Chapter 5
Influenza, Measles, SARS, MERS, and Smallpox

Daniel S. Chertow and Jason Kindrachuk

The Viruses

Influenza Biology

Influenza viruses are spherical or filamentous, enveloped, negative-sense, single-stranded RNA viruses of family *Orthomyxoviridae* of approximately 100 nm to 300 nm in diameter that include types A, B, C, and D [1, 2]. Influenza A and B viruses cause mild to severe illness during seasonal epidemics, and influenza A viruses cause intermittent pandemics. Influenza C viruses cause mild infections but not epidemics, and influenza D virus may cause subclinical infection [3, 4]. Influenza A viruses are classified into subtypes based on the combination of the surface glycoproteins hemagglutinin and neuraminidase, with 18 H and 11 N known subtypes [5–7]. Specific influenza strains are named according to the World Health Organization (WHO) convention designating influenza virus type, host of origin (if not human), geographic origin, strain number, year of isolation, and subtype (for influenza A viruses) (e.g., Influenza A/California/7/2009[H1N1]) [8].

Influenza A viruses have eight genome segments that code for structural and nonstructural proteins (Fig. 5.1a) [9]. Surface glycoproteins include hemagglutinin (HA), required for viral binding and entry, and neuraminidase (NA), required...
Precautions

$R_0$

$1$-$2$
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Fig. 5.1 Schematic of viral structures and key epidemiological features. (a) Influenza virus is spherical or filamentous in shape. Hemagglutinin (HA) and neuraminidase (NA) proteins are integrated into the host-derived lipid envelope and project from the viral surface. Matrix (M1) protein underlies the envelope, and M2 forms an ion channel within the envelope. Eight single-stranded RNA genome segments are coated with nucleoprotein (NP) and bound by the polymerase complex. Nuclear export protein (NEP) mediates export of viral RNA. Influenza has estimated reproductive number ($R_0$) between 1 and 2. Standard, droplet, and contact precautions are recommended to prevent nosocomial transmission. (b) Measles virus is pleomorphic in shape. Hemagglutinin (H) and fusion (F) proteins are integrated into the host-derived lipid envelope, and matrix (M) protein underlies the envelope. The single-stranded RNA genome is coated with nucleoprotein (N) and bound by the polymerase complex. Measles has an estimate $R_0$ between 9 and 18. Standard, airborne, and contact precautions are recommended to prevent nosocomial transmission. (c) Coronaviruses are spherical in shape. Spike (S), membrane (M), and envelope (E) proteins are integrated into the host-derived lipid envelope. The single-stranded RNA genome is coated with nucleoprotein (N). SARS and MERS have an estimated $R_0$ of <1–2. Standard, airborne, and contact precautions are recommended to prevent nosocomial transmission. (d) Poxviruses are oval to brick shaped. The biconcave viral core contains double-stranded DNA and several proteins organized as a nucleosome and surrounded by a core membrane. Two proteinaceous lateral bodies flank the core, and a single lipid membrane surrounds the cell-associated form of the mature virion (MV). A second host-derived lipid envelope covers the extracellular virion (EV). Smallpox has an estimated $R_0$ between 4 and 6. Standard, airborne, and contact precautions are recommended to prevent nosocomial transmission of smallpox.
Fig. 5.1 (continued)
Fig. 5.1 (continued)
for viral budding. Matrix (M1) protein underlies the host-derived lipid envelope providing structure, and M2 protein is an ion channel integrated into the envelope. Eight single-stranded RNA viral genome segments are coated with nucleoprotein (N) and bound by the polymerase complex, composed of basic polymerase 1 (PB1), PB2, and acidic polymerase (PA). Nuclear export protein (NEP) mediates trafficking of viral RNA segments and nonstructural protein (NS1) inhibits host antiviral responses. The virus can also express accessory proteins PB1-F2 and PA-x.
Measles (Rubeola Virus) Biology

Measles virus is a pleomorphic, enveloped, negative-sense, single-stranded RNA virus of family Paramyxoviridae of approximately 100 nm to 300 nm in diameter [2]. Measles virus causes mild to severe illness during seasonal outbreaks in endemic areas and intermittent outbreaks in nonendemic area [10]. Measles virus codes for six structural and two nonstructural proteins (Fig. 5.1b) [11]. Hemagglutinin (H) and fusion (F) glycoproteins project from the viral surface and facilitate viral binding to cellular receptors and fusion with the host cell membrane, respectively. Matrix (M) protein underlies the envelope providing structure. The inner nucleocapsid is composed of RNA coated by nucleoprotein (N), bound by the polymerase complex which includes the large (L) polymerase protein, and phosphoprotein (P), a polymerase cofactor. The remaining nonstructural proteins include C and V.

Coronavirus Biology

Coronaviruses are spherical, enveloped, positive-sense, single-stranded RNA viruses of family Coronaviridae of approximately 120 nm in diameter [12]. Coronaviruses are the causative agents of an estimated 30% of upper and lower respiratory tract infections in humans resulting in rhinitis, pharyngitis, sinusitis, bronchiolitis, and pneumonia [13]. While coronaviruses are often associated with mild disease (e.g., HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1), severe acute respiratory syndrome coronavirus (SARS-CoV), a lineage B betacoronavirus, and Middle East respiratory syndrome coronavirus (MERS-CoV), a lineage C betacoronavirus, are associated with severe and potentially fatal respiratory infection [14, 15].

SARS- and MERS-CoV transcribe 12 and 9 subgenomic RNAs, respectively, which encode for the spike (S), envelope (E), membrane (M), and nucleocapsid (N) structural proteins (Fig. 5.1c) [14]. S, E, and M are all integrated into the host-derived lipid envelope, and S facilitates host cell attachment to angiotensin-converting enzyme (ACE)-2 receptors for SARS-CoV and dipeptidyl peptidase (DPP)-4 receptors for MERS-CoV [16, 17]. The N protein encapsidates the viral genome to form the helical nucleocapsid. The viral replicase-transcriptase complex is made up of 16 nonstructural proteins (nsp1–16) including a unique proofreading exoribonuclease that reduces the accumulation of genome mutations [12].

Smallpox (Variola Virus) Biology

Poxviruses are oval-to-brick-shaped double-stranded DNA viruses of family Poxviridae that range in size from 200 to 400 nm [2]. Viruses within genus Orthopoxvirus that cause human disease include cowpox virus (CPXV), monkeypox virus (MPXV), vaccinia virus (VACV), and variola virus (VARV), the etiologic agent of smallpox [18].
Poxviruses contain a biconcave viral core where the DNA genome, DNA-dependent RNA polymerase, and enzymes necessary for particle uncoating reside (Fig. 5.1d) [19]. This nucleosome is surrounded by a core membrane that is flanked by two proteinaceous lateral bodies. A single lipid membrane surrounds the cell-associated form of the mature virion (MV). A second host-derived lipid envelope covers the extracellular virion (EV) [2, 19]. Poxvirus genomes are comprised of a large, linear double-stranded viral DNA genome that encodes ~200 genes. Highly conserved structural genes are predominantly found in the middle of the genome, whereas variable virulence factor genes that function in immune evasion, virulence, and viral pathogenesis are found at the termini of the genome [20].

Ecology and Epidemiology

Avian, Swine, Seasonal, and Pandemic Influenza A Viruses

Wild aquatic birds are natural reservoirs for nearly all influenza A virus subtypes, which spread to domestic avian species and mammals, including humans [5]. H17N10 and H18N11 subtypes are exceptions in that they have only been isolated from bats [6, 7]. Certain H5 and H7 subtypes are highly pathogenic to domestic poultry when transmitted from wild birds, known as highly pathogenic avian influenza (HPAI) viruses [21]. HPAI viruses cause spillover infections in humans that may be severe or fatal. Examples include outbreaks of H5N1 and H7N9 HPAI viruses in Asia with high case fatality among humans, although limited human-to-human transmission [22, 23] has been reported. HPAI virus adaptations might lead to sustained human-to-human transmission, and so poultry outbreaks are managed by flock depopulation [24]. Influenza A subtypes isolated in swine include H1 to H5, H9, and N1 and N2. Subtypes that spillover into humans cause mild to severe illness and are known as swine “variant” viruses [25].

Currently circulating seasonal influenza A subtypes H1N1 and H3N2 and influenza B viruses, Yamagata or Victoria lineage, cause annual epidemics during fall through spring in temperate regions and infections throughout the year in the tropics [26]. Antigenic drift of H and N surface glycoproteins drives annual epidemics. From 2017 to 2018, seasonal influenza caused approximately 49 million illnesses, 1 million hospitalizations, and 79,000 deaths in the United States alone [27]. When two or more influenza A viruses infect a common host, such as a bird or pig, individual gene segments may recombine to form a novel virus, known as antigenic shift. Influenza pandemics occur when novel viruses emerge into an immunologically naïve population and become adapted for sustained human-to-human spread. The 1918 “Spanish” influenza pandemic was the most severe on record, resulting in an estimated 50 million deaths [28]. Less severe pandemics occurred in 1957, 1968, and 2009. In an effort to improve preparedness and response to seasonal, pandemic, and zoonotic influenza, the World Health Organization (WHO) conducts global surveillance of influenza A and B isolates (Fig. 5.2a) [29].
Fig. 5.2 Viral disease burden reported by WHO region. (a) WHO global influenza surveillance of laboratory confirmed influenza A and B infections, 2008–2018. (b) Global measles cases reported to WHO, 2011–2018. Reported cases from 1980 are used as a reference. (c) Global cases of SARS- and MERS-CoV infections. (d) Global cases of smallpox from 1920 to 1970. Data represents the cumulative cases for that year. WHO regions are as follows: WPR Western Pacific Region, SEAR South-East Asia Region, EUR European Region, EMR Eastern Mediterranean Region, AMR Region of the Americas, AFR African Region. (Data courtesy of WHO)
Fig. 5.2 (continued)
**Endemic and Epidemic Measles**

Measles is pathogenic for humans and nonhuman primates, although sustained transmission occurs only among humans raising potential for global elimination [30]. Historically, measles infected an estimated 90% of children by age 5 years, resulting in approximately 2 million global deaths each year [10]. With the introduction of the measles vaccine in 1963 and advances in global vaccination programs, measles cases and mortality have drastically declined (Fig. 5.2b). By 2017, 85% of children worldwide had received at least one dose of the measles vaccine by age 1 year, and during 2000–2017, global measles mortality decreased by 80%, preventing an estimated 21 million deaths [31]. Of the 24 known measles genotypes, only five were detected in circulation during 2016–2017. Despite these gains, measles remains endemic in many regions of the world including Africa, Western Pacific, South East Asia, and Europe, and measles has resurfaced in previously low-incidence areas (e.g., regions within Europe and the Americas) with epidemics attributable to importation of cases and suboptimal immunization coverage [32–34]. An estimated 93% population immunity is required to prevent measles transmission within communities, a prerequisite for global elimination [35].

**SARS and MERS Epidemics**

Chinese horseshoe bats are the putative reservoir for SARS-CoV, and dromedary camels are thought to be the reservoir for MERS-CoV [36–43]. Animal-to-human transmission likely occurs following direct contact with intermediate hosts [38, 44]. During the 2003–2004 SARS epidemic, 8096 cases and 774 deaths were reported from 26 countries with no cases reported since (Fig. 5.2c) [45]. Human-to-human transmission of SARS-CoV occurred primarily in healthcare settings with healthcare workers comprising 22% and >40% of reported cases in China and Canada, respectively [45]. MERS was first reported in Saudi Arabia in 2012 with >2000 cases and >800 deaths reported from 27 countries through 2018 [46]. While most cases have been reported from the Arabian Peninsula, an imported case to South Korea in 2015 resulted in a large outbreak in multiple healthcare facilities [47]. MERS transmission occurs primarily in healthcare facilities and to a lesser degree within households [48, 49].

**Smallpox Eradication**

While the only known reservoir for VARV is humans, it has been postulated that the virus emerged from an ancestral rodent-borne poxvirus more than 10,000 years ago [18, 50]. Numerous smallpox epidemics have occurred throughout recorded
history including more than 300 million fatalities during the twentieth century alone [51–53]. Smallpox was eventually eradicated following the implementation of the Smallpox Eradication Program by the WHO from 1966 to 1980 (Fig. 5.2d) which was facilitated by the absence of a zoonotic reservoir for VARV [51].

**Pathogenesis**

**Influenza Transmission and Mechanisms of Disease**

Influenza viruses are transmitted by large respiratory droplets by coughing, sneezing, or talking or through contact with infected surfaces [54]. Influenza viruses bind to sugar moieties on the surface of airway epithelial cells where early viral replication, propagation, and shedding occur during an average 1–2 days of incubation period [55–57]. Peak viral replication typically occurs within 4 days of symptom onset and resolves within 7–10 days, lasting longer in children and immunocompromised hosts [58–60]. On average one person infects one to two additional people; however, this reproductive number ($R_0$) varies by viral strain and social and environmental factors [61]. Viral infection impairs the airway mucosal barrier and disrupts the alveolar-capillary membrane contributing to leakage of fluid and inflammatory cells into the alveolar space which impairs gas exchange resulting in hypoxemia [62, 63]. Bacterial coinfection often complicates severe cases contributing to respiratory failure and death, with *Staphylococcus aureus* and *Streptococcus species* as predominant copathogens [64]. Seasonal influenza virus infection is largely limited to the respiratory tract; however, H5 and H7 HPAI viruses have a polybasic cleave site within the hemagglutinin allowing for replication outside of the respiratory tract [65, 66]. Infection with one strain of influenza does not confer complete immunity to other strains or subtypes [67].

**Measles Transmission and Mechanisms of Disease**

Measles is among the most highly contagious respiratory infections, spread by exposure to large respiratory droplets through coughing, sneezing, or talking; by indirect contact with infected surfaces; or by small infectious droplets that can remain suspended in air for up to 2 hours [10, 68]. Respiratory tract dendritic cells, lymphocytes, and alveolar macrophages are early targets of infection where during an average 8- to 12-day incubation period measles replicates and spreads to local lymphatics and respiratory epithelium and then disseminates in blood via infected lymphocytes to epithelial and endothelial cells in most organs [69–71]. The infectious period begins with fever onset and extends for several days after rash appears
The estimated $R_0$ of measles is 9–18 dependent upon host susceptibility and social and environmental factors [73]. Measles infects and disrupts tissues throughout the body; however, severe disease is primarily due to lower respiratory tract and neurological complications [72]. Natural measles infection confers lifelong immunity, and passive transfer of maternal antibodies protects newborns during the early postnatal period [74]. Individuals who recover from measles infection are at increased risk of secondary infection [75, 76].

**SARS- and MERS-CoV Transmission and Mechanisms of Disease**

SARS-CoV is transmitted by large respiratory droplets and by contact with infected surfaces. Epidemiologic data also support small droplet airborne transmission of SARS-CoV although the estimated $R_0$ of 0.86–1.83 argues against this being a predominant route of spread [77, 78]. SARS-CoV binds to angiotensin-converting enzyme (ACE)-2 receptors on respiratory epithelial cells, pneumocytes, and alveolar macrophages resulting in diffuse alveolar damage and respiratory failure [79, 80]. SARS is a systemic infection with viremia detected in most cases affecting multiple cell types and organs [81, 82]. Acute kidney injury is multifactorial with evidence of acute tubule necrosis, vasculitis, and glomerular fibrosis, and central nervous system manifestations are at least in part attributable to direct infection of neurons resulting in edema and degeneration [83].

MERS-CoV is transmitted by large respiratory droplets and by contact with infected surfaces with an estimated $R_0$ of <1 to >1 outside of versus within healthcare settings, respectively [84]. MERS-CoV binds dipeptidyl peptidase 4 (DPP4) on respiratory epithelial cells and pneumocytes where it undergoes productive replication during a 2–14 days incubation period [16]. Viral shedding from the lower respiratory tract may persist for weeks [85, 86]. Viremia, while not documented in all cases, is associated with severe disease and productive infection of DCs, and macrophages is thought to facilitate immune dysregulation [87, 88]. DPP4 is broadly expressed on cells outside of the lung; however, few autopsy data are available to define viral distribution [16, 89].

**Variola Virus Transmission and Mechanisms of Disease**

VARV is transmitted primarily by large respiratory droplets and to a lesser degree through contact with contaminated objects such as scabs, bedding, or clothing or by airborne small respiratory droplets [90, 91]. VARV is thought to replicate in airway epithelium and spread to regional lymph nodes [92, 93]. VARV replicates within lymph nodes and disseminates via the bloodstream seeding distant sights including
Clinical Findings

Influenza Illness and Complications

Influenza infection manifests as acute onset of fever, chills, malaise, headache, and myalgias following an average 1–2 days asymptomatic incubation period [9]. Most infections are self-limited resolving within 1–2 weeks. Upper or lower airway complications include otitis media, sinusitis, bronchitis, and pneumonia with or without bacterial coinfection [63, 64, 102]. Risk factors for severe infection include age >65 years or <5 years; pregnancy; preexisting respiratory, cardiac, neurologic, or metabolic conditions; immunosuppression; and obesity. Progressive lethargy and shortness of breath, typically within 5 days of symptom onset, suggest development of lower respiratory tract complications which may rapidly progress to respiratory failure and death in severe cases [64]. Pneumonia due to influenza infection alone versus influenza and bacterial coinfection cannot be reliably distinguished by clinical or radiological grounds, and so a high index of suspicion is needed. Influenza complications outside of the respiratory tract include exacerbation of underlying heart disease including ischemic heart disease and heart failure, myocarditis, encephalopathy, and encephalitis [103].

Measles Illness and Complications

Measles infection manifests by acute onset fever, coryza, conjunctivitis, and cough [10]. Small white papules, Koplik spots, appear on the buccal mucosa within 3 days of fever onset, followed by development of diffuse maculopapular rash 1 or 2 days later. Diarrhea commonly begins shortly following rash onset and may result in dehydration. Symptoms typically resolve within 7 days of fever onset in self-limited illness. Groups at increased risk for measles complications include malnourished infants and those with vitamin A deficiency, adults >20 years old, and immunocompromised individuals [72]. Respiratory complications include otitis media, laryngotracheobronchitis (croup), and pneumonia. Pneumonia, often complicated by
bacterial coinfection, is the most common severe complication of measles contributing to respiratory failure and death [72, 104]. Predominant bacterial copathogens include *Streptococcus pneumonia*, *Staphylococcus aureus*, and *Haemophilus influenzae*.

Three rare but severe neurologic complications occur [105]. Acute disseminated encephalomyelitis (ADEM) is a demyelinating autoimmune process that occurs within weeks of acute illness in approximately 1 in 1000 cases. ADEM is characterized by fevers, seizures, and neurologic deficits. Measles inclusion body encephalitis is a progressive lethal brain infection occurring within months of acute illness primarily among individuals with impaired cellular immunity. Subacute sclerosing panencephalitis (SSPE) occurs 5–10 years following initial infection resulting in seizures and cognitive and motor decline resulting in death. SSPE affects an estimated 1 in 10,000 infants under 1 year of age and is attributed to host responses to defective viral particle production in the brain.

**SARS and MERS Illness and Complications**

Following an average 5-day incubation period, SARS-CoV infection presents with fevers, chills, dry cough, headache, malaise, and dyspnea commonly followed by watery diarrhea [106–108]. Age >60 years and pregnancy are associated with severe disease manifested by progressive respiratory failure within 2 weeks of illness onset [108, 109]. Common laboratory features of SARS included lymphopenia, thrombocytopenia, abnormal coagulation parameters, and elevated lactate dehydrogenase, alanine aminotransferase, and creatine kinase levels [110–112]. Acute kidney injury and proteinuria were observed in 7% and 84% of patients, respectively [113].

Initial symptoms of MERS-CoV infection include fever, chills, cough, shortness of breath, myalgia, and malaise following a mean incubation period of 5 days [114]. Gastrointestinal symptoms, including vomiting and diarrhea, occur in one-third of patients [115–118]. The median times from symptom onset to hospitalization, ICU admission, and death are 4, 5, and 12 days, respectively [118]. MERS patients present with a rapidly progressing pneumonia requiring mechanical ventilation and additional organ support with the first week of illness [109]. Severe disease has been linked to comorbidities including diabetes mellitus (68%), chronic renal disease (49%), hypertension (34%), chronic cardiac disease (28%), chronic pulmonary disease (26%), and obesity (17%) [114]. The median age of those with confirmed MERS is 50 years with a male-to-female ratio of 3.3:1 [114]. Laboratory abnormalities include lymphopenia, leukopenia, thrombocytopenia, elevated serum creatinine levels consistent with acute kidney injury, and elevated liver enzymes [114, 115, 117, 119, 120]. High lactate levels and consumptive coagulopathy have also been reported [119, 121]. Chest radiographic abnormalities are due to viral
pneumonitis with or without secondary bacterial pneumonia, and acute kidney injury occurs in up to 43% of patients [114, 119, 120, 122–124].

**Smallpox Illness and Complications**

As the smallpox disease course was related to the clinical presentation of disease, Rao proposed a clinical classification system [125] that was later adopted by the WHO in 1972 [51]. *Ordinary type smallpox* was the most common clinical type of smallpox. The incubation period was 7–19 days and was followed by fever onset (38.5–40.5 °C), headaches, backaches, vomiting, and diarrhea [51]. Lesions first appeared on mucous membranes (including the tongue, palate, and pharynx) ~1 day prior to macular rash development, where lesions began on the face followed by proximal regions of the extremities, the trunk, and the distal extremities. Lesion development followed a centrifugal dispersion pattern, typically most dense on the face, with papules appearing within 2 days of macular rash development. Papules became vesicular ~2–4 days later followed by a pustular stage (5–7 days postrash) that peaked ~10 days postrash. Pustule resolution quickly followed and was accompanied by lesion flattening, fluid reabsorption, hardening, and scab formation (14–21 days postrash). Rao proposed for ordinary type smallpox to be further subdivided based on the macular rash pattern [125]. These included *discrete ordinary-type smallpox*, characterized by discrete skin lesions; *confluent ordinary-type smallpox*, where pustular skin lesions were confluent on the face and extremities; and *semiconfluent ordinary-type smallpox*, where skin lesions were confluent on the face but disparate over the rest of the body. Modified-type smallpox, where lesions were less numerous than in ordinary-type smallpox, was primarily associated with vaccinated individuals and had an accelerated nonfatal disease course [125]. Flat-type and hemorrhagic-type smallpox were the most lethal forms of the disease but were also very rare (~7% and 3% of patients, respectively) [51]. Flat-type smallpox had high CFRs in both unvaccinated and vaccinated patients (97% and 67%, respectively). Hemorrhagic-type smallpox was nearly 100% fatal in both vaccinated and unvaccinated individuals, and death normally came prior to macular rash development. The clinical symptoms of flat-type smallpox were more severe during the prodromal period and did not subside. Skin lesions were flat and often black or dark purple. Respiratory complications were common and patients were febrile throughout disease. Death typically occurred 8–12 days post-fever onset. Hemorrhagic-type smallpox could be divided into early and late hemorrhagic-type smallpox. The *early form* was characterized by hemorrhage (primarily subconjunctival) early in the disease course. Generalized erythema, petechiae, and ecchymosis within 2 days of fever and flat matter lesions formed across the entire body surface. Lesions turned purple by day 4 with death by day 6 as a result of cardiac and pulmonary complications. In the late form, hemorrhages occurred following rash development and death followed between 8 and 10 days post-fever onset.
Diagnosis

**Influenza: Infection Control and Confirmatory Testing**

In healthcare settings, patients under evaluation for influenza should be isolated, and standard, droplet, and contact precautions should be implemented [126]. Traditional antigen-based rapid diagnostic assays (RDAs) for influenza lack sensitivity and cannot be relied upon to rule out infection [26]. Newer antigen-based RDAs that employ a digital scan of the test strip, and molecular assays that employ isothermal amplification technology have improved sensitivity and specificity that more closely approximates highly sensitive and specific reverse transcriptase polymerase chain reaction (RT-PCR)-based assays [127]. Acceptable sample types for influenza testing include nasopharyngeal swab or wash and bronchoalveolar lavage specimens. Individuals suspected of zoonotic influenza infection should have case evaluation and specimen testing coordinated through local or state public health authorities.

**Measles: Infection Control and Confirmatory Testing**

Measles should be considered in patients without preexisting immunity and a compatible febrile rash illness. Travel to a region with ongoing measles transmission or exposure to other individuals with a febrile rash illness should raise suspicion. Patients under evaluation for measles require isolation and implementation of standard, airborne, and contact precautions. Local or state health authorities should be contacted within 24 hours to assist with confirmatory testing, case finding, and infection control. Measles is typically confirmed by measles-specific IgM serology or detection of measles RNA in a nasopharyngeal, throat, or urine specimen by RT-PCR [10]. A fourfold or greater rise in measles IgG titers between acute and convalescent samples tested 2 or more weeks apart can assist with diagnostic uncertainty. Virus can also be cultured from respiratory, blood, and urine specimens in appropriate public health laboratories.

**SARS and MERS: Infection Control and Confirmatory Testing**

While SARS is no longer circulating, MERS should be suspected in individuals with a compatible febrile illness and an epidemiological risk factor [128]. Risk factors include travel to the Arabian Peninsula or contact with a confirmed or suspected case within 14 days of symptom onset. Patients under evaluation for MERS require isolation and implementation of standard, airborne, and contact precautions.
Confirmatory testing and infection control should be coordinated through local or state health authorities. MERS may be confirmed in designated public health laboratories by RT-PCR testing of lower respiratory tract specimens [129]. Multiple other specimen types including upper respiratory tract samples, serum, and stool should also be collected for testing. Serologic testing can be used to evaluate for suspected infection among individuals no longer shedding virus [129, 130].

Smallpox: Infection Control and Confirmatory Testing

Smallpox has not been observed in over 40 years; however, concerns remain for use as a bioweapon. Major and minor criteria have been established to assist clinicians in recognition of smallpox [131]. Individuals under evaluation should be isolated, and standard, airborne, and contact precautions should be implemented. Local or state health authorities should be contacted to assist with confirmatory testing and public health interventions. PCR identification of variola DNA or isolation of the virus from a clinical specimen is required to confirm a diagnosis in specialized high-containment laboratories.

Clinical Management

Influenza Prevention and Treatment

Annual seasonal influenza vaccination is recommended in the United States for all individuals aged 6 months or older and has been associated with decreased risk of pneumonia and death, particularly among high-risk groups [132–134]. Seasonal influenza vaccination does not provide protection against novel strains. Consequently, efforts are underway to develop a vaccine that would protect against most or all influenza strains [135]. Three classes of drugs are licensed for the treatment of influenza in the United States [136]. Adamantanes, including amantadine and rimantadine, are not currently recommended given resistance of circulating seasonal strains. Baloxavir morboxil, a cap-dependent endonuclease inhibitor, was recently approved for the treatment of uncomplicated influenza [137]. Neuraminidase inhibitors (NAI) include oral oseltamivir, inhaled zanamivir, and intravenous peramivir. Prophylactic use of NAIs is recommended in unvaccinated individuals with risk factors for severe disease and during institutional outbreaks to limit spread. Therapeutic use is recommended for individuals with suspected or confirmed influenza that have developed or are at high risk for influenza complications [26]. Influenza complications, including respiratory and multiorgan failure, are managed with supportive care. Bacterial coinfection should be considered and empirically treated early pending results of microbiologic testing among severe cases.
**Measles Prevention and Treatment**

Measles can be effectively prevented through vaccination, typically given in combination with vaccines for rubella (MR), mumps (MMR), or varicella (MMR-V). WHO recommends the first dose of measles vaccine be administered at 9 or 12 months of age in high and low prevalence settings, respectively [138]. A second dose should be administered after a minimum of 4-week interval. Nonimmune individuals that have been exposed to measles should receive post-exposure prophylaxis with MMR or immunoglobulin within 72 hours or 6 days, respectively, although not concurrently [139]. Clinical management of patients with measles consists of fluid, electrolyte, and nutritional support and early recognition and treatment of bacterial coinfection [10]. Two doses of vitamin A in children under 2 years have been associated with reduced risk of pneumonia and death [140]. WHO recommends administering 200,000 IU of vitamin A daily for 2 days in children aged 1 year and older, with reduced dosing in younger infants [141].

**SARS and MERS Treatment**

There are currently no licensed therapeutics or vaccines for SARS or MERS. Consequently, supportive care is the mainstay of treatment [142]. Renal replacement therapy is frequently required in severe illness [119, 143, 144]. Empiric antibiotics are often administered given potential for secondary bacterial infection. Ribavirin and pegylated interferon alpha 2b have been administered to MERS patients, although effectiveness data is lacking [144]. Aerosol-generating procedures including endotracheal intubation are associated with increased risk of healthcare worker infection necessitating strict adherence to infection control measures, including use of eye protection in addition to standard, airborne, and contact precautions [145].

**Smallpox Prevention and Treatment**

While routine smallpox vaccination ceased at the end of the smallpox eradication program, it is still employed for those at increased risk for exposure. First-generation vaccines comprise a significant proportion of both the US national and global vaccine stockpiles [146]. However, first-generation vaccines carry high risk of adverse events due to use of replication-competent VACV and potential manufacturing contaminants. Second-generation smallpox vaccines have reduced concerns for contaminants and are expected to have similar protective efficacy as first-generation vaccines. ACAM2000® has garnered US Food and Drug Administration licensure for vaccination of those at high risk for Orthopoxvirus exposure and is part of the US strategic national stockpile [147]. ACAM2000® and the Lister-derived vaccines
RIVM and Elstree-BN also contribute to the global stockpile. IMVAMUNE (MVA), a third-generation vaccine, is licensed in Europe and Canada and is part of the US national stockpile. Passive immunization with VIG has been employed to treat complications of vaccinations [148, 149]. There has also been increasing interest in the development and licensure of small molecule antivirals for treatment of Orthopoxvirus infections. CMX001 (brincidofovir), a DNA synthesis inhibitor, has demonstrated protection against lethal VARV in nonhuman primates [150] and has been granted orphan drug designation while also being included in the US Strategic National Stockpile. ST-246 (tecovirimat), which inhibits viral egress, has potent (IC50 < 0.010 μM) and selective (CC50 > 40 mM) inhibitory activities against multiple orthopoxviruses [151], is the only antipoxvirus therapeutic that has been granted approval in the US and has been added to the Strategic National Stockpile.

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