Emerging Zoonotic and Vector-Borne Viral Diseases

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Abstract

Many vector-borne and zoonotic diseases are considered to be emerging; since they are either newly reported to cause human disease, or are causing disease in geographical locations or species not previously documented. In the past 15 years, significant outbreaks of Severe Acute Respiratory Syndrome (or SARS) and Middle Eastern Respiratory Syndrome (or MERS), Nipah and Hendra, Ebola virus disease and Zika fever and others have been reported. In this chapter the clinical characteristics, epidemiological aspects, treatment and prevention and information related to the laboratory investigation of important zoonotic and vector-borne diseases that have emerged in the past 10 years, and how this affects children, will be discussed. Furthermore rabies, considered a neglected viral disease with the majority of victims in Africa being children, will also be addressed.

5.1 Hemorrhagic Fevers

The viral hemorrhagic fevers (VHF) are a specific group of diseases that have in common the propensity for human to human transmission particularly in the hospital setting, have high mortality and require early recognition and a public health response to prevent outbreaks. They are caused by unrelated RNA viruses belonging to the *Filovirus*, *Arenavirus, Bunyavirus* and *Flavivirus* genera (reviewed in [1, 2]) (Table 5.1). Subclinical or mild cases are commonly associated with for example Lassa fever, yellow fever and Crimean-Congo hemorrhagic fever (CCHF), contrasted by Ebola virus and Marburg virus disease (EVD and MVD) which are more often

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Table 5.1 Summary of medically important and most commonly occurring viral hemorrhagic fevers

Viral hemorrhagic fever	Crimean-Congo hemorrhagic fever	Marburg virus disease	Lassa fever	Yellow fever
Reported geographic distribution	Most wide spread tick-borne viral infection in humans. Reported from more than 50 countries in Africa, South East Europe, Middle East and Asia. Including China, Turkey, Bulgaria, Croatia, Greece, Iran, Iraq, Saudi Arabia, Kenya, Uganda, Tanzania, Egypt, Nigeria and South Africa	Angola, Democratic Republic of Congo, Kenya, Uganda, Zimbabwe	Sierra Leone, Guinea, Liberia and Nigeria	Endemic in more than 50 countries in tropical regions of Africa (44 countries) and South and Central America (12 countries)
Cumulative occurrence/ prevalence	Sero-prevalence of up to 20% in endemic areas in people with history of tick bites	Only 466 cases reported from 1967 to 2014 (including cases associated with exportation of infected monkeys to Europe, Russia and USA). Outbreaks often involve single cases. Two bigger outbreaks reported in DRC and Angola in 1998–2000 and 2004–2005, respectively	Up to 500,000 cases in West Africa per annum Sero-prevalence of up to 55% in certain communities in endemic areas	Up to 130,000 cases with hemorrhagic manifestation per year by estimation
Mode of transmission	Mostly through tick bites, or other contact with infected ticks, or infected tissues and blood. Nosocomial transmission has been reported, but human-to-human transmission limited	Spill over from cave dwelling bats, exact mode of transmission unclear Human-to-human transmission through direct and close contact with infected persons	Human contact with infected rodent urine and fecal material. The latter may be aerosolized and transmitted *via* this route	From day feeding *Aedes* mosquitoes, particularly *A. aegypti*

Reservoir host and vector	Domestic livestock and small mammals Ticks, particularly *Hyalomma* ticks	Believed to be cave dwelling bats such as *Roussettus aegyptiacus*	*Mastomys natalensis* (or the multimammate mouse)	Maintained in sylvatic cycle in nature involving certain primates and canopy dwelling mosquitoes. May establish in urban setting involving *Aedes aegypti*
Case fatality rate	Up to 30% in hospitalized cases	Up to 90% in outbreaks	Up to 20% in hospitalized cases, but up to 80% of people infected do not develop signs and symptoms of Lassa fever	Up to 50% in hospitalized cases
References	Uyar et al. [13], Ergönül [14], Bente et al. [15], Mardani and Pourkaveh [16], Elaldi and Kaya [17], Messina et al. [18], Shayan et al. [19], Leblebicioglu et al. [20]	Brauburger et al. [21], Olival and Hayman [22], Brainard et al. [23], Rougeron et al. [24]	Richmond and Baglole [25], Ogbu et al. [26]	Gardner and Ryman [27], Garske et al. [28]

Ebola virus disease is not included in this summary, but described in detail in the text. The geographical expanse provided for each disease related to reports of naturally occurring outbreaks and does for example not include exported cases of disease

associated with severe and fatal outcomes and case fatality rates of up to 90% recorded during outbreaks.

All of the HF viruses are naturally harbored in distinct animal or invertebrate reservoirs. Outbreaks of the disease are either associated with exposure to the virus through a vector species (for example ticks for CCHF virus or mosquitoes for yellow fever) and little or no human-to-human spread, or a single spill-over event from the animal reservoir with amplification of the outbreak through human-to-human transmission (for example spill-over of Ebola virus from bats or other infected forest dwelling animals to humans). Since these viruses are associated with an animal or invertebrate reservoirs and vectors, the diseases have a specifically geographical expanse, partly related to the distribution of these reservoir and vector species. Another observation is that historically, outbreaks of VHFs have been occurring in low resource settings with many of the outbreaks associated with health care facilities where poor infection control practices allow for the spread of these viruses. Recent outbreaks of yellow fever have occurred in high density urban areas with intense mosquito breeding. Infection prevention and control measures in hospitals remain the most important measure to contain a VHF outbreak [3–7]. This is in the absence of prophylaxis or treatment on the account of most of the VHFs. Currently, the only VHF for which a licensed vaccine is available is yellow fever. The vaccine is administered to children over 9 months of age of as part of the expanded program of immunization in a number of yellow fever endemic countries, in mass campaigns and in response to reported outbreaks. Documentation of a high rate of yellow fever vaccine-associated neurotropic disease in young infants during the 1960s led to institution of age <6 months as a contraindication for yellow fever vaccination except during epidemics when the risk of yellow fever virus transmission may be very high [8].

Ribavirin may be useful for treating Lassa fever and CCHF, although not proven in clinical trials [9–12].

A number of VHF infections such as CCHF are related to occupational exposure to infected vectors or animals so infections in children are less common.

For the purpose of this chapter further discussions will focus on aspects of Ebola virus disease (EVD).

5.1.1 Epidemiological Aspects of EVD

To date, natural outbreaks of EVD have only been recorded in central and west African countries. Before the outbreak of EVD in Guinea, Sierra Leone and Liberia from 2013 to 2015, outbreaks of the disease were limited to secluded and rural locations in central Africa [29]. A cumulative 31,139 cases with 12,890 deaths have been recorded since the first recognition of EVD in 1976–2015, more than 90% of these cases were reported during the West Africa outbreak [30, 31]. Single exported cases during outbreaks have been recorded in travellers with secondary transmission noted during four such events in South Africa, Nigeria, USA and Mali [29]. The common perception is that children are spared during EVD

outbreaks, and in fact this observation was made during several outbreak investigations [32]. This does however not mean that children are not affected. A retrospective study revealed that 20 of the 218 (9%) confirmed EVD cases during the 2000 Gulu, Uganda outbreak were in young children and adolescents [33]. Nearly 20% of the cases reported during the West Africa outbreak involved children below the age of 15 [34]. The putative index case of the West Africa outbreak was a 2 year old child that may have had exposure to bats whilst playing in the forest nearby his home [35, 36]. The risk of EVD in children may be related to cultural factors in handling and caring for ill persons within households. In communities where children are kept away from the sick the risk should be lower, but in many instances young children are co-admitted to hospital with their sick caregivers increasing the risk of them also being infected [33]. During the Gulu-outbreak, it was noted that the under-five age group was more affected during this outbreak than other children. Here children were typically co-admitted to hospital with their symptomatic parents [33].

The natural history of Ebola virus (EBOV) remains an enigma despite intensive research on the topic. Evidence is accumulating that certain forest dwelling fruit bat species (including *Hypsignathus monstrosus*, *Epomops franqueti, Myonycteris torquata* and possibly *Eidolon helvum*) are natural reservoirs of the virus although this occurrence is still not fully understood [37–39]. The source of EVD outbreaks has often been associated with direct contact with bushmeat [40]. The latter includes bats, chimpanzee, gorillas and duiker antelope [41]. The risk for contact with bushmeat appears to be related to slaughtering and preparation of the raw meat and not necessarily the consumption of cooked meat [41]. Outbreaks of EVD in the human population are amplified by human-to-human transmission through close and direct contact with infected individuals [23]. These outbreaks are perpetuated in the hospital setting but also in close family and friend circles where caring for the ill and traditional burial practices are the most prominent risk factor for contracting the virus.

5.1.2 Clinical Aspects of EVD

The initial stage of the clinical course of EVD is non-specific, complicating early diagnosis, and follows an incubation period of 2–21 days [42]. The difficulty of clinical diagnosis is compounded by a long list of possible differential diagnoses in the locations where EVD has been described. This includes other VHF such as Lassa fever, but also other infectious diseases such as malaria, cholera and typhoid [42–45]. EVD is characterized by sudden onset of fever (>40 °C (104 °F)), generalized weakness and anorexia, myalgia, headache and sore throat [42, 46, 47]. These were all common findings in children during the EVD outbreak in West Africa [34]. Noteworthy, is that all of the EVD cases reported in children during the 2000 Gulu outbreak reported fever [33]. Patients infected with EVD rapidly deteriorate and commonly present with gastrointestinal symptoms including vomiting, diarrhea and dehydration. Chertow et al. [48] reported profuse watery diarrhea in EVD patients

persisting for a week or more. As with other VHF, and contrary to the naming of the syndrome, most cases do not present with overt bleeding [33, 34, 42, 48]. Less than 20% of children diagnosed with EVD presented with bleeding which was reported as hematochezia, hematemesis, bleeding gums, epistaxis and oozing from needle puncture sites [33, 34]. Patients will then either recover or deteriorate, often displaying neurological signs. Patients typically succumb due to multi-organ failure and hypovolemic shock [42]. Common findings in EVD patients with a poor prognosis are rapidly developing leukopenia, thrombocytopenia and a decrease in coagulopathy markers [42, 49, 50].

The case fatality rate in children is high [51]. During the Gulu-outbreak, the reported case fatality rate among children and adolescents was 40% [33]. During the West Africa outbreak, the case fatality rate in the under-five group was significantly higher than other age groups, with the highest death rate reported in children under-1 year old (90%) [34].

Pregnant woman are more likely to develop severe EVD, and miscarriage is reported universally in pregnant woman diagnosed with EVD [48, 52]. A case report of EVD in a pregnant EVD woman that survived, but still aborted suggests that maternal immunity may have little effect on affording protection to the unborn [53].

5.1.3 Laboratory Diagnosis of EVD

Limited capacity for specialized laboratory diagnosis exists in most countries where EVD has been previously reported. This remains one of the biggest challenges in effective outbreak responses for the future [54, 55]. Laboratory investigations are typically carried out by national reference centres and involve specialized testing to detect the virus, or the body's response to the infection [24, 54, 56]. Specific laboratory confirmation is by reverse transcription (RT)-PCR which detects the viral RNA in a patient's sample. Antigen detection using enzyme immunosorbent assays (ELISA) are also commonly used. Live virus may also be isolated in cell culture, but typically serves as a complimentary assay and due to the time required for results, not always useful for diagnosis or a timely outbreak response. Detection of specific IgM responses or rise in specific IgG titre is also indicative of recent infection. The latter is tested using indirect immunofluorescence assays or ELISA. Some laboratories may offer additional testing such as electron microscopy and immunohistochemistry on tissue samples, but this may be viewed as complimentary testing in most cases. It is recommended that blood and tissues of suspected EVD cases be handled in biosafety level 4 facilities; although RT-PCR testing during the West Africa EVD outbreak was done under field conditions working under modified biosafety level 3 conditions. The West Africa outbreak has highlighted the need for rapid and sensitive tests for EVD. Tests that can be conducted at facility level or at the bedside will be helpful in directing clinical decisions [55, 57]. Although testing at reference laboratories may be laborious and more time consuming than facility-level testing, it is still recommended that all investigations be confirmed by

experienced reference laboratories. Several rapid EVD assays are being developed in response to the West Africa outbreak, but are not yet widely available [58–63].

5.1.4 Treatment and Prevention of EVD

Despite tremendous efforts during and following the West Africa outbreak to develop antiviral treatment and vaccines, neither are (widely) available yet [64–66]. Management remains supportive in most instances, although experimental treatment options have been applied for some [67, 68]. Fever and pain is managed with paracetamol and it is recommended to avoid nonsteroidal antipyretics [12]. Chertow et al. [48] who managed more than 700 EVD patients in Liberia in 2014 found that the use of antiemetics, antidiarrheal medications, and rehydration therapy was beneficial. Antimalarial treatment is recommended for all suspected EVD cases, and malaria testing is recommended to guide further actions [12]. Treatment with broad spectrum antibiotics is recommended especially in children, aged less than 5 years [12] as empiric treatment for possible bacterial sepsis. Fluid replacement will be required in many EVD patients and blood transfusions, in those with bleeding, may be beneficial [12].

The Ebola virus has been detected in breast milk up to 9 months after infection, and therefore it is not recommended that woman diagnosed with EVD breastfeed [12, 69].

Historically the use of hyperimmune serum for treatment of EVD, but also other VHF cases, has been reported [70–72]. During the West Africa outbreak, the WHO also approved the use of hyperimmune serum for the treatment of patients, although reportedly not widely used [73]. A limited clinical trial during the outbreak indicated the safety, acceptability and feasibility of treatment with hyperimmune sera [74]. Van Griensven and co-authors [74] also argued the scalability of such a product, particularly given the number of potential immune donors now available in Guinea, Liberia and Sierra Leone.

During the West Africa outbreak, experimental drug treatment of patients was also reported. Palich and co-workers [67] reported the survival of a 6 year old child diagnosed with EVD after treating with favipiravir (or T-705) until virus was cleared from his blood. The use of favipiravir in children older than 1 year has been suggested by Bouazza and co-workers [75], but data from ongoing trails are not yet available.

Other treatment option developments have focused on the use of antiviral drugs (such as favipiravir), type I interferon, anti-coagulant drugs, small interfering RNA, monoclonal antibodies and morpholino-oligomers [76–78]. A number of experimental vaccines have undergone safety and immunogenicity studies *in-vivo* in various populations, although children have largely not been included in these studies. In phase 3 studies using a ring vaccination approach for post exposure prevention of EBV disease in potential contacts (>18 years of age) a recombinant vesicular stomatitis virus based vaccine (rVSV-ZEBOV) showed very high efficacy [79]. Social mobilization, patient isolation, infection control and use of personal protection

equipment by health workers, contact tracing and monitoring for infection and safe burials are key traditional interventions in outbreaks.

5.2 Arboviral Diseases

Arboviruses are insect-transmitted viruses belonging to the *Flaviviridae*, *Togaviridae* and *Bunyaviridae* virus families. Hematophagous vectors such as mosquitos, ticks, midges and sandflies transmit the viruses to humans and other susceptible vertebrate hosts. More than 500 arboviruses have been catalogued worldwide, with a little more than a quarter of them reported to cause human disease [80]. The clinical spectrum of arboviral disease is vast ranging from asymptomatic infection to life-threatening febrile and hemorrhagic fever. Arboviral disease typically falls within one of four groups of clinical presentation, namely non-specific systemic febrile disease, encephalitis, polyarthralgia or hemorrhagic fever [81]. Most of the arboviruses are however, not limited to causing only one clinical syndrome. West Nile virus may for example cause unapparent infection in up to 80% of infected individuals but may also cause debilitating encephalitis in others [82]. The distribution of specific arboviruses is geographically defined based on insect vector distribution. Several instances of expanding vector distribution, for example, presumptively due to global climate changes, changes in land use patterns and global transportation have been increasingly linked with the emergence of arboviruses worldwide [83, 84]. Examples include the introduction of West Nile virus to North America in 1999 [85, 86], the re-emergence of dengue in South East Asia, South America and Sub-Sahara Africa [87], the emergence of chikungunya in Indian Ocean Islands and the Caribbean [88], and the emergence of Zika virus (ZIKV) in Latin America in 2014 [89].

Clinical diagnosis of arboviral disease is complicated, and under- or misdiagnosis related to the difficulty of clinical diagnosis in the absence of overt complications is common. In addition, the geographical spread of many arboviruses overlap and have similar clinical manifestations relating to complexity in clinical diagnosis [90]. Specialized diagnostic testing is required to confirm a suspicion of arboviral disease, but is not accessible in many countries where it is probably needed the most. Although RT-PCR detection or virus isolation provide definitive diagnosis, laboratory investigations for arboviral infections mostly rely on serological testing and interpretation due to the typically short viremic period associated with most arboviral infections. Interpretation of serological testing for arboviruses is also challenging and confounded by substantial antigenic cross-reaction between viruses belonging to the same family. The cross-reaction phenomenon particularly applies to flavivirus infections and may be further complicated by possible prior infection with a virus from the same family, or a vaccination for yellow fever or Japanese encephalitis.

For the purpose of this chapter the remainder of the discussion will focus on the newly emerging ZIKV.

5.2.1 Epidemiological Aspects of ZIKV

The WHO declared the ZIKV outbreak in the Americas a Public Health Emergency of International Concern [91]. This followed the rapid emergence of the virus in Brazil and virtually the entire South American subcontinent and the recognition of the potential link in the rise of the number of babies born with microcephaly and other neurological abnormalities observed [92].

The ZIKV was reported for the first time following yellow fever research conducted in the Zika Forest of Uganda in 1947 when it was isolated from a febrile rhesus monkey [93]. It was recognized as a disease causing agent in humans in 1954 when diagnosed in febrile patients in Nigeria [94]. In the years to follow, ZIKV remained mostly a research curiosity with a handful of studies that described its ecology and sero-prevalence in selected human populations and it caused sporadic cases and limited outbreaks without reported mortality or fetal effects [94–99] in a number of countries in Africa and Southeast Asia. In 2007, the first major outbreak of ZIKV was reported from the Yap Islands of Micronesia where more than 70% of the Island's population was affected [100–102]. This was followed by an outbreak in French Polynesia in 2013 and 2014, also affecting nearly 70% of the population [103–106]. The virus continued to spread westward, and was reported in Chile's Easter Island in February 2014 [107]. This was followed by detection of the virus in Brazil in May 2015, although molecular studies have suggested that the virus may have been introduced as early as late 2014 [108–110]. By September 2016, ZIKV was reported from more than 47 countries in Latin America and the Caribbean [111]. In addition, probably related to increased vigilance for the virus, outbreaks of the disease have been reported from Micronesia, Western Samoa, Figi, Singapore, Tonga, Samoa and the Marshal Islands, with possible endemic transmission reported in a dozen other countries in Southeast Asia and the Pacific since 2015 [111]. Although, these reports may relate to endemic occurrence of the virus, the possibility of autochthonous outbreaks due to translocation of virus from Latin America is under investigation for some of these outbreaks [111].

The ZIKV, a flavivirus, is transmitted to humans primarily through the bite of the female, day-feeding *Aedes aegypti* mosquito [112]. The role of other mosquito species in transmission of the virus to humans is disputed [113–121]. *Aedes* mosquitoes usually thrive during warm and wet seasons in the tropics and subtropics, with *Aedes aegypti* particularly well suited for breeding in urban settings, hence the risk of transmission of the virus from infected mosquitos to humans. Although, direct mosquito transmission is mostly implicated in transmission of the ZIKV to humans, transmission in-utero, intrapartum and through sexual transmission has been reported [111, 122–133]. Transmission in-utero has been most alarming with the probable link to congenital malformations and microcephaly (see Sect. 5.2.2). Rare cases of transmission through blood transfusion and laboratory exposures have also been reported [105, 134].

5.2.2 Clinical Aspects of ZIKV

Following the bite of an infected mosquito, an incubation period of up to 2 weeks follows, after which some infected individuals will develop the signs and symptoms of ZIKV infection [100]. An estimated 80% of humans becoming infected with the virus will not develop any clinical signs of disease. In the remainder, disease is typically acute but mild and self-resolving [100, 135]. This is marked by a low-grade fever (typically not above 38.5 °C (101.3 °F)), arthralgia, a maculopapular rash, conjunctivitis, headache and asthenia, much like dengue fever [100, 135]. Clinical diagnosis of ZIKV infection is complicated due to its non-specific presentation, but also due to the co-circulation of other arboviruses such as dengue and chikungunya viruses which cause clinically indistinguishable disease in most cases. Co-infection of ZIKV and dengue or chikungunya virus has also been reported [90, 136–138]. This is not entirely surprising given that these viruses are spread by the same species of mosquitoes. Additionally, other infectious etiologies may also present with similar clinical syndrome including parvovirus infection, rubella, measles, leptospirosis, malaria and rickettsiosis [139].

Hospitalization is rarely required for ZIKV infection [103, 140, 141]. The case fatality rate of ZIKV is considered low and probably associated with comorbidities in such cases [142]. Infants and children present with similar disease as adults and recovery with no sequelae noted in such cases [100, 140, 143, 144].

5.2.2.1 Complications of ZIKV Infection

Neurological complications have been implicated as untoward effects of ZIKV infection. Such neurological deficits have also been reported with other arboviral infections, albeit rarely [145–147]. Guillian-Barré syndrome has been reported as a rare complication of ZIKV infection, although the true extent of the association and occurrence remain to be determined [103, 141, 148]. In addition, rare cases of brain ischemia, encephalitis and myelitis have been reported following ZIKV infection [149–152].

A place and time association was noted with the outbreak of ZIKV in Brazil and concomitant rise in number of babies born with microcephaly in 2015 [153], but studies have subsequently reported significant evidence to support this hypothesis [154]. As such, current opinion is that ZIKV infection during pregnancy can be linked to microcephaly and other congenital neurological and developmental abnormalities, although Koch's postulates have not been applied to prove causality [155]. Reports of neonates with microcephaly and other malformations and abnormalities are accumulating since early 2016 [125, 130, 131, 156–158]. In conjunction with microcephaly, small brain size, ventriculomegaly, hypoplasia or agyria, agenesis of the cerebellar vermis, posterior fossa abnormalities and calcifications have been reported [125, 131, 156, 157]. Other abnormalities have included growth retardation, arthogryposis and ophthalmologic findings [125, 130–132, 156, 157, 159]. Fetal losses have also been reported, and a perinatal mortality rate of almost 27% was reported by Oliveira and co-workers

[130, 131] in a small cohort study conducted in Brazil. Continued longitudinal monitoring of the development of the birth cohort affected by the ZIKV outbreak will reveal the breadth of neurological damage possibly caused by the virus [160]. A retrospective study has indicated cases of microcephaly and other abnormalities in babies born during the ZIKV outbreak in French Polynesia [161]. The possible link between these cases and ZIKV infection was not made at the time, most likely due to the limited number of cases involved (i.e. the extent of the outbreak in Brazil and South America allowed for the possible correlation to be made).

The risk of the development of fetal abnormalities during pregnancy remains to be fully elucidated. The risk factors and the risk associated with infection at different stages of gestation are not clear yet [162]. It is suggested that infection during the first trimester is the most damaging, although infection at later stages of gestation have also reportedly resulted in malformations and neurodevopmental problems [162].

5.2.3 Laboratory Diagnosis of ZIKV

Specialized laboratory testing is required for confirmation of a ZIKV diagnosis. In some settings this service is provided by national reference laboratories, but with the extent of the problem in Latin America the growing availability of commercially available reagents, these tests are offered by an increasing number of laboratories. Testing is recommended for symptomatic individuals with possible exposure to the virus [163]. Asymptomatic pregnant woman at risk of infection should also be screened for possible infection [163].

It is recommended that laboratory tests for ZIKV infection include RT-PCR detection of the viral RNA in whole blood, serum, plasma or urine which are collected during the acute phase of illness (i.e. <7 days after onset of illness) [163, 164]. The virus has also been detected in saliva, cerebrospinal fluid, female genital tract secretions, semen and breast milk [122, 128, 129, 161, 165–169]. Detection of viral RNA in secretions such as semen and saliva has been noted for extended periods even after viremia in the blood has been cleared [122, 129, 168, 170]. Although viremia in the blood is typically cleared quickly, viral RNA has been detected in blood more than 2 months after onset of illness in a limited number of cases [126, 171].

Detection of ZIKV-specific IgM responses requires verification with plaque reduction assays in order to determine the specificity of such responses and mitigate the risk of erroneous diagnosis due to the high level of cross reactivity expected for the antibody responses to other flaviviruses or flavivirus vaccines [163].

Fetal infection has been confirmed by RT-PCR on amniotic fluid, placenta and fetal serum, cerebrospinal fluid and brain [125, 130, 131, 156, 157]. Immunohistochemistry and electron microscopy of brain tissue has also been reported.

5.2.4 Treatment and Prevention of ZIKV

No specific treatment is yet available for ZIKV infection. Treatment is supportive and constitutes bed rest, oral hydration, antipyretics and pain medication [164]. Aspirin should not be used to manage pain and fever in children under the age of 12 due to the risk of Reye's syndrome. Pregnant woman, symptomatic or asymptomatic, that may have had exposure to the virus should be screened for the infection [163]. Fetal monitoring including amniocentesis after 21 weeks of gestation and 6 weeks after exposure for microcephaly and other malformations is recommended [149, 164, 172].

No vaccines are currently available for ZIKV infection but current progress is encouraging [173]. Various approaches to the development of such a vaccine are currently underway, with more than 15 such projects initiated by June 2016 [174]. Prevention of infection in the absence of vaccination relies on preventing exposure to the mosquitos that may transmit the ZIKV. This may be achieved by for example applying insect repellents and staying indoors behind screened windows during peak mosquito activity. Many countries have issued travel warnings to pregnant woman, woman planning to become pregnant and their partners not to travel to ZIKV affected areas. Affected countries have advised woman to delay pregnancy at the time of the ZIKV outbreak, which is a difficult approach in countries where up to half of pregnancies are unplanned [175, 176].

5.3 Rabies

Rabies is the most fatal viral infection in recorded history, and although controllable in certain animal populations through vaccine programmes and largely preventable in humans through prevention of exposures and post exposure prophylaxis, clinical rabies disease cannot be treated [177–179]. Hampson et al. [180] estimated that 59,000 human cases of rabies occur in dog rabies affected countries annually. Dog rabies is most commonly reported from developing countries and typically affects poor communities where dog rabies control measures are inadequate. In addition, many epidemiological reports have indicated that children are particularly affected [181–184]. Human cases are underreported in many developing countries due to the lack of specialized diagnostic services to investigate such cases, but also due to the complexities of clinical diagnosis. Consequently, rabies remains an under-recognized and neglected disease in much of the world [180, 185].

The disease is marked by a progressive acute phase culminating in coma and followed by death within a short period in nearly all patients [186, 187]. The disease is caused by viruses belonging to the genus *Lyssavirus* of the family *Rhabdoviridae.* The lyssaviruses represent a diverse group of viruses with the International Committee on the Taxonomy of Viruses recognizing rabies lyssavirus and 13 rabies-related viral species in 2016 [188]. Additional lyssaviruses have been described but not classified taxonomically [189]. Not all of the lyssaviruses have been associated

with human cases, and by far the public health burden associated with rabies relates to infection with "classic" rabies viruses (previously denoted as genotype 1 viruses) (RABV) [180, 190]. The RABV circulates in diverse terrestrial mammals which vary by geographical location [185]. The public health burden associated with rabies however relates to rabies in domestic dogs since these animals serve as the most common vector of the disease to the human population [180, 185, 191, 192]. Therefore, most human rabies cases are reported from developing countries where dog rabies control efforts are suboptimal [180, 185].

5.3.1 Epidemiological Aspects

The occurrence of lyssaviruses has been reported virtually globally, with the exception of the poles and some islands [193]. Only one of the currently described lyssaviruses, namely the Mokola virus, has not been associated with a bat reservoir [193, 194]. Nonetheless, only single human cases of rabies have been associated with bat exposures related to European bat lyssavirus 1 and 2; Australian bat virus; Duvenhage virus and Irkut virus [190, 195]. No human cases have been associated with Aravan, Bokeloh bat; Ikoma; Khujand, Shimoni bat, West Caucasian bat lyssavirus or the unclassified Lleida Bat virus to date [196].

Uniquely, rabies virus is associated with insectivorous bat reservoirs in the Americas—this phenomenon has not been reported elsewhere [197–199]. In addition to bats, cycles of rabies are also reported in various terrestrial mammals in the Americas, for example in raccoons and skunks in the USA. Domestic dog rabies is reported mostly from developing countries in Asia and Africa [180], with elimination achieved in the US and various European countries. The role of wildlife rabies varies from region to region. It should however be noted that all mammalian species are susceptible to rabies and may serve as potential vectors of the disease and this should be considered when evaluating possible exposure.

5.3.2 Clinical Aspects

The virus is transmitted in the saliva of an infected animal. Bites, but any small nicks or scrapes or scratches that break the skin, may constitute exposures. Mucosal exposures, such as licking over the face with contact with the nose, eyes and mouth are also considered exposures. Incubation periods range from 4 days to several years and tend to be shortest with severe bites on the face, head and neck, especially in children [186, 187]. The average incubation period for the RABV is 20–90 days with rare cases reported with an extended incubation period [200, 201]. There are no diagnostic tests possible during this period to predict the likelihood of rabies disease following on a potential exposure. A wide range of non-specific prodromal features including fever, headache, myalgia, fatigue, and change in mood and itching at the initial rabies exposure site may be reported, and in the absence of a report of possible exposure to rabies the disease is difficult to diagnose clinically [186].

Human rabies can take two clinical forms [186, 187]:

- The more common, furious or agitated rabies which is characterized by hydrophobia, aerophobia and periods of extreme excitement alternating with lucid intervals, features of autonomic system dysfunction and finally by unconsciousness and complete paralysis. Initially spasms affect mainly the inspiratory muscles. Autonomic nervous system problems are frequently reported
- Dumb or paralytic rabies which affects the medulla, spinal cord and spinal nerves. Paralytic rabies is less common and more difficult to recognize as rabies. Neurological sign include quadriparesis which predominantly involves the proximal muscles, loss of reflexes and paralysis. Cranial nerve involvement may result in ptosis and external ophthalmoplegia. The course of the disease is less acute and even without intensive care patients may survive for up to 30 days before they succumb to bulbar and respiratory paralysis.

The fatal outcome of RABV infection is associated with a progressive encephalitis and eventual multi-organ failure [187, 202]. The differential diagnosis of rabies is broad. A detailed history of previous potential animal exposure is very important, but can also be inaccurate as animal contact may have been forgotten or unnoticed especially as often reported where bats have been involved in the exposures [203]. The differential diagnosis includes other viral causes of encephalitis and bacterial meningitis and cerebral malaria [182, 186]. Tetanus is important in the differential diagnosis and may also be linked to the same animal source, typically there is a short incubation period and the muscle rigidity is constant, without relaxation between spasms. Paralytic rabies can also be confused with poliomyelitis and Guillian-Barré syndrome [204, 205]. Drug intoxications, psychiatric disorders also form part of the differential diagnosis.

5.3.3 Laboratory Diagnosis

Specialized testing is required to confirm a clinical diagnosis of rabies. Ante-mortem demonstration of virus in saliva or nuchal skin biopsies may be helpful in some cases, but demonstration of virus using molecular or immunofluorescence techniques on post mortem brain tissue remains the gold standard. Most often these tests are provided only by national reference laboratories, but remain unavailable in many countries where human rabies cases still occur. Routine blood screens are not informative for rabies diagnosis and are expected to be within normal ranges [186]. Examination of cerebrospinal fluid may be unremarkable and is not specific. Magnetic-resonance imaging and computed topography may be useful for differential diagnosis, but no remarkable findings are expected for rabies [187].

Ante-mortem diagnosis of rabies can be confirmed through RT-PCR detection of viral RNA in saliva, nuchal biopsies and cerebrospinal fluid [8, 206, 207]. Detection of viral RNA in tears, urine and respiratory secretions has also been reported [208]. Serological investigations are not always useful to confirm a rabies diagnosis, but

the detection of virus neutralizing antibodies in the serum of a previously unvaccinated person or in cerebrospinal fluid are considered confirmatory findings [8]. The gold standard for rabies confirmation in humans (and animals) remains examination of brain tissue post mortem by PCR or immunofluorescence [8, 206, 207].

Every attempt should be made to confirm the diagnosis of human rabies as this provides critical information regarding the burden of disease, failed prevention and guides and stimulates improved rabies control in animals.

5.3.4 Treatment and Prevention

Clinical rabies disease remains untreatable and is limited essentially to palliative care through pain relief and sedation [186, 187]. Provision of intravenous morphine and benzodiazepines has been recommended [8, 187]. If the diagnosis of rabies is confirmed emotional support of the patient and their families is important. Standard infection control precautions are applied in the management of a suspected rabies patient. Transmission of the virus from patient to health care workers or family members has not been previously documented [8, 209]. Rabies post exposure prophylaxis (see below) should be provided to individuals bitten by an infected patient or who experience a mucosal exposure to patient saliva [8, 209].

Survival in an unvaccinated patient with rabies has been reported following the experimental treatment of a teenager in the USA in 2004 [210]. The patient, an adolescent girl, was exposed to rabies virus through contact with a bat, and was treated through the induction of coma. Remarkably, the patient mounted a potent natural immune response to the infection, an observation not commonly noted in unvaccinated rabies patients [210]. The protocol has since been repeated in a number of patients with discouraging results [177, 178, 211, 212]. Effective therapeutic interventions still remain to be expounded [178].

As humans are mostly exposed to the RABV through contact with domestic dogs, the vaccination of dogs presents a crucial intervention for prevention of the disease in humans [213, 214]. The latter should be complimented by promotion of responsible animal ownership and bite prevention programmes. Ensuring the availability and accessibility of post-exposure prophylaxis (PEP) for potentially exposed humans is key in the prevention of human rabies. Rabies PEP is highly effective in preventing rabies in persons exposed to RABV provided timeous administration of biologicals and recommended regimens are followed [8]. True failures of PEP are very rare [215, 216]. Modern rabies vaccines are highly purified, cell-derived inactivated vaccines with agreeable safety profiles, very few adverse reactions and are highly immunogenic [8]. Wound cleaning and PEP, done as soon as possible after suspected contact with a rabid animal can prevent the onset of rabies in virtually 100% of exposures. Intensive wound cleaning is a critical, affordable and manageable component of rabies prevention especially in communities without access to rabies biological prevention and may play some role in some cases in preventing progression to rabies disease. Management of the wound includes cleaning with copious amounts of water (even for small wounds) and soap. The wound should be

disinfected with 70% ethanol and iodine. Wound management should also include the use of antibiotics and provision of tetanus vaccination/booster vaccination as clinically required.

Rabies PEP should start as soon as possible following on an exposure to a suspected rabid animal. Even if there is a delay between exposure and visit to the healthcare facility, there is no cut off point after which it is too late to initiate rabies PEP. The decision to give PEP or not should also be made on the risk of RABV transmission, for example taking into account: the animal species, provoked versus unprovoked attack, animal behavior, animal health and category of exposure and history of rabies vaccination of the animal if possible and reliable. Vaccination is either through the intramuscular or intradermal route in accordance with WHO recommended regimens [8]. In wounds that drew any amount of blood (including small wounds such as scrapes that broke the skin) (also called category III exposures), rabies immunoglobulin (RIG) is essential. The latter provides passive immunity whilst immunity is mounted against the rabies vaccination. The use of RIG is crucial in prevention of rabies in category III exposures and failure to provide has culminated in prophylaxis failures [217]. Human or equine-derived rabies immunoglobulins are highly effective and generally safe to use [8]. It should be noted that the use of equine derived immunoglobulin should be used in facilities that are able to manage potential severe allergic reactions [8]. The RIG is infiltrated locally into wound site as much as possible. If injection locally into wound is painful, particularly in children; especially if the wound is on the head, face or neck, consider some sedation provided it can be done safely. The costs of RIG, and limited access and availability in many developing countries, limit the success of PEP in developing countries.

Pre-exposure vaccination is provided to individuals at high or continual risk of RABV exposure, such as veterinarians and laboratory workers [8]. Rabies vaccination is also provided to travellers visiting areas that are endemic for rabies and if their activities may put them at risk of potential exposure (for example only visiting hotel versus backpacking in the outdoors) [218–220]. Pre-exposure regimens using cell-derived vaccines either administered intradermally or intramascularly as three doses have been shown to induce good immune responses, which are long lasting and successfully boosted even after many years if there is specific exposure [8]. Pre-exposure vaccination obviates the need for post exposure rabies immunoglobulin, a generally scarce resource in many areas. The use of pre-exposure vaccines as part of the expanded program for immunization has been used in some areas with high exposure risks and shown to be immunogenic and safe, with persistence of rabies virus-neutralizing antibodies [221–223].

5.4 Conclusion

Emerging and vector-borne and neglected viral diseases pose a risk to communities particularly in resource poor settings. While adults are disproportionately affected by some of these as a result of occupational exposure, the burden of rabies and Zika

infections is borne by children and the fetus respectively. Treatment options overall are very limited or not possible, so early identification of emergence and prevention of spread, are key strategies. The development of vaccines for a number of emerging diseases show promise but clinical trials are still needed. A "One Health" approach addressing environmental, animal and human aspects of emerging and zoonotic diseases are key in prevention, early detection and control.

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