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# Prevention of Emerging Infections in Children



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## KEYWORDS

- Emerging infections • Prevention • Avian influenza
- Middle-East respiratory syndrome • Dengue • Chikungunya • Ebola

## KEY POINTS

- Emerging infectious diseases are major health challenges affecting children globally.
- The zoonoses avian influenza and the Middle East respiratory syndrome, mosquito-borne diseases dengue and chikungunya, and Ebola have been major causes of morbidity and mortality across Asia, Latin America, and Africa in recent years.
- Multiple strategies can be employed for prevention with transmission-targeted prevention, chemoprophylaxis, and vaccination.
- Although multiple vaccines are under development for all, the dengue vaccine is the only pediatric-specific vaccine approved, with potential public health impact if scaled up.

## INTRODUCTION

The prevention of emerging infections in children is a constantly dynamic arena, where substantial medical advances have enabled intervention and prevention of infection outbreaks. This article focuses on 5 infections causing significant morbidity and mortality across Asia, Latin America, and Africa in recent years. Because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reviewed extensively in a previous issue of this journal, it is not addressed in this article. Avian influenza and the Middle East respiratory syndrome (MERS) are highly contagious zoonoses spread through aerosol and droplets that have predominantly affected Asia. Dengue infection and chikungunya are extremely endemic mosquito-borne viruses in tropical regions across Asia, Latin America, and Africa, with vector control and vaccination central to efforts in their management. Ebola is a highly contagious virus spread through

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human-to-human contact. The latest information in clinical manifestations, infection, prevention control, chemoprophylaxis, vaccination, and other public health measures effective at controlling and preventing these infections is reviewed.

## **AVIAN INFLUENZA**

Avian influenza is a highly contagious viral disease affecting several species of birds and occasionally affects mammals, including humans. Avian influenza is classified into 2 types, low pathogenic avian influenza and highly pathogenic avian influenza (HPAI) strains. In 1997, human infections with the HPAI virus of type A of subtype H5N1 (A[H5N1]) virus were reported during an outbreak in poultry in Hong Kong SAR, China. Since 2003, this avian virus has spread from Asia to Europe and Africa and has become endemic in poultry populations in some countries. From January 2003 to May 2021, there were 862 cases of human infection with avian influenza A (H5N1) virus, including 193 children reported from 17 countries with a case fatality rate (CFR) of 53%.<sup>1,2</sup> In 2013, human infections with the Asian lineage avian influenza A (H7N9) virus were reported for the first time in China. The virus since has spread in the poultry population across the country and has resulted in more than 1500 reported human cases with high mortality rates. Compared with H5N1-infected children, lower severity and greater transmission have been found in the H7N9-infected children.<sup>3</sup> Other avian influenza viruses have resulted in sporadic human infections, including the avian influenza virus subtypes A(H5), A(H7N7), and A(H9N2) viruses.

The route of transmission from animals to humans is direct or indirect exposure to infected live or dead poultry or contaminated environments, such as live bird markets. Human-to-human transmission is rare; there previously have been reports of transmission in family clusters.<sup>4</sup> Because of the possibility of transmission and severity of disease, however, droplet and contact transmission-based precautions should be considered as well as aerosol transmission-based precautions in aerosol-generating procedures in health care settings.<sup>5</sup>

### ***Prevention and Control***

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#### ***Personal protective measures***

The best prevention measure is to avoid sources of exposure.<sup>6</sup> Several measures may be taken to prevent animal-to-human transmission, including avoidance of poultry farms, contact with wild and domestic birds in live poultry markets, entering areas where poultry may be slaughtered, and contact with any surfaces that may be contaminated with feces from poultry or other animals. Good food safety and hygiene practices also are advisable. Prevention of human-to-human transmission can be facilitated by handwashing with soap and water or alcohol-based sanitizer; good respiratory hygiene (covering the mouth and nose when coughing or sneezing and correct use and disposal of tissues); avoidance of touching eyes, nose, or mouth if hands are unwashed; and cleaning and disinfection of surfaces and objects. In terms of managing suspected index cases, practice of early self-isolation for symptomatic persons and avoidance of close contact with symptomatic persons are advisable.

#### ***Postexposure chemoprophylaxis***

According to Centers for Disease Control and Prevention (CDC) recommendations, chemoprophylaxis with influenza antiviral medications can be considered for persons with high-risk and moderate-risk exposure to avian influenza (household members, closed contact to or health care workers not protected with appropriate equipment during exposure to confirmed or probable cases).<sup>7</sup> Administration of chemoprophylaxis should begin as soon as possible (within 48 hours) after exposure with neuraminidase

inhibitors (oseltamivir and zanamivir). Instead of the once-daily typical chemoprophylaxis dosing for seasonal influenza viruses, administration of chemoprophylaxis for avian influenza should be administered twice daily. Chemoprophylaxis should continue for 5 days to 10 days depending on exposure time. There is a role for postexposure chemoprophylaxis in children with confirmed cases in household contacts. Detail on dosage is useful.

### ***Vaccination***

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The first avian influenza vaccine approved by the US Food and Drug administration (FDA) was a nonadjuvant subvirion H5N1 avian influenza vaccine in 2007. Conventional influenza vaccine platforms predominantly rely on production in embryonated chicken eggs and have low immunogenicity. In contrast, an ideal vaccine for an avian influenza pandemic should induce a robust protective immune response with minimal antigen use, provide cross-protection against viruses from different clades, and be rapidly producible if a pandemic occurs.<sup>8</sup> In response, new avian influenza vaccine development has expanded to several different platforms to overcome these issues. Use of adjuvants plays an important role in augmenting protective immunity by accelerating helper T-cell function. An oil-in-water emulsion (AS03)-adjuvant subvirion H5N1 avian influenza vaccine was approved for pre-pandemic use in the European Union (EU) in 2008 and in the United States in 2013.<sup>9</sup> AS03-adjuvant H5N1 vaccines not only are highly immunogenic against the homologous vaccine strain but also induce cross-clade neutralizing antibodies against circulating antigenically distinct H5N1 viruses,<sup>10,11</sup> including in children ages 6 months to 17 years.<sup>12</sup> The MF59-adjuvant tetravalent vaccine contains A/H5N1, and seasonal A/H3N1, A/H1N1, and B components also induce similar antibody responses and reactivity compared with administration of separate A/H5N1 and seasonal vaccines.<sup>13</sup> The modified vaccinia virus Ankara (MVA), a viral vector platform, also is well tolerated and immunogenic with approved use in adults by the World Health Organization (WHO) and EU.<sup>14,15</sup> Moreover, there are other platforms to develop avian influenza vaccines, such as virus-like particles (VLPs) and nonreplicating adenoviral vectored vaccines—stable double-stranded DNA genome and vectors, such as adenovirus (Ad5, Ad26, ChAdOx1, and BAdV-3) in clinical trials.<sup>16</sup>

Currently available H5N1 vaccines in children are the AS03-adjuvant vaccine for infants greater than 6 months and children and adolescents ages less than 17 years, administered 0.25 mL intramuscularly followed by a second 0.25-mL dose 21 days later, although the MF59-adjuvant vaccine can be administered as 0.5 mL intramuscularly followed by a second 0.5-mL dose 21 days later. There are no studies, however, of adjuvanted AS03-adjuvant or MF59-adjuvant vaccines among infants less than 6 months.<sup>17</sup>

Pre-pandemic vaccine production and stockpiling are important parts of preparedness planning when outbreaks occur. The limitation, however, is vaccine matching relative to actual antigenic diversity of circulating H5N1 viruses and regarding timing due to the uncertainty of when the next pandemic will occur and the shelf-life of stored bulk antigens. Another approach is pre-pandemic vaccination administration to specific segments of the population and single revaccination boosters in the future. The widespread use of pre-pandemic vaccines among the population, however, must weigh the potential risks of unexpected adverse reactions with the benefit of vaccinations. Therefore, this approach should be considered in those with high risk of exposure to pandemic influenza, such as health care workers, but not in children.

### **THE MIDDLE EAST RESPIRATORY SYNDROME**

MERS is an emerging respiratory virus caused by the MERS coronavirus (MERS-CoV) that first was identified in Saudi Arabia in 2012 with high case fatality rates. A major

outbreak occurred outside the Middle East in South Korea, and infections were reported in 27 countries in 2015.<sup>18</sup> MERS-CoV also occurs in children, most commonly from household contacts. Lower mortality has been observed in children compared with adults.<sup>19,20</sup> The mechanism of transmission from animals to humans is not fully understood, but dromedary camels are a major intermediate host for MERS-CoV and an animal source of infection in humans.<sup>21</sup> Strains of MERS-CoV that are identical to human strains have been isolated from dromedaries in several countries, including Egypt, Oman, Qatar, and Saudi Arabia. No history of exposure to camels, however, is present in more than half of patients with primary MERS-CoV infections.<sup>22,23</sup> There is evidence of human-to-human transmission from clustering of cases in hospitals and among household contacts.<sup>24–26</sup> Consequently, airborne, droplet, and contact transmission-based precautions are recommended for patients with suspected MERS-CoV infection by the WHO and CDC.

## ***Prevention and Control***

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### ***Personal protective measures***

General prevention measures are health education to promote community awareness of the disease. There are several strategies to prevent camel-to-human transmission<sup>21,27–29</sup>: avoid direct contact with camels (including nasal and eye discharge, urine, and feces) and camel products (eg, milk and meat), especially with symptomatic camels and during seasons of high transmission, usually between April and July. This is the season where new camel generations become susceptible to MERS-CoV infection after the decline of their maternal protective antibodies.<sup>30</sup> Frequent handwashing and use of personal protective equipment while handling dromedary camels are advised for those with occupational risk, such as farmers, veterinarians, market workers, and slaughterhouse workers. Educational campaigns can be implemented to target camel owners and the general public to inform them of the risks of consuming unpasteurized camel products (eg, milk) and undercooked meat. Furthermore, disease control in camels is essential and includes strict regulation of camel movements, including a requirement for MERS-CoV infection clearance prior to importation and transport of camels between farms or to slaughterhouses, and camels with detectable MERS-CoV RNA should be quarantined and tested at regular intervals.

Prevention of human-to-human transmission, particularly in household contacts, includes observation of respiratory etiquette during sneezing or coughing in suspected or confirmed MERS-CoV-positive patients, regular mask use, and minimal touching of surfaces near MERS-CoV-infected persons. Disposable glove use is advised when in contact with bodily fluids, including urine, stool, vomit, and respiratory secretions. All waste generated in the room of a MERS-CoV-positive patient should be bagged securely. Hand hygiene with alcohol-based hand rub should be performed by both the infected patient and caregiver following any contact with the patient or their environment. Household items in the MERS-CoV-positive patient room should be cleaned regularly with Environmental Protection Agency-approved commercial solution or diluted bleach (1 part bleach to 99 parts water).

### ***Postexposure chemoprophylaxis***

Although current studies of ribavirin and lopinavir/ritonavir for 14 days after high-risk exposure to patients with severe MERS-CoV preisolation pneumonia report a 40% decrease in the risk of infection,<sup>31</sup> there are no recommended regimens for pre-exposure or postexposure chemoprophylaxis.

## Vaccination

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There currently are no vaccines available for the prevention of MERS, although there are several vaccines in development in camels and humans.<sup>26,32,33</sup> Several challenges are present in MERS-CoV vaccine development, including absence of economic incentives; because MERS-CoV infections occur only sporadically in humans and are contained mostly in 1 geographic area, no suitable animal models exist for MERS-CoV disease for testing, and neutralizing antibodies titers wane rapidly over time in humans who recover from MERS-CoV infection, leaving uncertainty on the duration of its protection.<sup>34,35</sup>

There are multiple investigational vaccines developed against MERS-CoV2 in humans, however, no trial studies in children. Viral S proteins and their fragments are key vaccine targets in MERS-CoV. GLS-5300, a DNA vaccine expressing a full-length MERS coronavirus S-glycoprotein antigen, is well tolerated and immunogenic in humans.<sup>36</sup> The recombinant MVA vaccine with MVA-MERS-S has a favorable safety profile without serious or severe adverse events.<sup>37</sup> It induces both humoral and cell-mediated responses against MERS-CoV. ChAdOx1 MERS, a candidate simian adenovirus-vectored vaccine expressing a full-length spike surface glycoprotein, and is safe and well-tolerated.<sup>38</sup> A single dose is able to elicit both humoral and cellular responses against MERS-CoV. Several platforms of MERS-CoV vaccines have been developed further in response to the SARS-CoV-2 pandemic in 2021.

## DENGUE

Dengue is a global public health threat. It is common in more than 100 countries around the world, especially in endemic areas in Southeast Asia, the Western Pacific, Latin America, and Africa. Asia shares approximately 7% of the global burden of dengue.<sup>39</sup> There are 96 million people who have symptomatic dengue infection each year globally and an estimated 40,000 people die from severe dengue.<sup>40,41</sup> The number of dengue cases reported to the WHO increased more than 8-fold in the past 2 decades, from 505,430 cases in 2000 to more than 2.4 million in 2010, and 5.2 million in 2019.<sup>39</sup> Factors contributing to dengue infection transmission have included rapid urbanization, increased population density, globalization of trade and travel, and lack of effective prevention control methods available.<sup>42</sup>

Dengue is caused by dengue viruses, which are single-stranded RNA viruses with 4 serotypes: DEN-1, DEN-2, DEN-3, and DEN-4. The virus belongs to the genus *Flavivirus*, of the family *Flaviviridae*. Dengue virus is transmitted mainly to humans by the bite of infected *Aedes* mosquitoes, mainly *A. aegypti*.<sup>42</sup> Its clinical manifestations vary widely, ranging from mild febrile illness to severe and fatal disease. Severe complications are plasma leakage, severe hemorrhage, and organ dysfunction. There currently are no specific antiviral agents to treat dengue infection. Treatment remains adequate fluid management and supportive treatment.

## Prevention and Control

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The WHO recommends integrated vector management (IVM),<sup>43</sup> which is a process for managing vector populations for the optimal use of resources for vector control and vaccination.

## Mosquito Bite Prevention

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Measures to prevent mosquito bites are (1) wearing light-colored long pants and long-sleeved shirts when spending time outdoors or when traveling to endemic areas; (2) clothing, tents, and bed nets treated with permethrin (an insecticide), especially for young children and sick or older people; (3) mosquito coils or other insecticide

vaporizers, which also may reduce indoor biting; and (4) using mosquito repellents applied to exposed skin and clothing in strict accordance with product label instructions.<sup>44</sup> Products containing oil of lemon eucalyptus or para-menthane-diol should be avoided in children under 3 years of age, and application of insect repellent to the hands, eyes, mouth, cuts, or irritated skin should be avoided in all children.<sup>45</sup>

### **Vector control**

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Vector control is recommended by environmental management, chemical, and biological controls.

Environmental management is focused on elimination of potential mosquito breeding sites and reduction of standing water sites. Accumulation of stagnant water should be prevented, and containers with water necessary for use should be covered with a fine mesh to prevent mosquito entry. Emptying and cleaning of domestic water storage containers on a weekly basis should be conducted. These source reduction strategies are effective when performed regularly.<sup>43</sup>

Chemical control includes application of appropriate insecticides to outdoor water storage containers to kill immature larvae and use of insecticides to kill flying mosquitoes.<sup>43</sup>

Biological control against eggs, larvae, and mosquitoes are also essential and can be performed using larvivorous fish, such as *Poecilia reticulata* and *Mesocyclops formosanus*, and *Crustacean* to control larvae.<sup>46</sup> Using larvivorous fish is a cost-effective and eco-friendly strategy in controlling the population of *A aegypti*.<sup>47</sup> A novel method is genetic control of *Aedes* using *Wolbachia*, which is a bacterial agent genetically inserted into vectors to interfere with the reproductive system of the vector, resulting in suppression of vector populations and therefore limiting the transmission of mosquito-borne diseases.<sup>48</sup>

Vector surveillance includes larval surveys, adult surveys, landing/biting collections, and resting collections, which are important to prioritizing and planning areas and timing for vector control.<sup>43</sup>

### **Vaccination**

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To date, only 1 licensed vaccine is available (live, attenuated [recombinant] tetravalent vaccine with a yellow fever 17D backbone [CYD] tetravalent dengue vaccine [TDV], or Dengvaxia, Sanofi Pasteur Inc.). In 2015, CYD-TDV was approved for dengue prevention in persons ages 9 years to 16 years with laboratory-confirmed previous dengue infection. This recommendation was based on study results of combined analyses of phase 3 trials (CYD 14, CYD 15, and CYD 23/57).<sup>49</sup> Average vaccine efficacy (VE) at 25 months for virologically confirmed dengue (VCD) was 65.6% (95% CI, 60.7–69.9). Overall VEs against severe disease and hospitalization due to VCD were 92.9% (95% CI, 76.1–97.9) and 80.8% (95% CI, 70.1–87.7), respectively. Further post hoc retrospective analyses of long-term safety data revealed an increased risk of severe dengue disease in those who were seronegative at baseline.<sup>50</sup> In countries considering vaccination as part of their dengue control program, prevaccination screening is recommended, so only those with evidence of a past dengue infection are vaccinated.<sup>51</sup> The dengue vaccine also can be considered in areas with dengue seroprevalence rates of at least 80% by age 9 years.<sup>52</sup> A remaining important challenge is regarding vaccine implementation strategies in real-world settings. Dengue vaccination should be based on country-specific data in populations at greatest risk but can include people between ages 9 years and 45 years.<sup>53</sup> A recent study in 2021, a randomized controlled phase 2 noninferiority study (CYD65) among healthy individuals ages 9 years to 50 years demonstrated noninferiority of 2-dose versus 3-dose CYD-TDV for each serotype at both 28 days and 1 year among



dengue-seropositive participants. A 2-dose CYD-TDV regimen may be an alternative in individuals who are dengue seropositive at baseline and ages 9 years and older.<sup>54</sup> Although the dengue vaccine is needed for travelers entering endemic areas, there is limited practical use for the CYD-TDV due to the limited number of seropositive travelers and the long vaccination schedule of 3 doses 6 months apart.<sup>55</sup> Several other dengue vaccine candidates, including live, attenuated; purified inactivated; subunit; and DNA vaccines, currently are under clinical development (Table 1). There are 2 live, attenuated vaccines currently under evaluation in phase 3 trials.<sup>55,56</sup> Although CYD-TDV does not include nonstructural proteins of dengue, TAK-003 (Takeda) contains the dengue virus serotype 2 backbone, and the TV003/005 (National Institutes of Health [NIH] National Institute of Allergy and Infectious Diseases/Butantan Institute) vaccine contains 3 full genomes of the 4 dengue virus serotypes.<sup>55</sup> Data up to 18 months postvaccination from an ongoing phase 3 study in healthy children ages 4 years to 16 years showed an overall VE of 73.3 (95% CI, 66.5–78.8). TAK-003 was well tolerated and efficacious against symptomatic dengue in children regardless of serostatus before immunization.<sup>57</sup>

## CHIKUNGUNYA

Chikungunya is a mosquito-borne viral disease caused by an arbovirus. The name, chikungunya, derives from the Kimakonde language, meaning “that which bends up,” to describe the arthralgia that affected patients suffer from.<sup>58</sup> The first identified case of chikungunya was reported in Tanzania in 1952, and since, periodic outbreaks have occurred in Asia and Africa.<sup>59</sup> Since 2004, chikungunya has spread rapidly and been identified in more than 60 countries throughout Asia, Africa, Europe, and the Americas.<sup>60</sup> Factors held responsible for the resurgence of chikungunya include lack of herd immunity, inefficient vector control activities, and emergence of viral mutations in *A albopictus* mosquitoes as more efficient vectors.<sup>61</sup>

Chikungunya is caused by the chikungunya virus (CHIKV), which is a single-stranded RNA virus. The virus belongs to the genus *Alphavirus*, from the family *Togaviridae*. CHIKV is transmitted primarily to humans by the bite of infected mosquitoes, including *A aegypti* and *A albopictus*.<sup>62</sup> Less common transmission is mother-to-child transmission in mothers who acquire chikungunya infection during the second trimester or within 1 week before delivery, which can cause neonatal chikungunya infection. Chikungunya shares some clinical signs and symptoms with dengue and can be misdiagnosed in areas where dengue is common. The incubation period is 3 days to 7 days (range 1–12 days).<sup>62</sup> It is characterized by a triad of fever, rash, and symmetric polyarthralgia, particularly affecting small joints. Symptoms generally are self-limited and usually resolve within 7 days to 10 days, but chronic symptoms of arthralgia can occur and persist for many months to years. Children tend to have less arthralgia compared with adults and more neurologic and dermatologic manifestations, such as bullous rashes and pigment changes.<sup>63</sup> In areas where chikungunya is not endemic, the diagnosis should be considered in travelers recently returning from endemic areas with acute onset of fever and polyarthralgia.<sup>64</sup> There are no specific antiviral agents to treat chikungunya infection. Treatment is supportive care includes rest, antipyretics, and analgesics. The use of nonsteroidal anti-inflammatory drugs, corticosteroids, and physiotherapy may benefit patients with persistent joint pain.<sup>62</sup>

### Prevention and Control

Chikungunya is a mosquito-borne disease. Prevention, therefore, is focused on mosquito bite prevention and vector control in accordance with epidemiologic surveillance similar to dengue.<sup>46</sup> Details on vector control are discussed previously.



**Table 1**  
**Overview of current dengue vaccine clinical trials<sup>55-57</sup>**

Platform	Vaccine	Vaccine Structure	Doses	Clinical Trial Phase
Live, attenuated	CYD-TDV (Dengvaxia, Sanofi Pasteur)	Yellow fever backbone with prM and E proteins from DEN-1-4	3 doses (6 mo apart)	Licensed in 2015
	TAK-003 (DENVax, Takeda)	DEN-2 backbone with prM and E proteins of from DEN-1, 3, 4	2 doses (3 mo apart)	3
	TV003/T005 (Tetravax, US NIH)	Deletion of 3'UTR of DEN-1, DEN-3, DEN-4 and a chimeric DEN-2/DEN-4	1 dose	3
Purified inactivated	PIV	Purified formalin inactivated DEN-1-4 and adjuvants	2 doses (1 mo apart)	1/2
Subunit	V180	Recombinant truncated protein containing DEN-80E and adjuvants	3 doses (1 mo apart)	1
DNA	D1ME100	Recombinant plasmid vector encoding prM/E of DEN-1 and adjuvants	3 doses (0, 1, 5 mo)	1
	TVDV	Recombinant plasmid vector encoding prM/E proteins of DEN-1-4 and adjuvants	3 doses (0, 1, 3 mo)	1

*Abbreviations:* DENVax, live, attenuated tetravalent dengue vaccine; PIV, purified formalin-inactivated virus vaccine; TVDV, the tetravalent DNA vaccine.

## Vaccination

Currently, no CHIKV vaccine has been licensed, but several are in the pipeline of vaccine research in clinical and preclinical studies: live, attenuated; VLP; inactivated; and viral vector vaccines<sup>65</sup> (Table 2). The challenge of developing a CHIKV vaccine is reduction of side effects, such as secondary arthralgia following immunization with the attenuated virus.<sup>46</sup> The first live, attenuated CHIKV vaccine in clinical trials was the TSI-GSD-218. The study on TSI-GSD-218 was terminated, however, due to safety concerns, with 8% of study participants developing mild arthralgia.<sup>66</sup>

The only CHIKV vaccine candidate to enter phase 3 clinical trials is VLA1553. The VLA1553 is a monovalent single-dose, live, attenuated vaccine based on an infectious clone (CHIKV LR2006-OPY1) vaccine candidate attenuated by deleting a major part of the gene encoding the nonstructural replicase complex protein nsP3.<sup>67,68</sup>

The VLP, the VRC-CHKVLP059-00-VP, is one of the most advanced technologies to date. In a 3-dose escalation phase 1 trial, the VLP vaccine was found to be safe, well tolerated, and highly immunogenic, with a 100% seroconversion rate in all dose cohorts after booster immunizations and cross-protection seen against multiple CHIKV strains.<sup>69,70</sup> The candidate currently has finished phase 2 clinical trials (NCT02562482), and phase 3 trials are needed to assess clinical efficacy.<sup>71</sup>

## EBOLA

Ebolaviruses are negative-strand RNA viruses in the Filoviridae family, first identified in 1976. Of the 5 Ebola species known to date, 4, including the Sudan Ebola, Zaire Ebola, Bundibugyo Ebola, and Tai Forest Ebola viruses, are the known causes of epidemics in humans.<sup>72</sup> More than 20 outbreaks of Ebola disease have been identified in sub-Saharan Africa, mainly due to the Zaire and Sudan viruses. The largest outbreak occurred during 2013 to 2016 in West Africa, predominantly affecting Guinea, Sierra Leone, and Liberia.<sup>73</sup> Approximately 20% of Ebola virus disease (EVD) cases were reported in children.<sup>74</sup>

**Table 2**  
Chikungunya vaccines in clinical trials<sup>65–71</sup>

Platform	Vaccine	Vaccine Type	Clinical Trial Phase
Live, attenuated	VLA1553	CHIKV with nsP3 deletion	3
	MV-CHIK	Recombinant live, attenuated measles vaccine expressing CHIKV VLP structural proteins	2
VLP	VRC-CHKVLP059-00-VP (PXVX0317 CHIKV-VLP)	VLP with plasmid expressing CHIKV structural proteins (West African strain 37997)	2
Whole-virus inactivated vaccine	BBV87	Inactivated whole-virion vaccine based on East, Central, South, African genotype	1
Viral vector	ChAdOx1 Chik	Replication-deficient simian adenoviral vector expressing CHIKV antigens	1

EVD is a zoonotic disease, of which fruit bats are thought to be natural hosts. Humans likely are infected by handling infected forest animals or by contact with infected bats. Secondary human-to-human transmission can occur via direct contact with blood, secretions, or other body fluids from infected humans or corpses. The virus can persist in immunologically privileged sites, such as the testes, for weeks to months; therefore, sexual transmission by survivors of EVD can occur.<sup>75</sup>

The incubation period for EVD is 2 days to 21 days (mean 4–10 days).<sup>76</sup> Symptoms begin with dry symptoms, for example, fever, headache, muscle aches, and joint pain, followed by wet symptoms, for example, nausea, vomiting, and diarrhea, at approximately day 4 of illness.<sup>76</sup> Diarrhea can be severe, leading to severe dehydration and electrolyte imbalance, especially hyponatremia. Hemorrhagic manifestations usually occur during later stages of the disease, including epistaxis, hematemesis, and hematochezia. Laboratory findings in EVD include leukopenia, lymphopenia, and elevated transaminase levels. Persons with severe disease typically die due to multisystem organ failure by 7 days to 10 days after onset of disease.<sup>73,77</sup> In children, because clinical features of EVD are nonspecific, epidemiologic criteria of history of contact with patients with confirmed EVD is important. The gold standard laboratory diagnostic test is real-time reverse transcription–polymerase chain reaction from blood samples, usually 3 days to 6 days after the onset of the symptoms. Blood tests for ELISA IgM and IgG antibodies are quick laboratory methods for diagnosis or surveillance for EVD. Early supportive care with intravenous fluids, electrolyte supplementation, and nutritional support can reduce mortality rates to approximately 40%.<sup>77–79</sup> Isotonic intravenous fluids with or without added dextrose are recommended as marked hyponatremia is common in patients with EVD.<sup>80</sup> The only FDA-approved treatment of EVD caused by the *Zaire ebolavirus* in adult and pediatric patients is the triple monoclonal antibody REGN-EB3 (atoltivimab/maftivimab/odesivimab-ebgn, INMAZEB®, Regeneron Pharmaceuticals). A randomized trial of REGN-EB3 in the Democratic Republic of the Congo during 2018 to 2019 showed that patients receiving the triple monoclonal antibody REG-EB3 had lower 28-day mortality rates of 33.5% compared with 51.3% in the triple monoclonal antibody ZMapp group ( $P = .002$ ).<sup>81</sup>

### **Prevention and Control**

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Transmission of Ebola viruses occur through direct contact with blood or bodily fluids, most often in the context of providing care to a sick family member or patient, or participation in burial rituals that involve washing and touching corpses.<sup>82</sup> Therefore, risk of EVD in children is attributed to contact with sick parents, caretakers, and relatives. Pediatric EVD often occurs in children younger than 5 years of age. Transmission through breast milk and congenital transmission also have been documented.<sup>83</sup> Practices in reducing risk of human-to-human transmission include contact isolation, wearing of gloves and appropriate personal protective equipment while taking care of ill patients, and regular handwashing after patient contact. Contact tracing of people with unprotected direct contact with patients during the symptomatic phase of illness should be monitored daily for evidence of disease for 21 days after last contact. Confinement of asymptomatic people usually is not warranted, due to low risk of transmission during the incubation period; however, those who develop signs or symptoms compatible with EVD should be isolated immediately until the diagnosis can be excluded.<sup>84</sup>

### **Vaccination**

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The recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein (rVSVΔG-ZEBOV-GP, Ervebo®, Merck & Co., Inc., USA), a replication-competent,

live, attenuated vaccine, has been approved by the FDA for the prevention of EVD caused by the Ebola virus species *Z ebolavirus* (EBOV) in adults ages greater than or equal to 18 years. The rVSVΔG-ZEBOV-GP Ebola vaccine contains the vesicular stomatitis virus that has been modified to contain a protein from the *Z ebolavirus*. The vaccine is administered as a single intramuscular dose. Common adverse reactions include arthralgia, myalgia, rash, headache, fever, and fatigue. The Advisory Committee for Immunization Practices recommend preexposure vaccination with Ervebo for adults who are at highest risk for potential occupational exposure to EBOV because they are responding to an outbreak of EVD, working as health care personnel at Ebola treatment centers or as laboratorians. VE was evaluated among clusters of contacts of confirmed EVD patients in Guinea during the 2014 to 2016 Ebola outbreak in West Africa.<sup>85</sup> A study demonstrated that among 2108 participants vaccinated immediately, none developed EVD greater than or equal to 10 days after randomization. This is in contrast to the delayed vaccination group (21 days after randomization), where 10 of 1429 participants developed EVD greater than or equal to 10 days after randomization. VE in this study was 100% (95% CI, 63.5%–100%). The Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) trial, which combined phase II and phase III clinical trials to assess the safety and efficacy of rVSV-ZEBOV, found that no cases of Ebola were reported in the 7998 participants who were vaccinated.<sup>86</sup> rVSV-ZEBOV was used as a ring vaccination strategy during the 2016 outbreak in Guinea. There currently are 1510 individuals, including 303 children ages between 6 years and 17 years old, who have received vaccines through compassionate use. There were no secondary cases of EVD that occurred among those vaccinated. The most common adverse event was headache (12%), with myalgia (3%) and arthralgia in less than 1% in children, compared with 7% in adults.<sup>87</sup>

**Table 3**  
**Summary of prevention of emerging infections**

Disease	Prevention Control Measures		Vaccine/ Chemoprophylaxis
	Community Settings	Hospital Settings	
Avian influenza	Avoidance of poultry exposure during outbreaks	Droplet, contact, and airborne precautions	Oseltamivir chemoprophylaxis
MERS	Avoidance of camel exposure	Droplet, contact, and airborne precautions	Vaccines are in preclinical and clinical studies.
Dengue	Avoidance of mosquito bites Vector control and surveillance	Standard precautions	Licensed dengue vaccine approved in 2017
Chikungunya	Avoidance of mosquito bites Vector control and surveillance	Standard precautions	Vaccines are in preclinical and clinical studies
Ebola	Human-to-human transmission Burial ceremonies	Standard universal and contact precautions; in health care setting, it is important to use personal protective equipment and environmental infection control	Licensed Ebola vaccine approved in 2019

The Chimpanzee adenovirus type 3 vector vaccine (ChAd3-EBO-Z) was studied as a phase II clinical trial, using a single dose in 600 children and adolescents (ages 1–17 years) in comparison with MENACWY-TT in Mali and Senegal. The vaccine induced an anti-glycoprotein Ebola virus antibody response at day 30, which declined by 6 months postvaccination and remained relatively stable thereafter. At 12 months postvaccination, 99.7% of participants had antibody concentrations greater than 36.11 ELISA units/mL. Anti-glycoprotein Ebola virus antibody had the highest antibody geometric mean titer in those 1 year to 5 years of age. A hypothesis was made that preexisting immunity against the adenovirus vector of the vaccine could have augmented their vaccine response. The most common reactions seen were fever, which occurred with higher rates in children 1 year to 5 years of age. Future research studies plan to focus on multivalent approaches, targeting also the Sudan strain. In addition, heterologous prime-boost strategies, for example, using ChAd3-EBO-Z for priming and the MVA-based vaccines, are available.<sup>88</sup>

In conclusion, Ebola disease in children has lower case rates compared with adults due to lower exposure. Prevention is by avoidance of direct contact with people with confirmed EVD. The clinical diagnostic criteria include history of contact with patients with EVD and subsequent evidence of fever 2 days to 21 days after contact. Although there is a vaccine approved for Ebola disease, this is only available for adults. Children may benefit from vaccination during outbreaks using the ring vaccination strategy.

## SUMMARY

Emerging infectious diseases are undergoing a global health challenge. Multiple strategies can be employed for prevention with transmission-targeted prevention, chemoprophylaxis, and vaccination (**Table 3**).

## CLINICAL CARE POINTS

### Avian influenza

- From 2003 to 2021, there were 193 children infected with the H5N1 virus, with a CFR of 53%.<sup>1,2</sup>
- Avoidance of exposure to infected live or dead poultry is an important preventive measure.
- Prepandemic vaccine production and stockpiling are important preventive measures. The AS03-adjuvant subvirion H5N1 avian influenza vaccine is approved for use in the EU and the United States.<sup>9</sup>

### The Middle East respiratory syndrome

- MERS-CoV first was identified in Saudi Arabia in 2012 with very high case fatality rates.
- MERS-CoV in children usually occurs from household contacts from human-to-human transmission.
- There are vaccines in development targeting viral spike proteins, for example, ChAdOx1 MERS, a simian adenovirus-vector vaccine expressing full-length spike surface glycoproteins.<sup>38</sup>

### Dengue

- Dengue is public health priority, with more than 5.2 million case reports in 2019.<sup>39</sup>
- Prevention in children includes mosquito bite prevention with repellents, bed nets treated with permethrin, and vaccination.<sup>44</sup>
- CYD-TDV is a live, attenuated recombinant tetravalent vaccine with a yellow fever 17D backbone licensed in 2015. Vaccination is recommended for persons ages 9 years to 45 years with previous infection. The dengue vaccine also can be considered in areas with dengue seroprevalence rates of greater than 80% by age 9 years.<sup>52</sup>

**Chikungunya**

- Chikungunya is an emerging disease that has spread to more than 60 countries throughout Asia, Africa, Europe, and the Americas.<sup>60</sup>
- Prevention is focused on mosquito bite prevention and vector control.<sup>46</sup>
- Chikungunya vaccine development has progressed to phase 3 for the VLA1553, a monovalent single-dose, live, attenuated vaccine.<sup>63</sup>

**Ebola**

- EVD is a zoonotic disease affecting mainly West Africa.
- Human-to-human transmission occurs via direct contact with blood, secretions, or other bodily fluids. Children usually are infected from household contacts.
- Ervebo, a replication-competent, live, attenuated vaccine, is approved for use by the FDA in the prevention of EVD caused by the EBOV species in adults ages greater than or equal to 18 years. Ring vaccination strategies were used successfully during the 2016 outbreak in Guinea.

**DISCLOSURE**

The authors have nothing to disclose.

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