Chapter 5 EBOLA
Review for IDCNA

Title: Ebola Virus Disease (EVD): Epidemiology, Clinical features, Management and Prevention

Running title: Ebola Virus Disease

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Key points

- Ebola Virus Disease (EVD) is a deadly (25%-90% mortality) zoonotic disease caused by the Ebola Virus (EBOV) which was first discovered in 1976 near the Ebola River in the Democratic Republic of Congo. Since then several major outbreaks of EVD have occurred in sub-Saharan Africa.
- Bats are the most likely host reservoir of EBOV. Humans acquire infection through direct or indirect contact with blood, body fluids and tissues of infected bats.
- Human-to-human transmission of EBOV occurs via direct contact with an infected person or those who die from EVD, the virus getting through broken skin or mucous membranes of the eyes, nose, or mouth. Sexual transmission has been described
- The incubation period ranges from 1 to 21 days (average of of 5 to 9 days.
- Initial symptoms are non-specific, with severe headache, muscle pain, weakness, fatigue, diarrhea, vomiting, abdominal pain and bleeding or bruising which are often misdiagnosed as influenza or malaria. Suspicion of EVD should prompt isolation and infection control measures
- There is no specific treatment for EVD. Supportive care and management of complications (renal, respiratory and liver failure, bleeding and sepsis) are mainstay of treatment. Outbreak control requires a multidisciplinary team effort applying case management, infection prevention and control practices, surveillance and contact tracing, a good laboratory service, safe and dignified burials and social and community mobilization.
- Several novel EBOV-specific diagnostics, treatments and vaccines are under evaluation.

Abstract / Summary

Ebola Virus Disease (EVD) is a deadly zoonotic disease caused by the Ebola Virus (EBOV) which was first discovered in 1976 near the Ebola River in the Democratic Republic of Congo. Since then 10 major outbreaks of EVD have occurred in sub-Saharan Africa. EVD. The largest EVD epidemic recorded occurred in West Africa between 2013 and 2016. A total of 28,646 suspected cases and 11,310 deaths (39.5% mortality). The high case fatality rates have endowed Ebola a reputation as one of the most deadly viral zoonotic diseases of humans. There is no specific treatment for EVD. Supportive care and management of complications (renal, respiratory and liver failure, bleeding and sepsis) are mainstay of treatment. Effective outbreak control requires a multidisciplinary team effort applying case management, infection prevention and control practices, surveillance and contact tracing, a good laboratory service, safe and dignified burials and social and community mobilization. This review highlights the epidemiology, clinical features, diagnosis, management and prevention of EVD. The emerging field-friendly point-of-care rapid diagnostic technologies, rapid viral characterization; geospatial mapping of EVD transmission in urban and rural areas, and new treatments and vaccines under development and evaluation are discussed.

Introduction

Ebola virus disease (EVD), also known as Ebola hemorrhagic fever (EHF) or Ebola**,** is caused by the Ebola Virus (EBOV). EBOV is a linear non-segmented, single negative-stranded RNA virus and is a member of the Filoviridae virus family of which six species have been identified named after the region of discovery: *Zaire ebolavirus, Bundibugyo ebolavirus, Sudan ebolavirus, Reston ebolavirus, Taï Forest ebolavirus and Bombali ebolavirus*. The *Bundibugyos, Zaire , and Sudan* ebolaviruses are the cause of the large outbreaks in Africa. The Zaire ebolavirus caused the 2014–2016 West African epidemic (1). The high case fatality rates have endowed Ebola a reputation as one of the most deadly viral zoonotic diseases of humans. **Fig 1** shows the geographic distribution of Ebola in Africa.

The first human case of EVD case was described in 1976 near the Ebola River in the Democratic Republic of Congo (DRC). The first outbreak of EBOV affected 284 people, with a mortality rate of 53%. This was followed a few months later, by the second outbreak of EBOV in Yambuku, Zaire (now Democratic Republic of Congo (DRC). Until 2013, EBOV outbreaks consisted of small numbers of cases that were contained by basic public health and containment measures. The largest EVD epidemic occurred in West Africa between 2013 and 2016, and detection of EVD cases in the United Kingdom, Sardinia, Spain and the USA focused global attention on the epidemic.

On 1st August 2018, the Ministry of Health of the Democratic Republic of the Congo (DRC) declared a new outbreak of EVD in North Kivu Province. As of March 17, 2019, there have been a total of 867 confirmed cases with 587 deaths (1). The DRC outbreak demonstrates that public health and surveillance efforts remain inadequate (2) and EVD remains an important public health threat to global health securityThis review highlights the epidemiology, clinical features, diagnosis, management and prevention of EVD. We also review emerging field-friendly and easy-to-use point-of-care rapid diagnostic technologies, viral characterization; and geospatial mapping of EVD transmission in urban and rural areas; WHO standard-of-care and advanced clinical management of EVD patients; use of investigational new drugs and vaccines within compassionate use or phase II and III clinical trials; and a WHO draft "Ebola/Marburg R&D Roadmap" to prioritize the development of countermeasures (diagnostics, therapeutics and vaccines) that are most needed by EVD-affected countries (3)

Case Definition of Ebola Virus Disease

In 1999 the World Health Organization (WHO) proposed the use of a case definition for haemorrhagic fever using the following clinical criteria: body temperature ≥ 101°F (38.3°C) of <3 weeks duration; severe illness and no predisposing factors for haemorrhagic manifestations; and at least 2 of the

following haemorrhagic symptoms: haemorrhagic or purple rash, epistaxis, hematemesis, haemoptysis, blood in stools, or other haemorrhagic signs; and no established alternative diagnosis (4).

In 2009, a systematic review reported that only 58% of EVD patients in literature met the 2009 WHO case definition (5). During the 2013-2016 West African outbreak, fever was absent in at least 10% of the cases with no major haemorrhagic manifestations (6). This clinical presentation questions previous EVD case definitions, which including fever and haemorrhagic manifestations make it too specific, and not sensitive enough for case detection. Thus substantial changes have been proposed in the eleventh revision of the International Classification of Diseases (ICD-11) with an innovative EVD case definition that links epidemiological and clinical perspective including the presence of a severe disease with high case fatality and unusual prolonged disease manifestations (7,8).

A 'confirmed case' of EVD is now defined as a suspected case (patient with fever and no response to treatment for usual causes of fever in the area, with at least one of the following signs: bloody diarrhoea, bleeding from gums, bleeding into skin (purpura), bleeding into eyes and urine) with laboratory EBOV confirmation (positive IgM antibody, positive PCR or viral isolation).

Epidemiology of Ebola Virus Disease

Historical:

EVD was first recognized in 1976, when two separate outbreaks were identified in the DRC, (then Zaire) and in South-Sudan (then Sudan) (9). At that time, it was assumed that these outbreaks were a single event associated with the infected person travelling between the two regions. However, further investigations revealed that there were two genetically distinct viruses: Zaire ebolavirus and Sudan ebolavirus, which came from two different sources and spread independently in each of the affected areas.

The first case was reported on August 22, 1976. He was a 42-year-old headmaster of the Yambuku Mission School, Equateur Region, returned from a 2-week driving excursion to northern Zaire; along the route, he purchased antelope and smoked monkey meat. He presented on August 26, to the outpatient clinic of the 120-bed Yambuku Mission Hospital with chills and fever and was treated for malaria with apparent relief. One week later, he returned with severe headache, muscle pain, nausea, abdominal complaints, and intestinal bleeding. He died on September 6, after the occurrence of a severe haemorrhagic syndrome of unknown cause. The EBOV was first isolated in 1976 (isolate E718) from the blood sample of a 42-year-old Belgian nursing sister who was working at the Yambuku Mission Hospital, DRC (10). Karl Johnson, the International Commission scientific director, suggested the name "Ebola" virus. Ebola is a river part of the Congo River network, about

60 km apart from the first EVD affected area. It was chosen to ensure that the Yambuku affected community was not stigmatized. The name is a distortion of the local Ngbandi name *Legbala*, meaning "white water" or "pure water" (10).

EBOV Host reservoir:

The specific host reservoir for EBOV remains unknown. After first discovery of EBOV, studies of finding the host reservoir focused on animals, insects, and plants. Ebola appears to be introduced into the human population through close contact with the blood, secretions, meat, organs or other bodily fluids of infected animals such as bats, chimpanzees, gorillas, monkeys, forest antelope, and porcupines in rainforest. Whilst non-human primates and other mammals were implicated when the first cases of an EVD, and the host reservoir is not yet confirmed, it appears most likely that the candidate reservoir appears to be African fruit bats.

EVD outbreaks in Africa since 1976:

Table 1 summarises all EVD outbreaks recorded since first discovery. Until the 2013-2016 EVD epidemic in West Africa, EVD outbreaks occurred in relatively isolated remote areas and were contained quickly. In contrast, the 2013–2016 EVD epidemic also involved major urban areas (1). with a total of 28,646 suspected cases and 11,310 deaths (39.5% mortality). Approximately 20% of EVD cases occurred in children under 15 years of age. A range substantial portion of EBOV transmission events might have been undetected particularly in the first phase of the 2013-16 outbreak since there were cases of mild illness with minimal symptoms recorded (11). These data raise new insight into the transmission dynamics and risk factor that underpin EBOV spill over events.

During the 9th EVD outbreak in the first 2018 semester in Équateur Province in DRC, there was a total of 54 cases with 33 death (case fatality ratio, CFR: 61%). A vaccination strategy was successfully applied between May and June 2018 with a total of 3481 people vaccinated targeting front-line HCWs as priority categories, and EVD primary and secondary contacts (12).

Later, on August 1, 2018, the DRC Ministry of Health declared an outbreak of Zaire EBOV in the North Kivu province—the country's 10th outbreak since the discovery of EVD in 1976 (13). Since then, the EBOV epidemic has spread in the Ituri provinces. As of 28th March 2019, a total of 1044 cases (978 confirmed and 66 probable cases) and 652 deaths (586 confirmed and 66 probable) have been reported. (**Fig 2)**

https://mailchi.mp/sante.gouv.cd/ebola_kivu_28mar19?e=2ee85af345

Clinical features of EVD

The clinical features of EVD are detailed in **table 2**. The incubation period is between 5 and 9 days with a range from 1 to 21 days. A range of clinical manifestations of EVD occur from mild to the rapidly fulminant. Early symptoms of EVD may be similar to those of other causes of fever such as malaria, dengue, Lassa fever, Marburg, Crimean Congo haemorrhagic fever, typhoid, shigellosis, rickettsial diseases, borreliosis, leptospirosis, viral hepatitis among others.

The clinical presentations of patients in the Zaire and Sudan EVD outbreaks in 1976 were similar and characterized by initial unspecific febrile syndrome followed by vomiting, diarrhoea, impaired kidney and liver functions, and internal and external bleeding (9,10). The main differences involved the case-fatality rates, with values of 88% (280 deaths/318 cases) in Zaire and 53% (151 deaths/284 cases) in Sudan, and the high frequency of chest pain (83%) and cough (49%) in Sudan (1, 9, 10). In the 2013–2016 EVD outbreak in West Africa, severe presentations of EVD included severe gastro-enteritis with dehydration (14), severe sepsis, multiple organ failure (kidneys, liver, respiratory and coagulation systems) (15-18) and shock (19-20) **(Table 2)**. Bleeding was not commonly reported. EBOV viral load is an important prognostic factor. Patients who did not survive had 10-100 fold higher viral loads at the time of hospital admission compared to survivors (21, 22). Patients who survive appear to have lower average peak viremia levels, and exhibit faster decay in viremia than those who did not survive (6). In survivors, viremia will decrease to under the limit of RT-PCR detection around 2–3 weeks after symptom's onset. The host immune response appears important in influencing the outcome of EVD. Early antibody responses to EBOV, and reduced lymphocyte depletion are associated with effective EBOV viral clearance and survival.

Clinical management of EVD

There is no specific anti-viral treatment for EVD and recovery is dependent on supportive clinical care and treatment of complications (**Table 2**). Management guidelines (23) from previous EVD outbreaks in 2013, were primarily focused on health care worker (HCW) safety and delivering treatment and care in rural areas with limited access to medical care. The management of EVD cases was based on supportive therapy with oral hydration and on the strict application of infection control measures to prevent transmission to HCWs, other patients and relatives, and to the community. High-level isolation and containment procedures hampered the implementation of standard clinical interventions for critically ill patients infected with other life-threatening pathogens in high-resources countries (24).

Management of EVD is more challenging in both urban and rural settings. Management of EVD outbreaks requires strict and early implementation of infection prevention & control measures,

assembly of multidisciplinary teams of trained staff, biocontainment units, and engagement of community leaders and community HCWs. Treating EVD patients requires understanding of risk exposure of acquiring EBOV, training in infection prevention and control measures, and ability to work in difficult field conditions of extreme heat and humidity, whilst wearing complete personal protective equipment (PPE) (19, 24-26).

In the 2013-2016 West African EVD outbreak, aggressive supportive care and antiviral therapy improved patient outcomes. It is therefore likely that the dramatic fall of CFR from around 75% in the first 2014 months to less than 40% at the end of the outbreak reflected both care enhancement and less severe case mix at presentation (27-34). This lower CFR could gradually approximate the 18.5% CFR reported among HCWs evacuated to medical facilities in the United States and Europe (30). However, despite the use of new high-level deployable infectious disease units, high aggressive therapeutic strategies, innovative antivirals and vaccines in first-line HCWs and EVD contacts in the 10th EVD outbreak in DRC, the CFR still reaches unacceptable peaks as high as the 64%.

Advanced levels of care setting in resource-limited countries

In 2014, many EVD care groups operating in the field (27-28) endorsed the need for more aggressive symptomatic treatment, early identification of severe cases and prompt treatment of dehydration and related electrolyte imbalances and organ-supporting care. Human resources and funding, combined with experience from EVD treatment of patients transported to North America and Europe, strengthened the idea of critical care provision in resource-constrained settings (30). The Italian non-governmental organization EMERGENCY delivered care sequentially at two Ebola Treatment Centres (ETC) in Sierra Leone: first at Lakka, a general hospital medical care was provided to EVD patients based on fluids, symptomatic drugs, antibiotic, and antimalarial treatment. In Goderich, a well-equipped intensive care unit (ICU), capable of providing 24 h nursing and medical assessment and support, mechanical ventilation, intravenous vasoactive medications, and renal replacement therapy was constructed to implement the first ever, dedicated ICU-ETC in Africa (31). An ETC-ICU was setup in a very short time with limited resources and highly trained and skilled personnel. Intensive supportive treatment resulted in shorter time to discharge in survivors and survival advantage in patients with intermediate-severe EVD (31). High-level optimized care appears to improve outcome needs to be promoted to overcome perceptions that EVD is always fatal. The added value and the feasibility of hemodialysis, artificial ventilation, or hemodynamic support in low-resource settings require further studies (6).

EBOV-specific treatments

The 2013-2016 EVD outbreak gave an opportunity to evaluate specific antiviral drugs, although the clinical trials evaluating favipiravir (32) and Zmapp (33) started too late towards the end of the outbreak to give any meaningful results. Most of the patients evacuated to Europe or to North America for medical treatment received investigational therapies and two thirds of them of them received at least two experimental drugs under compassionate protocol (30).

During the current 10th RDC EVD outbreak, DRC health regulatory authorities established a committee to review and recommend investigational use of therapeutics in individual patients' care under expanded access or compassionate use, based on the WHO ethical framework (monitored emergency use of unregistered and experimental interventions (MEURI), WHO 2016) until approved protocols for clinical trials are available (**Table 3)**.

Currently, five agents for compassionate use in the treatment of patients diagnosed with EVD have been approved. The monoclonal antibody MAb114 was the first agent to be approved for use; then additional biologics (REGN-EB3 and ZMapp) and the antivirals remdesivir and favipiravir completed the approval processes (34-36). For most of these agents, efficacy studies involving Ebola virus challenges in nonhuman primates have been supportive. Very few data are available on the use of investigational new drugs during the 10th RDC EVD outbreak. At the end of 2018 a WHO situation report referred that investigational agents had been administered to 38 patients — MAb114 (22 patients), remdesivir (9 patients), and ZMapp (7 patients). Nineteen of these patients had been discharged, 12 had died, and 7 had remained hospitalized; those who died were in advanced stages of disease when treatment was initiated (World Health Organization. Ebola situation reports: Democratic Republic of the Congo (http://www.who.int/ebola/situation-reports/drc-2018/en/).

High-level Deployable Infectious Disease Units

The main function of the high-level infectious disease unit is to keep high-risk patients in one strictly selected and dedicated area. There are numerous challenges with implications for both staff safety and patient care in the plastic tents commonly used as high level infectious disease units: daytime temperatures typically are high with profuse sweating even before donning PPE to enter the high-risk zone; dehydration of staff is a constant concern; putting on PPE takes up to half an hour and each team member has to be carefully checked to ensure that there are no exposed skin areas at risk for infection. Every activity within the high-risk zone is performed according to written procedures and is strictly monitored. Different solutions to address these challenges have been proposed. Particularly, during the 10th DRC outbreak, a recent advance in the field of patient care and management was the use by the Alliance for International Medical Action (ALIMA) of individual air-conditioned biosecure cubicles, Cube, (manufactured by Securotec in France, http://www.securotec.fr/) in ETC

(37). With such cubicles, HCWs can provide intravenous fluids and therapeutics through specialized ports and are thus free from the burdensome personal protective equipment used during the 2013-2016 West African outbreak and able to spend more time with their patients (37). However, the role of the cubicle strategy is mostly recognized in the early phase of an EVD outbreak or in case of EVD patients without severe clinical presentation.

EBOV Vaccines

As of December 31, 2018, 58 clinical trials on Ebola vaccine are registered on ClinicalTrials.gov: of them, 40 trials are completed, seven active and not recruiting, and seven recruiting (38). However, clinical efficacy data are only reported in the Ebola Ça Suffit vaccination trial in Guinea (39). This trial evaluated vaccine effectiveness in EVD contacts, randomised for immediate or delayed vaccination with the recombinant, replication-competent, vesicular stomatitis virus-based vaccine expressing the glycoprotein of a Zaire Ebolavirus (rVSV-ZEBOV). Authors estimated a 100% vaccine efficacy in individuals vaccinated in the immediate group compared with those eligible and randomised to the delayed group. However, on days 0–9, incident cases occurred in vaccine recipients at a similar rate to that of controls. The real magnitude of this efficacy has been widely debated, but a likely substantial protection to immediate recipients appears to be warranted (40). Vaccination related adverse events are a major concern for rVSV-ZEBOV recipients. In a Swiss cohort study, despite a significant dose vaccine reduction strategy, ten (19%) of 53 vaccine recipients experienced arthritis (41). Female gender (OR 2.2, 95%CI 1.1–4.1) and a medical history of arthritis (2.8, 1.3–6.2) were independent risk factors for the development of arthritis post vaccination (41). Soon after the announcement of the 10th EVD outbreak in DRC, the vaccination with rVSV-ZEBOV began on August 8, 2018 implementing a ring protocol strategy. A cumulative number of 92.502 people have been vaccinated as of 18 March 2019 (Ministère de la Santé, DRC, see https://mailchi.mp/sante.gouv.cd/ebola_kivu_28mar19?e=2ee85af345)

Clinical sequelae and EBOV persistence in survivors

In EVD survivors, clinical sequelae such as uveitis, arthralgia and fatigue are common and can affect up to the two thirds of survivors (42). All studies from the 2013-2016 outbreak are consistently finding no association with EBOV viral load in plasma during the acute phase. However in a single longitudinal study in Port Loko a higher EBOV viral load at presentation was independently associated with uveitis (adjusted odds ratio [aOR] 3.33, 95% CI 1.87–5.91) and with new ocular symptoms or ocular diagnoses (aOR 3.04, 95% CI 1.87–4.94) (43). However, this finding was not confirmed in following studies (44), and EBOV was not identified by RT-PCR in ocular fluid or

conjunctivae in 50 EVD survivors with ocular disease (45). Clinical and laboratory evidence suggests that pathogenesis of eye disease involves blood–ocular barrier breakdown and the potential for EBOV to persist in monocytes, macrophages and retinal pigment epithelium (46).

Persistence of EBOV in survivors

The EBOV can persist in selected body compartments of EVD survivors, most notably in semen. EBOV has been isolated from the semen of an EVD survivor on day 83 after symptom onset (47), and Ebola virus RNA has been detected in the semen of 4 of 38 (11%) survivors up to month 15, and in 1 of 25 survivors (4%) up to month 18 (48). Although the potential contribution of sexual transmission to the scale of the epidemic is largely unknown, a case report has been published on EBOV sexual transmission about 470 days after symptoms onset in a survivor from Guinea with EBOV persistence in semen up to day 531 (49). Finally, of five male-to-female events associated with EBOV transmission from survivors, one of them, with at least 4 generations of secondary cases, was reported (50). Understanding the duration of Ebola virus shedding in EVD survivors and preventing further transmission is essential for promoting infection control public health measures and for controlling the Ebola epidemic. Finally, the central nervous system might also be a reservoir for EBOV, as described in the case of a patient who developed meningoencephalitis with EBOV detection 9 months after initial recovery from acute EVD Ebola virus disease (51).

Post exposure prophylaxis

The most effective method of protecting HCWs and laboratory workers from acquiring EBOV when managing EVD patients is the implementation of strict infection control measures with use of appropriate personal protective equipment. However, even when optimal measures are taken accidental exposures to EBOV have occurred (52). In these cases post-exposure prophylaxis has been considered,

Anti-viral Drugs: Among antiviral portfolio, favipiravir has reported a weak antiviral activity against EBOV at low viral load (32). This result can preclude its efficacy as therapeutic agent but not as post-exposure prophylaxis characterized by presumed low viremia settings. Favipiravir has been used as post-exposure prophylaxis in few HCWs during the 2013-2016 West Africa outbreak with no secondary cases (53). Two of them received additional monoclonal antibody therapy. Other small-molecule inhibitors are under development, including the nucleoside analogue BCX4430 and the nucleotide analogue GS-5734, but although promising, only in vivo data are available.

Prophylactic Vaccines: Development of the rVSV-ZEBOV vaccine offered the first opportunity for use of EVD post-exposure prophylaxis (PEP). It has been used in 8 HCWs with different EBOV

exposures, 7 of them during the west African outbreak (52). However, there are few concerns on use of vaccine as PEP. Firstly, when considering the 7-10 day EBOV incubation period, vaccine-induced immunity could be insufficiently rapid to prevent the disease, but could only attenuate or delay the symptom onset. Secondly, current vaccines are specific for Zaire EBOV and might offer less or no protection against other species.

EBOV diagnostic tests

During an outbreak situation, empirical EVD diagnosis is usually made based on unspecific febrile syndrome. It is the most frequently used clinical diagnostic tool used in low-resource settings and is not discriminatory in areas with a high incidence of malaria, Lassa fever virus, Yellow fever and other arbovirus infections.

Laboratory diagnosis of EBOV infection plays a critical role in patent management and outbreak response efforts. However establishing safe and testing strategies for this high-biosafety-level pathogen in resource-poor environments remains extremely challenging.

Over the past decade three basic methods for diagnosing EBOV infection have been developed (i) Serologic tests that detect anti-EBOV antibodies, (ii) Antigen tests that detect EBOV viral proteins, and (iii) Molecular tests that detect viral RNA sequences.

There are two types of diagnostic test for Ebola. Rapid diagnostic tests detect a viral protein (54) and those based on the polymerase chain reaction (PCR) to identify the virus's genomic material (55).

Serologic testing for antiviral antibodies is generally not used since antibodies can persist for many months after recovery and antibody responses during acute illness are variable. However, EBOV antigen detection and molecular tests have proven very effective for acute diagnosis, as virus levels in the blood typically rise to high levels within the first few days of infection. Some antigen diagnostic tests are designed to broadly detect Ebola virus infection, while others distinguish among the five known EBOV species. No tests have yet demonstrated the ability to detect Ebola antigen prior to the onset of symptoms.

During recent EVD outbreaks WHO approved *in vitro* reverse transcription polymerase chain reaction (RT-PCR) diagnostic product, RealStar® Filovirus Screen RT-PCR Kit 1.0 (Altona Diagnostics GmbH), which was assessed under an emergency quality assessment mechanism established by WHO to address the lack of Ebola tests, and to fast-track countries' access to reliable testing options.

This was successfully used to diagnose EBOV infections. However, its deployment and clinical impact was limited because of the infrastructure and training required to accurately run the assay. Capillary blood samples could serve as an alternative to venous blood samples for EBOV diagnosis

by RT-PCR even in cases when venepuncture is difficult to perform -for example, with new-borns and infants or when adult patients reject venepuncture for cultural or religious reasons (56). The above reported limitations highlighted the need for portable diagnostics with ambient temperature–stable reagents that can be deployed in low-resource settings. To bridge this gap, several diagnostic platforms and assays compatible with austere environments have been designed and approved for Emergency Use Assessment and Listing procedure by WHO (57).

Currently, 14 tests for EBOV are under development and evaluation as portable point of care portable and fully automated tests. HCWs and public health groups have not been able to access them quickly due high costs and it is takes staff at laboratories or health centres two to eight weeks to get hold of the tests. Recently the DPP Ebola Antigen System (Chembio Diagnostic Systems Inc.), is used with blood specimens, including capillary "fingerstick" whole blood has been approved by the US FDA (55).

Prevention, Surveillance and Control

Early case detection and isolation: Early diagnosis and isolation of EVD patients during outbreaks is important (58). A surveillance system is essential in guiding the control measures required to reduce morbidity and mortality due to EVD (59). Control strategies during an Ebola outbreak include proactive case detection, contact tracing and management, safe and dignified burials and prevention of new infections (60, 61). . Successful contact tracing requires skills in the assessment of EVD symptoms, interviewing techniques and counselling. Persons who conduct contact tracing should have investigative skills to find and track all potential contact and the ability to analyse the evidence (62), and their success is determined by the level of trust between the community and the public health system and the quality of the diagnostic and treatment services (63).

Community engagement and education: Control strategy efforts might be improved with data on the knowledge, attitudes and practices in the EVD affected populations (64). Health communication and social mobilization efforts to improve the public's knowledge, attitudes and practices regarding EVD were important in controlling the 2013–2016 outbreak (65). The 2018-2019 outbreak in eastern DRC differed from the 2013–2016 outbreak in several ways, including multiple previous EVD outbreaks in the country, longstanding violent conflict, large numbers of internally displaced persons living in temporary camps and availability of the new rVSV-ZEBOV vaccine (64). Despite the knowledge that transmission via infected corpses was high, the 8% of Congolese people involved in the survey would wash or touch the body if a family member died of suspected EVD. It suggests that an important minority of Congolese people might also engage in high-risk burial practices (64).

During an EVD epidemic, prevention and control measures include mandatory prompt and safe burial of the dead. The burial team refer to guidelines for dignified burial of Muslim and Christian patients. A safe burial can be accomplished by a trained burial team using appropriate personal protective equipment (PPE), placing the body in a puncture- and leak-resistant plastic body bag and burying the body in a grave. Ideally, used burial team PPE should be incinerated (66).

Preventing infection in healthcare workers: Healthcare workers can be exposed to health-care related EBOV infection when caring for EVD patients. During the 2014 EVD outbreak in DRC all 8 HCWs died, whereas during the 2013-2016 West African epidemic more than 890 HCW were infected, with a case fatality rate of 57% (67). Prior to working with EVD patients, all HCWs involved in the care of EVD patients must receive training and demonstrate competency in performing all Ebola related infection control practices and procedures, specifically in proper donning and doffing PPE (68). PPE should include double gloves, gown or coverall and apron, facemask (N95 mask or powered, air-purifying respirator (PAPR), eye protection (goggles or face shield), head cover and boots. PAPR may be preferable to the N95 mask during procedures that generate aerosols of body fluids. Use of PAPR, compared to the N95 mask, is more comfortable for the HCWs, but it could increase the contamination risk (69-70).

LEGENDS TO FIGURES AND TABLES

FIGURE 1: Geographic distribution of Ebola in Africa

FIGURE 2: Distribution of EVD cases by place of residence in the 2019 Ebola DRC outbreak

TABLE 1: Occurrence and Distribution of EVD outbreaks since 1976

TABLE 2: Clinical characteristics of EVD

TABLE 3: Newer treatments for EVD

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