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# BUNDIBUGYO VIRUS DISEASE REASSESSED VIROLOGY, EPIDEMIOLOGY AND CLINICAL MANAGEMENT OF THE 2026 CENTRAL AFRICAN OUTBREAK

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**Abstract**

Bundibugyo virus (BDBV), an emerging orthoebolavirus, was first detected in Uganda in 2007 and has historically received less scientific and public attention than Ebola virus and Sudan virus. The current outbreak in Central Africa provides an opportunity to reassess its epidemiology, clinical impact, molecular characteristics, and preparedness needs. This review consolidates current knowledge of BDBV from previous outbreaks and recent advances in molecular virology, reservoir ecology, diagnosis, clinical management, therapeutics, vaccines, and outbreak response. Available evidence indicates that BDBV has caused recurrent outbreaks, with estimated case-fatality rates ranging from 25% to 54.8%, while the 2026 outbreak has had a substantial regional impact. Genomic studies demonstrate considerable differences between BDBV and other orthoebolaviruses, particularly in the glycoprotein, which may contribute to limited cross-protection from Ebola virus-specific countermeasures. Although bats remain leading candidate reservoirs, a definitive natural host has not been identified. Diagnostic capacity is constrained by limited BDBV-specific assays and logistical challenges in conflict-affected settings, while the absence of licensed BDBV-specific therapeutics or vaccines limits available countermeasures. Experimental pan-ebolavirus monoclonal antibodies and multivalent vaccine platforms offer potential for broader cross-protection. Overall, the 2026 outbreak highlights how reservoir uncertainty, diagnostic limitations, incomplete

countermeasure coverage, and fragmented responses in conflict-affected settings can amplify regional public-health consequences. Strengthening One Health surveillance, deployable molecular diagnostics, broadly protective therapeutics and vaccines, and genomic surveillance should therefore be prioritized to improve preparedness for future BDBV emergence.

## 1. INTRODUCTION

### *1.1 Taxonomy and Neglect*

Bundibugyo virus belongs to the genus Orthoebolavirus in the family filoviridae and is one of six species of viruses belonging to the genus. In April 2023, the International Committee on Taxonomy of Viruses renamed this taxon together with the genus Orthomarburgvirus to Ebolavirus, making the species Orthoebolavirus bundibugyoense official [1]. BDBV is one of the most poorly studied human-pathogenic orthoebolaviruses, even after this taxonomic designation. Ebola virus has found its way into mainstream research and public interest since the 2014-2016 West African epidemic and the promise of better tools and candidate medical countermeasures (MCM) for Ebola has not been gained by other filoviruses, including BDBV. Since the 2014-2016 West African epidemic, research investment and public interest in Ebola virus have converged, and the promise of better tools and potential medical countermeasures (MCM) for Ebola has not yet been realized for other filoviruses, including BDBV. There are still significant gaps in the science regarding the filovirus family, many of which have been identified by expert appraisals and are the basis for the proposed prototype pathogen prioritization list [2].

### *1.2 Outbreak Record and Open Questions*

BDBV was first seen in an epidemic of viral haemorrhagic fever in Bundibugyo District in western Uganda in 2007 [3, 4]. In 2012, a second outbreak in the Democratic Republic of the Congo (DRC), in the village of Isiro, resulted in 38 laboratory confirmed cases and 13 deaths [5]. The reported case-fatality ratio also varies for the Ugandan outbreak, depending on the case definition and denominator: 34% [4]; a crude ratio of 25% [6]; and approximately 40% for laboratory confirmed cases [7]. BDBV seems to be less pathogenic than Ebola virus (case fatality 80-90%) and Sudan virus (case fatality 50-55%), but such differences in case-fatality rates are due to varying aspects of surveillance, clinical management and host factors, which makes it difficult to draw definitive conclusions about the relative species pathogenicity [3, 6]. Despite this, early epidemiology identified significant risk, with laboratory confirmation taking about three months after the start of the 2007 outbreak [4, 7], and most transmission associated with unprotected handling of the deceased (adjusted odds ratio 3.83, 95% CI 1.78–8.23) [4]. The animal reservoir has not been confirmed, although bats are repeatedly suggested as a reservoir, and communities in the Bundibugyo District have regular interactions with bat roosts [8]. A second genomic re-sequencing analysis revealed BDBV emergence in Isiro occurred about 50 days earlier than previously assumed, and that it was not a single spillover event [5].

### *1.3 Taxonomy and Molecular Virology of Bundibugyo Virus*

Bundibugyo virus is the type species of the Orthoebolavirus bundibugyoense species, which has a nonsegmented, negative-sense RNA genome encoding seven structure proteins and three characteristic gene overlaps, at VP35/VP40, GP/VP30 and VP24/L [9, 10]. The assignment to this species is based upon genomic criteria such as being at least 30% different from Ebola virus but less than 30% from the type virus of its own species [10]. Even though BBDV is formally classified as such, molecular

characterization of BBDV is limited when compared to other orthoebolaviruses with a limited number of complete genomes available for analysis [5].

### *1.4 Genomic organization and phylogenetic divergence*

The BDBV genome consists of a set of conserved 3′ leader and 5′ trailer sequences, and gene order 3′-NP–VP35–VP40–GP–VP30–VP24–L–5′, which carry the cis-acting signals for transcription and replication, and are interspersed by eight genes with one open reading frame (ORF) each, except for GP which has 3 overlapping ORFs [9]. The 2007 Bundibugyo isolate was initially sequenced and showed around 32% divergence from its closest known relative, Côte d'Ivoire ebolavirus, a level like the 35-45% level of divergence between previously defined ebolavirus species, making BDBV a new species [3]. The glycoprotein shows functional correlates as differences of over 27% and 35% at the amino acid level when compared with Côte d'Ivoire and Zaire ebolavirus glycoproteins, respectively, and of 23% and 25% with the immunosuppressive VP35 protein, respectively, which are expected to result in significant antigenic variation [3]. Additional patient-derived genomes from the 2012 outbreak also challenged earlier assumptions about evolution, as their analysis suggested that the BDBV had emerged in Isiro about 50 days before the accepted time and that the outbreak had not been caused by a single spillover event [5].

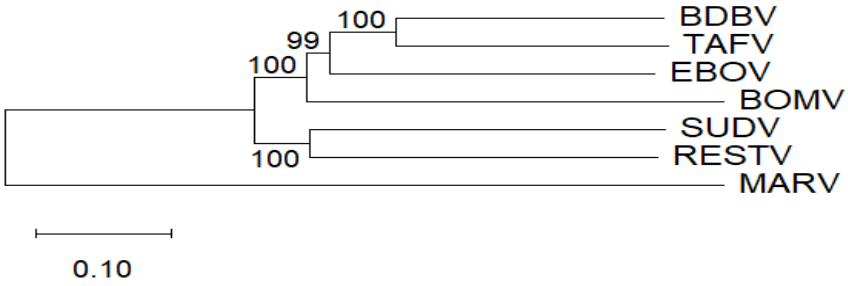



***Figure 1— Phylogenetic tree (BDBV vs. other Orthoebolavirus species)***

### *1.5 The structure of glycoproteins and its involvement in pathogenesis*

BDBV, like other orthoebolaviruses, expresses a single trimeric surface glycoprotein, which is synthesized as a precursor that is subsequently cleaved by furin into the receptor-binding subunit GP1 and the fusion subunit GP2 that is held together covalently [11]. The heptad repeat regions and the hydrophobic internal fusion loop are found in GP2, while GP1 has the putative receptor binding site, in addition to having a heavily glycosylated mucin-like domain [11, 12]. Structural studies throughout the family have shown that the mucin-like domain and glycan cap cover the receptor-binding site and suppress immune responses during natural infection, which helps to account for the lack of neutralizing antibodies [11, 13]. No atomic-resolution structure of BDBV GP exists but comparative data are used to establish both conservation and divergence. This hydrophobic pocket that is required to interact with the endosomal receptor NPC1 is shared among filoviruses and antibodies against this site can bind

cleaved GP from all filoviruses tested so far [14]. However, measurable differences in cross-protection were observed, as a vesicular stomatitis virus (VSV)–based vaccine expressing the Zaire ebolavirus GP protected 75% of nonhuman primates (NHP) from BDBV challenge, but an analogous vaccine based on Côte d'Ivoire ebolavirus GP protected only slightly more than mock vaccination [15]. On the other hand, the human antibody EBOV-520, that recognizes a conserved site at the GP base, neutralizes EBOV, Sudan virus, and BDBV, suggesting that there are conserved vulnerability hotspots despite overall divergence. As such, GP becomes a key factor in species-specific pathogenesis and the focus for broadly protective countermeasures.

**Table 1. Key characteristics of Orthoebolavirus species with Bundibugyo virus**

| Virus | Current species | First detection | Human disease | CFR | Vaccine status |
|---|---|---|---|---|---|
| **Ebola virus (EBOV)** | *Orthoebolavirus zairense* | 1976, Yambuku, DRC [16, 17] | Yes; recurrent outbreaks [18] | 60–90% [18]; pooled 66.6% [19] | Ervebo licensed for EBOV; Zabdeno/Mvabea also approved [20, 21] |
| **Sudan virus (SUDV)** | *Orthoebolavirus sudanense* | 1976, Nzara, Sudan [3] | Yes; recurrent outbreaks [18] | 53–69% [22]; pooled 48.5% [19] | No licensed vaccine; SUDV-specific candidates under development [23] |
| **Bundibugyo virus (BDBV)** | *Orthoebolavirus bundibugyoense* | 2007, Uganda [23] | Yes; outbreaks in Uganda and DRC [3, 5] | 25–51% [6, 17]; pooled 32.8% [19] | No licensed vaccine; experimental candidates show protective potential [15, 21] |
| **Taï Forest virus (TAFV)** | *Orthoebolavirus taiense* | 1994, Côte d'Ivoire [24, 25] | Yes; one non-fatal case [6] | 0% based on one reported case [19] | No licensed vaccine; experimental approaches investigated [15] |
| **Reston virus (RESTV)** | *Orthoebolavirus restonense* | 1989, Reston, USA [26] | No recognized clinical disease; | Not established | No licensed vaccine |

| | | | | | |
|---|---|---|---|---|---|
| | | | human infections reported [27] | | |
| **Bombali virus (BOMV)** | *Orthoebolavirus bombaliense* | 2018, Sierra Leone; detected in bats [28-30] | No documented human disease [31] | Not established | No licensed vaccine; pathogenicity remains under investigation [32] |

**2 Epidemiological Evolution: 2007 to 2026**

Bundibugyo virus disease now has a tripart epidemiological history that includes two contained outbreaks and an ongoing epidemic, covering both the persistence of BBDV as a human disease and the gradual evolution of outbreak science. When comparing the episodes, it is important to remember that each episode was investigated under different conditions of surveillance, so these comparisons help to illustrate the extent to which our estimates of the severity of each episode are influenced by case ascertainment.

***2.1 The Index Outbreak — Uganda, 2007***

There was a first recognized BVD outbreak in August 2007 – February 2008 in Bundibugyo District, in the west of Uganda [4, 33]. The number of cases reported by parallel investigations differed significantly: in a case-series investigation, 192 cases of suspected acute viral encephalitis were found, with 42 (22%) being laboratory-positive [4]; in an outbreak-response investigation, 131 cases of suspected acute viral encephalitis were identified, of which 56 (42%) were laboratory-positive [33]; and in a clinical surveillance investigation, there were 93 cases of suspected acute viral encephalitis, from which 56 (60%) were laboratory-positive [6]. These differences prefigure the central methodological principle of BVD epidemiology, which is that denominators shape measured severity. The crude case fatality rate ranged from 25% (37 deaths among 93 putative cases) to 34% [4], to approximately 40% among laboratory confirmed cases [33] and below 36% in the original description of the molecular case [3]; among hospitalized confirmed cases, the rate rose to 42% [6]. This was like the clinical signs of other orthoebolavirus infections, including non-bloody diarrhea (81%), severe headache (81%) and asthenia (77%) with only 27% of the assessed patients having a hemorrhagic sign [6]. Laboratory confirmation took about three months after the outbreak started, allowing for extended periods of transmission to people; most transmission was linked to the handling of dead bodies without using protection (adjusted odds ratio 3.83; 95% CI 1.78–8.23) [4, 33].

***2.2 The Isiro Outbreak — DRC, 2012***

In 2012, BDBV reappeared in Isiro, Haut-Uélé District, Province Orientale, DRC. On 2 August 2012, MSF was informed that four people had died of an unexplained febrile hemorrhagic illness; samples

from them were later confirmed to be BBDV by the Uganda Virus Research Institute [34]. There were 38 laboratory confirmed outbreaks with 13 deaths [5]. Four of the early isolates for which genomic sequencing was possible, plus seven more from the patients, led to the old idea of a single zoonotic spillover being challenged, and one patient record suggested that the initial emergence was around 50 days earlier than previously thought [5]. The nosocomial dimension of spread was further highlighted in the transmission modelling of the Isiro data, which showed differences in the infection dynamics in the Ebola treatment unit and the wider community [35]. It was in 2012 that the urban potential of BDBV was shown, as well as the ability of molecular epidemiology to help correct the timeline of outbreaks [5].

### *2.3 The 2026 Central Africa Epidemic*

Fourteen years after Isiro, BBDV initiated a larger regional outbreak: An outbreak of BBDV was declared a public health emergency of international concern in May 2026, marking the first time that this virus was designated under the terms of the Public Health Emergency of International Concern (PHIHC) [36].

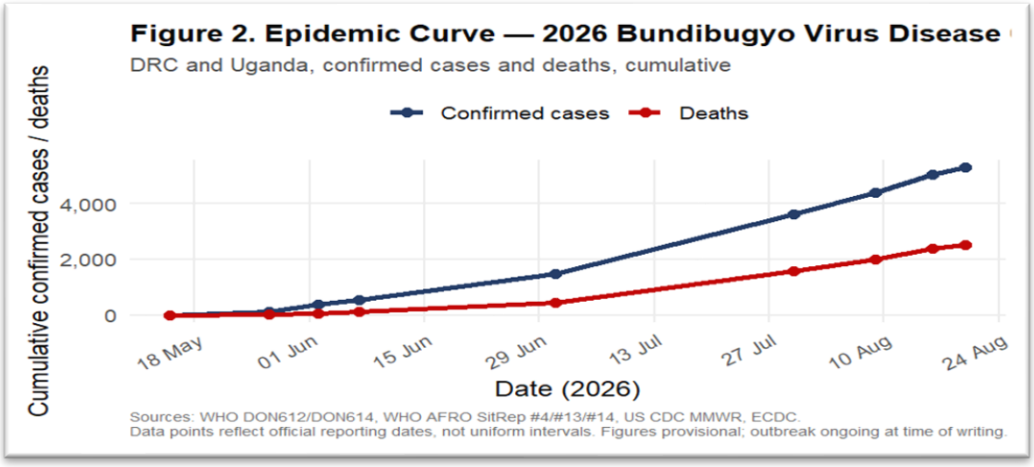



***Figure 2— Epidemic curve (weekly cases/deaths, 2026) ggplot graph***

From the same day, there was a quick international response, including travel ban, travel screening, and post-arrival quarantine, to prevent cross-border importation [36]. Such measures can then be quantitatively evaluated and vulnerabilities exposed. However, symptom-based screening can only detect the BBDV during the presymptomatic window, which has a mean of 6.3 days (95% CI 5.2-7.3 days) from infection to detection, and molecular screening is also limited by the time between infection and detection and the scarcity of BBDV-specific assays during the early response [36]. Modelling studies suggest arrival symptom screening would miss 67.6–86.3% of infected travellers when implemented alone in a steady-state outbreak, and a seven-day universal quarantine would miss 26.3% of travellers, while a combination of the two would still miss 17.8–22.7% [36]. Even a 21-day quarantine is expected to have gaps in effectiveness if the distribution of incubation is heavy-tailed [36]. The episode thus mirrors the structural lessons from earlier outbreaks: in 2007, the delayed confirmation allowed for it to silently spill over for about three months [4, 33], and in 2012, it emerged earlier and

more complex than initially appreciated, due to retrospective genomics [5]. The post-2014 pandemic structure (PHEIC, border measures, modeling-based policy making) has been institutionalized in the 2026 response and generic ebolavirus genomic surveillance protocols are now available for variant-agnostic sequencing [37]. However, the proven ineffectiveness of surveillance and the combination of the lack of diagnostics for BBDV has shown that gaps in surveillance are still persisting, and the ultimate cure for the virus will depend on continued diagnostic and response capacity in BBDV endemic areas of Africa [2, 37].

**Table 2. Comparison of reported Bundibugyo virus outbreaks**

| Characteristic | Uganda, 2007–2008 | Isiro, DRC, 2012 | DRC/Central Africa, 2026 |
|---|---|---|---|
| **Location** | Bundibugyo District, western Uganda [4] | Isiro, Haut-Uélé, DRC [34] | DRC; ongoing [36] |
| **Outbreak period** | August 2007–February 2008 [4] | August–November 2012 [34] | 2026; ongoing [36] |
| **Reported cases** | 93–192 cases were reported across different investigations, with laboratory confirmation varying between studies [3, 4, 6, 33] | 62 cases: 36 confirmed, 21 probable, and 5 suspected [34] | 5,794 confirmed cases [38] |
| **Deaths** | 37 deaths reported [4, 6] | 34 deaths overall [34] | 2,786 deaths [38] |
| **Case-fatality ratio** | Approximately 25–42%, depending on case definition and study population [4, 6, 33] | 54.8% overall [34] | 48.1% [38] |

### 3. Reservoir Ecology and Transmission Dynamics in Conflict-Affected Settings

Bundibugyo virus has not been conclusively associated with a natural host but there is convergent ecological evidence that suggests that it is a virus of bats. Bat or non-human primate carcass activities (hunting, butchering and consumption) are widely reported in community-level studies, and substantial roosting populations of Angolan soft-furred fruit bats (Lissonycteris angolensis ruwenzorii) and Sundevall's leaf-nosed bats (Hipposideros caffer) have been documented in Bundibugyo District [8, 39]. Bats are known to host over 60 viruses such as members of the Ebola, Nipah, Hendra and Lyssavirus genera and filovirus spillover events have been associated with seasonal reproductive and food abundance in reservoir hosts and habitat fragmentation [40, 41]. There are other, similar potential routes of exposure for Ebola virus: a 2007 index case of Luebo was associated with exposure to

bushmeat from bats; the 2013–2016 West African epidemic is thought to have started in a hollow tree where insectivorous bats reside [8, 41]. After spillover has happened, the secondary transmission picture is more strongly determined by the human contact network, and the capacity of the response. These limitations were demonstrated during the 2018-2019 EVD outbreak in eastern DRC, the first to occur in a war setting: around 55 million screenings, 12,591 contacts monitored, 112,485 vaccinations administered and approximately 280 samples processed daily were not enough to stop the spread of EVD and coincided with an increase in the incidence of the disease at the same time as direct attacks against treatment units occurred [42, 43]. In Butembo, the coordination hub, mathematical modelling indicated that the speed of case-isolation and uptake of vaccination at the community level depended on previous conflict events, and the strategy that was finally implemented, a combination of enlarged ring vaccinations around clusters and increased community engagement, was able to bring the main hotspot under control [44, 45]. On a larger scale, at North Kivu/Ituri, the frequency of conflict events was about 600 times higher in affected health zones than in other health zones of the DRC, with many deaths not being detected or reported and not occurring in treatment facilities [42, 43, 46]. Such structural vulnerabilities are repeated in the 2026 Central African's epidemic; in conflict affected areas, the time window for the transition between animal-to-human spillover to contained human-to-human transmission is therefore very short.

### *3.1 The clinical spectrum and pathogenesis*

In general, the clinical spectrum of Bundibugyo virus disease resembles that of other orthoebolaviruses but is of different proportions. The most common features at presentation were not specific (fever, severe headache, abdominal pain, myalgia, vomiting, diarrhea) and the case fatality rate was ~40%, intermediate between the case fatality rate of Ebola virus (~80–90%) and Sudan virus (~50–55%); overt hemorrhage was observed in a minority of cases in the 2007 outbreak of Bundibugyo compared to ~45% over historical EBOV outbreaks [3, 7]. The same factors have been noted in parallel clinical observations done during the outbreak of Isiro in 2012 [34] and in all the following literature on case management, supportive intensive care, electrolyte replacement and strict infection control have been emphasized as the operational standard [6]. The molecular mechanisms underlying the pathogenesis of BBDV are not completely understood. Comparative sequence analysis reveals that there are significant differences between BDBV's surface glycoprotein GP1 and its Zaire ebolavirus orthologs, as well as differences in the interferon antagonist VP35, and experimental infection shows that BBDV is measurably different from pan-ebolavirus interventions but also is intrinsically lethal in cynomolgus macaques [3, 47]. The glycan cap of GP, a feature that is conserved across pathogenic orthoebolaviruses, has been validated as important target for protective monoclonal antibodies, and recent host response investigations (using RNA-seq) have shown that transcriptomic signatures obtained during early infection in experimental BDBV infections statistically predict fatality at later time points, similar to biomarker data from Lassa virus cohorts and a small number of plasma proteins stratifying survivors and non-survivors with high statistical confidence [47, 48]. The distance between Ebola virus–specific

and pan-ebolavirus Immunotherapeutics is yet to be bridged for therapeutic translation. Only two antibody cocktails, ZMapp and REGN-EB3, have been tested with remdesivir in EVD patients, and EVD mortality is reduced to ~30% in treated patients; however, only the two-antibody cocktail mAb114 has protective efficacy against EBOV, SUDV, and BDBV in ferrets and nonhuman primates, and there is no report of any MBP134AF clinical trial endpoint for confirmed cases of BBDV [47, 49, 50]. The current investigation of Bundibugyo virus disease in 2026 thus has the potential to improve the available therapeutic envelope – supportive intensive care and available cross-protective monoclonal antibodies, and, following lab confirmation, remdesivir if it is available.

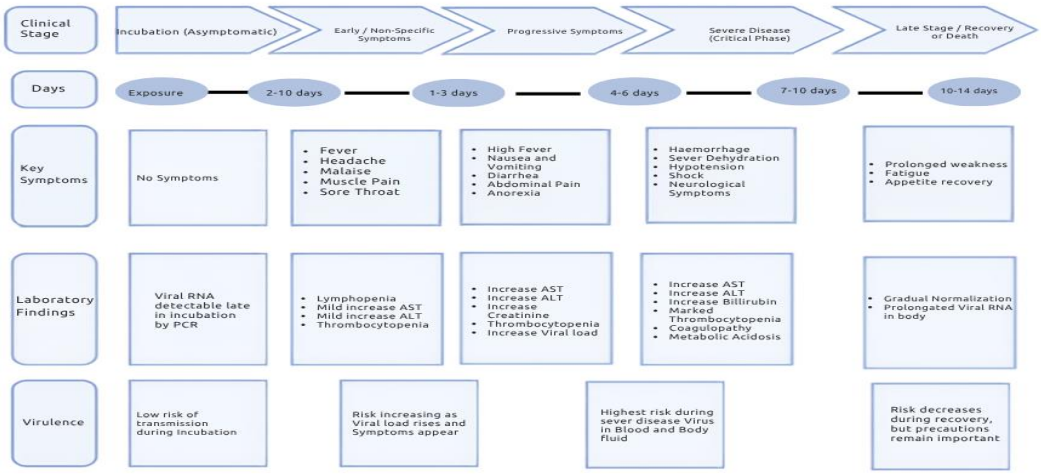



***Figure 3— Clinical progression / symptom timeline***

### *3.2. Effective, efficient communication with remote and insecure locations*

Molecular detection using reverse transcription PCR (RT-PCR) is the gold standard for filovirus diagnosis, but diagnosis capacity is consistently lagging in outbreak areas where there is conflict [51]. The decentralised platforms, Xpert Ebola, FilmArray and the Idylla Ebola Virus Triage Test, were all authorised for use during the West African epidemic that began in 2014, and give results in 1-2 hours, but require continuous electricity, temperature control and trained staff [51, 52]. In the context of the 2018–2019 EVD response in eastern DRC, the response was able to process about 280 samples per day in the face of ongoing armed conflict, and to operate in insecure areas at sustained logistical cost [43]; in Guinea, the molecular capacity was decentralized, with the deployment of MinION nanopore sequencing for variant-agnostic genomic surveillance [37, 53]. Rapid diagnostic tests designed for field use do not consistently measure the same thing. The SD Ebola Zaire Ag lateral-flow assay was highly sensitive (84.5%) and highly specific (99.0%) on whole-blood samples in the 2014–2016 West African evaluations, and in Sierra Leone a United Kingdom Defence Science and Technology Laboratory RDT was 100% sensitive (78.2–100% CI) with a specificity of 96.6% (91.3–99.1% CI) when using a higher test-line threshold [37, 53-55]. The 510(k)-cleared OraQuick Ebola Rapid Antigen Test (OQ EA) has demonstrated sensitivity of 84.0% on venous whole blood, 90.9% on fingerstick samples from infected nonhuman primates and 97.1% on cadaver buccal swabs [56]. The ReEBOV dipstick, which detects

VP40 antigen from Zaire, Sudan, and Bundibugyo viruses, has been shown to be 100% sensitive on high viral load specimens and is potentially cold-chain independent [57-59]. The diagnostic challenge for Bundibugyo virus is not the lack of an appropriate antigenic target (ReEBOV and OraQuick are cross-reactive with all pathogenic orthoebolaviruses) but rather fragility of supply, reliance on cold-chain consumables incompatible with active conflict and lack of BDBV-specific quantitative thresholds [36, 56].

**4. Therapeutic Landscape**

There is no therapeutic licensed for Bundibugyo virus disease and the licensed armamentarium is specific for Zaire ebolavirus [49]. The randomized PALM trial during the 2018-2019 North Kivu outbreak, demonstrated a survival benefit for both the single monoclonal antibody mAb114 and the triple-antibody cocktail REGN-EB3 compared to the comparator ZMapp, while the nucleotide analogue remdesivir did not [60, 61]. Both the antibody products were later approved for Ebola virus disease, but both were not targeting BBDV [49, 62]. The PALM design has also been informative: even in outbreak settings, when the efficacy of the comparator is highly questionable, randomized evaluation is viable at an interim analysis when the PALM is crossed [9, 60]. BDBV has been a relatively new and preclinical development. The glycan cap of GP was targeted by a human monoclonal antibody that was able to provide protection for nonhuman primates challenged with BBDV at a dose lethal for untreated animals, potentially as part of multi-antibody cocktails [47]. The most advanced is MBP134AF, a two-antibody pan-ebolavirus cocktail that is composed of antibodies that recognize conserved GP epitopes and has been shown to protect ferrets and nonhuman primates from Ebola, Sudan virus, and Bundibugyo virus; this is being tested in the present clinical trial, either alone or in combination with remdesivir, for Sudan virus disease in Uganda [49]. More broadly, the antibody EBOV-520 targets a vulnerable site that is found in the GP base and neutralizes all three pathogenic species including BDBV [63]. A key lesson that can be drawn from the PALM trial is that single- versus multi-antibody regimens have different pros and cons: while the former may lead to an escape, the latter are more likely to be favoured, as illustrated by the divergent outcome of the single versus multi-antibody arms of the PALM trial [9, 61];a comparative lesson that is repeated [49]. The resulting therapeutic landscape in 2026 is also asymmetric: while the Ebola virus disease can be treated with licensed antibody therapy, the Bundibugyo virus disease can be treated with supportive intensive care with electrolyte repletion [6], plus cross-reactive monoclonal antibodies under emergency-use provisions. The current epidemic in Central Africa, the first BDBV case since MBP134AF was brought into clinical development, might provide the first human efficacy data, which is a gap that remains the most noticeable in the field [2, 49].

**5. Vaccine Development**

Zaire-specific is also the case for licensed ebolavirus vaccines. The adenovirus/modified vaccinia Ankara vaccine (Ad26/MVA) was highly effective in a phase III ring vaccination study in Guinea (97.5% effective in preventing transmission [64], 95% CI 81.8–99.9), and it is approved by the US FDA

and European Medicines Agency [65, 66]. The evaluation of ZEBOV (followed by MVA-BN-Filo) has been carried out in adults and children by randomized trials [67]. However, there is some tempering of expectations from durability data in nonhuman primates: protection was at high levels at 4-8 months after rVSV-ZEBOV vaccination (88-93% survival) but dropped to 53% at 12 months despite ongoing antibody levels [68]. The focus of the design problem is cross-protection against BBDV. The rVSV expressing the Côte d'Ivoire GP was less protective than the rVSV expressing the Zaire GP, with only 75% of cynomolgus macaques being immune after a single dose of either vaccine [15]; subsequent testing showed that complete protection with monovalent heterologous vectors is challenging [69]. The one notable exception is a DNA/adenovirus vaccine encoding Zaire and Sudan glycoproteins, which uniformly protected primates from lethal challenge with BBDV, believed to be via potent cellular immunity [70]. Consideration of the breadth was intended; for example, a quadrivalent VesiculoVax formulation was developed to prevent multiple filoviruses and Lassa virus, and the rVSV backbone could be used to express BDBV GP [65]. Although replicating vectors [64] are safer than mRNA–lipid nanoparticle vaccines (mRNALPs), which have protected guinea pigs and mice [71, 72], no ebolavirus mRNA candidate has yet advanced into clinical trials [73]. First, a multivalent or conserved-epitope platform is thus the focus, as outbreaks of this virus occur years apart and in less secure areas, and the vectors should also be durable and single-dose practical, like the licensed vectors [49, 74].

**Table 3. Selected vaccines and therapeutics for ebolaviruses and their relevance to BDBV**

| Candidate | Platform / target | Development stage | Key evidence | Relevance to BDBV |
|---|---|---|---|---|
| **mAb114** | Human monoclonal antibody directed against EBOV GP | Licensed | In the PALM randomized clinical trial, mAb114 was associated with higher survival than ZMapp in patients with Ebola virus disease [61] | **No**; activity is directed against EBOV. |
| **REGN-EB3** | Three monoclonal antibodies targeting EBOV GP | Licensed | REGN-EB3 showed greater efficacy than ZMapp in the PALM trial [61] | **No**; evidence is specific to EBOV. |
| **Remdesivir** | Nucleotide analogue prodrug | Clinical evaluation | Clinical evaluation did not demonstrate improved survival compared with ZMapp [60] | **Not established** for BDBV. |

| | | | | |
|---|---|---|---|---|
| **MBP134AF** | Two monoclonal antibodies recognizing conserved epitopes on GP | Clinical trials | MBP134AF has provided protection against EBOV, SUDV, and BDBV in animal models, with clinical evaluation also extending to Sudan virus disease [49] | **Yes**; evidence supports cross-species protection. |
| **Glycan cap-specific mAb** | Human monoclonal antibody targeting the GP glycan cap | Preclinical | A glycan cap-specific monoclonal antibody protected nonhuman primates from lethal BDBV infection [47] | **Yes**; direct BDBV protection has been demonstrated. |
| **rVSV-ZEBOV** | Replication-competent VSV vector expressing EBOV GP | Licensed | High protective efficacy was demonstrated in ring-vaccination studies [64, 65] | **Partial**; evidence of protection against BDBV exists in NHPs. |
| **Ad26.ZEBOV + MVA-BN-Filo** | Viral-vector prime–boost vaccine | Clinical trials | Clinical studies have demonstrated acceptable safety and immunogenicity in both adults and children [67] | **Not established**; BDBV protection has not been sufficiently demonstrated. |
| **DNA/rAd5 (ZEBOV + SUDV GP)** | DNA prime followed by recombinant adenovirus boost | Preclinical | The vaccine regimen protected nonhuman primates against lethal BDBV challenge, indicating cross-species protective potential [70] | **Yes**; cross-species protection has been demonstrated. |
| **Quadrivalent VesiculoVax** | Multivalent rVSV-based vaccine platform | Preclinical | Protection against multiple filoviruses has been demonstrated in nonhuman primate studies [74] | **Potential**; the platform may accommodate BDBV GP. |
| **mRNA-LNP** | Lipid nanoparticle– | Preclinical | Animal studies have demonstrated protective | **Potential**; further BDBV-specific |

| | | | | |
|---|---|---|---|---|
| | encapsulated mRNA platform | | immune responses, although development for filovirus prevention remains comparatively limited [71-73] | evaluation is required. |

**6. Response and Containment of Public Health**

The first outbreak of orthoebolavirus in DRC, the 2018-2019 EVD outbreak in the east, established the operational limit of containment of filovirus in a situation of insecurity. Despite the response accumulating about 55 million screenings, watching 12,591 contacts, delivering 112,485 doses of vaccine and testing about 280 samples a day, there were direct attacks on Ebola treatment units that coincided with the declines in Ebola incidence and transmission remained for over two years [42, 43]. In the Butembo coordination hub, the speed at which cases were isolated and the level of vaccination at the population level were found to differ depending on previous conflict events, and an adjusted strategy of ring vaccination of cases with broadened size, and increased community engagement, eventually brought a major hotspot under control [44, 45]. The number of conflict events in affected health zones was 600 times higher than in other zones of the DRC, and many deaths in the affected areas have not been reported or detected and required safe burial [46]. Combined, these data reflect the quantitative limits of what filovirus response can accomplish in the event of a serious outbreak – and below which it will not stop transmission. That's the same envelope for the 2026 Bundibugyo response. While symptom-based travel bans, entry screening, and post-arrival quarantine are among the measures proposed by affected governments, quantitative evaluation shows that symptom-based entry screening would fail to capture 67.6–86.3% of infected travellers in a steady state outbreak, while a seven-day universal quarantine would still miss 26.3% and a combination of both would miss 17.8–22.7% [36]. The 21-day quarantine is less than ideal, as the incubation-period estimates are uncertain, and molecular screening is limited by the time required for the virus to be detectable after it has been acquired [36]. The clinical response architecture was based on a framework known as PALM, that showed that randomized evaluation during outbreaks is possible, and that an interim analysis precedent was established that is now part of outbreak-trial ethics [60, 61]. Pre-emptive genomic surveillance with generic filovirus assays provides a third layer, allowing for variant-agnostic sequencing in a matter of hours, as opposed to weeks [37]. At every level of intervention, the constraint identified in Uganda in 2007 is surveillance and diagnostic gaps prolong transmission [33] and there is no technical solution to this constraint.

***Discussion: How a "Minor" Filovirus became a "Major" Epidemic***

BDBV has been historically described as a ‘minor’ orthoebolavirus with a case fatality rate of ~25–42% (across reports) compared to Ebola virus (60–90%) and Sudan virus (40–60%) [22]. This framing, however, combines the level of severity in each case with the potential for an outbreak. The admission

of BDBV to the list of public health emergencies of international concern (PHIEC) — its first such listing for this virus — illustrates how relatively mild virulence of BBDV can grow into a regional public health emergency in suitable conditions [36]. In four intersecting ways this transition occurs. First, viral genetics. Species-specific countermeasures, such as ZMapp, mAb114, REGN-EB3 and rVSV-ZEBOV, are only partially or fully ineffective because of BDBV's ~32% nucleotide divergence from its closest species, Côte d'Ivoire ebolavirus, and >27% amino-acid divergence from GP and >35% amino-acid divergence from Zaire ebolavirus [3, 15, 62]. For example, the licensed rVSV-ZEBOV vaccine has been shown to provide only 75% protection against BDBV challenge in nonhuman primates leaving one in four animals unprotected unless pan-ebolavirus vaccines, or multivalent platforms, are used [15]. Second, reservoir uncertainty. Ecological evidence points to bats, but no definitive reservoir has been identified and repeated spillover events from wildlife to human are allowed to occur without actionable intervention [8, 39]; bats host more than 60 viruses and are the established reservoir of multiple filoviruses [40]. Thirdly the gaps in diagnosis and treatment. Lateral flow assays (LFA) that can detect antigens, like ReEBOV and OraQuick, cross-react with BDBV, but cross-reactive monoclonals are used under emergency-use provisions, and there is no therapeutic with BBDV-specific quantitative thresholds in use — patients rely on supportive intensive care [49, 56]. Fourth, ecological and political conditioning. Similarly, the geographic distribution of the current outbreak is in the filovirus 'spillover corridor' of forest fragmentation across equatorial Africa [41]. In conflict zones, there is a marked decline in surveillance, security of treatment units and simultaneous isolation of cases, all three of which are 600 times more common than in non-conflict areas [42, 46]. So, an uncharacterized reservoir, conflict-driven response fragmentation, neglected species-specific diagnostics and a modest per-case virus virulence can combine to scale up a modest virus into an epidemic, as seen in 2018–2019, where about 55 million viral tests and 112,485 doses of vaccination failed to provide an overall response to break DRC transmission [43]. To consider BBDV as a "minor" is to underestimate its zoonotic potential and what has become a reality after the 2026 event.

***Research Priorities and Preparedness Gaps***

In recent years, filovirus preparedness has been discussed in terms of four mutually reinforcing objectives—animal reservoir identification, improved diagnostics, broadened therapeutic options, and pan-ebolavirus vaccine construction [2, 75]. The 2026 Bundibugyo outbreak refocuses each into a research question. The priority for reservoir work is to conduct bat surveillance in the affected central African corridor using paired serologic and metagenomic sampling, alongside community-based One Health programmes to define bat-human exposure pathways [8, 39, 40]. This type of activity will not produce clear results in one funding period but is necessary to turn speculation into risk-assessment models that can be acted upon [41]. In terms of diagnostics, the focus is on point-of-care BDBV-specific PCR and antigen assays that do not require cold chain; isothermal platforms are already capable of detecting filovirus RNA in ~ 10 minutes at ambient temperatures and have been demonstrated to be useful to extend the diagnostic reach to insecure settings [57-59]. The use of randomized clinical trial

frameworks is also well known and widely used in standard operating procedures and thus can be adapted during the current outbreak [60, 61]. The therapeutic priority is to advance progress in MBP134AF, a two-antibody cocktail that has proven efficacy against nonhuman primates infected with Ebola, Sudan and Bundibugyo viruses, into registered clinical trials of patients with confirmed BDBV infection and to incorporate mAb114 style single antibodies into multi-target therapeutics to prevent viral escape [50, 62]. Multivalent or conserved-epitope vaccines are prioritized, as well as vaccines based on DNA/Ad5 vaccine platforms as they have been proven to provide uniform protection against BDBV in nonhuman primates, and mRNA-lipid nanoparticles are already being explored as a scalable platform for vaccine clinical translation [70, 71]. In terms of surveillance, generic filovirus amplicon sequencing allows for variant-agnostic surveillance in real time and is the most cost-effective protection against the next unexpected emergence [37]. Each of these priorities is a chance to be realized in the 2026 outbreak in a way that is the most productive it has been in almost 20 years before the cycle begins again.

***Conclusion***

Bundibugyo virus, which was first detected in Uganda in 2007 and was since confirmed as the cause of an outbreak in the Democratic Republic of the Congo in 2012, is resurgent as the first orthoebolavirus species to enter a Public Health Emergency of International Concern. Molecular characterization found ~32% divergence in nucleotides from its closest relative and significant divergence in the surface glycoprotein, making it difficult to achieve species-specific monoclonal antibody therapeutic and the licensed rVSV-ZEBOV vaccine was only moderately effective. Low case fatality ratios (CFRs, 25-42% in documented epidemics) make BBDV an intermediate per-case virulence, but the present epidemic shows that despite its relatively low pathogenicity, it can be significantly more virulent at the regional level if reservoir uncertainty, diagnostic gaps, vaccine partiality and/or response fragmentation due to conflict are present. This evidence over time has consistently identified a consistent trend: the delayed laboratory confirmation of cases prolonged transmission chains in the index outbreak, the retrospective genome sequencing in the 2012 Isiro outbreak adjusted the timeline, and quantitative analyses of border screening and quarantine operations suggest that presymptomatic travel, driven by a median incubation period of ~ 6.3 days, is a primary constraint on the ability to contain transmission by symptom-based surveillance. Future collective efforts to be prepared for the next emergence will need to rely on pan-ebolavirus monoclonal antibody cocktails that have been tested in humans, widely used vaccine platforms that activate conserved epitopes and avast vaccine platforms that offer multiple epitopes, and on multispecies or community-based One Health surveillance systems, with point-of-care diagnostics that can be deployed without a cold chain, along with prospective bat surveillance that can be carried out in conjunction with community-based One Health approaches. BDBV will be taking advantage of these same structural weaknesses that were discovered in 2007 until they can be patched.

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