Title: The Lancet Infectious Diseases Series on the Modern Landscape of Ebola: Bridging Scientific Discoveries and Clinical Application

Running Head: Modern advances in Ebola management

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Abstract

The west Africa (2014-2016) Ebola disease epidemic marked a historic change of course in patient care during emerging infectious disease outbreaks. The epidemic response was a failure in many ways – a slow, cumbersome, and disjointed effort by a global architecture that was not fit-for-purpose for a rapidly spreading outbreak. In the most affected countries, healthcare workers and other responders felt helpless – dealing with an overwhelming number of patients but with few, if any, tools at their disposal to provide high quality care. These inadequacies, however, led to attention and innovation. The decade since then has seen remarkable achievements in clinical care for Ebola disease, including the approval of the first vaccines and treatments. In this, the first article in a two-part series, we reflect on this progress and provide expert summary of the modern landscape of Ebola disease, highlighting the priorities and ongoing activities aimed at further improving patient survival and wellbeing in the years ahead.

Key Points

1. **Epidemiology**: The threat of Ebola has not reduced in the 10 years since the west Africa outbreak, although many subsequent outbreaks have been smaller – assisted by strong public health, community, and counter-measure responses.
2. **Vaccines:** Significant progress has been made in developing and trialling vaccines for EBOV, with the approval of rVSV-ZEBOV, which has demonstrated up to 100% efficacy. However, there are no licensed vaccines for other strains like SUDV, and so broader-spectrum vaccines are a priority.
3. **Therapeutics:** Monoclonal antibody treatments like REGN-EB3 and MAb114 reduce mortality in EBOV patients. However, no approved treatments exist for SUDV or other Ebola virus strains, or for post-Ebola syndrome.
4. **Vulnerable Populations:** There has been an important shift towards including pregnant women, children, and other vulnerable populations in clinical trials. Further interventions to improve maternal and peri-natal outcomes are lacking.
5. **Advances in Supportive Care:** The first GRADE based and WHO endorsed guidelines have been implemented to improve the standard of care for patients with Ebola disease. These improvements have helped reduce mortality but remain largely driven by expert consensus, with a limited evidence base.
6. **Post-Ebola Sequelae:** Post-Ebola syndrome is now better understood, with survivors often facing long-term symptoms such as uveitis and chronic pain. Viral persistence in immune-privileged sites is a particular challenge due to risk of sexual transmission, including for prolonged periods following acute infection.

Introduction

This year marks a decade on from the declaration of an outbreak of Ebola disease for the first time in west Africa. The world was caught by surprise and so much was lost during the ensuing epidemic. An unprecedented 11,000 people died from their infection, and many more from the consequent impact on already vulnerable local health systems.[1,2] This was compounded by the loss of over five hundred healthcare workers, including world experts in viral haemorrhagic fevers.[3] The three most affected countries, Guinea, Liberia and Sierra Leone, suffered prolonged setbacks in economic development, schooling, and poverty alleviation.[4–6] Responders to the outbreak were, at times, overwhelmed, and were criticised for a response that stigmatised patients and ignored communities.[7] The international public health infrastructure was exposed as too limited, cumbersome, and fragmented to meet the challenge of a rapidly spreading epidemic with resource limitations, governance and political failings, ineffectual community engagement, expertise limitations, shortages of public health surveillance capacities, and a long delay in responses highlighted as key issues.[8,9]

But too, the epidemic was a turning point. It galvanised the international community to focus on epidemic preparedness, response, and recovery following a decade of quiescence from global outbreaks.[10] Although major issues remain, ensuing innovations at the country and regional level in policy, governance, and coordination, such as the establishment of the Africa CDC, left us somewhat better prepared for COVID-19 and other future outbreaks.[11–13]

Specific to clinical care for Ebola disease, the west Africa epidemic heralded a new era. For the first time there were systematic efforts to apply internationally recognised standards of supportive and critical care, applying evidence from both low and high resource environments. In addition, the West Africa epidemic spurred a new approach to clinical research by accelerating the implementation of trials during emergencies, addressing ethical challenges, and leading to the creation of global frameworks like WHO's Research and Development Blueprint.[8]

Ebola has not left us; ten outbreaks have occurred since the west Africa epidemic.[1] During this period there has been consistent work to further improve care and correct the inadequacies and misdirections of the past.

A decade ago, we summarised the state of clinical science at that time. Now, in this two-part series, we reflect on the progress made in understanding Ebola disease and improving patient care since then. Most importantly, we look ahead with expert summaries of innovations in management which will be crucial for future filovirus outbreaks, and may serve as a template for future outbreaks. Specifically in this first article, we discuss clinical advances . These, and the remaining key scientific priorities are summarised across seven key areas—epidemiology, clinical characterisation, vaccines, therapeutics, special populations, supportive care, and post-Ebola sequelae (see Table 1). In turn in our second article, informed by the significant implementation gap between many of these innovations and the realities on the ground in affected communities, we seek to highlight many of the advances in patient-centred care approaches from involving communities in care and advances that facilitate rapid diagnosis to optimising dignified care delivery and infrastructure and finally through to advances in supporting survivors.

Table 1: Comparison of advances in understanding of Ebola disease since the west Africa Epidemic with ongoing scientific priorities.

Category	Advances	Scientific priorities
Epidemiology	Better availability of genomic data and phylogenetic analyses to understand outbreak dynamics Improved real-time data surveillance Broader modelling understanding of countries at risk of Ebola disease Taxonomy revision and new classification systems	Understanding animal reservoir hosts Identifying intra and between species transmission pathways Understanding survivor transmission risks One Health integration and better understanding of filovirus ecology Earlier identification of rare outbreaks in high infectious disease burden contexts
Clinical manifestations	Recognition of the predominance of gastro-intestinal symptoms and extent of multi-organ dysfunction with less haemorrhage that previously thought Understanding the clinical presentation of vaccinated patients who exhibit milder symptoms Understanding the key predictors of death including age extremes, confusion, haemorrhage, renal and hepatic dysfunction, and high viral load Harmonized data collection of risk factors, signs, and symptoms on patient arrival	Improving performance characteristics of case-definitions and adjusting case definitions and screening protocols to account for changes in symptomatology among vaccinated individuals Consistent data collection standards and definitions across outbreaks Understanding mechanisms of disease progression and the biochemical predictors of severe disease Understanding host-factors (including immunophenotypes) that lead to variability in disease severity and disease sequelae between individuals More systematic collection of data from SUDV outbreaks to better understand its clinical course and differences to EBOV infection
Vaccines	Successful clinical trials leading to approved vaccines for EBOV Two licenced vaccines for EBOV approved for clinical use A global stockpile of 450,000 doses established, with proven use in outbreaks. Three candidate vaccines for SUDV were shortlisted by WHO in 2022	Designing vaccines with broader protection (pan-orthoebolavirus or pan-filovirus) Determine the best vaccination strategies for rVSV-ZEBOV and Ad26.ZEBOV Address gaps in vaccine durability, with a focus on breakthrough infections and waning immunity Develop revaccination strategies, particularly for front-line workers, survivors, and other high-risk groups Expand vaccine stockpiles to ensure

		rapid availability during outbreaks Expanding post-regulatory approval access to vaccines and establishing effective funding mechanisms
Treatments	Successful clinical trials leading to approved therapeutics for EBOV Inclusion of special populations in therapeutic guidelines Encouraging evidence of remdesivir in reducing viral persistence	Designing and assessing SUDV specific, pan-orthoebolavirus, and pan-filovirus therapeutics Designing and assessing drugs that have an extended window of efficacy Assessing combination therapy, including host-directed therapies Developing therapeutics effective among patients with a high viral load Post-exposure chemoprophylaxis studies Dose-optimization studies for approved treatments Expanding post-regulatory approval access to therapeutics and establishing effective funding mechanisms
Supportive care	More specific approaches to supportive care, including oral rehydration and guided electrolyte repletion Development of consensus-based supportive care guidelines Availability and use of organ-support interventions in outbreak affected areas	Designing and evaluating potential optimisations in elements of supportive care (e.g. fluid resuscitation strategies, loperamide) Scaling and optimising supportive care practices in parallel with novel therapeutics and vaccines Addressing the logistical challenges of providing high-quality critical care in outbreak-prone regions (e.g., dialysis, oxygen supply, blood banks)
Special populations	Enrolment of special populations in clinical trials Inclusion of special populations in vaccine and treatment guidelines Better understanding of the clinical course and complications in paediatric Ebola disease	Understanding population specific responses to vaccinations and treatments Adapting and nuancing supportive care to meet needs of special populations Understanding of viral transmission risks via breast milk and amniotic fluid
Post-Ebola sequalae	Recognition of post-Ebola disease syndrome Recognition of viral sequestration and recrudescence	Understanding the duration and population level risk of sexual transmission Assessing the role of vaccines and therapeutics in reducing clinical symptoms or viral persistence

		Understanding sexual transmission risk (if any) from female survivors Understanding unintended consequences of treatments on viral persistence, or long-term side-effects Further well powered trials on treatments to eradicate virus from sanctuary sites

Epidemiology

The taxonomy of filoviruses has undergone substantial revision because various Ebola related terms were being used ambiguously.[14] Viruses in the filovirus family are members of either the genus *Orthoebolavirus* (including Ebola Zaire virus (EBOV) and Sudan virus (SUDV)) that cause the clinical syndrome termed Ebola disease, or are members of the genus *Orthomarburgvirus* (including Marburg virus) which causes a similar clinical pattern in Marburg disease. There are six orthoebolaviruses, with discovery of one new addition, Bombali virus, in the last decade.

While most outbreaks are believed to result from discrete zoonotic spillover events from reservoir species, likely bats, definitive identification of a specific animal reservoir remains elusive. The high biodiversity and geographical remoteness of some affected regions present challenges in pinpointing reservoir species.[15–17] Clear knowledge on filovirus ecology would facilitate targeted One Health campaigns – an approach that integrates human, animal, and environmental health – by improving our understanding of geographic and seasonal risks. This would allow for specific ecological interventions, such as habitat preservation and controlled land use, that reduce the likelihood of zoonotic spillovers.[18] Recent evidence indicates that, rarely, outbreaks can occur due to transmission from survivors of a previous outbreak (see Ebola Disease Sequelae section). This risk can be prolonged, for example, the 2021 outbreak in Guinea was linked to the west Africa epidemic.[19] How frequently outbreaks originate from survivors will be better understood as genomic sequencing becomes more broadly available in affected regions.

In the last decade there have been nine Ebola disease outbreaks caused by EBOV and one caused by SUDV[1] (figure 1). Modelling, using species distribution models with paired zoonotic infection data and environmental covariates, suggests as many as an estimated 22 million people in at least 22 African countries (shaded grey in figure 1) are at risk from these viruses.[20]

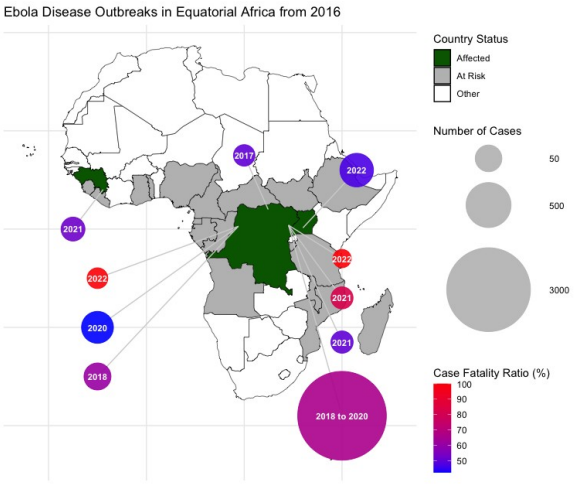

Figure 1: Outbreaks or clusters of Ebola disease since the west Africa epidemic with associated case fatality ratios. Red shading denotes countries affected by one or more Ebola disease outbreaks since 2016, while grey shading denotes countries potentially at risk of Ebola disease as determined via contemporary modelling strategies[20]

Post-2016, the Democratic Republic of the Congo (DRC) has been the epicentre of outbreaks, including significant outbreaks in Équateur Province (2018, 2020) and a major outbreak in the North Kivu, Ituri, and South Kivu Provinces (2018-2020). The latter was the second largest outbreak on record with over 2,200 deaths.[1] This contrasts with the May 2018 outbreak in Équateur Province which was contained to 54 patients. Active public-health measures and the early use of the recombinant vesicular stomatitis virus–EBOV vaccine among first- and second-line contacts have been identified as important in the control of this outbreak[21], however geographical and other factors may have played a role in containment of this outbreak and should not be discounted.

In contrast, controlling the North Kivu outbreak was particularly challenging due to its occurrence in a conflict zone. The presence of armed groups and regional instability led to mass internal displacement, impaired access, community mistrust, and direct violence against healthcare workers.[22,23] Modelling of this outbreak estimated that violent events increased the local reproductive number, *R*, by between 0·17 and 0·53 (crucially pushing *R* above one, the threshold needed to sustain an outbreak).[24] This is likely attributable to downstream effects of conflict including fragile and fragmented local health systems, mistrust in local and international authorities, and the logistical and safety challenges associated with delivering public health interventions and care in an active conflict zone.[7,25,26]

Outside the DRC, Guinea faced a resurgence of Ebola disease in 2021, originating in Nzérékoré with 23 reported cases (16 confirmed and 7 probable).[27] While the rapid establishment of Ebola Treatment Centres (ETCs), access to vaccination, and treatment with monoclonal antibodies were undoubtedly important in controlling this outbreak[27], other factors, such as the geographical isolation of the outbreak and potential pre-existing immunity[19], may also have contributed.

In 2022, Uganda experienced an outbreak of SUDV for which there is a noticeable lack of vaccine and therapeutic options.[28] Recognition the outbreak was delayed by at least six

weeks, which demonstrates the ongoing difficulty of early identification of these relatively rare outbreaks in the setting of a myriad of endemic infections with clinically overlapping presentations. Initially transmission was propagated by healthcare-associated transmission, but this changed to predominately household and community transmission.[29] This underscores the need to urgently improve national and international outbreak response preparedness through global programmes.

Clinical characterisation

The clinical presentation of Ebola disease was well described during the west Africa epidemic. It is primarily an acute febrile gastrointestinal illness characterized by early non-specific symptoms followed by vomiting, diarrhoea, severe dehydration and frequent multi-organ dysfunction.[30,31] Vomiting and diarrhoea cause complicating metabolic acidosis and hypokalaemia and can progress to renal insufficiency with hyperkalaemia.[30] Tachycardia and hypotension occur due to hypovolemia because of large fluid loss and may be worsened by vasodilatation leading to organ hypoperfusion and lactic acidosis.[32 33]

While coagulopathy-associated gastrointestinal haemorrhage occurs occasionally, it is not as common as previously believed.[33] The mechanisms underlying bleeding when it occurs remain poorly understood. Tissue factor and Von Willebrand Factor were elevated in patients with more severe disease in the west Africa epidemic[34] however, when fibrinogen levels were measured, they did not correlate with clinical outcomes or haemorrhagic complications[34,35] and data from 150 patients indicates that severe thrombocytopenia is generally absent[30]. Elevated thrombomodulin in plasma has been associated with severity in patients infected with EBOV[34], and with haemorrhagic complications in patients infected with SUDV[35]; it seems likely that the thrombomodulin from activated endothelial cells contributes to the endothelial dysfunction and coagulation disorders seen in Ebola disease, but this is only part of the picture.

The number of patients during the west Africa epidemic meant that predictors of death could be reliably calculated for the first time. These included demographics such as the extremes of age and clinical signs such as confusion and the presence of haemorrhage.[33] Renal and hepatic dysfunction occur frequently, are severe, and are strongly correlated with mortality.[30,36,37] High viral load at presentation continues to be one of the most important predictors of death.

However, most clinical descriptions of Ebola disease during west Africa were derived from the WHO case reporting forms which provide a standardised dataset at the time of admission. What was less well understood was the progression of clinical symptoms.[33] Subsequent large prospective longitudinal cohorts such asEVISTA[37] from eastern DRC have been valuable in better describing the progression of Ebola disease. For example, while the prevalence of haemorrhage at presentation in the EVISTA cohort (16%) was similar to west Africa, 39% of patients went on to experience haemorrhagic complications. Likewise, neurological manifestations became more common during patient follow up (from 12% to 27%) including over a quarter of patients with agitation or coma. Likewise, almost half of

patients went on to experience pulmonary symptoms and half were hypoxic ($Sp0_2$ <92%) at follow up.

The introduction of vaccines after the west Africa epidemic has altered the clinical presentation and course of illness. When vaccinated patients were compared to unvaccinated patients with *EBOV* infection in DRC, fewer signs and symptoms were present – including marked reductions in the frequency of haemorrhagic manifestations.[38] This has implications for identifying patients for isolation and testing given the symptom components of case definitions will likely perform worse for vaccinated patients.

Due to fewer and smaller outbreaks, data on the clinical manifestations of SUDV and how they differ from EBOV are sparse. SUDV is often described as less fatal disease, but the data for this are limited and difficult to interpret given contextual differences between outbreaks. The CFR for confirmed cases in the 2022 Uganda SUDV outbreak was 39%. A preprint from that outbreak reporting 160 of the 164 patients (142 confirmed and 22 probable) describes a broadly similar presentation with predominant symptoms of fever, weakness, vomiting, and diarrhoea (table 2).[29] Haemorrhagic symptoms were present in only 8% of patients at the time of presentation. The time between illness onset and first isolation continued to be relatively long (median of 5 days, IQR 3-8 days) presenting an ongoing challenge for treatment.
Table 2 compares symptomatology across three previously published cohorts from west Africa (EBOV infection), the 2018-20 DRC outbreak (vaccinated vs unvaccinated EBOV infection), and the 2022 Uganda outbreak (SUDV infection). Such comparisons across cohorts continue to be limited by inconsistent terminology, different minimum datasets, and the complex temporal nature of symptom onset – standardisation of which is a key priority for future outbreaks. Improving structured biological sampling and laboratory capacity in future outbreaks will continue to help us understand differences in illnesses and outcomes, why some patients get more severe disease or die, and identify potential targets for clinical interventions.

Table 2: Relative Prevalence of Selected Symptoms Across Three Separate Ebola Disease Cohorts Contrasting the west Africa epidemic, the 2018-20 DRC Outbreak Stratified by Vaccination Status, and the 2022 SUDV Outbreak in Uganda

	***EBOV* infection (West Africa, 2014-2016)[39]**			**Unvaccinated *EBOV* infection (DRC, 2018-2019)[38]**			**Vaccinated *EBOV* infection (DRC, 2018-2019)[38]**			***SUDV* infection (Uganda, 2022)[29]**		
Symptom[#]	Count/ Total	% of cases	95% CI	Count/ Total	% of cases	95% CI	Count/ Total	% of cases	95% CI	Count/ Total	% of cases	95% CI
Asthenia/ Fatigue	3098/3865	80·2%	78·9%-81·4%	704/846	83·2%	80·7%-85·7%	228/290	78·6%	73·9%-83·3%	89/160	55·6%	47·9%-63·3%
Chest pain	1179/2815	41·9%	40·1%-43·7%	175/822	21·3%	18·5%-24·1%	64/283	22·6%	17·7%-27·5%	47/160	29·4%	22·3%-36·4%
Fever	3440/3952	87·0%	86·0%-88·1%	402/831	48·4%	45·0%-51·8%	121/287	42·2%	36·4%-47·9%	135/160	84·4%	78·7%-90·0%
Headache	2122/3504	60·6%	58·9%-62·2%	453/840	53·9%	50·6%-57·3%	170/292	58·2%	52·6%-63·9%	74/160	46·2%	38·5%-54·0%
Joint pain	1616/3253	49·7%	48·0%-51·4%	366/825	44·4%	41·0%-47·8%	138/287	48·1%	42·3%-53·9%	49/160	30·6%	23·5%-37·8%
Myalgia	1694/3378	50·1%	48·5%-51·8%	310/826	37·5%	34·2%-40·8%	108/280	38·6%	32·9%-44·3%	49/160	30·6%	23·5%-37·8%
Abdominal pain	1764/3369	52·4%	50·7%-54·0%	416/838	49·6%	46·3%-53·0%	99/286	34·6%	29·1%-40·1%	64/160	40·0%	32·4%-47·6%
Anorexia	2685/3613	74·3%	72·9%-75·7%	617/845	73·0%	70·0%-76·0%	188/289	65·1%	59·6%-70·5%	62/160	38·8%	31·2%-46·3%
Diarrhoea	2307/3624	63·7%	62·1%-65·2%	341/840	40·6%	37·3%-43·9%	95/284	33·5%	28·0%-38·9%	81/160	50·6%	42·9%-58·4%
Vomiting and nausea	2402/3657	65·7%	64·1%-67·2%	422/847	49·8%	46·5%-53·2%	129/287	44·9%	39·2%-50·7%	93/160	58·1%	50·5%-65·8%

Dysphagia	721/2642	27·3%	25·6%-29·0%	171/831	20·6%	17·8%-23·3%	31/280	11·1%	7·4%-14·7%	10/160	6·2%	2·5%-10·0%
Sore throat	546/2510	21·8%	20·1%-23·4%	142/829	17·1%	14·6%-19·7%	28/280	10·0%	6·5%-13·5%	15/160	9·4%	4·9%-13·9%
Any bleeding/ Unexplained Bleeding	373/3138	11·9%	10·8%-13·0%	135/835	16·2%	13·7%-18·7%	17/286	5·9%	3·2%-8·7%	13/160	8·1%	3·9%-12·4%
[a]Where symptom nomenclature differed, best clinical judgement was used to consolidate symptoms across cohorts												

Vaccines

Vaccines have been successfully developed against *EBOV* with one - recombinant vesicular stomatitis virus-Zaire Ebola virus (rVSV-ZEBOV) - demonstrating up to 100% efficacy during the west Africa epidemic.[40] The vaccine is a recombinant, replication-competent viral vector vaccine. RVSV-ZEBOV is sold under the name Ervebo, and was licensed in 2019 by the European Medicines Agency (EMA), the United States Food and Drug Administration, and prequalified by WHO. In 2020, the EMA recommended conditional marketing authorization for a second vaccine—a two-dose regimen comprising Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo)—based on efficacy data from animal models and immuno-bridging studies[41] (summarised in table 3). There are however a number of outstanding questions in the field not least of all vaccine durability, with more recent data suggesting a significant level of breakthrough infection in previously vaccinated individuals - 155 of 620 (25%) patients with Ebola disease in the PALM treatment trial[42] and 175 of 533 (33%) of patients in the EVISTA cohort[37] reported prior vaccination with rVSV. In addition, it has been shown in PREVAIL trials in Liberia, that 18.5% of rVSV vaccine recipients did not have detectable antibodies one month post vaccination.[43] Given these data there it is important to develop revaccination strategies, especially for front-line healthcare workers redeployed to future outbreaks, paediatric, and immunocompromised individuals.[44] There is also a need to consider vaccination of survivors, due to the demonstration of onward transmission (albeit infrequently) which may be occurring due to waning immunity.[44] However, there is no clear consensus on when or how these revaccination approaches might be implemented, and while Ad26.ZEBOV is approved by the EMA to be used as a booster vaccine, rVSV-ZEBOV is not. There is therefore an ongoing need to address revaccination strategies including implementation, prioritisation, and the usefulness of heterologous immunisation.

Table 3: Comparison of the Current Availability of Vaccination and Treatment Options for Different Orthoebolaviruses

Category	EBOV	SUDV	Other Orthoebolaviruses
	Vaccination		
Approved vaccines	rVSV-ZEBOV (WHO, FDA, EMA) Ad26.ZEBOV & MVA-BN-Filo (WHO, EMA)	None. Access to candidates through clinical trials	None. Access to candidates through clinical trials
Special Populations	Pregnant Women: No restrictions on use Children: Restricted to 12+ months	None. Access to candidates through clinical trials	None. Access to candidates through clinical trials
	Treatment		
Supportive care	Optimized supportive care (WHO)	Optimized supportive care (WHO)	Optimized supportive care (WHO)
Approved targeted therapeutics	MAb114 (WHO, FDA) REGN-EB3 (WHO, FDA)	None. Access to candidates via clinical trials or monitored use where available	None, access via clinical trials or monitored use where available

Special Populations	Children: Neonates with maternal infection qualify for targeted treatment	Access via clinical trials or monitored use where available	Access via clinical trials or monitored use where available
	Recovery		
Post-Ebola (disease) Syndrome	No countermeasures available	No countermeasures available	No countermeasures available

In January 2021, a global stockpile of EBOV vaccines was initiated, led by the International Coordinating Group on Vaccine Provision. By May 2024, over 450 000 doses were available for rapid deployment in response to an outbreak. The stockpile has already proven its utility, with more than 7,000 doses of the Ervebo vaccine made available in response to outbreaks in the DRC. Doses can be requested from the stockpile for either outbreak responses or preventative campaigns.[45]

Whilst vaccines are available for *EBOV* there are no licensed products for *SUDV*. This represents a key unmet need. During the 2022 *SUDV* outbreak, the WHO Technical Advisory Group shortlisted three candidate vaccines. The panel considers safety, the potential for efficacy, the availability of doses and the ability to expedite manufacturing; notably all vaccines shortlisted used a viral vector platform technology.[46–48] Fortunately, public health measures were effective in controlling the outbreaks before the ring vaccination protocol could be implemented.

Future licensure of candidate filovirus vaccines may occur through conditional marketing authorization (i.e., based on animal efficacy, plus human immunogenicity and safety data alone) or clinical efficacy assessments. The WHO, in-country partners, and other stakeholders are utilising advances in clinical trial methods to test vaccine efficacy across multiple outbreaks. Consideration of adequate and diverse funding mechanisms to enable innovative clinical trial delivery, vaccine development, and stockpiling approaches are needed for a step-change in the field, including the development of a multivalent vaccine approach (offering protection against multiple filoviruses). There is an unmet need to understand the pathway to regulatory approval for such a vaccine. Multilateral partnerships, an extensive trial network, and strengthened infrastructure in at-risk countries, combined with expedited clinical trial delivery and outbreak responsiveness, remain the best strategies to achieve vaccine licensure.

Treatments

Historically, the mainstay of treatment for Ebola disease has been supportive care. Blood transfusion from convalescent patients was first tried during the 1995 Kikwit outbreak. However, treatment trials were instituted for the first time during the west Africa epidemic with a range of therapeutics tried including monoclonal antibodies (mAbs), small-molecule antivirals, convalescent plasma, and repurposed medications. Unfortunately, none of these trials found conclusive evidence of benefit[33]

MAbs have emerged as the leading treatment strategy over the last decade. The Pamoja Tulinde Maisha (PALM) trial[42] was a notable success. Conducted in the DRC during 2018-19, this randomized controlled trial aimed to evaluate the impact of potential treatments on 28-day survival. It investigated three therapies: the mAb cocktail REGN-EB3, the single mAb

MAb114, and the small-molecule antiviral remdesivir, compared against the mAb cocktail ZMapp (designated as the control group based on promising but inconclusive results from the west Africa epidemic). Ebola disease patients receiving MAb114 and REGN-EB3 had mortality rates of 35·1% and 33·5%, respectively, compared to around 50% in their control groups. These treatments are now FDA-approved and strongly recommended by WHO for patients with PCR-confirmed EBOV infection (including neonates less than seven days old born to mothers with confirmed infection).[49]

In PALM patients were stratified by viral load with high levels of viraemia notably associated with mortality. Even among the successful mAb arms mortality was 67% among patients with CT values below 22 as compared to 11% among patients with lower levels of viraemia at randomisation.[42] The importance of this "therapeutic window" before high viraemia is underscored by the 12% increase in mortality for each day's delay between symptom onset and admission to ETC across the study.[42] Management of these patients with high viral loads remains an important gap in the therapeutic landscape, as do challenges with the manufacturing, logistics, availability, and affordability of mAbs.[50]

Current mAbs are specific for *EBOV* and there are no recommended treatments for *SUDV* or other orthoebolaviruses. A promising pipeline for mAbs includes treatments that are broadly neutralising across all orthoebolaviruses. Leading candidates have shown efficacy in non-human primate studies[51,52] but no human trial data are yet available. Patients were treated with MBP 134, a cocktail of two mAbs that target epitopes conserved across *orthoebolavirus* species, during the 2022 SUDV outbreak in Uganda, but this was undertaken under a Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) protocol and so impacts on survival cannot be inferred. Pan-filovirus mAbs are also being developed but the pipeline is less advanced.[53]

Other therapeutic options are also being studied. While the direct acting anti-viral remdesivir alone did not show any evidence of efficacy in the PALM trial, it has shown to have survival benefit in non-human primate studies especially when used in combination with a mAb where it notably it extends the therapeutic window for mAbs.[54,55] Remdesivir has extensive safety data in COVID-19 and shows in-vitro and in-vivo efficacy for a broad array of filoviruses[56–58] which would make it an attractive agent if clinical efficacy is shown. In addition, Remdesivir has shown preliminary success in treating viral persistence[59], which may become more prevalent with expanded access to mAbs.

Therapies that improve helpful host responses to infection or mitigate against pathological host responses should also be investigated – these might include organ or tissue (e.g. endothelial) specific protection, immune-mediators, anti-inflammatories, and host-directed anti-virals.[60,61]

Priorities for future innovation include advancement of pan-filovirus treatments, testing of combination therapies, and improving the window for intervention. In addition, despite evidence of efficacy, there remain significant issues with access to the therapeutics already available, and substantial work is needed post regulatory approval to ensure therapeutics are utilised where they are needed.[62,63] Post-exposure chemoprophylaxis has been

understudied[64] and developments in the research and development pipeline (such as orally available drugs) means this is an increasingly feasible prospect.

Supportive care

Improved syndromic characterisation of Ebola disease has allowed a more specific approach to supportive care: oral rehydration solution when enteral intake is possible; clinically guided, balanced intravenous volume repletion; and laboratory test-informed electrolyte repletion are now considered critical.[32] With this improved clinical experience and standardisation of systematic fluid resuscitation, mortality in Africa fell to 40% across the outbreak.[65]

Since the west Africa epidemic there has been an increasingly systematic and evidence-based approach to developing guidelines for supportive care of patients with Ebola disease[66,67] - the first guidelines employing Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology were developed and published in 2018.[32] In these, eight interventions were strongly recommended, albeit with low-to-moderate confidence in the underlying evidence base, and largely extrapolated from sepsis literature. These included: oral rehydration, parenteral administration of fluids, systematic monitoring and charting of vital signs and volume status, measurement of serum biochemistry, prescribed staffing ratios, regular communication with patients' family and friends, analgesia and treatment of symptoms, and administration of antibiotics to patients with high illness severity. WHO now provides a 'living' document outlining standard operating procedures for clinical management of Ebola disease.[68]

While there is a limited Ebola disease-specific evidence-base for the care of critically ill patients, intravenous vasoactive medications, renal replacement therapy, oxygen administration and mechanical ventilation were employed for a small number of patients during the west Africa epidemic.[69] Treatment of critically ill patients in outbreaks after 2016 have evolved to provide higher levels of care including more frequent-to-continuous monitoring of vital signs, intravenous fluid administration through durable venous access, intravenous vasoactive medication to support blood pressure, oxygen administration, including through high-flow nasal cannula, and non-invasive positive pressure ventilation. As an example, in a cohort of just over 700 patients treated in the eastern DRC (2018-2019), 11% received inotropes, 38% received oxygen therapy and 14% received blood component transfusion.[37]

Providing high-quality critical care remains logistically challenging in areas prone to outbreaks. Practical limitations include providing dialysis; providing oxygen flows that exceed the capacity for typical concentrators; a lack of accessible safe blood banks; and a lack of ambient climate control for health care workers[70], and dependable power supplies.[71,72] High-quality clinical research to evaluate the feasibility and effectiveness of many elements of supportive care are essential to evolve our ability to provide best care. It is critical that these are prioritised alongside novel therapeutics and vaccines, because optimisations in supportive care can occur in parallel, and are cheap and scalable interventions. Standardisation also supports trials by ensuring that differences in trial groups are due to experimental treatment allocation rather than variations in care.

Special populations

Pregnancy was identified as a specific risk factor during the early DRC Ebola disease epidemics in 1976 and 1995, with a pregnancy-related mortality rate of 90%.[73] However, mortality rates in pregnancy during the west Africa and 2018-20 DRC outbreaks were lower, at 64% and 56%, respectively[74,75] and subsequent reviews are inconclusive regarding whether there is a higher risk of mortality in pregnant women – but hampered by a lack of high-quality data.[37]

The foundation of treatment for pregnant women remains - as for all patients - optimal supportive care. Notably, during the latter stages of the west Africa epidemic, pregnant women were included in trials of both convalescent plasma and favipiravir (and eligible for other trials).[76] During the 2018-20 DRC epidemics, pregnant women were also enrolled in the PALM trial.[42] Although the sample size of pregnant women was too small to draw specific conclusions about efficacy in this subpopulation, it is considered good clinical and ethical practice to offer these treatments to pregnant patients.[76] In this trial there were no serious adverse events related to pregnancy outcomes that were related to the study drugs.[42]

Pregnancy was an exclusion criterion in the rVSV-ZEBOV vaccine (Merck) trial in Guinea in 2015. Since 2016, the Strategic Advisory Group of Experts (SAGE) recommendations to WHO suggest including pregnant women in Ebola disease vaccination efforts, as was seen during the 2018-20 DRC epidemics. Nevertheless, there remains a scarcity of data on the safety and effectiveness of the different *EBOV* vaccines, and booster strategies, in pregnant and lactating women.[44,76]

Foetal losses during Ebola disease outbreaks are high, exceeding 70%.[77] Reports of neonates surviving transplacental orthoebolavirus exposure are rare. One notable case in Guinea in 2015 involved a neonate who was PCR positive at birth for orthoebolavirus and survived after treatment with remdesivir, ZMapp, and a survivor's buffy coat.[78] There have been four other case reports of neonates surviving transplacental exposure to orthoebolavirus; all tested PCR negative at birth.[79–81] One neonate received only prophylactic antibiotics, the others and their mothers received REGN-EB3 or mAb114; unfortunately, all three women died of Ebola disease. The neonates were discharged healthy with a negative PCR on day 21 or afterwards. Administering REGN-EB3 or mAb114 within the first hours after birth might have played an important role in their survival. WHO recommends providing these treatments to neonates born to infected mothers.

Amniotic fluid has shown persistent PCR positivity for up to 32 days after maternal viral clearance, though the infectivity of this fluid is unknown.[82] Similarly, viral RNA has been detected in breast milk during both symptomatic and asymptomatic infection and following recovery, however much remains unknown about the associated risk of transmission.[83,84] Patients who survive Ebola disease with their pregnancy intact should deliver in an ETC with appropriate infection prevention and control measures. Considering the pregnancy's very poor prognosis, it is essential to involve patients in decision-making around possible termination of pregnancy.

The survival rates for children under five with Ebola disease remain alarmingly low, with case-fatality rates of 70-83% in infants under 12 months.[85–87] The reasons for this are

multifaceted – children often present with higher viral loads and have an immature immune system, but they are also more susceptible to complications. For example, in a cohort of 73 children with EBOV infection in the eastern DRC in 2019, 36% experienced hypokalaemia, 52% hyperkalaemia, 74% hyponatraemia, and 27% hypoglycaemia.[88] Optimal supportive care therefore remains the cornerstone of treatment. However, the inclusion of children in the PALM trial, where 25% of participants were children, underscores the importance of involving this vulnerable population in research.[87]

Ebola disease sequelae

Given the high fatality rates, the term 'survivor' is particularly apt in Ebola disease. A reasonable, desired outcome is the elimination of replicating virus from the body and a return to health. While achievable for some survivors, many are left with chronic ill-health and persistent sequelae. In others, viral persistence or recrudescence continue to cause challenges even occasionally resulting in viral transmission.

Post-Ebola (disease) syndrome is now better understood.[89] Several studies conducted after the west Africa epidemic found that survivors reported symptoms such as urinary frequency, headache, fatigue, muscle pain, memory loss, and joint pain significantly more often than controls.[59,90] Viral persistence in aqueous humour was first identified in a survivor from the west Africa epidemic, and overall uveitis appears to be a relatively common complication, possibly associated with a higher viral load during acute illness.[91]

A retrospective, case-controlled cohort study in Sierra Leone showed higher odds of disability in survivors at one year compared to controls (78% versus 11%; adjusted OR 23·5, P<0.001), including disabilities in vision, mobility and cognition. Musculoskeletal pain was found to underlie most of the reported immobility. Survivors also had higher depression and anxiety scores (see part two of the series for further discussion).[92]

An important question is the duration of post-Ebola disease sequelae. A study of survivors in Liberia found that of 311 followed-up at five years after acute illness, 52% of patients had at least one symptom, with 29% reporting this interfered with their lives. Reassuringly, most symptoms decreased in frequency and severity over time.[93] Another study of 20 survivors from the 1995 DRC outbreak showed lower cognitive scores and more symptoms of depression and anxiety than controls, despite 22 years since their acute infection.[94]

Theories outweigh data in explaining sequelae occurrence in survivors. One possibility is an immunological predisposition. For example, the HLA-B27 allele is associated with uveitis, and the USA survivor described above was HLA-B27 positive.[95] More research is needed into individual immunophenotypes and their influence on clinical outcomes. Retained viral antigen in tissues, which may represent low-level, localised viral replication could result in humoral and cellular immune responses that rather than eradicating the virus instead result in inflammation at local and/or more distant sites.

Virus may find sanctuary in an immune-privileged sites, escaping clearance mechanisms during acute infection. EBOV identification in aqueous humour[95], semen[96,97], and CSF[98] after recovery from acute Ebola disease supports this theory of sanctuary sites. Novel therapies might also facilitate viral sequestration in survivors. Compared to those who did not receive any of the experimental treatments (mAb114, REGN-EB3, ZMapp, or remdesivir), treated

survivors in a Guinean study had later appearance of antibodies and a faster decline in antibodies; this was most marked in survivors who received mAb114.[99] The implications of these differences are unknown and require further study.

Most survivors do not pose a transmission risk; however, some have persistent infections (which may be asymptomatic), with potential to transmit virus. The most described scenario is sexual transmission by male survivors.[19,100,101] Prospective cohort data now demonstrate that viral persistence in semen is a frequent and prolonged phenomenon. One study estimated 75% positivity for EBOV RNA at 6 months following discharge from acute illness, with a median duration of 204 days although other data vary slightly.[96,97] Virus detection in semen might be intermittent for some[59], although the mechanisms behind intermittent reactivation or secretion of latent virus are unclear.

Sexual transmission has led to new outbreaks in Guinea, including a 2016 outbreak linked to a man who had detectable virus in semen more than 500 days after his illness.[101,102] One study examining the origins of 35 outbreaks suggested that up to one quarter may start from persistently infected survivors of a previous outbreak.[103] Understanding viral persistence is a critical public health priority. The PREVAIL IV trial[104], though underpowered, showed promising results, with a five-day course of remdesivir safely reducing EBOV RNA in the semen of Ebola survivors. However, further research is needed to explore and understand treatments that fully eliminate ongoing transmission risk and manage symptoms and sequalae secondary to viral persistence and recrudescence.

Conclusion

The vast experience of Ebola disease gained during and since the west Africa Epidemic has improved patient care. Leading initiatives have included successful trials of vaccines and treatments, and systematic observational clinical data collection to direct and augment supportive care. However, there are priority research questions that have not been met. The implementation of these scientific successes into practical benefits to patients is far from perfect and is limited by challenges in understanding context and operational constraints. In part two of this series, we will discuss efforts to embed emerging science into improved systems for early diagnosis, high-quality and dignified care, and support for survivors and affected communities.

Author contributions

AR, JD, PH contributed to conception and design of the study. All authors contributed to writing of the manuscript and reviewed the final draft. AR and PH were responsible for the decision to submit the manuscript for publication.

Conflicts of interest statement

TL received a grant to support the running of the UK Vaccine Taskforce from the National Institute of Health Research, was a consultant for Vaccitech on an unrelated project, and is named as an inventor on a patent application for a vaccine against SARS CoV-2. AR has received a Pump Priming grant and an AfOx catalyst grant from the University of Oxford and WHO supported travel to the building research readiness for a future filovirus outbreak workshop and the WHO R+D Pathogen shortlisting meeting. PH and AR are supported by the

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Figures:

Table 1: Comparison of advances in understanding of Ebola disease since the west Africa Epidemic with ongoing scientific priorities.

Category	Advances	Scientific priorities
Epidemiology	Better availability of genomic data and phylogenetic analyses to understand outbreak dynamics Improved real-time data surveillance Broader modelling understanding of countries at risk of Ebola disease Taxonomy revision and new classification systems	Understanding animal reservoir hosts Identifying intra and between species transmission pathways Understanding survivor transmission risks One Health integration and better understanding of filovirus ecology Earlier identification of rare outbreaks in high infectious disease burden contexts
Clinical manifestations	Recognition of the predominance of gastro-intestinal symptoms and extent of multi-organ dysfunction with less haemorrhage that previously thought Understanding the clinical presentation of vaccinated patients who exhibit milder symptoms Understanding the key predictors of death including age extremes, confusion, haemorrhage, renal and hepatic dysfunction, and high viral load Harmonized data collection of risk factors, signs, and symptoms on patient arrival	Improving performance characteristics of case-definitions and adjusting case definitions and screening protocols to account for changes in symptomatology among vaccinated individuals Consistent data collection standards and definitions across outbreaks Understanding mechanisms of disease progression and the biochemical predictors of severe disease Understanding host-factors (including immunophenotypes) that lead to variability in disease severity and disease sequelae between individuals More systematic collection of data from SUDV outbreaks to better understand its clinical course and differences to EBOV infection
Vaccines	Successful clinical trials leading to approved vaccines for EBOV Two licenced vaccines for EBOV approved for clinical use A global stockpile of 450,000 doses established, with proven use in outbreaks. Candidate vaccines for SUDV shortlisted by WHO	Designing vaccines with broader protection (pan-orthoebolavirus or pan-filovirus) Determine the best vaccination strategies for rVSV-ZEBOV and Ad26.ZEBOV Address gaps in vaccine durability, with a focus on breakthrough infections and waning immunity Develop revaccination strategies, particularly for front-line workers, survivors, and other high-risk groups

		Expand vaccine stockpiles to ensure rapid availability during outbreaks Expanding post-regulatory approval access to vaccines and establishing effective funding mechanisms
Treatments	Successful clinical trials leading to approved therapeutics for EBOV Inclusion of special populations in therapeutic guidelines Encouraging evidence of remdesivir in reducing viral persistence	Designing and assessing SUDV specific, pan-orthoebolavirus, and pan-filovirus therapeutics Designing and assessing drugs that have an extended window of efficacy Assessing combination therapy, including host-directed therapies Developing therapeutics effective among patients with a high viral load Post-exposure chemoprophylaxis studies Dose-optimization studies for approved treatments Expanding post-regulatory approval access to therapeutics and establishing effective funding mechanisms
Supportive care	More specific approaches to supportive care, including oral rehydration and guided electrolyte repletion Development of consensus-based supportive care guidelines Availability and use of organ-support interventions in outbreak affected areas	Designing and evaluating potential optimisations in elements of supportive care (e.g. fluid resuscitation strategies, loperamide) Scaling and optimising supportive care practices in parallel with novel therapeutics and vaccines Addressing the logistical challenges of providing high-quality critical care in outbreak-prone regions (e.g., dialysis, oxygen supply, blood banks)
Special populations	Enrolment of special populations in clinical trials Inclusion of special populations in vaccine and treatment guidelines Better understanding of the clinical course and complications in paediatric Ebola disease	Understanding population specific responses to vaccinations and treatments Adapting and nuancing supportive care to meet needs of special populations Understanding of viral transmission risks via breast milk and amniotic fluid
Post-Ebola sequalae	Recognition of post-Ebola disease syndrome Recognition of viral sequestration and	Understanding the duration and population level risk of sexual transmission Assessing the role of vaccines and

	recrudescence	therapeutics in reducing clinical symptoms or viral persistence Understanding sexual transmission risk (if any) from female survivors Understanding unintended consequences of treatments on viral persistence, or long-term side-effects Further well powered trials on treatments to eradicate virus from sanctuary sites

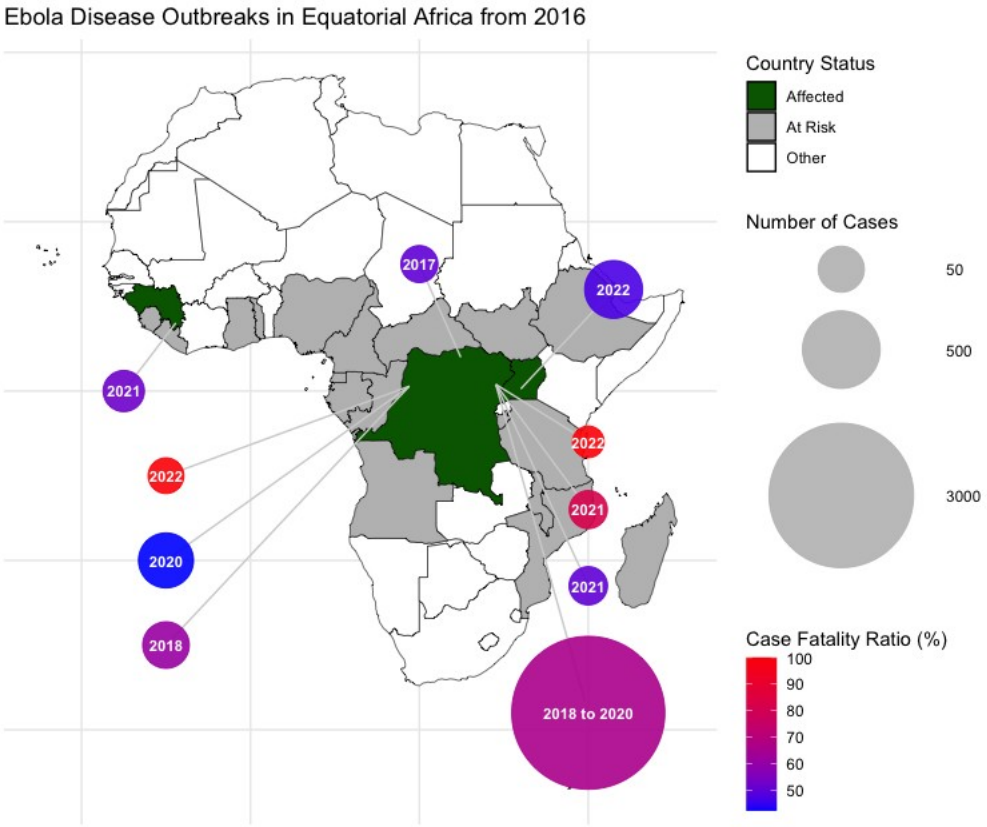

Figure 1: Outbreaks or clusters of Ebola disease since the west Africa epidemic with associated case fatality ratios. Red shading denotes countries affected by one or more Ebola disease outbreaks since 2016, while grey shading denotes countries potentially at risk of Ebola disease as determined via contemporary modelling strategies[20]

	***EBOV* infection (West Africa, 2014-2016)**[39]			**Unvaccinated *EBOV* infection (DRC, 2018-2019)**[38]			**Vaccinated *EBOV* infection (DRC, 2018-2019)**[38]			***SUDV* infection (Uganda, 2022)**[29]		
Symptom[#]	Count/ Total	% of cases	95% CI	Count/ Total	% of cases	95% CI	Count/ Total	% of cases	95% CI	Count/ Total	% of cases	95% CI
Asthenia/ Fatigue	3098/3865	80·2%	78·9%-81·4%	704/846	83·2%	80·7%-85·7%	228/290	78·6%	73·9%-83·3%	89/160	55·6%	47·9%-63·3%
Chest pain	1179/2815	41·9%	40·1%-43·7%	175/822	21·3%	18·5%-24·1%	64/283	22·6%	17·7%-27·5%	47/160	29·4%	22·3%-36·4%
Fever	3440/3952	87·0%	86·0%-88·1%	402/831	48·4%	45·0%-51·8%	121/287	42·2%	36·4%-47·9%	135/160	84·4%	78·7%-90·0%
Headache	2122/3504	60·6%	58·9%-62·2%	453/840	53·9%	50·6%-57·3%	170/292	58·2%	52·6%-63·9%	74/160	46·2%	38·5%-54·0%
Joint pain	1616/3253	49·7%	48·0%-51·4%	366/825	44·4%	41·0%-47·8%	138/287	48·1%	42·3%-53·9%	49/160	30·6%	23·5%-37·8%
Myalgia	1694/3378	50·1%	48·5%-51·8%	310/826	37·5%	34·2%-40·8%	108/280	38·6%	32·9%-44·3%	49/160	30·6%	23·5%-37·8%
Abdominal pain	1764/3369	52·4%	50·7%-54·0%	416/838	49·6%	46·3%-53·0%	99/286	34·6%	29·1%-40·1%	64/160	40·0%	32·4%-47·6%
Anorexia	2685/3613	74·3%	72·9%-75·7%	617/845	73·0%	70·0%-76·0%	188/289	65·1%	59·6%-70·5%	62/160	38·8%	31·2%-46·3%
Diarrhoea	2307/3624	63·7%	62·1%-65·2%	341/840	40·6%	37·3%-43·9%	95/284	33·5%	28·0%-38·9%	81/160	50·6%	42·9%-58·4%
Vomiting and nausea	2402/3657	65·7%	64·1%-67·2%	422/847	49·8%	46·5%-53·2%	129/287	44·9%	39·2%-50·7%	93/160	58·1%	50·5%-65·8%
Dysphagia	721/2642	27·3%	25·6%-29·0%	171/831	20·6%	17·8%-23·3%	31/280	11·1%	7·4%-14·7%	10/160	6·2%	2·5%-10·0%
Sore throat	546/2510	21·8%	20·1%-23·4%	142/829	17·1%	14·6%-19·7%	28/280	10·0%	6·5%-13·5%	15/160	9·4%	4·9%-13·9%
Any bleeding/ Unexplained Bleeding	373/3138	11·9%	10·8%-13·0%	135/835	16·2%	13·7%-18·7%	17/286	5·9%	3·2%-8·7%	13/160	8·1%	3·9%-12·4%
[#]Where symptom nomenclature differed, best clinical judgement was used to consolidate symptoms across cohorts												

Table 2: Relative Prevalence of Selected Symptoms Across Three Separate Ebola Disease Cohorts Contrasting the west Africa epidemic, the 2018-20 DRC Outbreak Stratified by Vaccination Status, and the 2022 SUDV Outbreak in Uganda

Table 3: Comparison of the Current Availability of Vaccination and Treatment Options for Different Orthoebolaviruses

Category	EBOV	SUDV	Other Orthoebolaviruses
	Vaccination		
Approved vaccines	rVSV-ZEBOV (WHO, FDA, EMA) Ad26.ZEBOV & MVA-BN-Filo (WHO, EMA)	None. Access to candidates through clinical trials	None. Access to candidates through clinical trials
Special Populations	Pregnant Women: No restrictions on use Children: Restricted to 12+ months	None. Access to candidates through clinical trials	None. Access to candidates through clinical trials
	Treatment		
Supportive care	Optimized supportive care (WHO)	Optimized supportive care (WHO)	Optimized supportive care (WHO)
Approved targeted therapeutics	MAb114 (WHO, FDA) REGN-EB3 (WHO, FDA)	None. Access to candidates via clinical trials or monitored use where available	None, access via clinical trials or monitored use where available
Special Populations	Children: Neonates with maternal infection qualify for targeted treatment	Access via clinical trials or monitored use where available	Access via clinical trials or monitored use where available
	Recovery		
Post-Ebola (disease) Syndrome	No countermeasures available	No countermeasures available	No countermeasures available

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