the aforementioned studies, may possess reasonable virucidal activity for norovirus when the contact time is prolonged for up to 30 s. Successful control of nosocomial outbreaks of norovirus by directly observed hand hygiene has been reported, especially during high-risk nursing care practices such as changing napkins and feeding (Cheng et al., 2009). A proactive infection control approach with the provision of 'added test' was implemented to prevent the occurrence of nosocomial outbreak

Table 3 Infection control measures for transmission-based precautions in resource-poor areas

Transmission-based precautions (example)	*Infection control measures in developed areas*	*Infection control measures modified in resource-poor areas*
Contact precautions (norovirus)	Patient placement: single room isolation or cohort nursing Patient care practice: hand hygiene with alcohol-based hand rub or soap and water if the hands are visibly soiled; personal protective equipment with glove and gown; use of dedicated medical equipment Environment disinfection: frequent disinfection with sodium hypochlorite (1000 ppm) to the high-touch surfaces and terminal disinfection after patient discharge from isolation facilities	Intrinsic limitation: single room isolation facilities, personal protective equipment, and dedicated medical equipment are not sufficient or not available Possible solution: nursed in the open cubicle or cohort nursing, performing regular hand hygiene round by designated healthcare workers at 2–3 h interval to all patients and healthcare workers; directly observed hand hygiene to conscious patients before meals and medications to reduce the risk of nosocomial transmission
Droplet precautions (influenza A virus H3N2, H1N1)	Patient placement: cohort nursing with spatial separation of at least 1 m between beds Patient care practice: hand hygiene with alcohol-based hand rub or soap and water if the hands are visibly soiled; personal protective equipment with surgical mask when caring patients within 1 m Environment disinfection: frequent disinfection with sodium hypochlorite (1000 ppm) to the high-touch surfaces and terminal disinfection after patient discharge from isolation facilities	Infection control requirement of droplet precautions should be able to perform in resource-limited setting
Airborne precautions (SARS-CoV)	Patient placement: airborne infectious isolation room with negative pressure of at least 12 air change per hours Patient care practice: hand hygiene with alcohol-based hand rub or soap and water if the hands are visibly soiled; personal protective equipment with N95 respirator when caring patients within 1 m Environment disinfection: frequent disinfection with sodium hypochlorite (1000 ppm) to the high-touch surfaces, and terminal disinfection after patient discharge from isolation facilities	Intrinsic limitation: lack of airborne infectious isolation room and N95 respirator Possible solution: natural ventilation in open space at tent shelter hanged up by tall post to ensure free air circulation from any wind directions; or in buildings with large windows opened to increase the air change per hour; or large extraction fans if electricity available; provide surgical mask to patient for source control

when the new variant of norovirus, genogroup II, type 4 (GII.4), was circulating in Hong Kong (Cheng et al., 2011). RT-PCR for norovirus was performed as an 'added test' by the microbiology laboratory for all fecal specimens that were requested for bacterial culture, *Clostridium difficile* culture or cytotoxin, and rotavirus antigen detection without a request for norovirus detection. During the study period, almost 50% of newly diagnosed norovirus infections were detected by the added test. Timely implementation of infection control measures by single room isolation of index case with strict contact precautions significantly reduced the incidence of hospital-acquired norovirus infection from 131 (baseline) to 16 cases per 1000 potentially infectious patient-days ($P < 0.001$) (Cheng et al., 2011).

Management of an Acute Emerging Infectious Disease Outbreak Such as SARS, Pandemic Influenza, and Ebola

SARS

The outbreak of SARS in 2003 was the first emergence of an important human pathogen in the twenty-first century. SARS emerged as an outbreak of atypical acute community-acquired pneumonia in the late 2002. The epidemic may have started when a bat SARS coronavirus jumped into caged palm civets in a wildlife market and became adapted and amplified to jump from civet to human. Infected chefs and animal handlers transmitted the adapted virus to healthcare workers and then the epidemic became amplified into the community. The epidemic was rapidly and globally disseminated when a 'super-spreader' of SARS, who was a medical professor from a teaching hospital in Guangzhou, went to Hong Kong on 21 February 2003. During his stay in hotel M, he transmitted SARS-CoV to other residents, and the secondary cases spread the disease to hospitalized patients in Hong Kong and to other countries including Vietnam, Singapore, and Canada. Eventually, a total of 8096 patients were infected in over 30 countries among 5 continents and 774 (9.5%) of them died (Cheng et al., 2007a). Nosocomial outbreaks were reported in many parts of the world including Toronto, Hong Kong, Guangzhou, Kaohsiung, Singapore, and Vietnam during the SARS epidemic. There were a total of 716 secondary and tertiary cases of SARS as a result of the admission of infected index patients. Healthcare workers constituted 410 (52.3%) of the secondary and tertiary cases (Cheng et al., 2013). As there were no known effective antiviral agents and vaccine for the treatment and prevention of SARS, infection control measures and extensive tracing to quarantine the contact person became the most important interventions for SARS control. The longitudinal follow-up of SARS patients revealed that the viral load gradually increased on day 5 after symptom onset and peaked at day 10. Early isolation of source patients can prevent ongoing transmission of SARS in the community. In hospitals, temporary suspension of clinical services in both inpatient and outpatient settings was adopted (Gopalakrishna et al., 2004; Liu et al., 2006; Nishiura et al., 2005; Reynolds et al., 2006), while home quarantine of healthcare workers who had contact with SARS patients was also mandated in some centers (Dwosh et al., 2003).

Provision of personal protective equipment (PPE) such as N95 respirators, gloves, gowns, and goggles and placement of suspected or confirmed cases of SARS in airborne infection isolation rooms were enforced when resources were available. The appropriate use of PPE was also important for staff protection. Many healthcare workers apparently lacked a clear understanding of how best to remove PPE without contaminating themselves. Little information about the appropriate sequence of removing PPE was available at that time (Puro and Nicastri, 2004).

Ebola Virus

Infection control measures are particularly important for emerging viral infections without effective antiviral therapy and vaccine. Recently, the largest outbreak of Ebola virus disease (EVD) in West Africa (Guinea, Sierra Leone, Liberia, Nigeria, and Equateur province of Democratic Republic of the Congo) has already resulted in a total of 27988 cases and 11299 deaths as of 16 August 2015.

Ebola virus is transmitted via contact with contaminated body fluid or the contaminated environment, and therefore, the practice of contact precautions with appropriate PPE is of utmost importance when handling suspected or confirmed EVD cases. Healthcare workers should preferably work in pairs so as to mutually observe against breaks in infection control measures. They are required to put on the PPE in the following sequence: N95 respirator, water-repellent cap or hood, full-length shoe cover or boot, water-resistant gown, face shield, and finally long nitrile gloves. If the patient has hemorrhagic symptoms, double nitrile gloves should be worn. In view of the high virulence and mortality, patients suspected to have EVD should be isolated in airborne isolation rooms, although the WHO allows cohorted nursing in designated areas with dedicated instruments, where access should be restricted in developing countries with limited isolation facilities.

Degowning remains the most critical procedure for healthcare workers. The most contaminated PPE should be removed first, starting with the long nitrite gloves, water-resistant gown, full-length shoe cover or boot, face shield, water-repellent cap or hood, and finally N95 respirator. Hand hygiene with alcohol-based hand rub should be performed in each step of degowning. When the hand is visibly soiled, it should be washed with soap and water. Healthcare workers must be well trained and audited for the proper procedure of gowning and degowning.

When the suspected or confirmed case of EVD dies, the healthcare and mortuary workers are required to wear PPE as described earlier. The dead body is placed in double bags with leakproof characteristic of no < 150 mm thick. Absorbent material should be put under the body and placed in the first bag. The surface of each body bag is wiped with 10 000 ppm sodium hypochlorite solution. The bags are sealed and labeled with the indication of highly infectious material (category 3) and moved to the mortuary

immediately. Viewing in funeral parlor, embalming and hygienic preparation are not allowed. The dead body should not be removed from the body bag and should be sent to cremation as soon as possible.

In August 2014, WHO declared the EVD outbreak in West Africa a public health emergency of international concern. Preparedness and response plans were made available by health authorities in nearly all countries worldwide. The aim was to detect the first imported case for early isolation in order to prevent local transmission in the community and healthcare settings. Therefore, risk assessment at ports, emergency rooms, and outpatient clinics for any patient fulfilling both clinical and epidemiological criteria for EVD is important. For the clinical definition, patient suffering from elevated body temperature or subjective fever or symptoms including severe headache, fatigue, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage should be alerted, while the epidemiological definition includes close contact with a confirmed or probable case of EVD or resided in or history of travel to an affected area or countries (Guinea, Liberia, Sierra Leone) within 21 days before symptom onset. Healthcare workers working in volunteer medical services or nongovernment organization, who have direct contact with patients in the affected areas or countries, should also perform medical surveillance or be placed in quarantine for at least 21 days after leaving the affected areas or countries. Medical evaluation should be sought promptly if there are any symptoms of fever, diarrhea, vomiting, or bleeding during quarantine or medical surveillance.

Control of Viral Outbreak in the Community

With reference to the experience in the community spread of pandemic influenza A virus infection, nonpharmacological interventions with social distancing, such as school closures, have been evaluated in previous modeling and epidemiological studies (Bell et al., 2009; Bootsma and Ferguson, 2007; Ferguson et al., 2006; Markel et al., 2007). During the influenza pandemic in 2009, school closures were practiced in the United States and Australia (Borse et al., 2011; Effler et al., 2010), because school closures were associated with a 65% reduction in the mean total number of contacts for each student as reported in a retrospective questionnaire survey in the United Kingdom (Jackson et al., 2011). In Hong Kong, kindergartens and primary schools were closed when local transmission of influenza A virus was identified in 2009, followed shortly afterward by secondary school closures for summer vacations. Influenza A virus transmission was estimated to be reduced by 25% (Wu et al., 2010). Home quarantine was also shown to reduce the incidence of pandemic influenza A in the workplace (Miyaki et al., 2011). In fact, home quarantine has been used to control the community spread of SARS in Beijing, Taiwan, Singapore, and Toronto (2003; Cava et al., 2005; Hsu et al., 2006).

Home quarantine can be considered for the control of the spread of Ebola virus in affected countries although in resource-limited settings, effectively implementing these strategies can be challenging. The local government and health authorities have already implemented home quarantine for 3 days as an urgent infection control measure. However, if it is technically and politically feasible, home quarantine may be extended for up to 21 days (one incubation period) for EVD. However, public health staff is expected to face unprecedented challenges in implementing an extensive quarantine policy, as they have a dual role of monitoring compliance and providing support to people in quarantine. Countries in close proximity to the affected areas require implementing border control measures to screen for any suspected case of Ebola virus, or even considering closing the border for 21 days. Although these measures may adversely affect international travel and local economies, it may be worthwhile to implement such strict measures to control this reemerging infectious disease with high mortality and psychological fear in a timely manner.

Antiviral and Convalescent Plasma Treatment in the Control of Viral Outbreaks

Currently available antiviral against influenza A include the adamantanes (amantadine and rimantadine), neuraminidase inhibitors (oseltamivir, zanamivir and peramivir), and a pyrazinecarboxamide derivative (favipiravir). Only the neuraminidase inhibitors and pyrazinecarboxamide derivatives are active against currently circulating influenza A viruses. Oseltamivir and favipiravir are available orally. Zanamivir is available either as dry powders and delivered by oral inhalation, or recently, intravenous formulation is available. Peramivir is only available in the intravenous formulation. Randomized controlled trial in patients with seasonal influenza suggested that the use of neuraminidase inhibitor can shorten the duration of illness by $\sim$1 day. A recent meta-analysis had demonstrated that early neuraminidase inhibitor treatment (within 2 days of symptom onset) was associated with a reduction in mortality (Muthuri et al., 2014). Two prospective clinical trials have demonstrated that treatment with convalescent plasma or hyperimmune intravenous immunoglobulin for patients with severe influenza infection was associated with lower viral load, cytokine level, and reduced mortality (Hung et al., 2011, 2013).

Clinical trials on various antiviral treatments against EVD are underway. These agents include BCX4430 (a novel nucleoside analog) (Julander et al., 2014), brincidofovir, favipiravir, TKM-Ebola, and ZMapp (a chimeric monoclonal antibody) in Guinea, Sierra Leone, and Liberia (Bishop, 2015).

Importance of Vaccination in the Control of Viral Outbreaks

When there is no highly effective antiviral for the treatment of a severe viral illness, especially in patients at the extremes of age or with medical comorbidities, and infection control measures are difficult to implement or comply with, vaccination is the final

option to prevent massive outbreaks. Influenza vaccine is the most widely used annual vaccine in the community and healthcare setting to protect at risk or any person to develop influenza-related complications and prevent institutional outbreaks. Seasonal influenza-related excess hospitalization and death were estimated to be 10 000 and 1100 per year in Hong Kong, a subtropical city (Chiu et al., 2002; Wong et al., 2004, 2006). In a meta-analysis assessing influenza vaccine efficacy and effectiveness in elderly patients, the inactivated influenza vaccine could reduce the risk of hospitalization as a result of pneumonia by 21–38% and cardiovascular disease by 18–30% and all cause of mortality by 39–56% (Nichol, 2008).

Control of virus disease outbreak by vaccination is particularly valuable for exposed individuals, when the viral diseases have a long enough incubation period so that the exposed individuals have sufficient time to develop protective immune responses before symptomatic disease set in. Measles (incubation period of 7–18 days), mumps (incubation period of 12–25 days), rubella (incubation period of 14–23 days), and varicella (incubation period of 10–21 days) are relevant examples. Reactive vaccination for measles outbreak has been shown to be an effective measure to reduce the scale of outbreaks. In the Democratic Republic of Congo, weekly reported cases reduced, respectively, by 89.3% and 68.9% in the 3 weeks following mass vaccination campaigns (Alberti et al., 2010). Similarly, nationwide mass vaccination interrupted the transmission of paralytic poliomyelitis in Albania. In 1996, a total of 138 paralytic cases occurred with an attack rate of 10 per 100 000 population among adults aged 19–25 years. The epidemic was controlled by two rounds of mass vaccination with trivalent oral poliovirus vaccine targeted to persons aged 0–50 years (Prevots et al., 1998).

Conclusion

While routine laboratory diagnostic tests and specific antimicrobial agents are generally available for the treatment of bacterial, fungal, and parasitic infections, we are just entering the stage when rapid nucleic acid tests and a greater array of antiviral agents are available for tackling viral infections. The broad array of viruses worldwide causes substantial morbidity and mortality, ranging from respiratory viruses, arthropod-related viruses, to the most deadly blood-borne viruses. Novel emerging or reemerging viruses are causing major epidemics from time to time especially in densely populated areas where human populations have close contact with wild animals (wildlife markets) and food animals (wet markets and abattoirs). Such epidemics such as the EVD can be explosive in countries with failed governance and poor health infrastructures. Currently, there is a lack of antiviral treatment for most of these infections. Therefore, prevention by implementing effective infection control and vaccination is of utmost importance to contain these viruses.

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