

Ebola Disease: An Updated Review in the Context of the 2026 Bundibugyo Virus Outbreak

Ebola Hastalığı: 2026 Bundibugyo virüsü Salgını Eşliğinde Güncel Bir Değerlendirme

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Abstract

Ebola disease (EBOD) is a severe viral illness with a high mortality rate caused by viruses of the genus *Orthoebolavirus* within the family *Filoviridae*. The emergence of a new outbreak caused by Bundibugyo virus (BDBV) in Ituri Province of the Democratic Republic of the Congo on May 15, 2026, along with the detection of cross-border cases in Uganda, has once again underscored the global public health significance of EBOD. This review provides a comprehensive overview of the current terminology and classification, pathogenesis, modes of transmission, clinical and laboratory findings, diagnostic methods, case definitions, treatment approaches, Infection prevention and control (IPC) measures, contact tracing, vaccination strategies, and long-term sequelae associated with EBOD. Currently licensed vaccines and monoclonal antibody therapies are approved only for *Orthoebolavirus zairense*, limiting treatment options during BDBV outbreaks. Accelerating the development of pan-filovirus vaccines and therapeutics, strengthening early diagnostic capacity, and improving IPC infrastructure remain key priorities.

Keywords: Ebola disease, Bundibugyo virus, *Orthoebolavirus*, filovirus, outbreak

Öz

Ebola hastalığı (EBOD), *Filoviridae* ailesine ait *Orthoebolavirus* türlerinin neden olduğu, yüksek mortaliteli ağır seyirli viral bir hastalıktır. 15 Mayıs 2026'da Demokratik Kongo Cumhuriyeti'nin Ituri Eyaleti'nde Bundibugyo virüsüne (BDBV) bağlı yeni bir salgının başlaması ve Uganda'da sınır ötesi olgular saptanması, EBOD'un küresel halk sağlığı güncelliğini yeniden ön plana taşımıştır. Bu derleme; EBOD'un güncel terminoloji ve sınıflandırması, patogenezi, bulaş yolları, klinik ve laboratuvar bulguları, tanı testleri, vaka tanımları, tedavi yaklaşımları, enfeksiyon önlem ve kontrolü, temaslı takibi, aşılama stratejileri ile uzun dönem sekeller konularını kapsamlı biçimde ele almaktadır. Mevcut lisanslı aşı ve monoklonal antikor tedavilerinin yalnızca *Orthoebolavirus zairense* için onaylı olması, BDBV kaynaklı salgınlarda tedavi seçeneklerini kısıtlamaktadır. Pan-filovirüs tedavi ve aşı geliştirme çalışmalarının hızlandırılması, erken tanı kapasitesinin güçlendirilmesi ve enfeksiyon kontrol altyapısının iyileştirilmesi öncelikli hedefler olmaya devam etmektedir.

Anahtar Kelimeler: Ebola hastalığı, Bundibugyo virüsü, *Orthoebolavirus*, filovirüs, salgın



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Introduction

Definition, Classification, and Current Terminology

Ebola disease (EBOD) is a severe viral illness caused by viruses of the genus *Orthoebolavirus* within the family *Filoviridae*. Under the current classification, the principal *Orthoebolavirus* species known to cause human disease include Ebola virus (*Orthoebolavirus zairense*, EBOV), Sudan virus (*Orthoebolavirus sudanense*, SUDV), Bundibugyo virus (*Orthoebolavirus bundibugyoense*, BDBV), and Tai Forest virus (*Orthoebolavirus taiense*, TAFV). The diseases caused by these viruses are designated Ebola virus disease (EVD), Sudan virus disease (SVD), Bundibugyo virus disease (BVD), and Tai Forest virus disease, respectively. Thus, the term “Ebola disease” is used as a broad designation for diseases caused by different *Orthoebolavirus* species^[1,2].

History and Epidemiology

EBOD was first recognized in 1976 during simultaneous outbreaks in present-day South Sudan and the Democratic Republic of the Congo (DRC), caused by SUDV and EBOV, respectively. Subsequent outbreaks occurred predominantly in Central and East Africa, particularly in the DRC, Uganda, Gabon, and Sudan. Although the magnitude and mortality of outbreaks have varied according to viral species and epidemiological context, EBOV outbreaks have generally been associated with higher case-fatality rates.

The 2014-2016 West African outbreak, initially reported in Guinea and subsequently spreading to Liberia and Sierra Leone, remains the largest EVD outbreak recorded to date, with more than 28,000 cases and 11,308 deaths. Limited healthcare capacity, inadequate surveillance systems, deficiencies in infection prevention and control (IPC), urban transmission, and extensive population mobility contributed to its rapid expansion. Travel-associated cases identified in Africa, Europe, and North America further underscored the potential for international dissemination of the disease.

Recurrent outbreaks have continued, particularly in the DRC, including the 2018-2020 outbreak, which resulted in 3,470 cases and 2,287 deaths. The 2022 outbreak in Uganda further underscored the persistent public health significance of SUDV^[3-5].

Mortality varies according to the causative viral species, access to healthcare, and the epidemiological and clinical characteristics of individual outbreaks. Comparative epidemiological characteristics, pooled case-fatality rates, and currently available vaccines and therapeutic options for EBOV, SUDV, and BDBV are summarized in Table 1.

Overall mortality was 61.3% among patients treated in sub-Saharan Africa, compared with 24.5% among those treated outside sub-Saharan Africa^[6]. Epidemiological risk is also shaped by the social context in which exposure occurs. Differences in exposure risk by sex and age appear to reflect social roles and caregiving responsibilities rather than established biological differences in susceptibility^[20].

Environmental Drivers and One Health Perspective

Environmental and social changes may influence both the risk of zoonotic spillover and the subsequent geographic spread of EBOD outbreaks. Changes in land use, including deforestation and other forms of forest conversion, may modify human-wildlife interfaces and increase opportunities for contact with potential animal reservoirs. A spatial analysis of 27 Ebola outbreak sites and 280 control locations in Central and West Africa found that outbreak occurrence near the margins of the rainforest biome was associated with dense forest loss during the preceding 2 years. However, this observational association does not demonstrate that forest loss alone causes EBOD outbreaks, and the mechanisms connecting environmental change, human-wildlife contact, and zoonotic spillover remain incompletely understood^[21].

Following a spillover event, transport connectivity and population mobility may facilitate geographic dissemination by connecting remote outbreak locations with other settlements and population centers. An analysis of EBOV outbreaks found that the extent of road and river networks surrounding spillover sites was significantly associated with the number of cases recorded during the first 100 days of an outbreak^[22]. The 2014-2016 West African epidemic further demonstrated how introduction into capital cities, extensive population mobility, and cross-border movement, coupled with weak surveillance, inadequate IPC, and strained healthcare systems, can facilitate sustained transmission and international spread^[3-5]. However, the infrastructure analysis did not incorporate indicators of population density, settlement size, or urban-rural status and therefore did not directly assess urbanization as an independent determinant of outbreak spread^[22]. Moreover, because the analysis included only EBOV outbreaks, these findings should be extrapolated cautiously to outbreaks caused by other *Orthoebolavirus* species.

Taken together, these findings support a One Health approach that integrates human disease surveillance with animal and environmental monitoring while fostering coordination among public health, veterinary, wildlife, and environmental authorities. Incorporating land-use and population-connectivity data into this multisectoral framework may improve assessment of spillover risk, facilitate early outbreak detection, and strengthen preparedness. Nevertheless,

Table 1. Comparative epidemiological characteristics and preventive and therapeutic options for EBOV, SUDV, and BDBV.

Characteristic	EBOV	SUDV	BDBV
Taxonomic designation and associated disease	Ebola virus (<i>Orthoebolavirus zairense</i>); Ebola virus disease (EVD)	Sudan virus (<i>Orthoebolavirus sudanense</i>); Sudan virus disease (SVD)	Bundibugyo virus (<i>Orthoebolavirus bundibugyoense</i>); Bundibugyo virus disease (BVD)
First recognized outbreak	1976, Yambuku, present-day DRC	1976, Nzara, present-day South Sudan	2007, Bundibugyo District, Uganda
Principal epidemiological pattern	Recurrent outbreaks mainly in Central Africa; responsible for the 2014-2016 West African epidemic and the 2018-2020 DRC outbreak	Outbreaks reported predominantly in Uganda and present-day South Sudan, including major outbreaks in Uganda in 2000 and 2022	Historically associated with outbreaks in Uganda and the DRC; responsible for the evolving 2026 outbreak in the DRC with cross-border cases detected in Uganda
Pooled case-fatality rate, 1976-2022 ^[6]	66.6%	48.5%	32.8%
Licensed or authorized vaccine availability	ERVEBO® is the only currently licensed and World Health Organization (WHO)-prequalified vaccine for EVD caused by EBOV. The former EU marketing authorization for the Ad26.ZEBOV/MVA-BN-Filo regimen (Zabdeno/Mvabea) was withdrawn in May 2026 for commercial reasons ^[7,8]	No licensed vaccine; candidate vaccines have undergone clinical evaluation	No licensed vaccine; candidate vaccine platforms are undergoing accelerated development and have been prioritized for clinical evaluation, but human efficacy has not been established
Licensed specific therapeutic options	Ansuvimab (mAb114; Ebanga™) and REGN-EB3 (Inmazeb™), supported by randomized human clinical trial evidence ^[9-11]	No licensed therapy with demonstrated clinical efficacy ^[12]	No licensed therapy with demonstrated clinical efficacy
Principal investigational therapeutic approaches	Broadly neutralizing and pan-filovirus antibodies and broad-spectrum antiviral combinations remain under investigation	Pan-ebolavirus monoclonal antibody therapy with MBP134/MBP431, alone or in combination with remdesivir, has demonstrated protection in non-human primate models ^[13,14]	The PARTNERS trial evaluates MBP134 and remdesivir, alone and in combination; maftivimab has also been prioritized for evaluation, and obeldesivir is being studied as post-exposure prophylaxis ^[12,15,16]
Current level of species-specific therapeutic evidence	Randomized human efficacy data are available for EBOV-specific monoclonal antibodies	Evidence remains predominantly preclinical; human efficacy has not been established	Human clinical trials are ongoing, but efficacy results are not yet available
Reported replication and disease kinetics	Faster <i>in vitro</i> replication and higher peak viral titers than BDBV; a shorter interval from symptom onset to death has been reported in available comparative data ^[17,18]	Direct comparative evidence remains limited	Slower <i>in vitro</i> replication, lower peak viral titers, and a longer interval from symptom onset to death than EBOV have been reported; however, species-specific human data remain limited ^[17,18]
Experimental susceptibility to remdesivir	<i>In vitro</i> activity is present, but monotherapy did not improve outcomes in the PALM trial ^[17,19]	Remdesivir-based combination therapy has shown protection in non-human primate models ^[14]	Greater <i>in vitro</i> inhibitory activity of remdesivir against BDBV than EBOV has been reported in experimental systems; this finding does not establish clinical efficacy ^[17]

Optimized supportive care remains the cornerstone of management for all three diseases. Pooled case-fatality rates represent estimates across outbreaks and should not be interpreted as fixed measures of intrinsic viral virulence, because outcomes are also influenced by outbreak setting, surveillance capacity, timing of diagnosis, and access to supportive care. Vaccine and therapeutic availability is reported as of July 2026. Investigational interventions should not be considered clinically effective until supported by appropriate human efficacy data. Experimental differences in replication kinetics and antiviral susceptibility should not be interpreted as direct measures of clinical virulence or treatment efficacy. Some comparisons are based on *in vitro*, minigenome, or animal model data, and direct species-to-species human evidence remains limited.

BDBV, Bundibugyo virus; BVD, Bundibugyo virus disease; DRC, Democratic Republic of the Congo; EBOV, Ebola virus; EVD, Ebola virus disease; SUDV, Sudan virus; SVD, Sudan virus disease.

evidence linking specific environmental and social drivers to Ebola emergence remains predominantly observational, and causal relationships have not been definitively established^[23].

The 2026 BVD Outbreak: Epidemiological Characteristics, Public Health Response, and Lessons Learned

On May 15, 2026, an outbreak of BVD was declared in Ituri Province in northeastern DRC, and outbreak-associated cases were subsequently identified in Uganda. As of July 21, 2026, the DRC had reported 2,536 laboratory-confirmed cases and 1,033 deaths among confirmed cases across Ituri, North Kivu, South Kivu, Haut-Uele, and Tshopo provinces. Uganda had reported 20 confirmed cases, including 2 deaths, and 1 probable case resulting in death. Fifteen confirmed infections were imported from the DRC, whereas 5 resulted from secondary transmission among contacts and healthcare workers. No sustained community transmission had been documented, and the most recent confirmed case in Uganda was identified on June 21, 2026. An imported case was also reported in France; the patient subsequently recovered, and no secondary transmission was detected. Because case investigations, laboratory confirmation, and data harmonization were ongoing, these reported figures should be considered provisional^[24-27].

Reported cases accumulated considerably faster than during previous major EBOD outbreaks. By mid-July, the World Health Organization (WHO) had characterized the event as the third-largest Ebola outbreak on record and reported that approximately 2,000 confirmed cases had been identified within about 2 months, whereas the 2018-2019 outbreak in the DRC required more than 10 months to reach a comparable case count. Nevertheless, the epidemic curve should be interpreted cautiously. The rapid increase in cumulative case counts may not reflect transmission occurring exclusively during the same period, because intensified case finding, expanded access to laboratory testing, and retrospective analysis of previously collected specimens may have incorporated earlier infections into the surveillance dataset. Ituri remained the principal epicenter, although the detection of cases across five provinces demonstrated the potential for continued national and regional spread^[15,26].

The response has unfolded in a complex setting in which multiple operational challenges have compounded one another. Armed conflict, population displacement, and restricted access to affected communities have coincided with limitations in healthcare services, laboratory capacity, IPC resources, and referral systems. Community mistrust, misinformation, and security incidents involving healthcare facilities and personnel have further disrupted surveillance and response activities. As of July 15, 2026, 119 confirmed infections, including 36 deaths, had been reported among

healthcare workers in the DRC. This substantial occupational burden indicates ongoing exposure in both healthcare and community settings and highlights gaps in the consistent implementation of IPC measures. Collectively, these conditions may delay case recognition, disrupt contact follow-up, compromise safe referral and clinical care, and allow transmission chains to remain undetected^[26].

On May 17, 2026, the WHO Director-General determined that the outbreak constituted a Public Health Emergency of International Concern under the International Health Regulations. The decision emphasized the need for coordinated international action in response to rapid geographic expansion, documented cross-border transmission, and continuing epidemiological uncertainty. The absence of licensed BDBV-specific vaccines and therapeutics further heightened the need for research and regulatory preparedness. Vaccine candidates were prioritized for expedited development, and clinical studies evaluating therapeutic and post-exposure prophylactic interventions were initiated during the outbreak. These approaches are discussed in the relevant sections below^[15,16,26,28].

The public health response has focused on three complementary objectives: achieving earlier case identification and isolation, reducing transmission associated with healthcare and community exposure, and strengthening coordination across affected provinces and national borders. Measures supporting these objectives have included expanding diagnostic capacity, conducting active contact follow-up, establishing safer referral and clinical care pathways, training and protecting healthcare workers, implementing community-based risk communication, ensuring safe and dignified burial practices, and facilitating more timely exchange of epidemiological information among neighboring countries. Maintaining dedicated isolation and treatment capacity and ensuring reliable access to appropriate personal protective equipment (PPE) have remained particularly important in newly affected areas^[26,29].

This experience demonstrates that standard containment measures may become less effective when delayed diagnosis, population mobility, insecurity, healthcare worker exposure, and limited health system capacity occur simultaneously. Preparedness for future outbreaks should therefore include decentralized laboratory networks that can be rapidly expanded, pre-established mechanisms for cross-border surveillance and data sharing, adequately trained and protected healthcare workers, predefined isolation and referral pathways, and community engagement structures led by trusted local stakeholders. Clinical research platforms with pre-approved protocols are also needed so that vaccine,

therapeutic, and prophylactic candidates can be evaluated without avoidable delays during an active outbreak^[26,29].

Rationale and Scope of the Review

This review provides a comprehensive evaluation of the terminology, epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, vaccination, and IPC strategies related to Ebola, drawing on evidence from previous outbreaks and current international guidance. Particular emphasis is placed on the evolving 2026 BDBV outbreak, its epidemiological and public health implications, and persistent species-specific gaps in prevention and treatment. In contrast to previous reviews, which have focused predominantly on EBOV, this review integrates the evolving epidemiology of the 2026 BDBV outbreak with species-specific evidence on diagnosis, prevention, investigational therapeutics, One Health-based surveillance, and practical clinical management.

Review Methodology

Search Strategy

A targeted literature search was conducted in PubMed/MEDLINE and Scopus from database inception through July 2026. The search strategy combined the terms “Ebola disease,” “Ebola virus disease,” “Bundibugyo virus,” “BDBV,” “Sudan virus,” “SUDV,” “*Orthoebolavirus*,” and “filovirus” with terms related to epidemiology, outbreaks, pathogenesis, transmission, clinical manifestations, diagnosis, case definitions, treatment, therapeutics, vaccination, IPC, contact tracing, and long-term sequelae. Boolean operators were used, and the reference lists of relevant reviews, guidelines, and key original studies were screened to identify additional publications.

Official guidelines, case definitions, surveillance updates, outbreak reports, and media briefings issued by the WHO and its regional offices, Africa Centres for Disease Control and Prevention (Africa CDC), Centers for Disease Control and Prevention (CDC), European CDC (ECDC), UK Health Security Agency (UKHSA), International Committee on Taxonomy of Viruses, Republic of Türkiye Ministry of Health, and other relevant public health and regulatory authorities were also reviewed. Selected conference abstracts and proceedings were considered only when they provided relevant historical or time-sensitive information unavailable in full peer-reviewed publications and contained sufficient methodological or outcome detail.

Eligibility Criteria

Peer-reviewed original studies, clinical trials, observational studies, systematic reviews, meta-analyses, authoritative guidelines, and official institutional reports relevant to human *Orthoebolavirus* infections were considered. Recent evidence and current international recommendations were prioritized,

whereas seminal historical publications were retained when necessary. Preclinical and animal studies were included only when they provided relevant evidence on pathogenesis, vaccine candidates, or investigational therapeutic approaches for which human data were limited.

The peer-reviewed literature search was restricted to articles published in English, although relevant national guidance published in Turkish was also considered. Duplicate records, dissertations, non-peer-reviewed commentaries, publications outside the clinical, epidemiological, diagnostic, preventive, or therapeutic scope of the review, and documents lacking sufficient relevant information were excluded.

Study Selection and Data Synthesis

Retrieved records were independently screened at the title and abstract levels by two authors, and the full texts of potentially relevant publications were independently assessed. Disagreements were resolved through discussion and consensus.

Given the narrative nature of this review, the evidence was synthesized qualitatively and organized into thematic sections. Particular attention was given to distinguishing EBOV-specific human evidence from findings related to other *Orthoebolavirus* species and from preclinical or animal data. No formal protocol registration, standardized risk-of-bias assessment, or quantitative evidence synthesis was performed. The thematic synthesis was designed to provide a comprehensive and critical overview of the current evidence, consistent with the scientific scope of the *Mediterranean Journal of Infection, Microbes and Antimicrobials*.

Pathogenesis

Orthoebolavirus species typically enter the body through mucosal surfaces, disrupted skin, or the parenteral route. Following entry, they initially replicate in immune cells, including monocytes, macrophages, and dendritic cells, before disseminating through the lymphatic system and bloodstream to the liver, spleen, adrenal glands, endothelium, and other tissues. Early suppression of the interferon response compromises host defenses, whereas the robust release of proinflammatory cytokines from infected cells promotes systemic inflammation. These processes contribute to hepatocyte necrosis, adrenal injury, lymphocyte apoptosis, endothelial dysfunction, and coagulation abnormalities. Consequently, increased vascular permeability, fluid loss, hypotension, shock, and multiorgan failure may develop^[30-32].

Although experimental studies have identified several mechanisms underlying filovirus immune evasion, species-specific differences in these mechanisms have also been reported^[31]. Human evidence regarding pathogenesis is

derived predominantly from EBOV infection, and the direct contribution of viral replication to organ-specific injury remains incompletely understood^[30,33]. Accordingly, the clinical relevance of these mechanisms to BDBV and SUDV infections should be interpreted with caution.

Modes of Transmission

Fruit bats of the family *Pteropodidae* are considered the natural reservoirs of *Orthoebolavirus* species. Zoonotic transmission to humans has been reported following close contact with the blood, body secretions, or organs of infected fruit bats, non-human primates, antelopes, and other wild animals^[2]. Infection of non-reservoir hosts, including humans, may facilitate cross-species transmission and initiate outbreaks^[22].

The primary risk factor for human-to-human transmission is direct contact with the blood and body fluids of symptomatic patients. Although blood, feces, and vomitus are among the principal sources of transmission, viral RNA has also been detected in several other body fluids, including breast milk, saliva, urine, semen, cerebrospinal fluid, and ocular fluid. However, detection of viral RNA by real-time reverse transcription polymerase chain reaction (RT-PCR) does not necessarily indicate the presence of viable, infectious virus. Therefore, the potential for transmission through specific body fluids may vary according to the stage of disease and viral load^[2,34]. Patients are generally not considered infectious before symptom onset, with infectiousness beginning when clinical manifestations develop^[2,5].

Laboratory studies have demonstrated that *Orthoebolavirus* species can be transmitted through droplet inoculation via the oral and conjunctival routes; however, the relevance of these experimental findings to routine human transmission remains uncertain^[35]. The risk of transmission increases substantially during the acute phase of illness, when viral load is highest, particularly among patients with severe symptoms such as vomiting and during the period immediately after death^[36]. Mother-to-child transmission of EBOD has been documented, and maternal EVD during the 2014-2016 West African outbreak was associated with extremely high rates of fetal loss and neonatal mortality^[37,38]. The detection of EBOV RNA and, in rare cases, viable virus in the semen of male survivors indicates that sexual transmission may occur during the convalescent phase. Accordingly, semen testing and counseling regarding safer sexual practices are recommended as components of survivor programs^[39].

Experimental transmission observed under controlled conditions should not be interpreted as evidence that airborne transmission represents a major route of person-to-person spread. Nevertheless, enhanced respiratory protection

remains appropriate during aerosol-generating procedures because such procedures may increase the risk of occupational exposure.

Clinical and Laboratory Findings

Clinical Findings

EBOD is a severe systemic filovirus infection that typically presents with sudden-onset, non-specific symptoms following an incubation period of 2-21 days. Because the precise timing and route of exposure are often uncertain, estimates of the interval between exposure and symptom onset remain limited^[40]. In an analysis of published human exposure data, the mean incubation period for EBOD was reported as 6.22 ± 1.57 days across all routes of transmission, 5.85 ± 1.42 days following percutaneous exposure, and 7.34 ± 1.35 days following person-to-person or infected animal contact^[41]. A meta-analysis reported that the incubation period for BVD caused by BDBV, the virus responsible for the current 2026 outbreak, may range from 5.7 to 11.3 days. Species-stratified random-effects analyses suggested that BDBV infection may be associated with a longer interval from symptom onset to death and a shorter interval from symptom onset to recovery than the corresponding estimates for other *Orthoebolavirus* species; however, BDBV-specific data remain limited^[18].

The clinical course generally follows a recognizable but variable pattern. During the early phase of infection, typically within the first 1-3 days after symptom onset, patients present with non-specific manifestations such as fever, loss of appetite, weakness, headache, myalgia, and arthralgia^[40]. During the 2013-2016 West African EVD outbreak, fatigue, loss of appetite, abdominal pain, diarrhea, vomiting, fever, and muscle pain were among the most frequently reported clinical manifestations^[40,42-44].

In its clinical guidance, the CDC pragmatically categorizes EBOD manifestations as “dry” and “wet” symptoms. During the early stage, non-specific “dry symptoms,” including fever, myalgia, headache, weakness, and fatigue, predominate. Approximately 4-5 days after symptom onset, gastrointestinal involvement becomes more prominent, and “wet symptoms,” such as diarrhea, vomiting, abdominal pain, and unexplained bleeding, may develop^[45]. Although this distinction does not represent a formal staging system, it provides a practical clinical framework for field triage, early case recognition, and timely implementation of IPC measures.

As “wet” symptoms emerge, gastrointestinal fluid losses may become profound and may reach 5-10 L/day in some patients^[30,45]. The resulting hypovolemia, electrolyte disturbances, hypotension, and shock are major contributors to mortality. Gastrointestinal manifestations are therefore

important not only for case recognition but also as indicators of the need for early and intensive supportive care^[30,45].

Maculopapular exanthema is a characteristic but variably reported finding in filovirus infections. In EBOD, a rash usually appears on days 5-7 of illness. It is generally erythematous, non-pruritic, and maculopapular; may involve the trunk, neck, face, and upper extremities; and may resolve with desquamation during recovery^[40,45]. The frequency of rash in previous EBOD outbreaks has been reported to range from 25% to 52%^[46]. However, its diagnostic value is limited because the rash may be difficult to detect, particularly in individuals with darker skin, and because reporting has been inconsistent across outbreaks. Therefore, rash should be regarded as a supportive clinical finding in EBOD, but its absence does not exclude the disease^[30,45,47].

Although bleeding manifestations are considered one of the classic features of EBOD, they do not occur in all cases and are more commonly observed in severe or advanced disease. Petechiae, ecchymoses, epistaxis, oozing from vascular access sites, and mucosal bleeding are among the milder hemorrhagic manifestations, whereas gastrointestinal bleeding, disseminated intravascular coagulation (DIC), and shock occur more frequently in severe cases. During the West African outbreak, blood in the stool was reported in approximately 6% of patients, whereas clinically significant bleeding occurred predominantly during the late phase of illness and in pregnancy^[47].

Bleeding manifestations were reported more frequently during the 1976 Yambuku outbreak than during many subsequent EVD outbreaks, including the West African outbreak^[30,45,48]. In the EVISTA cohort from the 10th EVD outbreak in the DRC, the prevalence of bleeding at admission was approximately 16%, similar to that observed during the West African outbreak, whereas bleeding complications developed in 39% of patients during follow-up^[19]. These findings indicate that, despite the term “hemorrhagic fever,” the absence of bleeding does not exclude EBOD and that the reported frequency of bleeding may vary according to disease severity, timing of clinical assessment, outbreak setting, and data collection methods. Whether clinically meaningful differences in bleeding manifestations exist among *Orthoebolavirus* species remains insufficiently defined.

Neurological manifestations are less common but represent an important clinical component of severe disease. They may result from direct central nervous system involvement, metabolic disturbances, shock, hypoglycemia, or multiorgan failure. Confusion, delirium, altered consciousness, seizures, and encephalitis have been reported^[30]. In the EVISTA cohort from the DRC, the prevalence of neurological manifestations

increased from 12% at admission to 27% during follow-up, and severe manifestations, including agitation and coma, were reported in more than one-quarter of patients^[19].

In severe cases, death usually occurs within 6-16 days after symptom onset as a result of septic shock, DIC, and multiorgan failure. During the West African outbreak, the mean interval from symptom onset to death was approximately 7.5 days^[30,45]. Among survivors, clinical recovery generally begins toward the end of the first week; however, fatigue, arthralgia, myalgia, uveitis, and other post-acute symptoms may persist for weeks or months^[45].

Vaccination may modify the clinical presentation of EVD. Observational studies comparing vaccinated and unvaccinated patients with EBOV infection in the DRC reported lower frequencies of several clinical manifestations, particularly hemorrhagic manifestations, among vaccinated individuals. These findings suggest that the sensitivity of symptom-based case definitions may be reduced in vaccinated populations^[49,50]. Most detailed descriptions of clinical progression and prognostic markers are derived from EBOV cohorts. Therefore, the frequency and prognostic significance of individual clinical manifestations should not be assumed to be identical in BDBV or SUDV infections, for which species-specific clinical data remain limited.

Laboratory Findings

Laboratory findings in EBOD varies according to the stage and clinical severity of the disease. Leukopenia and marked lymphopenia are typical findings during the early phase, whereas neutrophilia may develop as the disease progresses. Thrombocytopenia is a common laboratory abnormality, with platelet counts typically ranging from 50,000 to 100,000/mm³. Elevation of liver enzymes is also common, and transaminase levels may exceed 1,000 IU/L. In severe and fatal cases, the increase in aspartate aminotransferase (AST) is more pronounced than that in alanine aminotransferase (ALT), and AST levels may reach 7-12 times those of ALT.

Elevated amylase levels may indicate pancreatic involvement or systemic inflammation, while increased creatine kinase levels may result from muscle injury. Marked fluid loss due to severe vomiting and diarrhea may lead to electrolyte and acid-base disturbances, including hypokalemia, hyponatremia, hypocalcemia, and metabolic acidosis. In severe cases, the coagulation system is also affected; prolonged prothrombin time and activated partial thromboplastin time, together with increased fibrin degradation products and D-dimer levels, may be consistent with DIC^[30,45,51]. These laboratory abnormalities are not specific to EBOD and should therefore be interpreted in the context of the clinical phase, disease severity, and epidemiological setting. Moreover, most detailed laboratory

descriptions are derived from EBOV cohorts, and whether the frequency or prognostic significance of these abnormalities differs in BVD or SVD remains insufficiently defined. The clinical, laboratory, and diagnostic features of EBOD according to disease phase are summarized in Table 2.

Diagnostic Tests

The diagnosis of EBOD is based on a combination of clinical findings, epidemiological risk, and laboratory diagnostic testing. Because the early manifestations of EBOD are non-specific, the differential diagnosis should be guided by the travel itinerary, the interval between travel or exposure and symptom onset, and relevant patient, animal, vector, food, water, and environmental exposures. The principal differential diagnoses and distinguishing clinical features in travelers returning from Ebola-affected regions are summarized in Table 3.

Malaria should be investigated urgently in every febrile traveler returning from a malaria-endemic region affected by Ebola. However, identification of malaria or another infection should not, by itself, preclude further evaluation for EBOD when a compatible epidemiological exposure has been identified^[35,58,60]. In some outbreak settings, up to 95% of suspected cases have tested negative for EBOD, underscoring the need to maintain a broad differential diagnosis that includes other endemic febrile illnesses^[62].

According to current WHO guidance, nucleic acid amplification test (NAAT)-based methods, particularly RT-PCR, remain the reference standard for laboratory confirmation in individuals who meet the EBOD case definitions. Because viral RNA levels may be below the detection threshold during the early phase of illness, a negative result from a specimen collected within the first 72 hours after symptom onset does not reliably exclude EBOD. Therefore, repeat testing with a second specimen is

Table 2. Clinical, laboratory, and diagnostic features of EBOD according to disease phase^[9,10,52,53].

Disease phase ^[54-56]	Approximate timing	Clinical findings	Laboratory findings	Diagnostic test interpretation/case classification ^[35]
Incubation period	2-21 days after exposure	No symptoms are present. Infectiousness is generally not expected	No specific laboratory abnormalities are usually present	Routine testing is not recommended for asymptomatic contacts; symptom monitoring should be performed for 21 days
Early phase/dry symptoms	First 1-3 days	Fever, weakness, fatigue, headache, myalgia, arthralgia, loss of appetite, and sore throat	Leukopenia, lymphopenia, early thrombocytopenia, and elevated transaminases may develop	NAAT (+): acute confirmed case. NAAT (–) or not performed + IgM (+): acute confirmed case. If NAAT is negative within the first 72 hours and clinical suspicion persists, repeat testing is required
Gastrointestinal phase/wet symptoms	Usually, after day 4-5	Nausea, vomiting, watery diarrhea, abdominal pain, and marked fluid loss; bleeding may occur in some cases	Electrolyte disturbances, metabolic acidosis, worsening thrombocytopenia, and elevated AST/ALT levels	NAAT (–) >72 hours after symptom onset: discarded case. Ag-RDT may support triage but should be confirmed by NAAT.
Severe disease phase	End of the first week and thereafter	Shock, altered mental status, confusion, seizures, severe bleeding, DIC, and multiorgan failure	Neutrophilia, marked thrombocytopenia, AST-predominant transaminase elevation, renal dysfunction, prolonged PT/aPTT, and elevated D-dimer levels	High viral load; NAAT (+): acute confirmed case. Once the diagnosis is confirmed, isolation, treatment, and contact tracing should be initiated promptly
Post-symptomatic/convalescent phase	Weeks to months	Fatigue, arthralgia, myalgia, headache, uveitis, visual or hearing problems, and psychosocial effects	Acute-phase abnormalities may resolve; viral RNA persistence may occur in immunologically privileged sites	NAAT (–) or not performed + IgM (+) + IgG (+): confirmed convalescent case. NAAT (–) or not performed + IgM (–) + IgG (+), >3 months, with clinical/epidemiological compatibility: confirmed convalescent case
Indeterminate serological interpretation	Early post-symptomatic period, especially <3 months	Clinical findings may have resolved; history is important	Acute laboratory abnormalities may have resolved	NAAT (–) or not performed + IgM (–) + IgG (+), <3 months, with clinical/epidemiological compatibility: indeterminate

NAAT/RT-PCR is the main diagnostic method for acute disease. A negative result within the first 72 hours does not definitively exclude EBOD; testing should be repeated if clinical suspicion persists. The distinction between “dry” and “wet” symptoms is not a formal staging system but a practical clinical approach. Ag-RDT, rapid antigen diagnostic test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation; EBOD, Ebola disease; IgG, immunoglobulin G; IgM, immunoglobulin M; NAAT, nucleic acid amplification test; PT, prothrombin time; aPTT, activated partial thromboplastin time; RT-PCR, real-time reverse transcription polymerase chain reaction.

Table 3. Differential diagnosis of suspected EBOD in travelers returning from an Ebola-affected region^[2,56-61].

Disease	Key epidemiological or exposure clues	Features shared with EBOD	Distinguishing clues	Principal diagnostic tests
EBOD	Travel to or residence in an affected area within 21 days; contact with a symptomatic or deceased case, body fluids, health care settings, unsafe burial practices, or potentially infected wildlife	Fever, profound fatigue, headache, myalgia, vomiting, diarrhea, thrombocytopenia, organ dysfunction, shock, and possible bleeding	Compatible with high-risk exposure; gastrointestinal “wet symptoms” often become prominent as illness progresses. Bleeding may be absent, particularly early in the disease	Species-specific <i>Orthoebolavirus</i> RT-PCR/NAAT
Malaria	Travel to a malaria-endemic area; mosquito exposure; incomplete or absent chemoprophylaxis	Fever, headache, myalgia, fatigue, vomiting, thrombocytopenia, jaundice, altered consciousness, and multiorgan dysfunction	Parasitemia, anemia, and hemolysis may be present. Clinical findings alone may not reliably distinguish malaria from early EBOD	Thick and thin blood films and malaria rapid diagnostic test
Enteric fever	Consumption of contaminated food or water	Fever, headache, fatigue, abdominal pain, vomiting, diarrhea, or constipation	A more gradual onset and sustained febrile illness may occur; gastrointestinal bleeding generally develops later when present	Blood culture, preferably before antimicrobial therapy; stool culture or molecular testing when appropriate
Shigellosis	Contaminated food or water; fecal-oral exposure	Fever, abdominal pain, diarrhea, dehydration, and occasional blood in the stool	Frequent small-volume stools, dysentery, mucus, and tenesmus are more suggestive of shigellosis	Stool culture or gastrointestinal molecular testing
Cholera	Exposure to unsafe water or food, particularly during a local cholera outbreak	Profuse diarrhea, vomiting, severe dehydration, hypotension, and shock	Abrupt, high-volume watery diarrhea with little or no fever; systemic inflammatory and hemorrhagic manifestations are usually absent	Stool culture, molecular testing, or validated rapid diagnostic testing
Leptospirosis	Exposure to floodwater, freshwater, mud, or environments contaminated with animal urine	Fever, headache, myalgia, vomiting, jaundice, acute kidney injury, bleeding, and shock	Conjunctival suffusion, prominent calf or lumbar muscle tenderness, and combined jaundice and renal dysfunction may provide diagnostic clues	PCR during early illness; IgM serology or microscopic agglutination testing according to illness stage
Rickettsiosis	Tick or other arthropod exposure; rural or safari travel	Fever, headache, myalgia, rash, thrombocytopenia, and elevated transaminases	An inoculation eschar, regional lymphadenopathy, or a characteristic rash may be present	PCR from an eschar or appropriate specimen and paired serology
Bacterial sepsis or meningococcemia	Possible respiratory, urinary, intra-abdominal, catheter-related, skin, or central nervous system source	Fever, hypotension, shock, thrombocytopenia, purpura, coagulopathy, and multiorgan failure	A focal source, meningismus, rapidly progressive purpura, or microbiological evidence of bacterial infection may be present	Blood cultures and source-directed cultures or molecular tests; cerebrospinal fluid testing when clinically appropriate and safe
Acute viral hepatitis	Food- or waterborne, bloodborne, sexual, or parenteral exposure depending on the hepatitis virus	Fever, fatigue, nausea, vomiting, abdominal discomfort, jaundice, and elevated transaminases	Jaundice and hepatocellular injury usually dominate the clinical picture; marked ALT-predominant elevations may support acute viral hepatitis	Virus-specific serology and NAAT when indicated

Table 3. Continued

Disease	Key epidemiological or exposure clues	Features shared with EBOD	Distinguishing clues	Principal diagnostic tests
Crimean-Congo hemorrhagic fever	Tick bite; contact with livestock, animal blood, or tissues; slaughterhouse exposure; residence in or travel to an endemic region, including Türkiye	Sudden fever, headache, myalgia, thrombocytopenia, elevated transaminases, bleeding, shock, and multiorgan failure	Clinical overlap with EBOD is substantial; tick- and livestock-related exposures and geographic epidemiology are therefore particularly important	CCHFV RT-PCR during acute illness and virus-specific serology according to illness stage
Other viral hemorrhagic fevers (VHFs)—including Marburg virus disease, Lassa fever, dengue, and yellow fever	Marburg: cave, mine, or bat exposure; Lassa: residence in West Africa or rodent exposure; dengue/yellow fever: mosquito exposure and relevant geography	Fever, headache, myalgia, gastrointestinal symptoms, thrombocytopenia, hepatic dysfunction, bleeding, and shock	Marburg virus disease may be clinically indistinguishable from EBOD; pharyngitis or facial edema may suggest Lassa fever; retro-orbital pain and hemoconcentration may suggest dengue; prominent jaundice may suggest yellow fever	Agent-specific RT-PCR/NAAT, antigen testing, and serology according to the suspected pathogen and illness stage

Clinical findings alone cannot reliably confirm or exclude EBOD. Isolation precautions, public health notification, and Ebola-specific testing should not be delayed in patients meeting the relevant epidemiological and clinical criteria. CCHFV, Crimean–Congo hemorrhagic fever virus; EBOD, Ebola disease; NAAT, nucleic acid amplification test; RT-PCR, reverse transcription polymerase chain reaction; VHF, viral hemorrhagic fever.

recommended when clinical and epidemiological suspicion remains high^[57].

In surviving patients, ethylenediaminetetraacetic acid (EDTA) whole blood or plasma is the preferred specimen, whereas oral or buccal swabs are used for deceased individuals. Oral swabs are not recommended for living patients because their sensitivity for detecting viral RNA is substantially lower than that of blood samples. Venous blood should be collected in an EDTA tube, with a recommended minimum volume of 5 mL. Blood specimens may be stored at room temperature for up to 24 hours or at 0°C–5°C for up to 1 week; specimens requiring longer storage should be maintained at -20°C or -70°C^[63,64].

Because species identification has direct clinical, therapeutic, and epidemiological implications, current WHO guidance emphasizes diagnosis at the species level. Diagnostic algorithms may therefore incorporate sequential pan-filovirus, genus-specific, and species-specific NAAT assays. Serological tests, including immunoglobulin (Ig)M- and IgG-based assays, are not recommended as stand-alone tests for acute diagnosis but may contribute to the identification of previous infections and epidemiological investigations^[57].

Rapid antigen diagnostic tests (Ag-RDTs) may support outbreak triage and postmortem screening, particularly in settings with limited access to centralized molecular testing. However, their diagnostic performance is lower than that of RT-PCR-based testing, and they should not be used as stand-alone tests to confirm or exclude acute EBOD^[65,66]. The principal value of Ag-RDTs is operational. They may facilitate rapid initial triage and decentralized screening, but a negative result should be

interpreted in the context of symptom duration, specimen type, viral load, and pretest probability.

Whole-genome sequencing is a complementary method that may help identify viral variants, investigate the origin of an outbreak, and establish epidemiological links among cases. However, it does not replace NAAT-based testing for the initial confirmation of acute infection^[57].

The processing of specimens from suspected cases requires strict biosafety precautions. WHO recommends a risk-based biosafety approach, with procedures involving non-inactivated specimens performed in appropriately equipped laboratories using validated containment measures. Because viral culture requires high-containment facilities and carries substantial biological risk, it is not recommended for routine diagnostic use^[57].

Case Definitions

An analysis based on Ebola treatment data from the DRC showed that each one-day delay in supportive care was associated with an 11% increase in the probability of death, highlighting the critical importance of rapid case detection and timely initiation of patient care^[67]. Field data from the 2014-2015 West African EVD outbreak also demonstrated that admission to an Ebola treatment unit within 24 hours of symptom onset was associated with approximately half the mortality risk observed among patients admitted later, further supporting the importance of early isolation and specialized supportive care^[68]. Taken together, these findings underscore the need for case definitions that facilitate rapid case identification, isolation, diagnostic testing, and referral while maintaining adequate sensitivity during outbreak response.

The case categories included in the 2014 WHO guideline on Ebola and Marburg case definitions continue to serve as the fundamental case-classification framework in the current WHO outbreak toolbox. These definitions are based on clinical findings, epidemiological exposure, and laboratory confirmation. Accordingly, EBOD cases are classified as suspected, probable, confirmed, or discarded cases.

A suspected case is defined as a person with sudden-onset high fever and a history of contact with an EBOD case or a sick or dead animal; a person with sudden-onset fever and at least three symptoms, including headache, weakness, loss of appetite, muscle or joint pain, abdominal pain, dysphagia, vomiting, dyspnea, diarrhea, or hiccups; or a person with unexplained bleeding or sudden unexplained death.

A probable case is defined as a suspected case evaluated by a clinician or a deceased suspected case with an epidemiological link to a confirmed case for whom a laboratory specimen could not be obtained.

A confirmed case is defined as a case in which viral RNA is detected by RT-PCR or EBOV-specific IgM antibodies are detected.

A discarded case refers to a suspected or probable case with negative laboratory test results^[55,69].

Although WHO case definitions are essential surveillance tools for outbreak management, their clinical performance remains limited. A systematic review and meta-analysis reported pooled sensitivity and specificity values of 81.5% and 35.7%, respectively, for WHO EBOD case definitions, indicating the potential for both missed cases and false-positive classifications. In the same study, a history of contact was identified as a strong predictor, whereas severe fatigue was the most sensitive symptom. The diagnostic value of fever varied according to the threshold applied and the stage of disease. These findings highlight the importance of using case definitions in conjunction with laboratory confirmation and epidemiological risk assessment rather than as stand-alone diagnostic tools^[30,70,71]. Increasing clinical experience from the 2013-2016 West African EVD outbreak further suggests that more specific combinations of symptoms may improve diagnostic assessment^[72].

In the 2025 surveillance case definition, the CDC places EBOD within the broader category of VHFs. A suspected case is defined as a case with clinical findings consistent with acute disease onset and an epidemiological link, or a case in which VHF or a VHF-causing agent is identified on the death record. A confirmed case requires laboratory evidence, including VHF-specific NAAT, genome sequencing, IgM positivity, a fourfold rise in IgG titer, or viral isolation^[53].

In response to the 2026 BDBV outbreak in the DRC, the ECDC published an interim case definition for use in the European Union/European Economic Area. Similar to the WHO framework, the ECDC definition incorporates clinical, epidemiological, and laboratory criteria but additionally introduces a dedicated high-risk exposure category and a “person under investigation” classification. These additional categories are intended to strengthen surveillance, facilitate early case detection, and support risk assessment activities^[73].

In the guidelines of the Republic of Türkiye Ministry of Health, clinical findings and epidemiological risk history are assessed together, consistent with the approaches used by WHO and the CDC. However, unlike the WHO framework, the Turkish guidelines do not define a separate “suspected case” category. Cases meeting at least one epidemiological criterion and at least one clinical criterion are classified as “probable cases,” whereas those confirmed by laboratory diagnostic testing are classified as “confirmed cases”^[56]. Because these frameworks were developed for different surveillance, jurisdictional, and operational contexts, their criteria should not be considered fully interchangeable. Instead, the case definition specified by the relevant outbreak response framework and public health authority should be applied. A comparison of the case definitions used by WHO, CDC, ECDC, the Republic of Türkiye Ministry of Health, and UKHSA is presented in Table 4. A practical algorithm for the initial assessment and management of patients who meet the applicable clinical and epidemiological criteria for suspected EBOD is presented in Figure 1.

Treatment

Supportive Care and EBOV-Specific Therapies

Optimized supportive care was the cornerstone of EBOD management before the availability of specific therapeutics and remains essential even when species-specific therapies are available. During the West African EVD outbreak, early and comprehensive supportive care provided in advanced treatment centers was associated with survival rates of up to approximately 82%, underscoring the prognostic importance of timely, optimized care^[75,76].

Optimized supportive care includes individualized fluid and electrolyte replacement, management of hypovolemia and shock, maintenance of adequate oxygenation, monitoring of glucose levels and renal function, and treatment of concomitant or secondary infections. Substantial crystalloid replacement may be required, particularly in patients with severe fluid loss resulting from vomiting and diarrhea; however, fluid therapy should be guided by repeated clinical and laboratory assessments. Early correction of hyponatremia, hypokalemia, and other electrolyte disturbances remains

Table 4. Comparison of EBOD case definitions.

Organization/ guideline	Scope	Case categories	Suspected/probable case approach	Confirmed case	Distinctive features
WHO ^[55,69]	Outbreak case definition for Ebola and Marburg diseases	Suspected, probable, confirmed, and discarded cases	A suspected case is defined as a person with sudden-onset high fever and a history of contact with an EBOD case or a sick or dead animal; a person with sudden-onset fever and at least three symptoms, including headache, weakness, loss of appetite, muscle or joint pain, abdominal pain, dysphagia, vomiting, dyspnea, diarrhea, or hiccups; or a person with unexplained bleeding or sudden unexplained death. A probable case is a suspected case evaluated by a clinician or a deceased suspected case with an epidemiological link to a confirmed case for whom a laboratory sample could not be obtained	Confirmed by detection of viral RNA by RT-PCR or EBOV-specific IgM antibodies.	Used for early case detection, isolation, and contact tracing in outbreak settings. Combines clinical findings, epidemiological exposure, and laboratory confirmation. Suspected or probable cases with negative laboratory results are classified as discarded cases
CDC ^[53]	General surveillance definition for VHF, including Ebola	Suspected and confirmed cases	A suspected case is a case with compatible acute-onset clinical findings and an epidemiological link, or a case in which VHF or a VHF-causing agent is listed on the death record	A case with confirmatory laboratory evidence such as VHF-specific NAAT/genome sequencing, IgM positivity, a fourfold rise in IgG titer, or viral isolation	Not specific to Ebola; used for standardized classification of VHF cases in U.S. public health surveillance. Provides a broader VHF framework than the WHO definition
ECDC ^[73]	Interim surveillance case definition for the 2026 BVD outbreak in the DRC for use within the EU/EEA	PUI, probable, and confirmed cases	A PUI is a person who meets the clinical and epidemiological criteria or a person with a high-risk exposure who develops any compatible symptom, including fever of any grade. A probable case is a person fulfilling both the clinical and high-risk exposure criteria. Epidemiological criteria include travel to an affected area or contact with a probable or confirmed case within the previous 21 days	Laboratory confirmation by detection of BDBV nucleic acid with confirmatory testing or isolation of BDBV from a clinical specimen	Introduces a dedicated high-risk exposure category and a PUI classification to support surveillance and risk assessment activities
MoH-Türkiye ^[56]	National guidelines for EVD	No separate suspected case category; probable and confirmed cases are defined	A probable case is a case meeting at least one epidemiological criterion and at least one clinical criterion. Epidemiological criteria include contact with the blood/body fluids of an EVD case within the previous 21 days, residence in or travel to an area with active transmission, contact with bats/rodents/primates in endemic regions, or risky contact with sexual secretions of recovered patients. Clinical criteria include unexplained death, fever $\geq 38^{\circ}\text{C}$, or at least three compatible clinical findings	A case meeting the probable case definition and confirmed by laboratory diagnostic tests for EVD is classified as a confirmed case	Similar to the WHO and CDC definitions, it evaluates clinical findings together with epidemiological risk history. Unlike the WHO framework, it does not define a separate "suspected case" category. Because a single probable case is considered an outbreak, rapid notification is emphasized
UKHSA ^[74]	Case classification for health protection teams managing Ebola and Marburg cases	Possible, probable, and confirmed cases	A probable case is a person without laboratory results who has a clinically compatible illness and a history of high-risk exposure within the previous 21 days. Clinical findings may include fever $> 37.5^{\circ}\text{C}$, severe weakness, headache, myalgia, abdominal pain, sore throat, vomiting, diarrhea, or unexplained bleeding. A possible case is a deceased person with epidemiological risk, or a person with compatible clinical illness and travel to an affected area or contact while using appropriate PPE	A positive real-time PCR result from blood or another body fluid is considered confirmation of a case	There is no "suspected case" category. Unlike the WHO framework, possible and probable cases are separated according to exposure risk level. The fever threshold is $>37.5^{\circ}\text{C}$

CDC, Centers for Disease Control and Prevention; DRC, Democratic Republic of the Congo; EBOD, Ebola disease; EVD, Ebola virus disease; ECDC, European Centre for Disease Prevention and Control; EU/EEA, European Union/European Economic Area; IgG, immunoglobulin G; IgM, immunoglobulin M; MoH-Türkiye, Republic of Türkiye Ministry of Health; NAAT, nucleic acid amplification test; PPE, personal protective equipment; PUI, person under investigation; RT-PCR, real-time reverse transcription polymerase chain reaction; UKHSA, UK Health Security Agency; VHF, viral hemorrhagic fever; WHO, World Health Organization; BDBV, Bundibugyo virus; EBOV, Ebola virus.

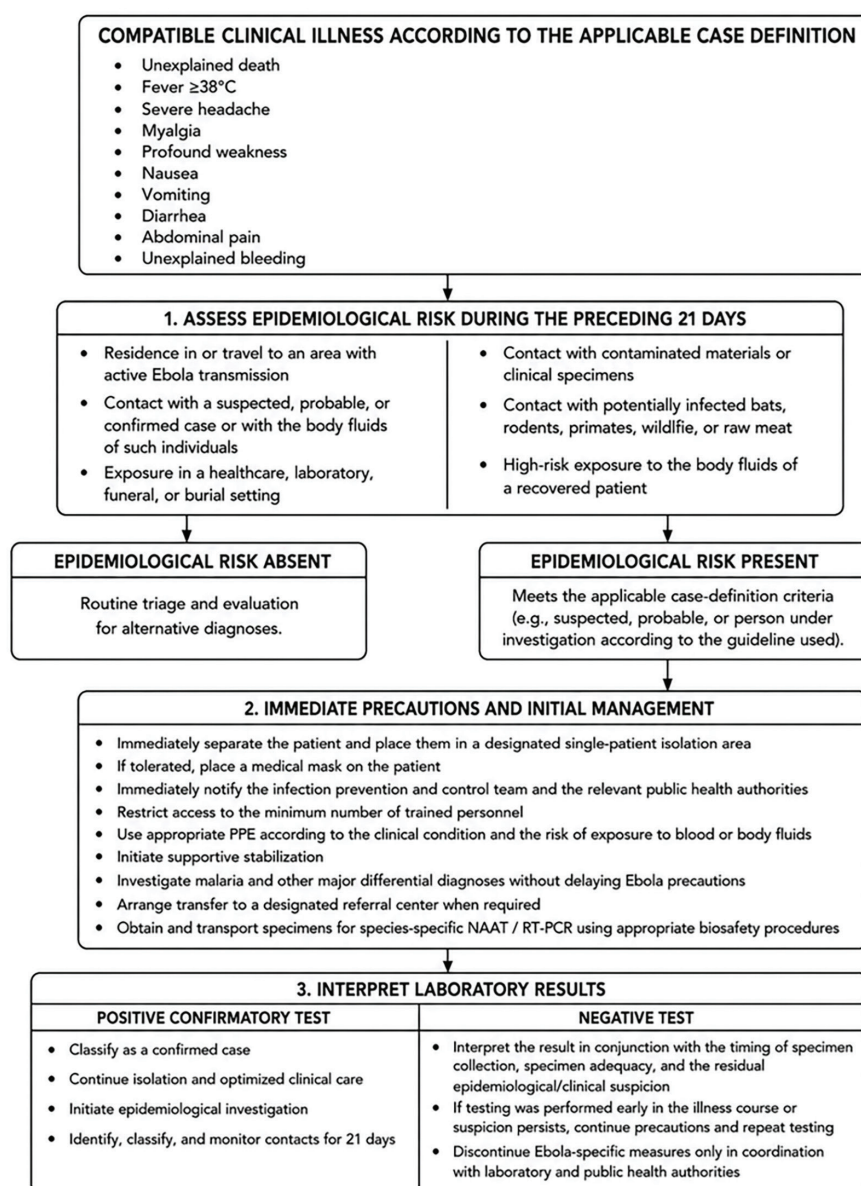


Figure 1. Practical algorithm for the initial assessment and management of a patient with suspected EBOD. The algorithm was developed by the authors based on current WHO guidance on diagnosis and infection prevention and control, relevant CDC clinical guidance, and the Republic of Türkiye Ministry of Health guideline for EVD. Case-category terminology varies across guidelines (WHO: suspected/probable/confirmed/discarded; CDC: suspected/confirmed; ECDC: PUI/probable/confirmed; Republic of Türkiye Ministry of Health: probable/confirmed; UKHSA: possible/probable/confirmed). Clinical findings are non-specific, and the identification of malaria or another infection does not necessarily exclude concomitant EBOD in the presence of compatible epidemiological exposure. NAAT, nucleic acid amplification test; RT-PCR, real-time reverse transcription polymerase chain reaction; PPE, personal protective equipment; PUI, person under investigation; EBOD, Ebola disease; WHO, World Health Organization; EVD, Ebola virus disease; ECDC, European Centers for Disease Control and Prevention; UKHSA, UK Health Security Agency.

critically important. WHO guidelines also identify early enteral nutrition, symptom control, empirical antimicrobial therapy when clinically indicated, and vasopressor support for refractory hypotension unresponsive to fluid resuscitation as components of optimized supportive care^[77].

A major therapeutic advance emerged from the PALM trial conducted in the DRC. In this randomized controlled trial,

mAb114 and REGN-EB3 reduced 28-day mortality compared with ZMapp, with mortality rates of 35.1% in the mAb114 group and 33.5% in the REGN-EB3 group^[9,10]. Based on these findings, both monoclonal antibody therapies received approval from the U.S. Food and Drug Administration (FDA) for the treatment of EVD caused by EBOV. The 2022 WHO guideline strongly recommends either mAb114 (ansuvimab; Ebanga™) or REGN-

EB3 (atoltivimab, maftivimab, and odesivimab; Inmazeb™) for patients with RT-PCR-confirmed EBOV infection. These agents should be administered as early as possible, and both therapies should be delivered as a single intravenous infusion^[11].

Remdesivir did not demonstrate clinical benefit as monotherapy in the PALM trial. Although preclinical and limited clinical evidence suggests potential roles for remdesivir in combination regimens and in the management of EBOV persistence, these uses remain investigational^[14,78]. The evidence supporting mAb114 and REGN-EB3 is comparatively robust because it is based on randomized clinical trial data. However, this evidence is specific to EBOV and should not be extrapolated to BDBV or SUDV.

Treatment outcomes are also strongly influenced by disease stage and baseline viral load; in the PALM trial, higher viral load was strongly associated with mortality^[9,79].

Investigational Therapies for SUDV and BDBV

Unlike EVD caused by EBOV, no approved therapeutic with demonstrated clinical efficacy is currently available for SVD or BVD^[11,12].

For SVD, available evidence for candidate therapies remains predominantly preclinical. MBP134, a two-antibody pan-ebolavirus cocktail, reversed advanced SUDV disease in non-human primates when administered as a single intravenous or intramuscular dose^[13]. In a separate non-human primate study, remdesivir combined with a pan-ebolavirus monoclonal antibody provided protection against advanced SUDV disease^[14]. Although these findings provide a rationale for clinical evaluation, they do not establish therapeutic efficacy in humans^[13,14].

For BVD, a WHO-convened Technical Advisory Group prioritized MBP134, maftivimab, and remdesivir for evaluation in clinical trials and recommended investigating remdesivir in combination with monoclonal antibody therapy^[12]. In July 2026, the PARTNERS platform trial began enrolling patients with confirmed BVD in the DRC to evaluate MBP134 and remdesivir as monotherapies and in combination. Because the trial has only recently begun, BDBV-specific human efficacy data are not yet available, and these agents remain investigational^[16].

For post-exposure prophylaxis, the WHO prioritized obeldesivir, an orally administered broad-spectrum antiviral candidate, for clinical evaluation in contacts of patients with confirmed BVD^[12]. In non-human primate models, oral obeldesivir provided post-exposure protection against lethal EBOV infection when treatment was initiated 24 hours after exposure. However, these findings do not establish efficacy against BDBV in humans^[80]. In July 2026, a separate clinical trial was initiated to evaluate obeldesivir as post-exposure

prophylaxis in individuals who had been exposed to confirmed BVD cases but had not yet developed disease^[15].

Beyond the candidates currently undergoing clinical evaluation, broadly neutralizing and bispecific antibodies targeting conserved glycoprotein epitopes across multiple *ebolavirus* species and other filoviruses represent another promising therapeutic strategy. However, most of these approaches remain in the preclinical or early clinical development stages, and their safety and efficacy against SVD or BVD in humans have not yet been established^[81].

Infection Prevention and Control

IPC is a central component of preparedness for and response to EBOD outbreaks. Drawing on experience from previous filovirus outbreaks, WHO issued an updated IPC guideline for Ebola and Marburg diseases in 2026, with recommendations developed using the GRADE methodology^[39]. The guideline emphasizes standard precautions, hand hygiene, protection of the eyes, nose, and mouth, fluid-resistant protective clothing, and appropriate respiratory protection during aerosol-generating procedures^[39].

The WHO guideline does not limit IPC to the use of PPE. Instead, it adopts a hierarchy-of-controls approach that integrates engineering controls, environmental measures, administrative interventions, and appropriately selected PPE. The guideline provides a framework for screening and triage, patient placement, risk-based PPE selection, healthcare worker safety, environmental decontamination, occupational exposure management, and contact monitoring^[39].

WHO recommends screening individuals presenting to healthcare facilities in outbreak-affected areas at the first point of contact, preferably using a “no-touch” approach, followed by prompt triage and isolation of suspected cases. Suspected or confirmed cases should preferably be placed in single rooms. In screening areas where a distance of at least 1 m can be maintained and direct contact with the patient or the patient’s environment is not anticipated, additional PPE beyond standard precautions may not be required. This risk-based approach aims to provide adequate protection while avoiding unnecessary PPE use, which may contribute to heat stress and fatigue and create communication difficulties and challenges during safe doffing^[39].

When physical distancing cannot be maintained during screening, PPE should be selected according to the anticipated degree of contact and exposure. Direct care of patients with suspected or confirmed Ebola requires protection of the mucous membranes, along with fluid-resistant protective clothing and gloves. Additional protective barriers, including double gloves, should be used when warranted by the

procedure or the anticipated degree of exposure to blood and body fluids^[39].

For healthcare facilities in the United States, CDC guidance also stratifies PPE requirements according to clinical stability and the likelihood of exposure to blood or body fluids. For clinically stable patients with suspected VHF who do not have bleeding, vomiting, or diarrhea, the minimum recommended ensemble includes a single-use, fluid-resistant gown or coverall, a facemask, a full-face shield, and two pairs of gloves. For patients with confirmed disease or suspected disease accompanied by clinical instability, bleeding, vomiting, or diarrhea, PPE should fully cover the skin and clothing and prevent exposure of the eyes, nose, and mouth. Care should be provided by trained personnel, with donning and doffing performed under the supervision of a trained observer^[82].

CDC recommends placing patients with suspected or confirmed VHF in a single-patient room with a private bathroom, restricting access to essential personnel, and using dedicated patient-care equipment whenever possible. Aerosol-generating procedures should be avoided unless clinically necessary. When such a procedure is required, the number of personnel present should be minimized, and the procedure should be performed in a private room, ideally in an airborne infection isolation room when feasible. Healthcare workers should use a fit-tested N95 or higher-level respirator or a powered air-purifying respirator, together with the recommended barrier PPE^[83].

One important update in the WHO guideline is the concept of the IPC ring approach. The IPC ring approach involves rapid assessment and targeted strengthening of IPC practices in healthcare facilities, households, and other sites epidemiologically linked to confirmed cases. Activities may include screening and isolation, environmental cleaning and disinfection, healthcare worker training, identification of IPC gaps, and rapid implementation of corrective measures. This targeted approach has been incorporated into recent filovirus outbreak responses, including the response to the 2022 Uganda SVD outbreak^[39,84].

The continuing burden of infection among healthcare workers during the 2026 BVD outbreak illustrates the challenges of consistently implementing IPC measures in conflict-affected and resource-constrained settings. As of July 15, 2026, WHO had reported 119 confirmed infections and 36 deaths among healthcare workers in the DRC, highlighting persistent occupational and community exposure, as well as ongoing gaps in IPC implementation^[26].

Accordingly, WHO does not recommend routine whole-body spraying of chlorine or other disinfectants onto PPE-clad healthcare workers before or during doffing. Evidence

supporting the effectiveness of this practice in reducing contamination is insufficient, and spraying may cause skin or respiratory irritation while creating a false sense of security. Instead, visible contamination should be managed through validated, targeted decontamination procedures and safe doffing practices. For environmental cleaning, wiping methods that mechanically remove organic material are preferred to indiscriminate spraying. Alcohol-based hand rub or soap and water should be used for hand hygiene rather than chlorine solutions^[39].

Environmental studies have detected viral RNA on gloves and frequently touched surfaces even in the absence of visible contamination. Although detection of viral RNA does not necessarily demonstrate the presence of viable virus, these findings support systematic cleaning and disinfection of potentially contaminated surfaces^[39].

The evidence supporting several IPC interventions remains limited because comparative studies are ethically and operationally difficult to conduct during high-risk filovirus outbreaks. Consequently, some recommendations are necessarily based on a combination of indirect evidence, accumulated outbreak experience, feasibility, occupational safety considerations, and precautionary principles rather than on comparative effectiveness trials alone^[39].

Contact Tracing

According to WHO, a contact is a person who has had direct contact with the blood, body fluids, secretions, or contaminated surfaces of a patient with EBOD during the symptomatic period. Living in the same household, unprotected contact during healthcare provision, laboratory exposure, unsafe burial practices, and contact with infected animals are also considered contact events. Contacts should be actively monitored for symptoms for 21 days after the last exposure, and individuals who develop compatible symptoms should be rapidly isolated and evaluated through laboratory testing^[39]. Because the likelihood of detecting viral RNA in contacts who have not developed symptoms is low, routine diagnostic testing is not recommended for asymptomatic individuals^[57]. Consistent with the WHO approach, the guideline of the Republic of Türkiye Ministry of Health also recommends classifying contacts as high-, intermediate-, or low-risk according to the level of exposure; implementing direct active monitoring of asymptomatic high- and intermediate-risk contacts; applying restrictions such as avoiding travel, public transportation, and crowded settings; and discontinuing follow-up on day 21 in contacts who remain asymptomatic^[56].

Updated ECDC guidance for air travel-associated Ebola exposures recommends contact tracing only when the index case was symptomatic during the flight and was identified

within 21 days of travel. For confirmed cases, contact tracing is generally limited to passengers seated within one seat of the index case, cabin crew members working in the same cabin section, cleaning personnel, and individuals with direct exposure to body fluids^[85]. Although contact tracing is central to outbreak containment, its effectiveness depends on timely case detection, complete identification of contacts, community trust, population mobility, data-sharing capacity, and the availability of trained personnel.

Vaccines

ERVEBO® (rVSVΔG-ZEBOV-GP) is a replication-competent, recombinant vesicular stomatitis virus (rVSV)-based live-vector vaccine that expresses the glycoprotein of EBOV belonging to the species *Orthoebolavirus zairense*. Following a positive assessment by the European Medicines Agency, ERVEBO® received EU-wide conditional marketing authorization in 2019 and was subsequently prequalified by WHO. ERVEBO® has been approved by the U.S. FDA for the prevention of disease caused by EBOV in individuals aged 12 months and older. It is currently the only licensed and WHO-prequalified vaccine available for EVD and does not provide protection against disease caused by other *Orthoebolavirus* species^[7,86,87].

The two-dose Ad26.ZEBOV/MVA-BN-Filo regimen, comprising Zabdeno and Mvabea, received EU marketing authorization under exceptional circumstances in 2020. However, the marketing authorizations for both vaccines were withdrawn in May 2026 at the request of the marketing authorization holder for commercial reasons^[8].

The PREVAIL I and PREVAC trials demonstrated that antibody responses were largely maintained for up to 12 months after vaccination. However, these immunogenicity findings do not establish the duration of clinical protection or determine the need for or optimal timing of booster vaccination^[88,89].

In the United States, the Advisory Committee on Immunization Practices recommends pre-exposure vaccination with ERVEBO® for high-risk adults aged 18 years and older. These groups include responders to active EBOV outbreaks, personnel working with specimens that may contain replication-competent EBOV in BSL-4 or Laboratory Response Network laboratories, and healthcare workers involved in the care or transport of patients with suspected or confirmed EVD in Ebola treatment centers or special pathogen treatment centers. The vaccine should not be administered to individuals with a history of anaphylaxis to vaccine components or rice protein, and vaccination should be deferred in the presence of acute systemic infection or febrile illness. Decisions regarding vaccination during pregnancy, breastfeeding, and immunosuppression should be individualized according to the anticipated exposure risk and the potential benefits and

harms^[86,90].

During EBOV outbreaks, the ring vaccination strategy using ERVEBO® is based on the rapid identification and vaccination of close contacts of confirmed or probable EVD cases, as well as contacts of those contacts. In the ring vaccination trial conducted in Guinea, no cases of EVD with symptom onset occurring 10 days or more after randomization were observed among participants who received immediate vaccination. Vaccination outcomes during the outbreak that began in the DRC in 2018 further supported the effectiveness of this strategy for outbreak control^[91,92]. However, the available evidence on clinical vaccine effectiveness is specific to EBOV and should not be extrapolated to SUDV or BDBV. No vaccine is currently licensed for SVD or BVD. In 2026, WHO concluded that the available evidence was insufficient to determine whether ERVEBO® provides clinically meaningful protection against BDBV and recommended against its programmatic use during BVD outbreaks outside controlled research settings^[93].

Post-Ebola Syndrome and Long-Term Sequelae

Following recovery from acute EVD, EBOV RNA and, in some anatomical compartments, replication-competent virus may persist for prolonged periods in immunologically privileged or anatomically sequestered sites, including the testes, intraocular compartments, and central nervous system^[39,78]. This is important not only because of potential late clinical complications but also because of the risk of sexual transmission, particularly as a result of viral persistence in semen. Because some cases reported during the later stages of the 2014–2016 outbreak were epidemiologically and molecularly linked to sexual transmission, WHO and CDC recommend semen testing, counseling on safer sexual practices, consistent condom use when abstinence is not chosen, and hand hygiene after contact with semen^[94,95].

Post-Ebola syndrome may include multisystem sequelae such as fatigue, myalgia, arthralgia, headache, visual and auditory disturbances, neuropsychiatric symptoms, and uveitis. Uveitis is particularly important because it may lead to vision loss, and a high viral load during acute illness has been associated with an increased risk of ocular complications. In addition to physical sequelae, psychosocial outcomes, such as post-traumatic stress disorder, depression, anxiety, and stigmatization, are frequently reported among EVD survivors^[3,96].

Although long-term sequelae following EBOV infection have been well characterized, data on long-term outcomes after BVD caused by BDBV remain limited. In a recent study evaluating survivors 16 years after the 2007–2008 outbreak in Uganda, persistent multisystem symptoms were reported, with neurological and musculoskeletal complaints representing the most common sequelae. Headache (35%) and visual

impairment (22.5%) were prominent findings, while 57.5% of participants reported persistent stigmatization. Hearing loss and gastrointestinal dysfunction, which are more commonly reported among EBOV survivors, were not prominent in this cohort. Although these findings suggest that some long-term manifestations may be shared across diseases caused by different *Orthoebolavirus* species, the evidence is derived from a limited observational survivor cohort and does not establish definitive species-specific differences in the spectrum or frequency of sequelae^[97].

Future Challenges and Perspectives

Future research on EBOD should not be limited to agents with direct antiviral activity but should also encompass therapeutic strategies aimed at modulating the host response and reducing organ damage. In this context, immunomodulatory and other host-directed therapies represent important areas of investigation; however, their clinical role and optimal timing remain uncertain, particularly in BVD^[3,98,99].

One of the most important limitations of current treatment options is that approved monoclonal antibodies have demonstrated efficacy only against EBOV infection. The PARTNERS trial has begun enrolling patients with confirmed BVD to evaluate MBP134 and remdesivir, administered as monotherapies and in combination^[16]. A separate trial is evaluating obeldesivir as post-exposure prophylaxis among contacts of confirmed cases who have not yet developed the disease^[15]. These studies may provide the first controlled human evidence on these interventions in BVD; however, their results are not yet available.

Therefore, the development of pan-filovirus therapeutics, clinical evaluation of broadly neutralizing *Orthoebolavirus* antibodies, investigation of antiviral-monoclonal antibody combination therapies, and development of interventions with wider therapeutic windows remain key priorities for future research^[3,81,98].

Nevertheless, the development of effective treatments alone is not sufficient. Timely and equitable access to licensed therapies in outbreak-affected regions remains a major challenge. Therefore, post-approval implementation processes, including procurement, distribution, cold-chain infrastructure, cost, and health system capacity, must be strengthened^[100,101].

For post-exposure chemoprophylaxis, EBOV-specific monoclonal antibodies, including REGN-EB3 and mAb114, have been used in limited case-based experiences. The absence of EBOD among 23 unvaccinated individuals with intermediate- or high-risk exposure supports the potential utility of this approach; however, the small sample size and

uncontrolled study design mean that the available evidence remains insufficient to support routine use^[102].

Conclusion

EBOD remains a major global public health threat because of its potential for recurrent outbreaks, high mortality, and the capacity of outbreaks to expand rapidly in settings characterized by population mobility, insecurity, limited laboratory access, and inadequate IPC capacity. The evolving 2026 BVD outbreak underscores that advances achieved for EBOV, including licensed vaccines and effective EBOV-specific monoclonal antibody therapies, cannot automatically be extrapolated to other *Orthoebolavirus* species.

Future preparedness should include earlier case detection, scalable and decentralized laboratory networks, strengthened IPC, protected healthcare workforces, pre-established cross-border data-sharing mechanisms, and pre-approved clinical research platforms that enable the rapid evaluation of candidate vaccines and therapeutics during emerging outbreaks. In parallel, the development of vaccines and therapeutics that are effective against multiple *Orthoebolavirus* species remains a major priority.

Footnotes

Authorship Contributions

Concept: A.B., Design: F.M.G.K., A.B., Data Collection or Processing: F.M.G.K., Analysis or Interpretation: F.M.G.K., A.B., Literature Search: F.M.G.K., A.B., Writing: F.M.G.K., A.B.

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