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Supplementary information

Therapeutic and prophylactic strategies for Ebola caused by Bundibugyo virus

In the format provided by the authors and unedited

Supplementary Table 1 | Existing and candidate therapeutic, prophylactic and vaccine options for Bundibugyo Ebola virus disease

Treatment and clinical-care countermeasures for Bundibugyo Ebola virus disease

Product/ strategy/Class	Proposed role in BVD	Mechanism of action / therapeutic rationale	Evidence base	Key uncertainties	Operational requirements	Priority action(s)
Optimised supportive and critical care Clinical-care platform	Foundation of treatment for all suspected and confirmed cases	Corrects the physiological consequences of Ebola disease, including dehydration, electrolyte disturbance, shock, hypoxia, co-infections, bleeding, pain, nutritional compromise and organ dysfunction	Early high-quality supportive care is lifesaving in Ebola disease and is the ethical foundation for all therapeutic trials	Minimum care package; best delivery model in insecure or under-resourced settings; referral thresholds	Requires trained staff, PPE, safe isolation, fluids, electrolytes, oxygen, point-of-care testing, blood products where indicated, waste management and psychosocial care	Treat supportive care as an active therapeutic intervention; standardise minimum care protocols; resource Ebola treatment units and mobile care teams
MBP-134 Broadly active monoclonal antibody cocktail	Treatment of confirmed BVD; possible future PEP candidate	Two broadly neutralising human monoclonal antibodies target conserved regions of ebolavirus glycoprotein, aiming to block viral entry and provide broader activity across ebolaviruses than Zaire-specific antibodies	WHO advisory groups prioritised MBP-134 for BVD clinical evaluation; preclinical data support broad activity across multiple ebolaviruses	Human efficacy in BVD; optimal dose; timing; safety in pregnancy and children; effect in late presenters; viral escape	Likely requires parenteral administration, cold chain, trained staff, infusion monitoring and trial infrastructure	Evaluate urgently in adaptive clinical trials with virological, clinical and safety endpoints
Maftivimab Monoclonal antibody; component of atoltivimab–maftivimab–odesivimab	Treatment of confirmed BVD cases; potential cross-species antibody candidate	Antibody targeting ebolavirus glycoprotein; selected component of a three-antibody Zaire ebolavirus treatment being evaluated for possible cross-species neutralising activity	WHO advisory groups prioritised maftivimab for BVD treatment trials; selected antibody components may have cross-species activity	Clinical efficacy against Bundibugyo virus; whether single-antibody use is sufficient; resistance risk; optimal pairing with antivirals or other antibodies	Parenteral delivery, supply constraints, cold-chain requirements, infusion capacity and monitoring	Evaluate only within research protocols; consider comparative or combination arms where feasible
Remdesivir Intravenous nucleotide analogue antiviral	Treatment of confirmed BVD; possible combination partner with monoclonal antibodies	Prodrug of an adenosine nucleotide analogue that inhibits viral RNA-dependent RNA polymerase after intracellular activation, thereby reducing viral RNA synthesis	WHO advisory groups prioritised remdesivir for confirmed BVD cases; prior filovirus preclinical and Ebola outbreak trial experience	Human efficacy in BVD; optimal timing; benefit in high viral-load or late disease; renal/hepatic safety; interaction with antibody therapy	Requires IV administration, infusion staff, laboratory monitoring and repeat dosing	Evaluate as monotherapy and in combination with monoclonal antibodies; collect pharmacokinetic, virological and clinical outcome data
Monoclonal antibody plus remdesivir Combination antiviral–antibody therapy	Treatment of confirmed BVD cases	Combines antibody-mediated viral neutralisation with polymerase inhibition; complementary mechanisms may improve viral suppression, reduce treatment failure and limit emergence of escape variants	WHO advisory groups recommended evaluation of monoclonal antibody–remdesivir combination therapy	Additive or synergistic benefit; toxicity; optimal timing; feasibility; cost-effectiveness; best antibody partner	More complex than monotherapy; requires coordinated drug supply, administration schedules and monitoring	Include in adaptive platform trials; predefine stopping rules, safety monitoring and virological endpoints
Ansuvimab/ mAb114 and REGN-EB3 Licensed/recommended monoclonal antibodies for Zaire ebolavirus disease	Established treatment for Zaire ebolavirus disease; not approved for BVD	Ansuvimab is a single monoclonal antibody targeting Zaire ebolavirus glycoprotein; REGN-EB3 is a three-antibody cocktail targeting distinct glycoprotein epitopes to neutralise virus and reduce escape risk	PALM trial demonstrated survival benefit in Zaire ebolavirus disease; WHO recommends these products for Zaire ebolavirus disease	Cross-species activity uncertain; clinical benefit in BVD unproven; risk of inappropriate extrapolation	Existing stockpiles do not solve the BVD therapeutic gap	Maintain for Zaire ebolavirus preparedness; do not use as substitute for Bundibugyo-specific evaluation unless evidence supports it

Product/ strategy/Class	Proposed role in BVD	Mechanism of action / therapeutic rationale	Evidence base	Key uncertainties	Operational requirements	Priority action(s)
Host-directed therapies Diverse range of products Adjunctive treatment targeting host response	Severe disease adjunct, especially for shock, endothelial injury, vascular leak, coagulopathy or dysregulated inflammation	Targets host pathways contributing to severe disease, including immune dysregulation, endothelial dysfunction, vascular leakage, coagulation abnormalities and organ failure	Biological rationale is strong, but Ebola-specific clinical evidence is limited	Which pathways to target; timing; safety; risk of harmful immune modulation; endpoint selection	Requires disease staging, monitoring capacity, biomarker support where feasible and careful inclusion criteria	Prioritise only biologically plausible candidates; evaluate in staged protocols, not uncontrolled use
Coagulation /endothelial-support strategies	Management of bleeding, vascular leak, shock and coagulopathy	Supports vascular integrity, haemostasis and organ perfusion in severe disease; may include blood products, correction of anaemia/coagulopathy and shock management	Severe filovirus disease can involve endothelial dysfunction, thrombocytopenia, coagulopathy and multiorgan failure	Which interventions improve outcomes; resource feasibility; transfusion risks	Requires laboratory testing, blood products, safe transfusion systems and trained staff	Include in standardised supportive-care protocols and observational outcome datasets
Nutritional and micronutrient supplements Host-resilience and supportive-care Adjunct as host-directed therapy	Support for patients with malnutrition, food insecurity or severe catabolic illness	Supports host immune function, tissue repair and recovery; may be especially relevant where conflict, displacement, poverty and food insecurity worsen baseline vulnerability	Strong clinical rationale, but limited Ebola-specific interventional evidence	Which nutritional interventions improve outcomes; baseline deficiency assessment; dosing and timing	Requires food and supplement supply chains, safe feeding protocols, monitoring and integration with clinical care	Incorporate nutrition into minimum care packages; evaluate pragmatic nutritional and micronutrient strategies where deficiencies are likely
Treatment of co-infections and comorbidities Supportive holistic/ adjunctive clinical care	Management of malaria, bacterial infection, pregnancy-related complications, HIV, tuberculosis or other comorbidities	Reduces preventable mortality and diagnostic confusion from common co-infections and comorbidities that can worsen clinical outcomes	Standard clinical practice; not Ebola-specific drug efficacy evidence	Best diagnostic algorithms; drug interactions; safe treatment in pregnancy and children	Requires diagnostic capacity, essential medicines and trained clinical teams	Standardise assessment and treatment of common co-infections and comorbidities in BVD care protocols
Convalescent or hyperimmune plasma Polyclonal antibody - immune strategy	Possible bridging or emergency research option	Provides polyclonal antibodies from survivors that may neutralise virus and support viral clearance if antibody titres are adequate	Historically used in Ebola outbreaks; controlled evidence has not shown clear benefit when titres are not standardised	Variable antibody titres; uncertain efficacy; transfusion risk; standardisation; donor availability	Requires blood collection, screening, compatibility testing, cold chain and transfusion capacity	Consider only within rigorous protocols if high-titre, safe, standardised products can be generated
Small-molecule antiviral pipeline beyond remdesivir/ obeldesivir Direct-acting antivirals	Early treatment, outpatient therapy or PEP	Targets viral replication, entry or other conserved viral functions; oral or simplified agents could improve field deployability	Mostly preclinical or early-stage; broad filovirus activity remains to be established clinically	Preclinical-to-human translation; resistance; safety; dosing; activity against Bundibugyo virus	Field use requires stability, affordability, simple dosing and minimal monitoring	Prioritise broad, oral, stable candidates with animal efficacy and human safety data
RNA-based approaches RNA interference, antisense or gene-expression platforms	Future therapeutic or rapidly adaptable platform	Uses sequence-directed silencing or inhibition of viral RNA, or engineered nucleic-acid platforms to block viral gene expression or replication	Earlier Ebola RNA/antisense approaches generated safety and proof-of-concept data but no established clinical efficacy	Delivery, safety, manufacturing, durability, cost and field feasibility	Complex administration and monitoring may limit outbreak use	Keep in strategic pipeline; do not overemphasise for immediate BVD response

The above portion of the table summarizes treatment and clinical-care countermeasures for Bundibugyo Ebola virus disease, including their proposed role, mechanism of action or therapeutic rationale, evidence base, key uncertainties, operational requirements and priority actions. The table distinguishes virus-directed therapies, antibody-based interventions, host-directed and supportive-care strategies, and longer-term therapeutic platforms, emphasising that no treatment is currently licensed specifically for Bundibugyo virus disease. References for this portion of the table are provided below. The WHO 28 May 2026 advisory committee confirmed the key BVD candidates: MBP134/MBP-134, maftivimab, remdesivir, monoclonal antibody–remdesivir combination therapy, obeldesivir PEP, rVSV Bundibugyo vaccine, and ChAdOx1 Bundibugyo vaccine.

BVD, Bundibugyo virus disease; DRC, Democratic Republic of the Congo; EBOV, Ebola virus or Zaire ebolavirus, depending on context; IPC, infection prevention and control; IV, intravenous; mAb, monoclonal antibody; PCR, polymerase chain reaction; PEP, post-exposure prophylaxis; PPE, personal protective equipment; R&D, research and development; RNA, ribonucleic acid; WHO, World Health Organization.

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Prophylaxis, vaccines, diagnostics and implementation adjuncts for Bundibugyo Ebola virus disease

Product or strategy	Class	Proposed role in BVD	Evidence base and rationale	Key uncertainties	Operational considerations	Priority action
Obeldesivir	Oral nucleoside analogue antiviral	PEP among contacts of confirmed or probable BVD cases; possible future early-treatment candidate	WHO advisory groups identified obeldesivir as a priority PEP candidate; oral administration makes it attractive for field deployment	Human protective efficacy; exposure window; dose; duration; adherence; resistance; safety in pregnancy, children and co-morbidities	Depends on rapid contact tracing, exposure classification, informed consent, drug distribution, adherence support and follow-up	Evaluate in PEP protocols among defined high-risk contacts; integrate with contact tracing, safety monitoring &virological follow-up
Monoclonal antibody-based PEP	Passive immunoprophylaxis	Possible future PEP for high-risk contacts, health-care workers or laboratory exposures	Antibody-based products can provide immediate passive protection; relevant if broadly active products are available	Protective efficacy after exposure; timing; dose; duration; safety; feasibility; cost	Parenteral delivery, cold chain and monitoring may limit field use	Consider only within defined PEP protocols; compare feasibility with oral antiviral PEP
Vaccine plus PEP strategy	Combined immediate and durable protection	High-risk contacts, health-care workers and burial teams	PEP could provide immediate protection while vaccination induces longer-term immunity	Optimal sequence; safety; efficacy; interactions; operational complexity	Requires careful communication to avoid false reassurance; needs follow-up and adherence	Develop protocols for combined PEP–vaccination evaluation when suitable products are available

Product or strategy	Class	Proposed role in BVD	Evidence base and rationale	Key uncertainties	Operational considerations	Priority action
Candidate Bundibugyo vaccines	Species-specific vaccine candidates	Potential prevention for contacts, health-care workers and at-risk populations; possible ring-vaccination candidates	Candidate vaccines are being developed or reviewed for possible outbreak evaluation including the single-dose sVSV Bundibugyo vaccine and ChAdOx1 Bundibugyo	Immunogenicity, efficacy; time to protection; dosing; safety; manufacturing scale-up; need for further animal data for some candidates	Requires trial readiness, cold chain, ring-vaccination logistics, consent and pharmacovigilance	Prepare for evaluation through outbreak-ready vaccine protocols when products become available
Existing Zaire ebolavirus vaccines	Licensed vaccines for Zaire ebolavirus disease	Prevention of Zaire ebolavirus disease; uncertain role in BVD	Existing Zaire vaccines transformed Zaire ebolavirus outbreak response	Cross-protection uncertain; risk of false reassurance if used without evidence	Ring-vaccination infrastructure exists but requires a species-appropriate product	Do not deploy outside research settings unless evidence and WHO guidance support use; current WHO advice is that Zaire ebolavirus vaccines should not be used for BVD outside research settings unless supportive evidence emerges.
Multivalent or pan-ebolavirus vaccines	Broad preventive vaccine platforms	Longer-term prevention across Zaire, Sudan, Bundibugyo and other ebolaviruses	Addresses repeated species-specific preparedness gaps	Breadth, durability, immune correlates, regulatory pathway, manufacturing and cost	Requires sustained R&D beyond the outbreak cycle	Advance as strategic preparedness products aligned with WHO priority-pathogen and regional stockpile needs
Rapid diagnostics linked to therapeutic allocation	Diagnostic-enabling intervention	Species confirmation, triage and eligibility for trials, treatment or PEP	Treatment decisions depend on identifying the ebolavirus species and confirming infection or exposure	Turnaround time; decentralisation; genomic confirmation; integration with clinical trials	Requires sample transport, biosafety, trained staff, data linkage and quality assurance	Integrate diagnostics, genomics and treatment/PEP protocols from the start
Infection prevention and clinical observation for contacts	Non-pharmacological prevention platform	Standard management of contacts, with or without PEP	Contact tracing, symptom monitoring and IPC remain essential even if PEP is evaluated	Completeness of contact lists; mobility; stigma; adherence to monitoring	Requires community trust, local health workers, data systems and safe referral pathways	Pair any PEP evaluation with strengthened contact tracing, IPC and community engagement
Occupational-health pathways for exposed staff	Workforce-protection platform	Rapid risk assessment, testing, PEP and follow-up for health-care workers, burial teams, cleaners and laboratory staff	Frontline workers face repeated high-risk exposures and are essential for outbreak control	Under-reporting, stigma, confidentiality, return-to-work criteria	Requires exposure reporting systems, counselling, testing, PEP access and psychosocial support	Integrate occupational exposure pathways into all PEP and clinical-research protocols
Psychosocial and community-support interventions linked to care	Care-delivery adjunct	Improve acceptance of treatment, PEP, vaccination and follow-up	Fear, isolation, burial restrictions and mistrust undermine uptake of care and trials	Best models for engagement; measuring impact; sustainability	Requires local leadership, communication teams, survivor networks and social support	Embed in all therapeutic, PEP and vaccine protocols as part of ethical implementation
One Health surveillance and upstream prevention	Spillover-prevention platform	Reduce risk of future zoonotic emergence and improve early warning	Human–animal interactions, ecological disruption, conflict, displacement, poverty and food insecurity can increase exposure risks and delay detection	Best surveillance models; sustainable community participation; wildlife-reservoir uncertainty	Requires integration of human, animal, environmental and community surveillance systems	Link countermeasure preparedness with One Health surveillance, early warning and interventions addressing structural drivers of spillover

The above portion of the table summarizes prevention and implementation strategies relevant to Bundibugyo Ebola virus disease, including obeldesivir PEP, antibody-based PEP, vaccine–PEP strategies, candidate Bundibugyo vaccines, existing Zaire ebolavirus vaccines of uncertain relevance to BVD, multivalent or pan-ebolavirus vaccines, rapid diagnostics linked to treatment allocation, infection prevention, contact monitoring, occupational-health pathways, psychosocial and community-support interventions, and One Health surveillance. It highlights how prophylaxis, vaccination, diagnostics, community engagement and upstream prevention should be integrated with therapeutic preparedness. References for this portion of the table are provided below.

BVD, Bundibugyo virus disease; DRC, Democratic Republic of the Congo; EBOV, Ebola virus or Zaire ebolavirus, depending on context; IPC, infection prevention and control; IV, intravenous; mAb, monoclonal antibody; PCR, polymerase chain reaction; PEP, post-exposure prophylaxis; PPE, personal protective equipment; R&D, research and development; RNA, ribonucleic acid; WHO, World Health Organization.

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Supplementary Table 2 | Platform requirements and outbreak opportunities for rapid evaluation of Bundibugyo Ebola countermeasures

Platform element	Why it matters	Application to BVD countermeasures	Key design or implementation issues	Priority action
Standing master protocols	BVD outbreaks are sporadic, geographically difficult and often too short for protocols to be developed only after an outbreak begins	Enables rapid evaluation of MBP-134, maftivimab, remdesivir, antibody–remdesivir combination therapy, obeldesivir PEP and candidate vaccines	Pre-specified eligibility criteria, consent procedures, endpoints, randomisation, adaptive rules, safety monitoring and amendment pathways	Maintain pre-approved, locally owned master protocols between outbreaks, with rapid amendment procedures for new candidates
Adaptive platform trial design	Candidate products, case numbers, product supply and outbreak geography may change rapidly	Allows treatment, PEP or vaccine arms to be added, dropped, combined or prioritised according to interim evidence and feasibility	Multi-arm, multi-stage design; Bayesian or frequentist adaptive rules; independent DSMB; stopping rules for futility, efficacy or harm	Use adaptive designs suited to rare outbreaks; predefine decision rules and pool data across sites or countries where appropriate
Rapid case confirmation and species-level diagnosis	Treatment choice depends on confirming BVD because Zaire-focused products cannot be assumed to work	Confirms trial eligibility; supports treatment allocation; identifies source cases for contact-based PEP and vaccine studies	PCR confirmation, species-specific assays, Ct values, genomic sequencing where feasible, and linkage to clinical and exposure data	Deploy decentralised testing where possible; link diagnostics, genomics and trial enrolment in real time
Exposure classification for PEP	PEP benefit depends on identifying true high-risk exposures within an actionable time window	Defines eligibility for obeldesivir PEP or future antibody-based PEP	Standardised exposure categories: household caregiving, direct body-fluid exposure, unsafe burial exposure, health-care exposure, laboratory exposure, cleaning or waste exposure	Use standard exposure definitions; train community-based contact-tracing teams; involve local leaders and survivor networks
Timing of intervention	Early treatment and early PEP are likely to be most effective, but diagnosis and presentation are often delayed	Captures time from symptom onset to treatment and time from exposure to first PEP dose	Stratification by symptom duration, viral load, disease severity, exposure timing and exposure intensity	Build rapid referral, dispensing and follow-up pathways into surveillance and contact-tracing systems
Clinical endpoints	Mortality is important but may be difficult to interpret when sample sizes are small or care quality varies	Supports evaluation of treatment efficacy and PEP or vaccine prevention of confirmed disease	Mortality, disease progression, organ dysfunction, length of care, development of confirmed disease among contacts, breakthrough infection and adverse events	Harmonise endpoints across DRC, Uganda and future outbreaks to allow pooled analyses
Virological endpoints	Viral kinetics can provide early efficacy signals when clinical endpoints are underpowered	Measures baseline viral load, viral decline, time to PCR negativity and breakthrough infection	Standard sampling schedule, Ct values, sequencing for resistance or escape, and linkage to pharmacokinetic data	Use simplified virological sampling protocols with reference-laboratory support and quality assurance
Safety monitoring and pharmacovigilance	Candidate products may be used in acutely ill patients or asymptomatic contacts during an emergency	Applies to mAbs, remdesivir, obeldesivir, vaccines and combination regimens	Infusion reactions, renal or hepatic toxicity, hypersensitivity, drug interactions, adherence, pregnancy outcomes and serious adverse events	Use pragmatic safety schedules, mobile follow-up teams, pregnancy registries and standard adverse-event definitions
Pregnancy and paediatric inclusion	Pregnant women and children are affected by Ebola but often excluded from trials despite high risk	Generates dosing, safety, efficacy and feasibility data for treatment, PEP and vaccination	Age- or weight-based dosing, pregnancy monitoring, maternal–fetal outcomes, assent or consent, and safeguarding	Plan inclusion prospectively with safeguards rather than default exclusion
Combination-therapy evaluation	Antibody and antiviral mechanisms may be complementary and may reduce treatment failure or viral escape	Enables evaluation of monoclonal antibody plus remdesivir for confirmed cases and possible PEP–vaccine strategies	Drug–drug interaction assessment, optimal sequencing, toxicity, efficacy, cost and field feasibility	Prioritise combinations with strong biological rationale and evaluate them through adaptive protocols
Obeldesivir PEP pathway	WHO has prioritised oral obeldesivir for PEP evaluation among contacts of confirmed and probable cases	Core opportunity to test whether drug-based PEP can reduce secondary BVD cases	Exposure risk, timing from exposure, dose, duration, adherence, safety, resistance and breakthrough-case investigation	Establish contact-based PEP protocols with clear allocation criteria, adherence support and virological follow-up
Candidate Bundibugyo vaccine pathway	No vaccine is licensed specifically for BVD	Candidate vaccines could be evaluated among contacts, health-care workers and high-risk groups	Ring-vaccination or occupational-risk design; immune endpoints; time to protection; safety; possible sequencing with PEP	Prepare vaccine protocols in parallel with therapeutic trials; avoid using Zaire-focused vaccines outside research unless evidence supports use

Platform element	Why it matters	Application to BVD countermeasures	Key design or implementation issues	Priority action
Supportive-care standardisation	Differences in clinical care can confound trial results and affect mortality	Ensures that all participants receive best available care regardless of trial arm	Minimum care package: rehydration, electrolytes, oxygen, co-infection treatment, pain control, nutrition, psychosocial support and safe referral	Define, resource and document a minimum supportive-care standard before trial activation
Host-directed and adjunctive-care evaluation	Severe disease reflects viral replication, immune dysregulation, endothelial injury, coagulopathy, shock and organ dysfunction	Supports evaluation of host-directed therapies, coagulation/endothelial support, nutritional support and treatment of co-infections	Disease-stage definitions, biomarkers, safety monitoring, interaction with antivirals or mAbs, and pragmatic endpoints	Restrict to biologically plausible candidates and standardised supportive-care packages; avoid uncontrolled use
Community engagement and trust platform	Mistrust can undermine early care-seeking, contact tracing, PEP uptake, vaccination and trial participation	Supports informed consent, randomisation, adherence, follow-up and acceptance of investigational products	Community advisory boards, survivor networks, local leaders, culturally appropriate communication and feedback loops	Embed engagement before and during trial activation; communicate eligibility, allocation and uncertainty transparently
Ethics and regulatory readiness	Delayed approvals can make outbreak trials impossible	Enables rapid activation of treatment, PEP and vaccine protocols	Pre-reviewed protocols, emergency amendments, regulatory reliance, material-transfer agreements, indemnity and pharmacovigilance	Develop regional ethics and regulatory reliance mechanisms with national leadership and WHO-supported templates
Data governance and local leadership	Outbreak research must avoid extractive models and ensure durable benefit for affected countries	Applies to treatment, PEP, vaccine, diagnostic and implementation datasets	Data-sharing agreements, authorship plans, sample governance, privacy protection, benefit sharing and local scientific leadership	Establish African-led governance structures before enrolment and define authorship and data-use plans prospectively
Product supply and fair allocation	Trials fail if products arrive late, are insufficient or appear inequitably allocated	Determines availability of MBP-134, maftivimab, remdesivir, obeldesivir, vaccine candidates and trial materials	Forecasting, importation, customs, expiry, cold chain, accountability and transparent allocation criteria	Pre-position investigational products where feasible and publish allocation criteria for treatment, PEP and vaccine candidates
Cold-chain and delivery infrastructure	Biologics, IV antivirals and vaccines may be difficult to deliver in remote or insecure settings	Affects mAbs, remdesivir, candidate vaccines and sample handling; less limiting for oral obeldesivir	Storage, transport, infusion supplies, power supply, waste disposal, biosafety and staffing	Prioritise stable formulations; establish regional logistics hubs and mobile trial teams
Occupational-health integration	Health-care workers, burial teams, cleaners and laboratory staff face repeated high-risk exposures	Enables rapid exposure assessment, testing, PEP, treatment and follow-up for frontline workers	Confidential reporting, rapid risk assessment, counselling, safe return-to-work protocols and psychosocial support	Create occupational-exposure pathways linked to PEP, testing, counselling and workforce protection
Cross-border coordination	Regional spread and population movement can fragment response and research	Harmonises protocols, case definitions, endpoints, contact tracing, product allocation and follow-up across DRC and Uganda	Shared data dictionaries, laboratory networks, sample-transfer agreements and regulatory alignment	Establish cross-border research coordination with DRC, Uganda, WHO, Africa CDC and regional partners
Integration with IPC and contact monitoring	Therapeutics and PEP cannot substitute for infection prevention and control	Prevents risk compensation and supports safe delivery of treatment, PEP and vaccines	PPE, safe triage, isolation, waste management, safe burials, symptom monitoring and referral of contacts	Pair therapeutic, PEP and vaccine protocols with IPC supplies, training and monitoring
Emergency-use data capture	Some products may be used before definitive efficacy evidence exists	Ensures that compassionate or emergency use contributes safety, virological, clinical and implementation data	Minimal datasets, standard case-report forms, follow-up schedules and linkage to laboratory data	Require systematic data capture for all investigational use, including use outside randomised trials
Regional stockpiling and manufacturing capacity	Product development is ineffective if countermeasures are unavailable when outbreaks begin	Supports rapid deployment of therapeutics, PEP products, vaccines, diagnostics and supportive-care supplies	Stockpile composition, replenishment, expiry, financing, quality assurance, fill–finish capacity and technology transfer	Create species-inclusive filovirus stockpiles and strengthen African manufacturing, diagnostics and fill–finish capacity where feasible
Implementation-science and equity framework	Efficacy alone will not ensure outbreak impact or community trust	Measures whether products reach the right people early enough and equitably	Uptake, timeliness, adherence, acceptability, cost, health-system impact, fair allocation and access for vulnerable groups	Include pragmatic implementation and equity endpoints in all treatment, PEP and vaccine protocols
Outbreak-to-interoutbreak learning system	Lessons are often lost once outbreaks end and funding declines	Converts trial, PEP, vaccine and implementation experience into future preparedness	After-action reviews, pooled analyses, protocol updates, sustained networks and guideline revision	Maintain standing filovirus R&D networks between outbreaks and update protocols after each deployment

This table outlines the clinical-trial, regulatory, operational, ethical, logistical and implementation-science requirements needed to rapidly evaluate treatment, post-exposure prophylaxis and vaccine candidates during Bundibugyo Ebola virus disease outbreaks. It emphasises standing master protocols, adaptive platform designs, rapid species-level diagnostics, exposure classification, clinical and virological endpoints, safety monitoring, pregnancy and paediatric inclusion, combination-therapy evaluation, obeldesivir post-exposure prophylaxis, candidate vaccine evaluation, supportive-care standardisation, host-directed adjunctive care, community engagement, ethics and regulatory readiness, African-led data governance, product supply, cold-chain logistics, occupational-health pathways, cross-border coordination, infection prevention, emergency-use data capture, stockpiling, manufacturing, implementation research, equity and outbreak-to-interoutbreak learning.

BVD, Bundibugyo virus disease; Ct, cycle threshold; DRC, Democratic Republic of the Congo; DSMB, data and safety monitoring board; IPC, infection prevention and control; IV, intravenous; mAb, monoclonal antibody; PCR, polymerase chain reaction; PEP, post-exposure prophylaxis; PPE, personal protective equipment; R&D, research and development; WHO, World Health Organization.

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Supplementary Table 3 | Therapeutic interventions tried or considered for Ebola virus disease since 1976

Intervention or product	Class / mechanism	Ebola species or outbreak context	Human use evidence	Outcome / interpretation	Current relevance
Optimised supportive and critical care	Standard clinical-care platform: fluids, electrolytes, oxygen, haemodynamic support, treatment of shock, co-infections, pain, nutrition and psychosocial care	All Ebola virus disease species	Progressive improvement in outbreak care; formal guidelines developed after West African epidemic	Essential and lifesaving; not virus-specific but central to survival	Should be standard of care in all outbreaks and the foundation for therapeutic trials
Convalescent whole blood	Polyclonal antibodies and other plasma components from survivors	Zaire ebolavirus, Kikwit, DRC, 1995	Eight patients received transfusions; uncontrolled observational report	High survival reported, but no randomised control and strong confounding; efficacy uncertain	Historical importance; not sufficient as modern evidence
Convalescent plasma	Survivor plasma containing polyclonal antibodies	Zaire ebolavirus, Guinea, 2014–2015	Nonrandomised comparative Ebola-Tx trial	No significant survival benefit when antibody titres were not standardised	Possible research/ bridging option only if high-titre, standardised and safely delivered
Hyperimmune immunoglobulin /polyclonal antibody preparations	Concentrated polyclonal antibodies	Mainly Zaire ebolavirus; preclinical & limited emergency use rationale	Limited human evidence; mostly preclinical or historical	Not yet established as effective treatment	Largely superseded by defined monoclonal antibody products
ZMapp	Triple chimeric monoclonal antibody cocktail	Zaire ebolavirus, West Africa 2014–2016; PREVAIL II trial	Randomised controlled trial compared ZMapp plus standard care versus standard care	Mortality numerically lower but did not reach conventional statistical significance; later inferior to mAb114 and REGN-EB3 in PALM	Important bridge therapy and comparator; not preferred where mAb114/REGN-EB3 available for Zaire ebolavirus disease
mAb114 / ansuvimab	Single human monoclonal antibody targeting Ebola glycoprotein receptor-binding domain	Zaire ebolavirus, eastern DRC, 2018–2020	Phase 1 safety study and PALM randomized controlled trial	Reduced mortality versus ZMapp; one of two clearly effective therapies for Zaire ebolavirus disease	Approved/recommended for Zaire ebolavirus disease; not established for Bundibugyo or Sudan viruses
REGN-EB3 / atoltivimab–maftivimab–odesivimab	Three-antibody monoclonal antibody combination targeting Ebola glycoprotein	Zaire ebolavirus, eastern DRC, 2018–2020	PALM randomized controlled trial; regulatory approval	Reduced mortality versus ZMapp; clearly effective for Zaire ebolavirus disease	Approved/recommended for Zaire ebolavirus disease; individual components, including maftivimab, require evaluation for non-Zaire ebolaviruses
Maftivimab	Individual monoclonal antibody component of REGN-EB3	Candidate for Bundibugyo virus disease evaluation, 2026	WHO-prioritised for BVD clinical evaluation; no established BVD efficacy	Cross-species activity is plausible but unproven	Priority candidate for BVD treatment trials
MBP-134	Experimental pan-ebolavirus monoclonal antibody cocktail	Preclinical Zaire, Sudan and Bundibugyo ebolavirus models; emergency-use consideration in Sudan virus outbreak; BVD 2026 candidate	No definitive human efficacy data	Strong preclinical rationale; clinical efficacy against BVD unproven	WHO-prioritised candidate for BVD clinical evaluation
MIL77E and related monoclonal antibody products	Monoclonal antibody cocktail derived from ZMapp-like antibodies	Mainly Zaire ebolavirus; limited emergency-use contexts	Limited human evidence; mostly emergency use or preclinical	Not established by randomized trial	Historical/contingency relevance; not a preferred evidence-based product
Favipiravir	Oral RNA-dependent RNA polymerase inhibitor	Zaire ebolavirus, Guinea, JIKI trial, 2014–2015	Historically controlled, single-arm trial	No clear overall survival benefit; possible signal in patients with lower viral loads; pharmacokinetic concerns	Not established for Ebola treatment; illustrates need for PK/PD and viral-load stratification
Remdesivir / GS-5734	Intravenous nucleotide analogue prodrug	Zaire ebolavirus, PALM trial; preclinical filovirus models; BVD 2026 candidate	PALM trial arm stopped when mAb114 and REGN-EB3 showed superiority; no established role in BVD	Inferior to mAb therapies for Zaire ebolavirus disease in PALM; preclinical rationale remains	WHO-prioritised for BVD clinical evaluation, including combination with mAbs
Remdesivir plus monoclonal antibody combination	Direct antiviral plus antibody-mediated neutralisation	Preclinical filovirus models; BVD 2026 candidate	No definitive human Ebola efficacy data for combination strategy	Biologically plausible; may improve efficacy in severe or late-presenting disease, but unproven	WHO-prioritised for BVD clinical evaluation

Intervention or product	Class / mechanism	Ebola species or outbreak context	Human use evidence	Outcome / interpretation	Current relevance
Obeldesivir / GS-5245	Oral prodrug of GS-441524; nucleoside analogue	Preclinical Sudan, Zaire and Marburg virus models; BVD 2026 PEP candidate	No established human BVD PEP efficacy	Oral route is attractive for field PEP; human efficacy and safety in exposed contacts remain to be established	WHO-prioritised for PEP evaluation among contacts of confirmed/probable BVD cases
Brincidofovir	Oral lipid conjugate of cidofovir; DNA-virus antiviral repurposed during West Africa outbreak	Zaire ebolavirus, Liberia, 2015	Very small open-label trial; terminated early	No efficacy conclusions possible; all four enrolled patients died; development for EVD stopped	Historical example of emergency repurposing without adequate evidence
TKM-130803 / TKM-Ebola	Small interfering RNA lipid nanoparticle targeting Ebola virus genes	Zaire ebolavirus, Sierra Leone, 2015	Single-arm phase 2 trial	Results not encouraging; efficacy not demonstrated	RNA therapeutics remain conceptually interesting but this product is not established
AVI-6002 / AVI-7537 and related PMO antisense oligomers	Phosphoro-diamidate morpholino oligomer antisense therapeutics targeting viral genes	Zaire ebolavirus; early development and phase 1 safety	Human phase 1 safety/ pharmacokinetic studies in healthy volunteers; no efficacy trial in EVD	Safety data generated, but no demonstrated clinical efficacy in Ebola patients	Historical nucleic-acid platform; not an established therapy
Interferon-β-1a	Host-directed innate immune modulator	Zaire ebolavirus, Guinea, West Africa outbreak	Historically controlled, single-arm proof-of-concept study	Possible signal but not definitive; no established efficacy	Host-directed therapy remains experimental and requires controlled evaluation
Other interferons / innate immune modulators	Host-directed antiviral immune modulation	Mostly in vitro, animal models or theoretical	No definitive human efficacy	Effects vary by timing, dose and disease stage; immune modulation may be harmful if mistimed	Research-only; should not be used outside protocols
rNAPc2	Recombinant nematode anticoagulant protein c2; tissue factor pathway inhibition	Zaire ebolavirus non-human primate model	No Ebola human efficacy trial	Partial protection in non-human primates	Supports host-directed/coagulation-targeted rationale, but not established in humans
Recombinant human activated protein C	Anticoagulant/ anti-inflammatory host-directed therapy	Zaire ebolavirus non-human primate model	No Ebola human efficacy trial	Partial protection in non-human primates; product withdrawn from sepsis use	Historical host-directed rationale only
Coagulation/endothelial support	Blood products, correction of coagulopathy, endothelial/vascular support	All severe Ebola disease	Part of advanced supportive care; not evaluated as a single antiviral therapy	Important for severe disease management but not virus-specific	Should be integrated into standardised care packages and outcome datasets
Nutritional and micronutrient support	Host-resilience and supportive-care adjunct	All Ebola disease, especially conflict, displacement and food-insecure settings	Limited Ebola-specific interventional trial evidence; strong clinical rationale	May influence immune function, recovery and tolerance of illness, but efficacy as a distinct intervention is not defined	Should be part of minimum care; pragmatic evaluation warranted where deficiencies are likely
Treatment of co-infections and comorbidities	Adjunctive clinical care	All Ebola outbreaks	Standard clinical practice; not Ebola-specific trial evidence	Essential to avoid preventable mortality and diagnostic confounding	Should be embedded in standard care and trial protocols
Therapeutic vaccines	Vaccines used after infection onset as treatment	Primarily Zaire ebolavirus vaccine platforms	No established therapeutic role once Ebola disease is established	Vaccines are preventive; post-exposure or peri-exposure use remains distinct from treatment	Do not frame as treatment; evaluate as prevention/PEP or ring-vaccination strategy
Vaccine plus PEP strategy	Combined immediate and durable protection	Proposed for high-risk contacts; species-dependent	No definitive BVD efficacy data	Could pair rapid antiviral/antibody PEP with longer-term vaccine protection	Requires trial protocols, exposure classification and careful communication
T-cell therapies / adoptive cellular therapies	Cellular immune therapy	Conceptual or preclinical; no established Ebola clinical pathway	No credible clinical efficacy evidence for Ebola treatment	Not part of current outbreak response or standard R&D pathway	Mention only as speculative/future immunotherapy; not a priority for BVD response

Intervention or product	Class / mechanism	Ebola species or outbreak context	Human use evidence	Outcome / interpretation	Current relevance
Broad-spectrum small-molecule antiviral pipeline	Direct-acting antivirals targeting viral polymerase, entry or replication	Mostly preclinical filovirus studies	No established human efficacy apart – only from failed/ inconclusive repurposed agents	May become important if oral, stable, broad and safe products are developed	Prioritise candidates with animal efficacy, human safety data and field-feasible dosing
BDBV-specific survivor-derived antibodies, including BDBV289-N	Candidate monoclonal antibody from Bundibugyo survivor response	Bundibugyo virus disease candidate	Current candidate; human efficacy not established	Potential species-specific relevance, but requires evaluation	Consider in BVD-specific pipeline if supported by WHO/regulatory review

Therapeutic approaches for Ebola virus disease since its discovery in 1976 have included convalescent blood and plasma, polyclonal and monoclonal antibodies, small-molecule antivirals, RNA and antisense platforms, interferons, host-directed coagulation and immune-modulating strategies, and optimized supportive care. However, only ansuvimab/mAb114 and REGN-EB3 have shown clear survival benefit in a randomized trial, and this evidence applies to Zaire ebolavirus disease. The therapeutic record therefore reinforces the need for species-inclusive countermeasures for Bundibugyo virus disease.

BDBV, Bundibugyo virus; BVD, Bundibugyo virus disease; DRC, Democratic Republic of the Congo; EBOV, Ebola virus or Zaire ebolavirus, depending on context; EVD, Ebola virus disease; GP, glycoprotein; IV, intravenous; mAb, monoclonal antibody; NHP, non-human primate; PCR, polymerase chain reaction; PEP, post-exposure prophylaxis; PK/PD, pharmacokinetics/pharmacodynamics; PMO, phosphorodiamidate morpholino oligomer; PPE, personal protective equipment; RNA, ribonucleic acid; siRNA, small interfering RNA; SUDV, Sudan virus; WHO, World Health Organization; ZEBOV, Zaire ebolavirus. PALM, Pamoja Tulinde Maisha; PREVAIL, Partnership for Research on Ebola Virus in Liberia; JIKI, favipiravir Ebola trial in Guinea.

Trial registration numbers: PALM, Pamoja Tulinde Maisha, NCT03719586; PREVAIL II, ZMapp plus standard of care versus standard of care for Ebola virus disease, NCT02363322; JIKI, favipiravir trial in Guinea, NCT02329054; Ebola-Tx, convalescent plasma for Ebola virus disease, NCT02342171; TKM-130803 Ebola siRNA trial, PACTR201501000997429; mAb114 phase 1 trial, NCT03478891;

REGN-EB3 phase 1 trial, NCT03576690. Trial registration numbers are listed for interventional clinical studies where a verified registry identifier is available; historical uncontrolled reports, preclinical studies, guidelines and emergency-use programmes are not assigned trial registration identifiers.