Ebola Virus Disease

Epidemiology, Clinical Features, Management, and Prevention

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KEYWORDS

• Ebola • Ebola virus diseases • Ebola hemorrhagic fever • Epidemiology • Diagnosis • Treatment • Prevention • Vaccines

KEY POINTS

- Ebola virus disease (EVD) is a severe zoonotic disease caused by the Ebola virus (EBOV), first discovered in 1976 near the Ebola River in the Democratic Republic of Congo.
- Bats are the most likely host reservoir of EBOV. Humans acquire infection through direct or indirect contact with blood, body fluids, and tissues.
- Human-to-human transmission of EBOV occurs via direct contact with an infected person. Sexual transmission has been described.
- Initial symptoms are nonspecific often misdiagnosed as influenza or malaria. Suspicion of EVD should prompt isolation and infection control measures.
- Outbreak control requires a multidisciplinary team effort applying case management, infection prevention and control practices, surveillance and contact tracing, good laboratory service, safe and dignified burials, social and community mobilization.

Conflicts of interest: All of the authors have an interest in global public health and emerging and reemerging infections. The authors have no other conflict of interest to declare.

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Infect Dis Clin N Am 33 (2019) 953–976
https://doi.org/10.1016/j.idc.2019.08.005
id.theclinics.com

INTRODUCTION

Ebola virus disease (EVD), also known as Ebola hemorrhagic fever or Ebola, is caused by the Ebola virus (EBOV). EBOV is a linear, nonsegmented, single negative-stranded RNA virus and is a member of the Filoviridae virus family, of which 6 species have been identified named after the region of discovery: Zaire EBOV, Bundibugyo EBOV, Sudan EBOV, Reston EBOV, Tai Forest EBOV, and Bombali EBOV. The Bundibugyo, Zaire, and Sudan EBOVs are the cause of the large outbreaks in Africa. The Zaire EBOV caused the 2014 to 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 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 of 53%. This outbreak was followed a few months later by the second outbreak of EBOV in Yambuku, Zaire (now 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 United States focused global attention on the epidemic.

Fig. 1. Geographic distribution of Ebola in Africa.

On August 1, 2018, the Ministry of Health of the 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 shows that public health and surveillance efforts remain inadequate[2] and EVD remains an important public health threat to global health security. This article highlights the epidemiology, clinical features, diagnosis, management, and prevention of EVD. It also reviews emerging field-friendly and easy-to-use point-of-care rapid diagnostic technologies, viral characterization, geospatial mapping of EVD transmission in urban and rural areas, World Health Organization (WHO) standard-of-care and advanced clinical management of patients with EVD, use of investigational new drugs and vaccines within compassionate use or phase II and III clinical trials, and a WHO draft Ebola/Marburg research and development (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 WHO proposed the use of a case definition for hemorrhagic fever using the following clinical criteria: body temperature greater than or equal to 38.3°C (101°F) for less than 3 weeks'; severe illness and no predisposing factors for hemorrhagic manifestations; and at least 2 of the following: hemorrhagic symptoms of hemorrhagic or purple rash, epistaxis, hematemesis, hemoptysis, blood in stools, or other hemorrhagic signs; and no established alternative diagnosis.[4]

In 2009, a systematic review reported that only 58% of patients with EVD in the literature met the 2009 WHO case definition.[5] During the 2013 to 2016 West African outbreak, fever was absent in at least 10% of the cases with no major hemorrhagic manifestations.[6] This clinical presentation questions previous EVD case definitions, which, including fever and hemorrhagic 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 epidemiologic 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 of usual causes of fever in the area, with at least 1 of the following signs: bloody diarrhea, bleeding from gums, bleeding into skin [purpura], bleeding into eyes and urine) with laboratory EBOV confirmation (positive immunoglobulin M antibody, positive polymerase chain reaction [PCR] or viral isolation).

EPIDEMIOLOGY OF EBOLA VIRUS DISEASE

Historical

EVD was first recognized in 1976, when 2 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 an infected person traveling between the 2 regions. However, further investigations revealed that there were 2 genetically distinct viruses: Zaire EBOV and Sudan EBOV, which came from 2 different sources and spread independently in each of the affected areas.

The first case was reported on August 22, 1976. The patient was a 42-year-old headmaster of the Yambuku Mission School, Équateur 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 hemorrhagic 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 from the first EVD-affected area. It was chosen to ensure that the Yambuku community was not stigmatized. The name is a distortion of the local Ngbandi name Legbala, meaning white water or pure water.[10]

Ebola Virus Host Reservoir

The specific host reservoir for EBOV remains unknown. After the first discovery of EBOV, studies to find the host reservoir focused on animals, insects, and plants. Ebola seems 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 rain forest. Although nonhuman primates and other mammals were implicated in the first cases of EVD, and the host reservoir is not yet confirmed, the candidate reservoir seems most likely to be African fruit bats.

Ebola Virus Disease Outbreaks in Africa Since 1976

Table 1 summarizes all EVD outbreaks recorded since the first discovery. Until the 2013 to 2016 EVD epidemic in West Africa, EVD outbreaks occurred in fairly isolated remote areas and were contained quickly. In contrast, the 2013 to 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 less than 15 years of age. A substantial portion of EBOV transmission events might have been undetected, particularly in the first phase of the 2013 to 2016 outbreak because there were cases of mild illness with minimal symptoms recorded.[11] These data bring new insight into the transmission dynamics and risk factors that underpin EBOV spillover events.

During the ninth EVD outbreak in the first 2018 semester in Équateur Province in DRC, there was a total of 54 cases with 33 deaths (case fatality ratio [CFR], 61%). A vaccination strategy was successfully applied between May and June 2018, with a total of 3481 people vaccinated, targeting frontline health care workers (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 March 28, 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 EBOLA VIRUS DISEASE

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,

Table 1
Occurrence and distribution of Ebola virus disease outbreaks since 1976

	Date	Country	Virus	Cases (N)	Deaths (N)	CFR (%)	Description	Reference
1	Jun–Nov 1976	Sudan	SUDV	284	151	53	First outbreak in Sudan: index cases were workers in a cotton factory: 37% infected workers. Many medical care personnel infected	WHO,[71] 1978
2	Aug 1976	Zaire	EBOV	318	280	88	First outbreak in DRC, ex Zaire, in Équateur province in Yambuku and surrounding areas: 38% serologically confirmed survivors	WHO,[9] 1976
3	Jun 1977	Zaire	EBOV	1	1	100	Second outbreak in DRC, ex Zaire, with no known connection with the 1976 outbreak	Heymann et al,[72] 1980
4	Aug–Sep 1979	Sudan	SUDV	34	22	65	Second outbreak at the same site as the 1976 Sudan epidemic	Baron et al,[73] 1983
5	1989	Philippine	Reston	3	0	0	High mortality in the cynomolgus macaques with 3 asymptomatic infected individuals	Miranda et al,[74] 1991
6	1990	United States	Reston	4	0	0	Linked to monkeys imported from Philippines with 4 asymptomatic infected individuals	CDC,[75] 1990
7	1994	Cote d'Ivoire	Tai Forest	4	0	0	High mortality in the chimpanzee population in the Tai Forest, with 1 recovered scientist in Switzerland	Le Guenno et al,[76] 1995
8	Dec 1994 to Feb 1995	Gabon	EBOV	52	31	60	First outbreak in Gabon in Makoku in gold-mining camps in the rain forest along the Ivindo River, initially thought to be yellow fever	Georges et al,[77] 1999

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Table 1
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	Date	Country	Virus	Cases (N)	Deaths (N)	CFR (%)	Description	Reference
9	May–Jul 1995	Zaire	EBOV	315	250	79	Third outbreak in DRC, ex Zaire, in Kikwit. Transmission was halted once PPE and other measures were used	Khan et al,[78] 1999
10	Jan–Apr 1996	Gabon	EBOV	60	45	75	Second outbreak in Gabon in the village of Mayibout and neighboring areas after eating a chimpanzee found dead	Georges et al,[77] 1999
11	Jul 1996 to Mar 1997	Gabon	EBOV	37	21	57	Third outbreak in Gabon in the Booué area with transport of patients to Libreville. The index patient was a hunter in a forest timber camp	Georges et al,[77] 1999
12	Oct 2000 to Jan 2001	Uganda	SUDV	425	224	53	First outbreak in Uganda, in the Gulu, Masindi, and Mbarara districts. Three main risk factors: attending funerals, having contact with affected patients, and providing medical care without PPE	Okware et al,[79] 2002
13	Oct 2001 to Jul 2002	Gabon, Republic of Congo	EBOV	124	96	77	Occurred on both sides of the border between Gabon (fourth outbreak) and the RC; first outbreak). Abnormal number of animals found dead in Gabon	WHO et al,[80] 2003
14	Dec 2002 to Apr 2003	Republic of Congo	EBOV	143	128	90	Second outbreak in RC in of Mbomo and Kéllé districts in the Cuvette Ouest Department	Formenty et al,[81] 2003

15	Nov–Dec 2003	Republic of Congo	EBOV	35	29	83	Third outbreak in RC in Mbomo villages	WHO,[82] 2004
16	Apr–Jun 2004	Sudan	SUDV	17	7	41	Third outbreak in Yambio county concurrent with an outbreak of measles	WHO,[83] 2005
17	April 2005	Republic of Congo	EBOV	12	10	83	Fourth outbreak in RC in Etoumbi medical centers: most cases among hunters, caregivers, or funeral attendees	—
18	Aug–Nov 2007	DRC	EBOV	264	187	71	Fourth outbreak in DRC in the Kasai-Occidental province	WHO,[84] 2007
19	Dec 2007 to Jan 2008	Uganda	BDBV	149	37	25	Second outbreak in Uganda in the Bundibungyo district; this was the first identification of the BDBV	MacNeil et al,[85] 2011
20	Dec 2008 to Feb 2009	DRC	EBOV	32	15	47	Fifth outbreak in DRC in the Mweka and Luebo health zones in the Kasai-Occidental province	WHO,[86] 2009
21	May 2011	Uganda	SUDV	1	1	100	Third outbreak in Uganda in the Luwero district	Shoemaker et al,[87] 2012
22	Jun–Aug 2012	Uganda	SUDV	17	7	41	Fourth and fifth outbreaks in Uganda in 2 sites: Luwero, Jinja, and Nakasongola districts, and Orientale province	Albarino et al,[87] 2013

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Table 1
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	Date	Country	Virus	Cases (N)	Deaths (N)	CFR (%)	Description	Reference
23	Jun–Nov 2012	DRC	BDBV	35	13	36	Sixth outbreak in DRC in the Orientale province. No epidemiologic link with 2012 outbreak in Uganda	Albarino et al,[88] 2013
24	Dec 2013 to Jan 2016	West Africa, mainly Liberia, Sierra Leone, and Guinea Conakry	EBOV	28,616	11,310	39	The largest Ebola outbreak in terms of human patients, fatalities, and multiple-site involvement in different countries in both urban and rural settings. It began in Guéckédou, Guinea, in December 2013	Baize et al.[89] 2014
25	Aug–Nov 2014	DRC	EBOV	66	49	74	Seventh outbreak in DRC in Équateur province	Maganga et al,[90] 2014
26	May 2017	DRC	EBOV	8	4	50	Eighth outbreak in DRC in the Likati health zone in Bas-Uélé province close to central African Republic	Nsio et al,[99] 2019
27	May–Jul 2018	DRC	EBOV	54	33	61	Ninth outbreak in DRC in the north-western towns of Bikoro and Mbandaka in Équateur province. VSV-ZEBOV vaccine has been used to contain the outbreak	Ebola outbreak team,[91] 2018
28	August 2018 to present	DRC	EBOV	3099	2074	66.9 ongoing	10th outbreak in DRC started on August 1, 2018: the second largest outbreak in North Kivu and, as of March 1, 2019, it is still ongoing	WHO, 2019[100]

Abbreviations: BDBV, Bundibungyo virus; CDC, US Centers for Disease Control and Prevention; CFR, case fatality ratio; PPE, personal protective equipment; RC, Republic of the Congo; SUDV, Sudan EBOV; VSV-ZEBOV, vesicular stomatitis virus–Zaire EBOV.

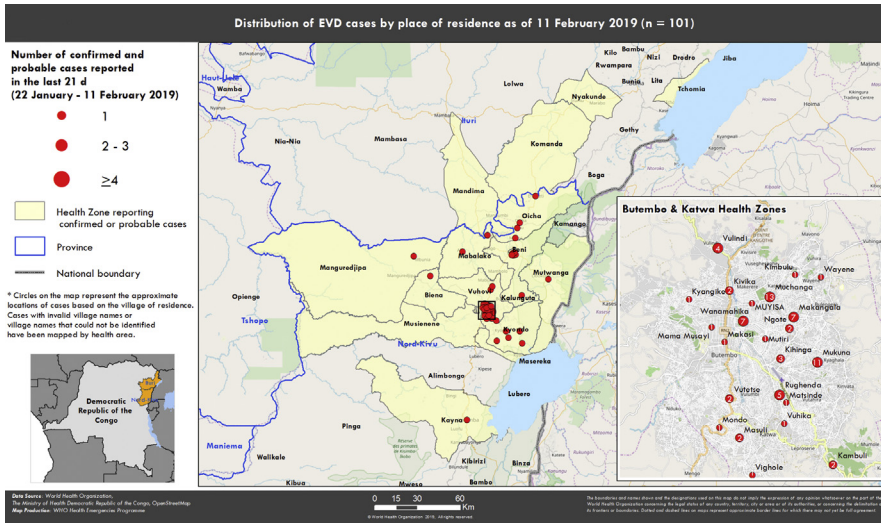

Fig. 2. Distribution of EVD cases by place of residence in the 2019 Ebola DRC outbreak. (*Courtesy of* the World Health Organization, Geneva, Switzerland, https://www.who.int/csr/don/08-august-2019-ebola-drc/en/ ; with permission.)

Crimean Congo hemorrhagic fever, typhoid, shigellosis, rickettsial diseases, borreliosis, leptospirosis, and viral hepatitis.

The clinical presentations of patients in the Zaire and Sudan EVD outbreaks in 1976 were similar and were characterized by initial unspecific febrile syndrome followed by vomiting, diarrhea, 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 from 318 cases) in Zaire and 53% (151 deaths from 284 cases) in Sudan, and the high frequency of chest pain (83%) and cough (49%) in Sudan.[1,9,10] In the 2013 to 2016 EVD outbreak in West Africa, severe presentations of EVD included severe gastroenteritis with dehydration,[14] severe sepsis, multiple organ failure (kidneys, liver, respiratory and coagulation systems),[15–18] and shock[19,20] (see **Table 2**). Bleeding was not commonly reported. EBOV viral load is an important prognostic factor. Patients who did not survive had 10-fold to 100-fold higher viral loads at the time of hospital admission compared with survivors.[21,22] Patients who survive seem to have lower average peak viremia levels, and show faster decay in viremia than those who did not survive.[6] In survivors, viremia decreases to less than the limit of reverse transcription (RT) PCR detection around 2 to 3 weeks after symptom's onset. The host immune response seems 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 EBOLA VIRUS DISEASE

There is no specific antiviral treatment of EVD, and recovery depends on supportive clinical care and treatment of complications (see **Table 2**). Management guidelines[23] from previous EVD outbreaks in 2013 were primarily focused on HCW safety and delivering treatment and care in rural areas with limited access to medical care. The management of patients with EVD was based on supportive therapy with oral hydration

Table 2
Clinical characteristics of Ebola virus disease

Phase of EVD	Duration	Clinical Disease Progression	Symptoms	Clinical Features	Treatment
Prodromal phase	1–3 d, following an incubation period of 5–9 d (range: 1–21 d)	Nonspecific febrile syndrome	Sudden onset of fever, tiredness, headaches, sore throat, muscular pain, weakness, loss of appetite, skin rash, cough	Feverish (<38°C) or remittent fever, lethargy, myalgia	Antipyretics, oral hydration
Systemic involvement	3–10 d	Gastrointestinal, liver, adrenal, pancreatic, and kidney involvement	Persistent fever, tiredness, abdominal pain, nausea, vomiting, profuse watery diarrhea, bruising and bleeding from gums Agitation and irritability	High temperature with pulse-temperature dissociation (relative bradycardia), progressive drowsiness, partial response to simple orders Patients unable to take care of themselves and may require intensive care Bleeding from gums and stools Hepatomegaly, splenomegaly Hematuria, proteinuria Low white cell count (lymphopenia), low platelet count, and abnormal liver and renal function tests. Both ALT and AST levels are increased (AST increases more than ALT) Urgent tests: malaria, Ebola RT-PCR, full blood count, serum creatinine and urea, liver function tests, arterial blood gases, coagulation studies, blood cultures	Early detection of systemic involvement and isolation with strict infection control measures. Use of PPE Instituting best supportive care measures Antipyretics, oral and aggressive intravenous hydration, antimalarials, antibiotics EBOV-specific therapy: Zmapp or REGN-1EB3 or mAb11
	—	Neurologic involvement	Persistent high temperature with confusion, panic, seizures, hallucinations, agitation, and irritability Reduced or no response to simple orders with advancing disease	Deep prostration, mood alterations, rarely seizures, coma Completely dependent on caregivers in the community and acute/critical care setting in hospitals	Antipyretics, aggressive intravenous hydration, antimalarials, antibiotics with good CNS penetration EBOV-specific therapy: Zmapp or REGN-1EB3 or mAb11 plus remdesivir

Multiorgan failure (25%–90% mortality)	7–16 d	Systemic involvement	Nonresponsive and comatose, no response to simple orders. Bleeding from all mucous membranes and all orifices Hiccups (sign of terminal illness)	Hypovolemic, severe sepsis or septic shock, acute renal insufficiency	Intensive care with circulatory/ hemodynamic and ventilatory support, renal dialysis, transfusions EBOV-specific therapy: Zmapp or REGN-1EB3 or mAb11 plus remdesivir
		Adult respiratory distress syndrome	Shortness and rapid breathing, cough, chest pain, and bluish skin coloration	Severe dyspnea at rest, central and peripheral cyanosis, drowsiness, jaundice	All previous therapy plus noninvasive or invasive mechanical ventilation

See **Table 3** for details on specific treatment of Ebola viral disease.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; RT-PCR, reverse transcription polymerase chain reaction; CNS, central nervous system.

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 and control measures, assembly of multidisciplinary teams of trained staff, biocontainment units, and engagement of community leaders and community HCWs. Treating patients with EVD 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 while wearing complete personal protective equipment (PPE).[19,24–26]

In the 2013 to 2016 West African EVD outbreak, aggressive supportive care and antiviral therapy improved patient outcomes. It is therefore likely that the dramatic decrease 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, highly aggressive therapeutic strategies, and innovative antivirals and vaccines in first-line HCWs and EVD contacts in the 10th EVD outbreak in DRC, the CFR still reaches unacceptable levels (as high as 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 nongovernmental organization EMERGENCY delivered care sequentially at 2 Ebola treatment centers (ETCs) in Sierra Leone: the first at Lakka, where general hospital medical care was provided to patients with EVD based on fluids, symptomatic drugs, antibiotics, and antimalarial treatment. In Goderich, a well-equipped intensive care unit (ICU), capable of providing 24-hour 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 set up 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 seems to improve outcomes and 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]

EBOLA VIRUS–SPECIFIC TREATMENTS

The 2013 to 2016 EVD outbreak gave an opportunity to evaluate specific antiviral drugs, although the clinical trials evaluating favipiravir[32] and Zmapp[33] started too late in 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 received at least 2 experimental drugs under compassionate protocol.[30]

During the current 10th DRC EVD outbreak, DRC health regulatory authorities established a committee to review and recommend investigational use of therapeutics in individual patient's 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**).

At present, 5 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 EBOV challenges in nonhuman primates have been supportive. Very few data are available on the use of investigational new drugs during the 10th DRC EVD outbreak. At the end of 2018, a WHO situation report stated 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 (WHO. Ebola situation reports: DRC; 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 1 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 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 ETCs.[37] With such cubicles, HCWs can provide intravenous fluids and therapeutics through specialized ports and are thus free from the burdensome PPE used during the 2013 to 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 patients with EVD without severe clinical presentations.

EBOLA VIRUS VACCINES

As of December 31, 2018, 58 clinical trials on Ebola vaccine are registered on ClinicalTrials.gov: of them, 40 trials are completed, 7 are active and not recruiting, and 7 are 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, randomized for immediate or delayed vaccination with the recombinant, replication-competent, vesicular stomatitis virus–based vaccine expressing the glycoprotein of a Zaire EBOV (rVSV-ZEBOV). Investigators estimated a 100% vaccine efficacy in individuals vaccinated in the immediate group compared with those

Table 3
Newer treatments for Ebola virus disease

Ebola Treatment	Mode of Action	Protection	Human Use	EVD Clinical Phase	Drug Company	Web Site	Bibliography
Convale -scence sera	Human serum obtained from EVD survivors	Ebola NtAb titer increases in survivors compared with deceased patients; also in vitro data	Used since the KiKwit outbreak but no efficacy in 2016 clinical trial	Phase III	NA	http://www.who.int/bloodproducts/brn/brn_positionpaperconvplasmafiloviruses_finalweb14august2014.pdf	Van Griensven et al,[92,93] 2016
Zmapp[a]	Human/mouse chimeric triple monoclonal antibody mixture (c13C6, h-13F6, and c6D8) produced on cellular lines obtained from tobacco plants	Postexposure protection in NHP up to day 5	It seems beneficial but no significant efficacy in PREVAIL trial	Phase II	Mapp Biopharma-ceuticals	www.mappbio.com	Qiu et al,[94] 2014; PREVAIL II Writing Group; Multi-National PREVAIL II Study Team,[33] 2016
REGN-1EB3	Specific anti- EBOV triple antibody mixture by immunizing VelocImmune mice	Postexposure protection by IV single dose in NHP up to day 5	Anecdotal use	Phase I–II	Regeneron	https://www.regeneron.com/perspectives/making-ebola-drug	Pascal et al,[95] 2018

mAb114	Single human monoclonal antibody identified from a survivor of the 1995 Kikwit outbreak, approximately 11 y after infection	Postexposure protection by IV single dose in NHP	Anecdotal use. Safe and well tolerated in humans	Phase I	Ridgeback Biothera-peutics by US NIAID license	http://www.ridgebackcap.com	Corti et al,[36] 2016; Gaudinski et al,[96] 2019
Remdesivir, GS-5734,	A monophosphoramidate prodrug of adenosine analogues, inhibits EBOV RNA-dependent RNA polymerase	Postexposure protection by IV infusion in all NHP at day 3–15	Anecdotal use and use in survivors with viral persistence in semen	Phase II	Gilead Sciences	www.gilead.com/science-and-medicine/pipeline	Warren et al,[97] 2016; Jacobs et al,[51] 2016
Favipiravir, T-705	Influenza viral RNA polymerase inhibitor, could share antiviral activity against other RNA viruses such as Ebola	Postexposure protection in laboratory mouse up to day 6	Stockpile available, limited efficacy in low to moderate viremia, well tolerated	Phase III	MediVector per Fujifilm	http://www.medivector.com/	Furuta et al,[98] 2013; Sissoko et al,[32] 2016

Abbreviations: IV, intravenous; NA, not available; NHP, non-human primate; NIAID, National Institute of Allergy and Infectious Diseases; NtAb, neutralizing antibody.

[a] In a few anecdotal cases, ZMab (a murine monoclonal Ab mixture) and Mil 77 (a monoclonal antibody produced by MabWorks in China) was used in the 2013 to 2016 outbreak.

The preliminary data of the WHO/NIAID/INRB multi-drug randomized control trial (PALM study) to evaluate the safety and efficacy of four drugs (ZMapp, remdesivir, mAb114 and REGN-EB3) used for treatment of Ebola patients in the Democratic Republic of the Congo (DRC) have been released on August 12, 2019. The data and safety monitoring board (DSMB) recommended that the study be stopped and that all future patients be randomized to receive either REGN-EB3 or mAb114 in what is being considered an extension phase of the study. This recommendation was based on the fact that an early stopping criterion in the protocol had been met by one of the products, REGN-EB3. The preliminary results in 499 study participants indicated that individuals receiving REGN-EB3 or mAb114 had a greater chance of survival compared to participants in the other two arms.[101]

The reported mortality was 49% in patients receiving ZMapp, 53% in those who received remdesivir, 34%, in the group that received mAb114, 29% in those on REGN-EB3. In the patients who sought treatment early after infection and had lower viremia the mortality was 6% in the Regeneron antibody group and 11% with mAb114, versus 24% and 33% in patients treated with ZMapp and remdesivir respectively.[102]

eligible and randomized to the delayed group. However, on days 0 to 9, incident cases occurred in vaccine recipients at a similar rate to that in controls. The magnitude of this efficacy has been widely debated, but a likely substantial protection to immediate recipients seems 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, 10 (19%) of 53 vaccine recipients experienced arthritis.[41] Female gender (odds ratio [OR], 2.2, 95% confidence interval [CI], 1.1–4.1) and a medical history of arthritis (OR, 2.8; 95% CI, 1.3–6.2) were independent risk factors for the development of arthritis after vaccination.[41] Soon after the announcement of the 10th EVD outbreak in DRC, vaccination with rVSV-ZEBOV began on August 8, 2018, implementing a ring protocol strategy. A cumulative total of 92,502 people have been vaccinated as of March 18, 2019 (Ministère de la Santé, DRC; see https://mailchi.mp/sante.gouv.cd/ebola_kivu_28mar19?e=2ee85af345).

CLINICAL SEQUELAE AND EBOLA VIRUS 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 to 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 OR [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 subsequent 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 EBOLA VIRUS 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 EBOV 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] In addition, of 5 male-to-female events associated with EBOV transmission from survivors, 1 of them, with at least 4 generations of secondary cases, was reported.[50] Understanding the duration of EBOV shedding in EVD survivors and preventing further transmission is essential for promoting infection control public health measures and for controlling the Ebola epidemic. In addition, 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.[51]

POSTEXPOSURE PROPHYLAXIS

The most effective method of protecting HCWs and laboratory workers from acquiring EBOV when managing patients with EVD is the implementation of strict infection control measures with the use of appropriate PPE. However, even when optimal measures are taken, accidental exposures to EBOV have occurred.[52] In these cases, postexposure prophylaxis has been considered.

Antiviral Drugs

In the antiviral portfolio, favipiravir is reported to have a weak antiviral activity against EBOV at low viral load.[32] This result can preclude its efficacy as a therapeutic agent but not as postexposure prophylaxis characterized by presumed low viremia settings. Favipiravir was used as postexposure prophylaxis in few HCWs during the 2013 to 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 postexposure prophylaxis. It has been used in 8 HCWs with different EBOV exposures, 7 of them during the West African outbreak.[52] However, there are a few concerns about the use of vaccines as postexposure prophylaxis. First, when considering the 7-day to 10-day EBOV incubation period, vaccine-induced immunity could be insufficiently rapid to prevent the disease, and might only attenuate or delay the symptom onset. Second, current vaccines are specific for Zaire EBOV and might offer less or no protection against other species.

EBOLA VIRUS DIAGNOSTIC TESTS

During an outbreak, empiric 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 testing strategies for this high-biosafety-level pathogen in resource-poor environments remains extremely challenging.

Over the past decade, 3 basic methods for diagnosing EBOV infection have been developed: (1) serologic tests that detect anti-EBOV antibodies, (2) antigen tests that detect EBOV viral proteins, and (3) molecular tests that detect viral RNA sequences.

There are 2 types of diagnostic test for Ebola. Rapid diagnostic tests detect a viral protein[54] and those based on PCR identify the virus's genomic material.[55]

Serologic testing for antiviral antibodies is generally not used because antibodies can persist for many months after recovery, and antibody responses during acute illness are variable. However, EBOV antigen detection and molecular tests have proved very effective for acute diagnosis, because virus levels in the blood typically increase to high levels within the first few days of infection. Some antigen diagnostic tests are designed to broadly detect EBOV infection, whereas others distinguish among the 5 known EBOV species. No tests have yet shown the ability to detect Ebola antigen before the onset of symptoms.

During recent EVD outbreaks, the WHO approved an in vitro 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 the WHO to address the lack of Ebola tests, and to fast track countries' access to reliable testing options.

This product was successfully used to diagnose EBOV infections. However, its deployment and clinical impact were 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 in which venipuncture is difficult to perform; for example, with newborns and infants or when adult patients reject venipuncture for cultural or religious reasons.[56] These limitations highlight 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 as Emergency Use Assessment and Listing procedures by the WHO.[57]

At present, 14 tests for EBOV are under development and evaluation as point-of-care portable and fully automated tests. HCWs and public health groups have not been able to access them quickly because of high costs and it takes staff at laboratories or health centers 2 to 8 weeks to obtain the tests. The recently developed DPP Ebola Antigen System (Chembio Diagnostic Systems Inc.) is used with blood specimens, including capillary fingerstick whole blood, and has been approved by the US Food and Drug Administration.[55]

PREVENTION, SURVEILLANCE, AND CONTROL

Early Case Detection and Isolation

Early case diagnosis and isolation of patients with EVD during outbreaks is important.[58] A surveillance system is essential in guiding the control measures required to reduce morbidity and mortality caused by 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 counseling. Persons who conduct contact tracing should have investigative skills to find and track all potential contacts and the ability to analyze 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 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 to 2016 outbreak.[65] The 2018 to 2019 outbreak in eastern DRC differed from the 2013 to 2016 outbreak in several ways, including multiple previous EVD outbreaks in the country, long-standing 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, 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 PPE, placing the body in a puncture-resistant 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 Health Care Workers

HCWs can be exposed to health care–related EBOV infection when caring for patients with EVD. During the 2014 EVD outbreak in DRC, all 8 HCWs died, whereas during the

2013 to 2016 West African epidemic more than 890 HCWs were infected, with a case fatality rate of 57%.[67] Before working with patients with EVD, all HCWs involved in the care of patients with EVD must receive training and show 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 with the N95 mask, is more comfortable for the HCWs, but it could increase the contamination risk.[69,70]

ACKNOWLEDGMENTS

This study was supported by the Italian Ministry of Health. E. Nicastri, F. Vairo, C. Montaldo, and G. Ippolito acknowledge support from the Italian Ministry of Health, grants to Ricerca Corrente linea 1 to National Institute for Infectious Diseases Lazzaro Spallanzani, IRCCS. L. Mboera, R. Ansumana, F. Vairo, C. Montaldo, A. Zumla, and G. Ippolito acknowledge support from the PANDORA-ID-NET Consortium, which is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP2) programme (EDCTP Grant RIA2016E-1609), which is supported under Horizon 2020, the European Union's Framework Programme for Research and Innovation. E. Nicastri, F. Vairo, and G. Ippolito are Professors at Saint Camillus International University of Health and Medical Sciences in Rome.

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