Standard of care for viral haemorrhagic fevers (VHFs): a systematic review of clinical management guidelines for high-priority VHFs

Ishmeala Rigby, Melina Michelen*, Andrew Dagens*, Vincent Cheng, Dania Dahmash, Eli Harriss, Eika Webb, Erhui Cai, Samuel Lipworth, Alexandra Oti, Valeria Balan, Helen Piotrowski, Robert Nartowski, Amanda Rojek, Helen Groves, Peter Hart, Muge Cevik, Henry Kyobe Bosa, Lucille Blumberg, Tom E Fletcher, Peter W Horby†, Shevin T Jacob†, Louise Sigfrid†*

The Sudan virus disease outbreak in Uganda in 2022 showed our vulnerability to viral haemorrhagic fevers (VHFs). Although there are regular outbreaks of VHFs with high morbidity and mortality, which disproportionally affect low-income settings, our understanding of how to treat them remains inadequate. In this systematic review, we aim to explore the availability, scope, standardisation, and quality of clinical management guidelines for VHFs. We identified 32 guidelines, 25 (78%) of which were low quality and did not have supporting evidence and eight (25%) of which had been produced or updated in the past 3 years. Guidance on supportive care and therapeutics had little detail and was sometimes contradictory. Guidelines based on uncertain evidence are a risk to patients, an ethical challenge for clinicians, and a challenge to implementing trials due to heterogeneous standards of care. We recommend a standard living guideline framework to improve the quality, scope, and applicability of guidelines. Furthermore, investments into trials should aim to identify optimal treatment strategies for VHFs and prioritise affordable and scalable interventions to improve outcomes globally.

Lancet Infect Dis 2023; 23: e240–52

Published Online February 6, 2023 https://doi.org/10.1016/S1473-3099(22)00874-X

*Joint first authors

†Joint senior authors

GloPID-R Research and Policy Team (L Sigfrid PhD), **International Severe Acute Respiratory and Emerging Infection Consortium, Pandemic Sciences Institute** (I Rigby MSc, M Michelen MSc, A Dagens MBChB, D Dahmash PhD, E Cai MD DPhil, V Balan BSc, H Piotrowski MA, R Nartowski PhD, Prof P W Horby PhD, L Sigfrid), **Bodleian Health Care Libraries** (E Harriss MSc), **and Nuffield Department of Medicine** (S Lipworth DPhil), **University of Oxford, Oxford, UK; Department of Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (S Lipworth); **Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK** (V Cheng DPhil); **Department of Veterinary Medicine, University of Cambridge, Cambridge, UK** (A Oti MBBS); **Emergency Department, Royal Melbourne Hospital, Melbourne, Australia** (A Rojek MBBS PhD); **Centre for Integrated Critical Care, University of Melbourne, Melbourne, Australia** (A Rojek); **Department of Clinical Sciences, Imperial College London, London, UK** (E Webb MBBS); **Wellcome Trust, London, UK** (H Groves PhD, P Hart PhD); **Department of Global Health and Infection Research, School of Medicine, University of St Andrews, St Andrews, UK** (M Cevik MD); **Ministry of Health, Kampala, Uganda** (H K Bosa MBChB); **Makerere University Lung Institute, Makerere University College of**

Introduction

Despite the high morbidity and mortality associated with most viral haemorrhagic fevers (VHFs), our understanding of how to manage these diseases is still sparse. Human VHFs are caused by genetically distinct viruses. WHO has designated Ebola disease, Marburg virus disease (MVD), Lassa fever, Crimean–Congo haemorrhagic fever (CCHF) and Rift Valley fever (RVF) as high-priority VHFs for research and development.[1] Ebola disease and MVD are caused by filoviruses, CCHF and RVF by bunyaviruses, and Lassa fever by arenaviruses.[2,3] There are six known ebolaviruses, four of which are known to cause human disease (ie, Bundibugyo virus, Sudan virus, Taï Forest virus, and Ebola virus).[4] Ebola disease outbreaks have most commonly been caused by Ebola virus and Sudan virus.[5] These six viruses are distinct, which can result in VHF in humans, characterised by symptoms such as fever, fatigue, muscle pain, headache, vomiting, diarrhoea, rash, or impaired kidney and liver function.[6] More severe illness can include internal and external bleeding, with case fatality ratios in past outbreaks ranging from 25% to 90% for Ebola disease,[7] from 24% to 88% for MVD,[8] approximately 1% for Lassa fever[9] and RVF,[10] and from 10% to 40% for CCHF.[11]

Although many of these VHFs predominantly affect populations in regions of Africa,[2,8] CCHF is also widespread in regions of Asia and the Middle East,[12] and has emerged in new regions in Europe in the 21st century.[13] Global travel, trade, climate change, and changes in human behaviour have contributed to an increase in VHF outbreaks and emergence in new areas.[14] Globally, clinicians should be alert to the risk of travel-imported cases to detect them quickly, reduce risk of transmission, and improve patient outcomes. Because the majority of VHFs have a high case fatality rate, management is a crucial component for patient survival. Early treatment, supportive care, and clinical management of complications are integral to improve outcomes. For example, during the Ebola virus disease outbreak in west Africa (2013–16), mortality among patients evacuated to well resourced, high-income countries for treatment was considerably lower compared with patients who were treated in west Africa (18·5% *vs* 40–70%).[15,16] This difference was probably influenced by the provision of high-level critical care (eg, invasive ventilation, renal replacement therapy, and intensive nursing),[16,17] as well as access to experimental therapies that were generally unavailable to patients in west Africa. Variation in case fatality rates between high-income and low-income settings has also been observed for MVD and Lassa fever.[17,18] However, the elements of optimal supportive care that have the most effect on improving survival are not clear. Studies done to a high ethical standard during outbreaks could enable access to experimental therapies locally, provide improvement in disease outcomes, and inform our understanding about the best approach to management. For example, the Pamoja Tulinde Maisha (PALM) trial in the Democratic Republic of the Congo during the 2018 outbreak of Ebola virus disease showed monoclonal antibodies MAb114 and REGN-EB3 to be superior to ZMapp in reducing Ebola virus disease mortality.[19] The antiviral remdesivir reduced the presence of Ebola virus RNA in the semen of people who had survived Ebola virus disease in another trial.[20] Ribavirin has been widely used to treat Lassa fever since the 1980s, despite no robust evidence supporting its use.[21] Likewise, there is no clear evidence on effectiveness of ribavirin for CCHF.[22]

Health Sciences, Kampala, Uganda (H K Bosa)**; National Institute for Communicable Diseases, Johannesburg, South Africa** (L Blumberg PhD)**; Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK** (T E Fletcher PhD, S T Jacob MD)

Correspondence to: Dr Louise Sigfrid, International Severe Acute Respiratory and Emerging Infection Consortium, Pandemic Sciences Institute, University of Oxford, Oxford OX3 7LG, UK
louise.sigfrid@ndm.ox.ac.uk

See Online for appendix

Clinical management guidelines are important tools for guiding clinical decision making and standardising care to benefit patient outcomes.[23] Guidelines can be particularly relevant for priority pathogens, such as those causing VHFs, for which outbreaks tend to occur sporadically and with risk of emergence in new geographical areas where clinicians might not have previous experience with the disease. During 2018–19, the PALM Ebola virus disease treatment trial in the Democratic Republic of the Congo showed that variation in access and administration of appropriate standard of supportive care across sites was a challenge in the design, implementation, and analysis of the trial.[19] Even when the evidence base is small, guidelines are integral for standardising supportive care between sites and can reduce the risk of inappropriate, non-evidence-based treatment to benefit patient care and outcomes and facilitate implementation of much needed trial responses to outbreaks. The aims of this systematic review are to assess the availability of evidence-based clinical guidelines for high-priority VHFs of public health importance and to establish consensus on evidence-based supportive care and treatment recommendations for different, at-risk populations globally.

Methods

This is a systematic review of the availability, inclusivity, scope, and quality of guidelines for high-priority VHFs.[1] It is registered with the International Prospective Register of Systematic Reviews (CRD42020167361),[24] follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews,[25] and uses the methodological guide for the design and conduct of systematic reviews produced by Johnston and colleagues.[26]

Eligibility criteria

We defined guidelines as documents that provided recommendations on medical treatments including supportive care (eg, fluid resuscitation, oxygen delivery, and symptomatic treatments to stabilise the vital signs of patients), following the WHO definition of guidelines.[27] These guidelines contain recommendations to guide practice and provide statements that are designed to help end users make informed decisions regarding interventions with the aim of having the best possible individual health outcomes. Guidelines providing supportive care or medical treatment recommendations focused on WHO's blueprint priority VHFs for research and development (Ebola disease, Lassa fever, MVD, CCHF and, RVF were included). We excluded local hospital standard operating procedures and public health or microbiology guidelines if they did not provide any treatment guidance. Guidelines were not excluded based on language. Only the latest version of a guideline was included.

Search strategy and selection criteria

We searched MEDLINE, Embase, Ovid Global Health, Scopus, Web of Science Core Collection, and WHO Global Index Medicus from database inception to Sept 14, 2022, for guidelines published in English. Inception ranged from 1788 to 1974 for the different databases (appendix pp 1–4). We identified keywords and phrases from an initial set of VHF guidelines that were identified via manual searches in the planning stage. From these guidelines, we defined associated MeSH and Emtree terms, subject headings, and indexes from specific databases. The search strings were then tested against the initial standard set to ensure the quality of the final search strings (appendix pp 1–4). Database search strategies applied the Canadian Agency for Drugs and Technology in Health search filter, with no limits applied to search results. Recognising that most clinical guidelines were not published in peer-reviewed journals, we complemented this with a grey literature search from database inception to Sept 22, 2022. The grey literature searches of Google Scholar were done in Arabic, English, Mandarin, Russian, and Spanish. Furthermore, we searched Ministry of Health and national public health websites in each G20 nation and requested clinical management guidelines from the Ministry of Health when none were identified on their websites. We also contacted VHF experts and requested available clinical management guidelines.

Screening and data extraction

After deduplication, three reviewers (AD, IR, and MM) screened the search results for inclusion—first title and abstract, then full text—using Rayyan (Qatar Computing Research Institute, Doha, Qatar).[28] For non-English records identified through the peer-reviewed and grey literature search, the documents were translated into English with Google Translate, screened, had data extracted, and were appraised by a reviewer (ie, AD, AO, DD, EC, EW, IR, MM, or VB) with good to excellent knowledge of the original publication language. Data were extracted with a standardised form (appendix pp 8–9).[29] Data on source, year issued, inclusivity (ie, children, pregnant women, adults, people older than 60 years, and people living with HIV), scope (ie, medical treatment and supportive care recommendations), and methods used to formulate the recommendations (ie, systematic, expert consensus, a combination of methods, or based on other guidelines) were extracted by one reviewer and checked by a second reviewer (ie, AD, DD, EW, IR, or MM). Any conflicts were resolved through consensus or by a third reviewer (LS).

Quality assessment

Two reviewers (ie, AD, AO, DD, EC, EW, IR, MM, or VB) independently assessed the quality of the guidelines using the Appraisal of Guidelines for Research and

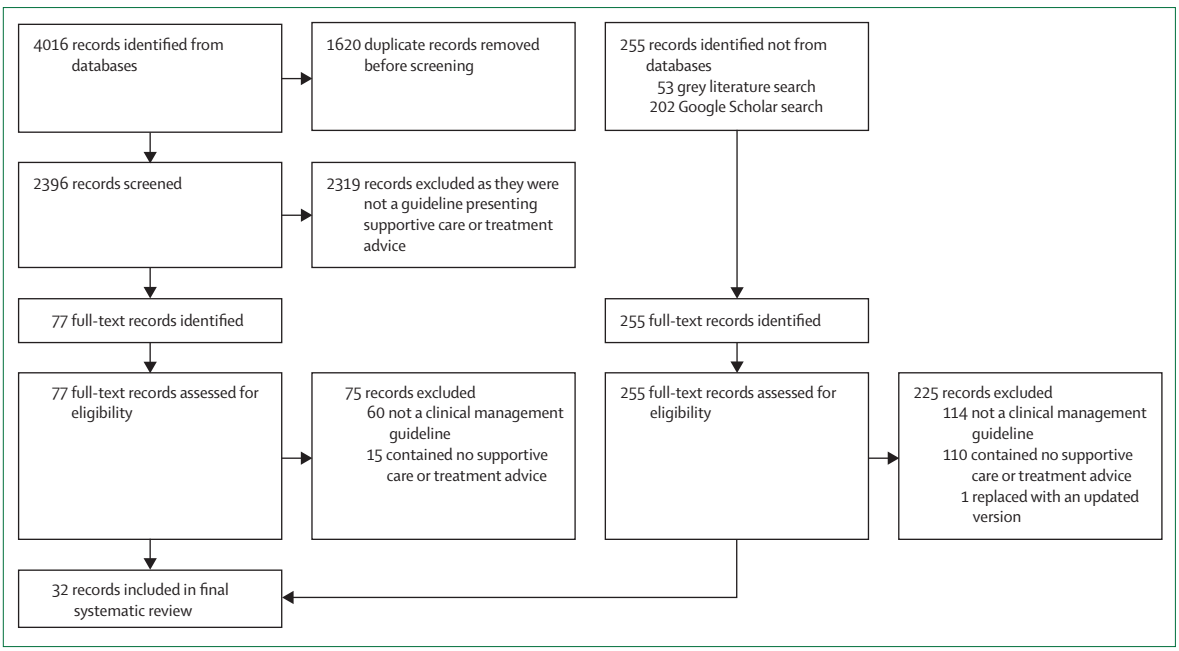

Figure 1: **Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart**

Evaluation (AGREE) II tool.[30] The AGREE II tool provides an objective, gold-standard framework to assess the quality of clinical guidelines. It consists of 23 criteria across six domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. There are also two global rating items (ie, overall guideline quality and recommendation for use).[30] The assessment scoring for each item was completed by two assessors (ie, AD, AO, DD, EC, EW, IR, MM, or VB) using a seven-point scale from 1 (strongly disagree) to 7 (strongly agree). A score of 100% was achieved if each reviewer scored the best score of 7 for all items in a domain and a score of 0% was achieved if each reviewer scored the worst score of 1 for all items in a domain.[30] If there was no information about the methods of the guideline, efforts were made to search for any additional information via associated websites. Concordance between scores of the reviewers was calculated with Cohen's κ.[31] Scores differing by more than three points between reviewers were reconciled via consensus. Overall domain scores were calculated as per the AGREE II tool user manual,[30] converting the sum of individual scores from each reviewer into a standardised percentage for each domain. The clinical guidelines were considered to be high quality if they scored more than 60% in domain three (rigour of development) as it is considered a high-quality indicator, as well as two other, non-specified domains. If a guideline scored more than 60% in any three or more domains, not including domain three, it was considered moderate quality. If a guideline did not meet any of these criteria, it was considered low quality.

Data analysis

The synthesis of data sought to identify areas of congruence and incongruence between guidelines. The availability of clinical management guidelines was established on the basis of whether guidelines were identified for different countries and regions. The guidelines were considered inclusive if they contained clinical guidance for the care of different population groups (ie, children, adults, pregnant women, people older than 60 years, or people living with HIV or immunosuppression). Descriptive analysis was done in R (R Core Team, Vienna, Austria) version 4.0.2 and graphics were produced with the ggplot2 library and Tableau.

For **R** see https://www.R-project.org/

For **ggplot2** see https://ggplot2.tidyverse.org

Patient–public involvement

There was no patient–public involvement in this systematic review due to ongoing COVID-19 pandemic constraints.

Results

Of the 4271 documents screened, 32 guidelines met the inclusion criteria and were included in the systematic review (figure 1; appendix pp 11–12).[32–64] Most were produced in English (81%, 26 of 32);[34,36,37,40–51,53–60,62–64] others were produced in French (6%, two of 32),[35,52] Russian (6%, two of 32),[33,38] Chinese (3%, one of 32),[39] and Japanese (3%, one of 32).[61]

Availability

16 (50%) of the 32 guidelines focused on the management of Ebola disease,[35,37–40,44,46,52,54,55,58–62,64] of which three (19%) were specific for Ebola virus,[44,46,64] and eight (50%)[38,40,52,58–61,64]

	Organisation	Country or region to which the guideline aims to apply	Year of guideline publication	People for whom the guideline includes recommendations	Quality of the guideline*
CCHF[33]	Russia MoH	Russia	2014	Children, adults, and pregnant women	High
CCHF[34]	Afghanistan MoPH and WHO	Afghanistan	2012	Children, adults, and pregnant women	Low
CCHF[36]	NIH and WHO	Pakistan	2013	Adults and pregnant women	Low
CCHF[63]	US CDC, NIH Pakistan, and WHO	USA	2013	Adults	Low
Ebola disease[64]	CCCS	Canada	2014	Children and adults	Low
Ebola disease[61]	Japan MoHLW	Japan	2015	Adults	Low
Ebola disease	Lamontagne et al[62]	Global	2018	Children and adults	High
Ebola disease[35]	Mission Coordination Opérationnelle Risque Épidémique et Biologique nationale	France	2019	Children and adults	Low
Ebola disease[38]	Russia MoH and SSMU	Russia	2014	Children, adults, and pregnant women	Low
Ebola disease[52]	MoHSA	Senegal	2015	Children, adults, and pregnant women	Low
Ebola disease[40]	MoHSW	Liberia	2014	Children, adults, pregnant women, and people living with HIV or who are immunocompromised	High
Ebola disease[39]	NHC China	China	2008	Adults	Low
Ebola disease[60]	Queensland Health and Queensland Government	Australia	2014	Children, adults, and pregnant women	Low
Ebola disease[59]	SCC and WFPICCS	USA	2015	Infants, children, and adults	Low
Ebola disease[58]	SOGC	Canada	2015	Adults and pregnant women	Low
Ebola disease[37]	UpToDate	Global	2021	Adults and pregnant women	High
Ebola disease[46]	US CDC	USA	2021	Children, adults, and pregnant women	Low
Ebola disease[44]	WHO therapeutics guideline (to be used alongside WHO supportive care guideline)[54]	Global	2022	Infants, children, adults, pregnant women, people aged 60 years or older, and people living with HIV or who are immunocompromised†	High
Ebola disease[55]	WHO (for use in pregnancy)	Global	2020	Infants and pregnant women	High
Ebola disease[54]	WHO supportive care guideline (to be used alongside WHO therapeutics guideline)[44]	Global	2019	Children, adults, and pregnant women	Low
FHF[47]	MSF	Global	2008	Children, adults, and pregnant women	Low
Lassa fever[48]	Nigeria CDC	Nigeria	2018	Children, adults, and pregnant women	Low
Lassa fever[57]	US CDC	USA	2014	Adults	Low
MVD[53]	UpToDate	Global	2022	Adults	High
MVD[41]	US CDC	USA	2021	Adults	Low
RVF[43]	US CDC	USA	2020	Adults	Low
VHFs (ie, EVD, MVD, Lassa fever, and RVF)[42]	BICHAT	Luxembourg	2004	Adults, and pregnant women	Low
VHFs (ie, CCHF, EVD, MVD, Lassa fever, and RVF)[45]	South Africa DoH	South Africa	2015	Children and adults	Low
VHFs (ie, CCHF, EVD, MVD, Lassa fever, and RVF)[50]	ENIVD	Europe	2001	Adults	Low
VHFs (ie, CCHF, EVD, MVD, Lassa fever, and RVF)[56]	MSF	Global	2021	Children and adults	Low
VHFs (ie, CCHF, EVD, MVD, Lassa fever, and RVF)[51]	San Francisco DoPH	USA	2008	Children, adults, and pregnant women	Low
VHFs (ie, CCHF, EVD, MVD, and Lassa fever)[49]	WHO	Global	2016	Children, adults, and pregnant women	Low

AGREE=Appraisal of Guidelines for Research and Evaluation. BICHAT=Biological and Chemical Agent Threats. CCHF=Crimean–Congo haemorrhagic fever. CCCS=Canadian Critical Care Society. CDC=Centers for Disease Control and Prevention. DoH=Department of Health. DoPH=Department of Public Health. ENIVD=European Network for Diagnostics of Imported Viral Diseases. EVD=Ebola virus disease. FHF=filovirus haemorrhagic fever. MoH=Ministry of Health. MoHLW=Ministry of Health, Labour, and Welfare. MoHSA=Ministry of Health and Social Action. MoHSW=Ministry of Health and Social Welfare. MoPH=Ministry of Public Health. MSF=Médecins Sans Frontières. MVD=Marburg virus disease. NHC=National Health Commission. NIH=National Institutes of Health. RVF=Rift Valley fever. SCC=Society of Critical Care Medicine. SOGC=Society of Obstetricians and Gynaecologists of Canada. SSMU=Smolensk State Medical University. VHF=viral haemorrhagic fever. WFPICCS=World Federation of Paediatric Intensive and Critical Care Society. *As per the AGREE II. †Infants are defined as age 7 days or younger. Children are defined as aged between 7 days and 5 years. Adults are defined as aged between 18 years and 59 years.

Table 1: **VHF guideline characteristics, inclusivity, and quality**

were produced during the 2013–16 west African Ebola virus disease epidemic. The remaining guidelines focused on CCHF (13%, four of 32),[33,34,36,63] Lassa fever (6%, two of 32),[48,57] MVD (6%, two of 32),[41,53] and RVF (3%, one of 32);[43] seven (22%) of 32 included more than one VHF (table 1).[42,45,47,49–51,56] Only 10 (31%) of 32 had been

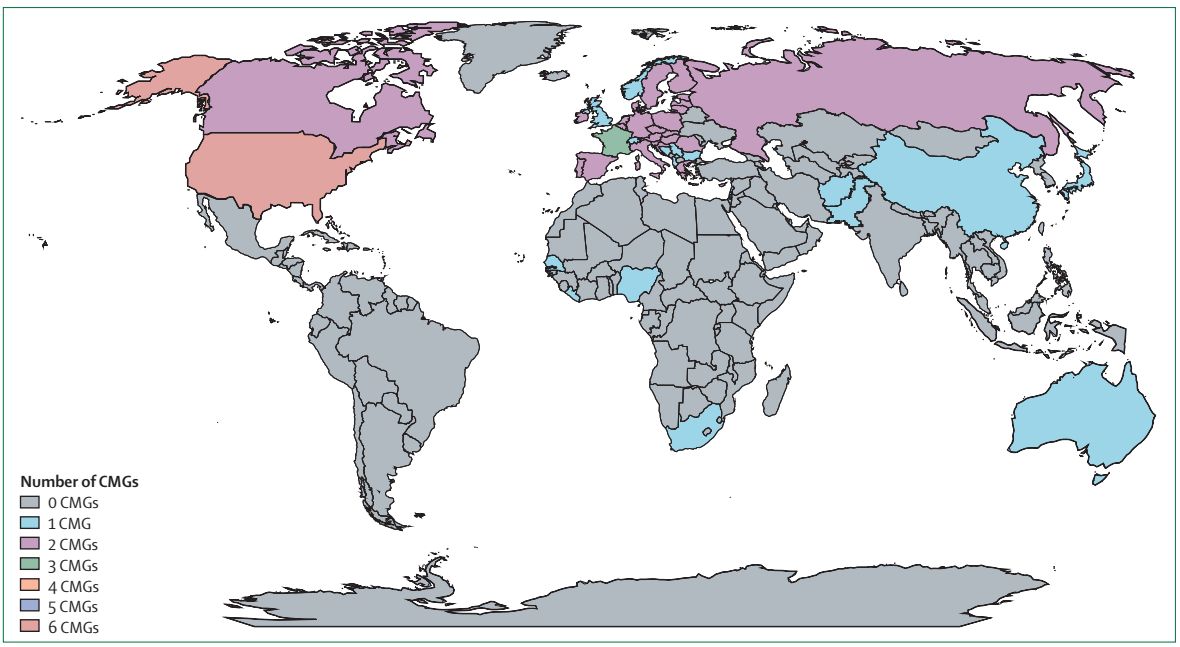

Figure 2: **Availability of VHF guidelines**
Locations where identified guidelines were produced. The colour represents the number of identified guidelines produced in each country. There were ten guidelines that aimed for implementation in regional or global settings. CMG=clinical management guideline. VHF=viral haemorrhagic fever.

produced since 2019 (table 1).[35,37,41,43,44,46,53–56] The guidelines were produced for use in North America (28%, nine of 32),[41,43,46,51,57–59,63,64] Europe and central Asia (16%, five of 32),[33,35,38,42,50] sub-Saharan Africa (13%, four of 32),[40,45,48,52] east Asia and the Pacific region (9%, three of 32),[39,60,61] south Asia (6%, two of 32),[34,36] or for global use (28%, nine of 32; figure 2; table 1).[37,44,47,49,53–56,62] 21 (67%) of 32 were produced by national organisations, including governments, and 11 (34%) of 32 were produced by international organisations (table 1).

Quality

25 (78%) of 32 guidelines were assessed as low quality (overall score ≤3)[34–36,38,39,41–43,45–52,54,56–61,63,64] and 7 (22%) were assessed as high quality.[33,37,40,44,53,55,62] The median overall quality score was 2 (range 1–7; figure 3). There was a high degree of concordance between reviewer scores (overall weighted Cohen's κ 0·86, 95% CI 0·86–0·86). There were substantial variations across the individual domain scores. The highest scoring domains were clarity of presentation (median 61%, IQR 45–67) and scope and purpose (median 54%, IQR 31–69). There were particular deficits in the domains for rigour of development (median 17%, IQR 9–38), applicability (median 24%, IQR 15–38), stakeholder involvement (median 28%, IQR 6–44), and editorial independence (median 0%, IQR 0–18; figure 3). The low scores for editorial independence could be partly attributed to little or no information provided regarding competing interest.

Many guidelines provided sparse or no information about the methodology used and links to evidence supporting the recommendations. Seven (22%) of the 32 guidelines[33,37,44,53,54,58,62] specified the use of systematic methods to search for evidence and seven (22%)[38,40,45,47,50,59,64] used expert consensus to inform the recommendations. Five (16%) of 32 used the Grading of Recommendations, Assessment, Development, and Evaluations framework for assessing the strength of the evidence alone or in combination with expert consensus.[37,44,53,55,62] 11 (34%) of 32[33,35,37,42,44,48,53,55,58,62,64] were peer-reviewed before publication. 12 (38%)[33,37,40,44,51–53,55,56,60,62,64] stated plans for regular updates, but only one outlined clear criteria and a timeframe for the update.[55]

Inclusivity

Several guidelines made specific recommendations for different at-risk populations, including pregnant women (56%, 18 of 32)[33,34,37,38,40,42,44,46–49,51,52,54,55,58,60] and children (63%, 20 of 32).[33–35,38,40,44–49,51,52,54–56,59,60,62,64] However, only one (3%) provided specific guidance for people older than 60 years[44] and two (6%) provided specific guidance for people living with HIV (table 1).[40,44]

Supportive care and treatment

Patients with VHFs can have fluid loss from pyrexia, haemorrhage, or gastrointestinal losses, and supportive care is an integral treatment (tables 2, 3).[65] There was a broad consensus on the need for intravenous fluid replacement in patients with VHF and a recognition that fluid resuscitation largely depends on the clinical condition of a patient. Despite the agreement that fluids

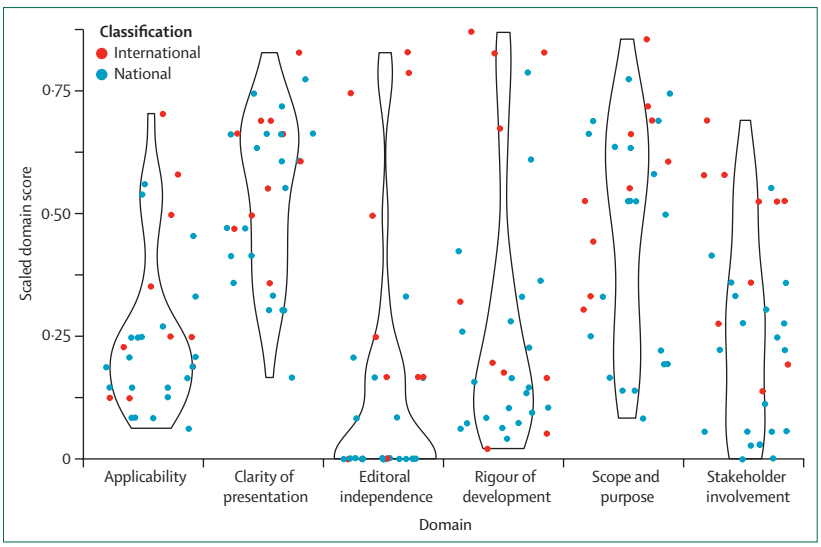

Figure 3: **AGREE II domain scores**
Violin plot depicting the individual scores of the guidelines in each domain. Each dot represents the proportional score per domain of each guideline. The width of each curve represents the frequency of guideline scoring in each region. The dots indicate whether guidelines were produced for international or regional and national use. AGREE=Appraisal of Guidelines for Research and Evaluation.

are needed, there was no agreement on ideal resuscitation strategy (table 3).

11 (34%) of 32 guidelines advocated for fluid resuscitation with crystalloids (eg, normal saline or Ringer's lactate).[33,37,40,48,49,52–54,56,60,64] Three (9%) clinical guidelines advised the use of human albumin solution in persistently hypovolaemic patients.[39,45,64] Four (12%) recommended fluid resuscitation with bolus infusions as part of a so-called fluid challenge approach, especially for patients in shock.[48,49,54,64] One (3%) of the guidelines advocated for initial 20 ml per kg fluid boluses, followed by repeated administration of 250–500 ml boluses every 30 min for adults.[48] Another guideline (3%) specified that hypotensive patients should be administered initial boluses of Ringer's lactate at 20 ml per kg, to be repeated until symptoms of hypotension are no longer apparent.[64] Three (9%) guidelines recommended liberal fluid resuscitation.[48,49,64]

The recommendations of guidelines were vague about the endpoint of fluid resuscitation. One (3%) guideline made it clear that total fluid volume is not to exceed 60 ml per kg in the first 2 h of presentation and advocated for continuing fluid resuscitation until systolic blood pressure (SBP) is more than 90 mmHg and monitoring of target variables (eg, heart rate <100 beats per minute, urinary output >30 ml per h, capillary refill time (CRT) <3 s, absence of skin mottling, easily palpable pulses, and improved mental status).[49] Two (6%) of 32 guidelines advocated for targeting an SBP of more than 90, absence of skin mottling, and normal CRT.[48,49] Another guideline (3%) incorporated heart rate, blood pressure, and parameters of end-organ perfusion.[64] It was rare for guidelines to make any specific mention of resource barriers to fluid resuscitation. Only three (9%) of 32 guidelines advised the central line for access and monitoring purposes;[35,55,64] two (9%) of these were specifically produced for high-income settings.[35,64] One (4%) of these guidelines stated that central line access will probably benefit pregnant women with Ebola virus disease.[55]

Similarly, there was no clear consensus between guidelines on administration of inotropes and vasopressors. 12 (38%) of 32 guidelines advocated for the use of inotropes or vasopressors if clinically appropriate.[33,37,46,48,49,53–55,59–61,64] One (3%) of 32 specified an indication (eg, when fluid resuscitation has failed despite administration of 30 ml per kg fluid in the first 3 h of administration or signs and symptoms of fluid overload).[54] Two (6%) guidelines recommended noradrenaline when hypotension persisted;[37,53] another (3%) recommended adrenaline or dopamine if adrenaline was unavailable.[48] One (3%) guideline detailed that noradrenaline infusion should be used to target a mean arterial pressure of 65–70 mm Hg,[64] with adrenaline as a second-line agent, and to avoid dopamine due to its association with increased frequencies of cardiac arrhythmias and mortality.[64]

11 (34%) of 32 guidelines provided guidance on the role of renal replacement therapy,[35,37,38,46,51,53,55,60,61,63,64] and four (13%)[54,55,61,64] advised that its use is resource dependent. For instance, the Canadian Critical Care Society guidelines advised that haemodialysis can be safely used in a high-income setting.[64]

Blood products

Recommendations on the use of blood products were similarly heterogeneous, with little detail. Although there was a recognition that patients with VHFs are at risk of anaemia, different target haemoglobin thresholds for transfusion were set (eg, 7 g per dl, 8 g per dl, or 5 g per dl).[33,43,46,47,52,57,62] There was no agreement on the use of plasma or platelets. One (3%) guideline of 32 advocated for the use of plasma to obtain an international normalised ratio of less than 1·5 and platelets more than 50×10^9 per L.[54] Two (6%) guidelines suggested treatment with fresh frozen plasma as required, but without further guidance.[35,39] Another (3%) guideline recommended vitamin K and tranexamic acid for people with active haemorrhage.[48]

Symptom management

Symptom management recommendations were provided, including four (12%) of 32 guidelines recommending benzodiazepines for anxiety[35,52,54,64] and six (19%) recommending ondansetron for nausea.[35,40,49,54,56,64] Analgesics (eg, paracetamol and opioids) were recommended for pain relief in 14 (44%) guidelines,[33,35,37,39,40,47,49,52–54,56,59,61,62] whereas 10 (31%) advised against aspirin or non-steroidal anti-inflammatory drugs.[37,38,47,51–54,56,59,60]

	Arenavirus: Lassa fever (n=2)	Bunyavirales		Filoviruses			Generic: multiple VHFs (n=6)
		CCHF (n=4)	RVF (n=1)	Ebola disease (n=16)	Ebola disease and MVD (n=1)	MVD (n=2)	
Percentage of basic supportive care (n)							
Fluid resuscitation	100% (2)	75% (3)	..	93% (14)	100% (1)	100% (2)	83% (5)
Fluid choice	50% (1)	25% (1)	..	47% (7)	100% (1)	50% (1)	33% (2)
Fluid administration	50% (1)	..	..	33% (5)	..	50% (1)	33% (2)
Fluid endpoint guidance	50% (1)	..	..	13% (2)	..	..	17% (1)
Supplemental oxygen	50% (1)	50% (2)	..	33% (5)	..	100% (2)	17% (1)
Blood products	50% (1)	50% (2)	..	60% (9)	..	100% (2)	33% (2)
Symptom control	..	25% (1)	..	87% (13)	100% (1)	50% (1)	33% (2)
Percentage of treatments (n)							
Antimalarials	..	..	..	27% (4)	100% (1)	..	17% (1)
Antibiotics	50% (1)	..	..	47% (7)	100% (1)	50% (1)	33% (2)
Antivirals	100% (2)	75% (3)	..	13% (2)	..	..	100% (6)
Percentage of advanced supportive care (n)							
Invasive monitoring	50% (1)	25% (1)	..	26% (4)	100% (1)	50% (1)	..
Renal replacement therapy	50% (1)	..	..	60% (9)	..	50% (1)	17% (1)
Vasopressors and inotropes	50% (1)	25% (1)	..	53% (8)	..	50% (1)	17% (1)

CCHF=Crimean–Congo haemorrhagic fever. MVD=Marburg virus disease. RVF=Rift Valley fever. VHF=viral haemorrhagic fever.

Table 2: **Overview of type of supportive care and treatments recommended for different diseases**

Physiological monitoring as part of standard of care

There was little agreement on the gold standard of patient monitoring. 12 (38%) of the 32 guidelines recommended repeated physical observations,[37,40,45,47,48,53,54,56,59,61,62,64] but there was no consensus on which observations to take, a baseline acceptable rate of observations, or frequency of vital sign observations. 11 (34%) of 32 only provided vague advice to monitor fluid balance, with no further details.[33,41,45,49,50,52,56,57,61–63] Seven (22%) provided more detailed guidance,[37,40,48,53,54,59,64] with one (3%) advising an examination of fluid status on admission to hospital and then at least once per day weights for monitoring urine balance in children.[54] There were disagreements about the role of urinary catheterisation, with one (3%) guideline[48] opposing its use and another (3%) advocating for its use to monitor urine output in critically ill patients.[64] 23 (72%) of 32 did not mention invasive physiological monitoring.[33,34,36,38–46,49–52,56–60,62,63] One (3%) guideline explicitly advised that invasive procedures should only be carried out in adequately safe conditions.[47] There was also no agreement on optimal biochemical investigations. 11 guidelines (34%)[41,45,48,49,54,57,59,60,62–64] recommended monitoring of electrolytes or renal functioning. Of these 11, four (36%) suggested monitoring once per day of urea and electrolytes,[45,48,49,64] ideally with point-of-care-testing.[26] One (9%) of these 11 guidelines suggested laboratory monitoring every 5 days,[48] and a guideline on Lassa fever emphasised liver function monitoring.[48] Seven (22%) guidelines mentioned the importance of haemoglobin monitoring, at least on admission to hospital or an Ebola virus treatment unit, alongside a coagulation test.[45,48,54,59,60,62,64]

Therapeutics

13 (41%) of the 32 guidelines provided guidance on antiviral use (table 3).[33,35,36,38,42,45,48–51,56,57,63] The two (6%) Lassa-fever-focused guidelines recommended ribavirin,[48,57] but only one (3%) explicitly stated the target population (appendix p 13).[48] Ribavirin was also recommended by all four (13%) CCHF-specific guidelines.[33,34,36,63] Of these, one (25%) specifically stated that ribavirin should be considered for pregnant women and children due to high risk of severe disease,[33] whereas two (50%) stated that pregnancy was a contraindication.[34,36] There were no targeted therapeutic recommendations for MVD and RVF.[41,43,53] 12 (32%) of the 32 guidelines suggested empirical use of antibiotics,[37,45–49,51,53,54,58,59,61] whereas one (3%) guideline stated that antibiotic prophylaxis is not indicated[39] and five (16%) stated that antibiotic use should be probabilistic[31] based on evidence of bacterial infection,[32,33] development of bacterial complications,[29] or consultation with an infectious disease doctor.[54] Nine guidelines (28%) discussed convalescent plasma;[34,40,42,45,51,55,59,60,64] one (3%) recommended its use for patients with Ebola virus disease "when necessary",[40] whereas eight (25%) highlighted that convalescent plasma therapy is experimental[34,42,45,51,55,59,60,64] and one (3%) stated that it should only be used as part of a controlled trial.[59] An MVD guideline published in 2022 stated that convalescent plasma use was of no or unclear benefit to patients.[53] Four (13%) Ebola virus disease guidelines discussed monoclonal antibodies (eg, mAb114 or REGN-3) to be considered alongside supportive care.[37,44,46,55] Two (6%) of these were specific for Ebola virus.[44,46] One (25%) of these four Ebola virus disease guidelines recommended that

	Year of guideline publication	Country or region for which the guideline is developed	Authorising organisation	Basic supportive care				Antimicrobials			Advanced supportive care		
				Fluid resuscitation	Supplemental oxygen	Blood products	Symptom control	Antimalarials	Antibiotics	Antivirals	Invasive monitoring	Renal replacement therapy	Vasopressors and inotropes
CCHF	2018	Pakistan	NIH Pakistan and WHO[36]	..	..	..	..	..	..	Yes	Yes	..	..
CCHF	2013	USA	US CDC[63]	Yes	Yes	..	..	..	..	Yes	..	Yes	..
CCHF	2014	Russia	MoH[33]	Yes	Yes	Yes	Yes	..	Yes	Yes	..	..	Yes
CCHF	2012	Afghanistan	MoPH, WHO, and WHO Health Clusters[34]	..	..	Yes	..	..	..	..	..	..	..
Ebola disease	2021	Global	UpToDate[37]	Yes	Yes	Yes	Yes	..	Yes	..	Yes	Yes	Yes
Ebola disease	2021	USA	US CDC[46]	Yes	..	..	Yes	..	Yes	..	..	Yes	Yes
Ebola disease	2020	Global	WHO[55]	Yes	..	..	..	..	..	..	..	Yes	Yes
Ebola disease	2019	Global	WHO[54]	Yes	..	Yes	Yes	Yes	Yes	..	Yes	..	Yes
Ebola disease	2022	Global	WHO[44]	..	..	..	..	..	..	..	..	..	..
Ebola disease	2019	France	Mission Coordination Opérationnelle Risque Épidémique et Biologique nationale[35]	Yes	..	Yes	..	Yes	Yes	Yes	Yes	Yes	..
Ebola disease	2018	Global	Lamontagne et al [62]	Yes	..	..	Yes	..	Yes	..	..	..	..
Ebola disease	2015	Canada	SCOG[58]	Yes	..	..	..	..	Yes	..	..	..	..
Ebola disease	2015	Japan	MoHLW[61]	Yes	..	Yes	Yes	Yes	Yes	..	Yes	Yes	Yes
Ebola disease	2015	Senegal	MoHSA[52]	Yes	..	..	Yes	Yes	Yes	..	..	..	..
Ebola disease	2014	Liberia	MoHSW[40]	Yes	..	Yes	Yes	Yes	Yes	..	..	..	..
Ebola disease	2014	Canada	CCCS[64]	Yes	..	Yes	Yes	Yes	..	..	Yes	Yes	Yes
Ebola disease	2014	Russia	MoH[38]	..	..	..	Yes	..	Yes	Yes	..	Yes	..
Ebola disease	2015	Global	SCC and WFPICCS[59]	Yes	Yes	Yes	Yes	..	Yes	..	..	..	Yes
Ebola disease	2014	Australia	Queensland DoH[60]	Yes	..	Yes	Yes	..	..	..	..	Yes	Yes
Ebola disease	2008	China	NHC[39]	Yes	..	Yes	Yes	..	..	..	..	..	..
EVD and MVD	2008	Global	MSF[47]	Yes	..	..	Yes	Yes	Yes	..	Yes	..	..
Lassa fever	2014	USA	US CDC[57]	Yes	Yes	..	..	..	..	Yes	..	..	..
Lassa fever	2018	Nigeria	Nigeria CDC[48]	Yes	..	Yes	..	Yes	Yes	Yes	Yes	..	Yes
MVD	2021	USA	US CDC[41]	Yes	Yes	Yes	..	..	..	..	..	..	..
MVD	2022	Global	UpToDate[53]	Yes	Yes	Yes	Yes	..	Yes	..	Yes	Yes	Yes
RVF	2020	USA	US CDC[43]	..	..	..	..	..	..	..	..	..	..
VHF	2021	Global	MSF[56]	Yes	..	..	Yes	..	..	Yes	..	..	..
VHF	2016	Global	WHO[49]	Yes	..	Yes	Yes	..	Yes	Yes	..	..	..
VHF	2015	South Africa	MoH[45]	Yes	..	Yes	..	..	Yes	Yes	..	..	..
VHF	2008	USA	San Francisco DoPH[51]	..	..	..	..	..	..	Yes	..	Yes	..
VHF	2004	Europe	BICHAT[42]	..	..	..	..	..	..	Yes	..	..	..
VHF	2001	Europe	ENIVD[50]	..	..	..	..	Yes	..	Yes	..	..	..

BICHAT=Biological and Chemical Agent Threats. CCCS=Canadian Critical Care Society. CCHF=Crimean–Congo haemorrhagic fever. CDC=Centers for Disease Control and Prevention. DoH=Department of Health. DoPH=Department of Public Health. ENIVD=European Network for Diagnostics of Imported Viral Diseases. EVD=Ebola virus disease. MoH=Ministry of Health. MoHLW=Ministry of Health, Labour, and Welfare. MoHSA=Ministry of Health and Social Action. MoHSW=Ministry of Health and Social Welfare. MoPH=Ministry of Public Health. MSF=Médecins Sans Frontières. MVD=Marburg virus disease. NHC=National Health Commission. NIH=National Institutes of Health. RVF=Rift Valley fever. SCC=Society of Critical Care Medicine. SOGC=Society of Obstetricians and Gynaecologists of Canada. VHF=viral haemorrhagic fever. WFPICCS=World Federation of Paediatric Intensive and Critical Care Society.

Table 3: **Supportive care and treatment recommendations for each VHF guideline**

monoclonal antibodies should be considered for pregnant women and in the context of research.[55] One (6%) of 16 Ebola disease guidelines, published in 2019, recommended Zmapp—a combination of three monoclonal antibodies—alone or in combination with remdesivir as first-line therapy.[35] Favipiravir was recommended as an alternative if these therapies were unavailable.[35] The WHO Ebola virus disease therapeutic guideline released in August, 2022, recommends mAB114 and REGN-EB3.[44] Both REGN-EB3 (a combination of three human monoclonal antibodies that target Ebola virus glycoprotein: atoltivimab [REGN3470], maftivimab [REGN3479], and odesivimab [REGN3471])[66] and mAb114 (a single monoclonal antibody that binds to the core receptor binding domain of the Ebola virus surface protein, preventing the virus from infecting human cells) have been approved by the US Food and Drug Administration for Ebola virus disease on the basis of the results of the PALM trial in 2018.[66–68]

Discussion

Our findings identified a clear deficit in availability of clinical management guidelines providing evidence-based treatment recommendations for VHFs. Most of the identified guidelines had few treatment details and had low-quality methods. 16 (50%) were developed for Ebola disease and, of those, three (19%) provided specific treatment recommendations for Ebola virus disease.[44,46,64] There were no specific guidelines for Sudan virus disease or Bundibugyo virus disease; only two (6%) guidelines were specific for MVD and one (3%) was specific for RVF. Our data highlight the scarcity of evidence on effective therapeutics and optimal supportive care strategies that are available for priority VHF pathogens. Our results also highlight little consensus on disease-modifying treatments. Ribavirin was recommended by all four CCHF guidelines (13%),[33,34,36,50] despite a 2018 Cochrane review concluding that there is insufficient reliable evidence on its effectiveness.[69] Likewise, ribavirin was recommended by both (6%) guidelines for Lassa fever,[48,57] despite little evidence of effectiveness and studies indicating that it increases mortality risk in patients without increased aspartate aminotransferase.[70–72] The variations in treatment recommendations for pregnant women are another cause for concern shown by the conflicting guidance on ribavirin for CCHF, with one (25%) of four CCHF guidelines stating that ribavirin is contraindicated in pregnancy but still recommending it, referring to the high mortality risk from CCHF.[33] One (25%) CCHF guideline explicitly stated that ribavirin should be avoided in pregnancy,[34] and two (50%) stated that pregnancy should be avoided for up to 6 months after completing a course of ribavirin.[34,36]

Despite a consensus on the need to administer fluids in the guidelines providing supportive care recommendations, there was no clear consensus regarding strategies on how best to resuscitate patients in shock. Three (9%) guidelines recommended liberal fluid resuscitation,[48,49,64] although the appropriateness of such a strategy has been challenged by fluid resuscitation trials involving patients treated in hospital with sepsis in sub-Saharan Africa.[73,74] Although the volume, rate, and composition of resuscitation fluids is an active topic of research globally, there are reasons that extrapolation of findings from large trials for other conditions could be unfounded for patients with different VHFs as the pathology, demographics, and comorbidity profiles of patients might differ. The optimal rate of resuscitative fluids is likely to be different for different VHFs; even within a specific disease, the pathogenesis of shock might change as the disease progresses. With improvement in the administration of advanced care for VHFs shown in several settings (eg, intensive care units in high-income countries and introduction of biosecure emergency care units during the 2018–19 Ebola virus disease outbreak in the Democratic Republic of the Congo),[15,16] investigating fluid, antibiotic, antimalarial, and anti-inflammatory choices in high-quality clinical trials should be prioritised, particularly as these strategies are not dependent on protracted and expensive drug pipelines.

Considering the high case fatality rates of most VHFs,[7–9,75,76] even if there is no evidence or poor-quality evidence on effective therapeutics, clinical management guidelines are crucial in guiding supportive care and discouraging inappropriate treatments. As was observed during the COVID-19 pandemic, there can be a tendency to recommend any drugs in emergency situations.[77] Guidelines are important tools to provide evidence-based information during outbreaks and public health emergencies if they are up to date, easily accessible, and trusted by front-line clinicians. There were a few examples of high-quality guidelines developed with systematic methods and grading of the evidence,[37,44,53,55,62] but most were of low methodological quality. Furthermore, there was a tendency for guidelines to be developed rapidly in response to outbreaks and not revisited.[77] Ensuring that guidelines are up to date is crucial to sustain their evidence base, validity, and credibility; guideline development frameworks recommend regular reviews and updates every 3–5 years. For emerging infectious diseases, in which the epidemiology and new evidence might change rapidly, guidelines should be flexible and adaptive.[66]

The number of guidelines providing recommendations that were not evidence-based was high and needs to be addressed. Treatment recommendations based on uncertain or no evidence might not only be ineffective but potentially harmful to patients, and could provide ethical dilemmas for clinicians.

We advise that recommendations are supported by an indication of the strength of the evidence and the decision process behind the recommendation. Tools, such as the Evidence to Decision Framework,[78] can facilitate this process. Further consideration is warranted

for opportunity costs, especially in low-income settings, where most of the VHFs are causing outbreaks. Other factors that affect implementation of guidelines should be considered. For example, few guidelines in our analysis discussed how frequently monitoring should occur for a patient, which for Ebola disease guidelines might partly reflect the scarcity of clinical resources in the early stages of the west Africa Ebola virus disease outbreak. Patient monitoring processes have improved due to better resources, new technology, and clinical trials. Likewise, few guidelines included recommendations of interventions for organ support (eg, mechanical ventilation and renal replacement therapy). Identifying optimal supportive care and treatment recommendations, and the identification of patients most likely to benefit from different treatment strategies, will aid health service planning and effective prioritisation of resources, as well as patient outcomes.

This systematic review has limitations. Although substantial efforts were made to identify guidelines, including searches in different languages, we might have missed national clinical guidelines that were not readily accessible. There might be guidelines for endemic countries that were not identified through our search due to language limitations or not being publicly available. Some countries or sites might rely on guidelines published by international organisations. Two high-quality guidelines were produced by UpToDate,[37,53] an organisation that produces guidelines for subscribers to their service. Although UpToDate might provide high-quality guidelines, they are not freely available. Further studies are recommended to assess access to clinical management guidelines and implementation of recommendations in different contexts to inform guideline development, dissemination, and effective implementation. Some of the included guidelines were in a language other than English,[33,35,38,39,52,61] and although these were assessed by a reviewer with good knowledge of that language, there could have been nuances lost in translation. Furthermore, the AGREE II tool assesses methodological aspects relevant to guideline development, but not the validity of the clinical management recommendations. Therefore, conclusions about the validity of the clinical guidance cannot be derived from the AGREE II assessment.

However, through our extensive searches we identified several guidelines from different regions that highlight concerning limitations in availability, scope, quality, and standardisation of high-priority VHF guidelines. The COVID-19 pandemic has shown the need for rapid access to clinical management guidance even when the evidence is scarce, as well as the effects of optimal supportive care strategies on survival rates. Close collaboration between guideline developers, stakeholders (eg, clinical trial networks), and health-care professionals from endemic regions should be considered as part of guideline development frameworks for the rapid identification of new evidence to inform guidance and care. Developing evidence-based guidelines is resource intensive, requiring stakeholder engagement, evidence appraisals, and resources for regular reviews and updates. VHFs disproportionally affect low-income settings, where such resources might not always be readily available. Guideline development for other, more common infections might be prioritised if resources are scarce. International, high-quality, easily accessible guidelines that can be adapted to different settings could overcome these issues and provide coordinated, sustainable models as long as implementation of recommendations is supported. To achieve these models, guidelines should be adapted for different endemicity, risk factors, and drug resistance in different regions. Global coordination could reduce poorly developed or low-quality guidelines, save valuable resources, and facilitate standardisation of care between sites. Further research to explore the implementation and effects of VHF guidelines in different settings is recommended to inform development frameworks.

The 2022 Sudan virus disease outbreak highlighted that preparedness to respond to and treat VHF infections should be strengthened. Our data highlight an urgent need to invest in and prepare for effective implementation of trials at the outset of outbreaks to identify optimal therapeutic and supportive care strategies, and for new evidence to be incorporated into accessible guidelines. The new WHO living treatment guidance published in August, 2022, is a good example of a high-quality guideline providing holistic and comprehensive treatment recommendations with regular updates to ensure the relevancy of guidance.[44]

Conclusion

Our data highlight a scarcity of standardised, high-quality clinical management guidelines for high-priority VHFs globally. Heterogeneous treatment recommendations based on uncertain evidence are a risk to patients and a challenge for implementation of trials. Our data highlight an urgent need to invest in research to identify optimal treatment strategies. Investments in health-care systems and innovation to improve capacity for critical care interventions in low-income settings are also needed. We recommend a living, evidence-based guideline framework to improve the quality and standardisation of evidence-based recommendations to benefit patient care and outcomes globally.

Contributors

PH, STJ, LB, TEF, LS, VC, AD, HG, HKB, EH, and PWH conceptualised the study. AD, SL, VC, LS, EH, IR, and MM developed the study protocol. IR, MM, AD, and LS wrote the manuscript with input from all co-authors. EH and AD did the database search. IR, MM, AO, EW, EC, DD, and AD did the grey literature searches and screened the articles. MM, DD, EC, IR, VB, AO, EW, and AD extracted the data and completed the risk of bias analyses. MM, IR, SL, VC, AD, DD, AR, HP, RN, MC, and LS led the data analysis, interpretation, and

presentation of findings. PWH, STJ, and LS provided overall supervision, leadership, and advice. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

This work was supported by funding from the UK Foreign, Commonwealth and Development Office; Wellcome Trust (215091/Z/18/Z); and the Bill & Melinda Gates Foundation (OPP1209135). The Global Research Collaboration for Infectious Disease Preparedness Secretariat is a project that receives funding from the EU Horizon 2020 research and innovation programme under a grant agreement (874667). PH is a Senior Research Advisor and HG is a Research Manager at the Wellcome Trust, which provided part of the funding for this study; neither had a role in data collection, analysis, or interpretation of findings. Wellcome supports a range of research funding activities including awards made to the International Severe Acute Respiratory and Emerging Infection Consortium. TEF and STJ have received funding through a sub-award between Oxford University and Liverpool School of Tropical Medicine. All other authors declare no competing interests.

Data sharing

All data generated or analysed during this study can be accessed through request to the corresponding author.

Acknowledgments

We thank the International Severe Acute Respiratory and Emerging Infection Consortium Global Support Centre for logistical and administrative support, all the members of the International Severe Acute Respiratory and Emerging Infection Consortium Global Clinical Research Network, and the external experts who completed the survey and submitted guidelines.

References

1 WHO. Prioritizing diseases for research and development in emergency contexts. https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts (accessed June 28, 2022).

2 UK Government. Viral haemorrhagic fevers: origins, reservoirs, transmission and guidelines. 2018. https://www.gov.uk/guidance/viral-haemorrhagic-fevers-origins-reservoirs-transmission-and-guidelines (accessed Aug 16, 2022).

3 Cobo F. Viral haemorrhagic fevers. In: Cobo F, ed. Imported infectious diseases. Cambridge: Woodhead Publishing, 2014: 243–55.

4 Centers for Disease Control and Prevention. What is Ebola virus disease? 2021. https://www.cdc.gov/vhf/ebola/about.html (accessed Oct 25, 2022).

5 Kozlov M. Ebola outbreak in Uganda: how worried are researchers? *Nature* 2022; published online Oct 7. https://doi.org/10.1038/d41586-022-03192-8.

6 Centers for Disease Control and Prevention. Signs and symptoms. 2021. https://www.cdc.gov/vhf/ebola/symptoms/index.html (accessed June 28, 2022).

7 WHO. Ebola disease. https://www.afro.who.int/health-topics/ebola-disease (accessed Oct 25, 2022).

8 WHO. Marburg virus disease. 2021. https://www.who.int/news-room/fact-sheets/detail/marburg-virus-disease (accessed Aug 16, 2022).

9 WHO. Lassa fever. http://www.who.int/mediacentre/factsheets/fs179/en/ (accessed Oct 25, 2022).

10 Ikegami T, Makino S. Rift Valley fever virus. *Uirusu* 2004; **54:** 229–35 (in Japanese).

11 WHO. Crimean–Congo haemorrhagic fever. https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever (accessed Oct 26, 2022).

12 Chinikar S, Ghiasi SM, Hewson R, Moradi M, Haeri A. Crimean–Congo hemorrhagic fever in Iran and neighboring countries. *J Clin Virol* 2010; **47:** 110–14.

13 Negredo A, de la Calle-Prieto F, Palencia-Herrejón E, et al. Autochthonous Crimean–Congo hemorrhagic fever in Spain. *N Engl J Med* 2017; **377:** 154–61.

14 Redding DW, Atkinson PM, Cunningham AA, et al. Impacts of environmental and socio-economic factors on emergence and epidemic potential of Ebola in Africa. *Nat Commun* 2019; **10:** 4531.

15 Uyeki TM, Mehta AK, Davey RT Jr, et al. Clinical management of Ebola virus disease in the United States and Europe. *N Engl J Med* 2016; **374:** 636–46.

16 Fischer WA 2nd, Crozier I, Bausch DG, et al. Shifting the paradigm—applying universal standards of care to Ebola virus disease. *N Engl J Med* 2019; **380:** 1389–91.

17 Sigfrid L, Moore C, Salam AP, et al. A rapid research needs appraisal methodology to identify evidence gaps to inform clinical research priorities in response to outbreaks—results from the Lassa fever pilot. *BMC Med* 2019; **17:** 107.

18 Brauburger K, Hume AJ, Mühlberger E, Olejnik J. Forty-five years of Marburg virus research. *Viruses* 2012; **4:** 1878–927.

19 Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019; **381:** 2293–303.

20 Higgs ES, Gayedyu-Dennis D, Fischer WA, et al. PREVAIL IV: a randomized, double-blind, 2-phase, phase 2 trial of remdesivir *vs* placebo for reduction of Ebola virus RNA in the semen of male survivors. *Clin Infect Dis* 2021; **73:** 1849–56.

21 Cheng HY, French CE, Salam AP, et al. Lack of evidence for ribavirin treatment of Lassa fever in systematic review of published and unpublished studies. *Emerg Infect Dis* 2022; **28:** 1559–68.

22 Soares-Weiser K, Thomas S, Thomson G, Garner P. Ribavirin for Crimean–Congo hemorrhagic fever: systematic review and meta-analysis. *BMC Infect Dis* 2010; **10:** 207.

23 Tello J, Barbazza E, Yelgezekova Z, et al. Glossary of terms: WHO European Primary Health Care Impact, Performance and Capacity Tool (PHC-IMPACT). 2019. https://apps.who.int/iris/handle/10665/346481 (accessed Aug 16, 2022).

24 Dagens A, Horby P, Jacobs S, et al. A systematic review of the availability, quality and inclusivity of supportive care guidelines in the management of high consequence infectious disease. 2021. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=167361&VersionID=1485505 (accessed Feb 16, 2022).

25 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372:** n71.

26 Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. *J Clin Epidemiol* 2019; **108:** 64–76.

27 WHO. WHO guidelines. https://www.who.int/publications/who-guidelines (accessed Aug 3, 2022).

28 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev* 2016; **5:** 210.

29 Dagens A, Sigfrid L, Cai E, et al. Scope, quality, and inclusivity of clinical guidelines produced early in the COVID-19 pandemic: rapid review. *BMJ* 2020; **369:** m1936.

30 Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE reporting checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016; **352:** i1152.

31 Revelle W. Procedures for psychological, psychometric, and personality research. 2021. https://personality-project.org/r/psych-manual.pdf (accessed Dec 12, 2022).

32 Deardorff A. Tableau (version 9.1). *J Med Libr Assoc* 2016; **104:** 182–83.

33 Ministry of Health of the Russian Federation. Clinical recommendations Crimean hemorrhagic fever (caused by the Congo virus) in adults. 2014. https://crb.velizh.ru/cr/%D0%B8%D0%BD%D1%84%D0%B5%D0%BA%D1%86%D0%B8%D1%8F/%D0%9A%D1%80%D1%8B%D0%BC%D1%81%D0%BA%D0%B0%D1%8F%20%D0%B3%D0%B5%D0%BC%D0%BE%D1%80%D1%80%D0%B0%D0%B3%D0%B8%D1%87%D0%B5%D1%81%D0%BA%D0%B0%D1%8F%20%D0%BB%D0%B8%D1%85%D0%BE%D1%80%D0%B0%D0%B4%D0%BA%D0%B0%20%D1%83%20%D0%B2%D0%B7%D1%80%D0%BE%D1%81%D0%BB%D1%8B%D1%85.pdf (accessed June 29, 2022; in Russian).

34 Ministry of Public Health Afghanistan, WHO, WHO Health Clusters. Operational guideline for prevention and control of Crimean–Congo haemorrhagic fever in Afghanistan. 2012. https://www.humanitarianresponse.info/sites/www.humanitarianresponse.info/files/documents/files/operational_guideline_for_prevention_and_control_of_cchf_in_afghanistan.pdf (accessed June 29, 2022).

35 Mission Coordination Opérationnelle Risque Épidémique et Biologique nationale. Therapeutic management of a patient with confirmed Ebola virus disease (EVD) in France. 2019. https://www.coreb.infectiologie.com/UserFiles/File/coreb/20190313-rpmo-tt-ebola-vf13mars19.pdf (accessed June 29, 2022; in French).

36 National Institute of Health, WHO. Guidelines for Crimean–Congo hemorrhagic fever (CCHF). 2013. https://www.nih.org.pk/wp-content/uploads/2018/03/Guidelines-for-Crimean-Congo-Haemorrhagic-Fever-CCHFUpdated-September-2013..pdf (accessed June 29, 2022).

37 Chertow DS, Bray M, Palmore TN. Clinical manifestations and diagnosis of Ebola virus disease. 2021. https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-ebola-virus-disease?search=Clinical%20manifestations%20and%20diagnosis%20of%20Ebola%20virus%20disease&source=search_result&selectedTitle=1~42&usage_type=default&display_rank=1 (accessed June 29, 2022).

38 Ministry of Health of the Russian Federation. Guidelines for the diagnosis, treatment and prevention of the disease caused by the Ebola virus. 2014. https://old.minzdravao.ru/sites/default/files/metodicheskie_rekomendacii_ebola.pdf (accessed June 29, 2022; in Russian).

39 National Health Commission of the People's Republic of China. Notice of the General Office of the Ministry of Health on issuing Ebola hemorrhagic fever and other infectious disease prevention and control guideline and clinical diagnosis and treatment plan. 2008. http://www.nhc.gov.cn/wjw/gfxwj/201304/f190209e05634aa0bdd880f177c55257.shtml (accessed June 29, 2022).

40 Ministry of Health and Social Welfare. Liberia Ebola virus disease clinical management manual. 2014. https://reliefweb.int/report/liberia/liberia-ebola-virus-disease-clinical-management-manual (accessed June 29, 2022).

41 Centers for Disease Control and Prevention. Marburg—treatment. 2021. https://www.cdc.gov/vhf/marburg/treatment/index.html (accessed June 29, 2022).

42 Bossi P, Tegnell A, Baka A, et al. BICHAT guidelines for the clinical management of haemorrhagic fever viruses and bioterrorism-related haemorrhagic fever viruses. *Euro Surveill* 2004; **9:** 29–30.

43 Centers for Disease Control and Prevention. Rift Valley fever—treatment. 2020. https://www.cdc.gov/vhf/rvf/treatment/index.html (accessed June 29, 2022).

44 WHO. Therapeutics for Ebola virus disease. 2022. https://www.who.int/publications-detail-redirect/9789240055742 (accessed Sept 29, 2022).

45 Department of Health, South Africa. National guidelines for recognition and management of viral haemorrhagic fevers. 2015. https://www.nicd.ac.za/wp-content/uploads/2017/08/vhfguidelinefinal7dec2015-1.pdf (accessed June 29, 2022).

46 Centers for Disease Control and Prevention. Ebola virus disease information for clinicians in US healthcare settings. 2021. https://www.cdc.gov/vhf/ebola/clinicians/evd/clinicians.html (accessed June 29, 2022).

47 Médecins Sans Frontières. Filovirus haemorrhagic fever guideline. 2008. https://www.nursingworld.org/globalassets/practiceandpolicy/work-environment/health--safety/medicins.pdf (accessed Aug 3, 2022).

48 Nigeria Centre for Disease Control. National guidelines for Lassa fever case management. 2018. https://ncdc.gov.ng/themes/common/docs/protocols/92_1547068532.pdf (accessed June 29, 2022).

49 WHO. Clinical management of patients with viral haemorrhagic fever: a pocket guide for front-line health workers: interim emergency guidance for country adaptation. 2016. https://apps.who.int/iris/handle/10665/205570 (accessed June 29, 2022).

50 European Network for Diagnostics of Imported Viral Diseases. Management and control of viral haemorrhagic fevers and other highly contagious viral pathogens. 2001. http://www.enivd.de/FS/fs_encdiseases.htm (accessed June 29, 2022).

51 San Francisco Department of Public Health. Disease prevention and control. 2008. https://www.sfcdcp.org/wp-content/uploads/2018/01/VHF-Binder-Chapter.2008.FINAL-id316.pdf (accessed June 29, 2022).

52 Republic of Senegal Ministry of Health and Social Action. Ebola standard operating protocols. 2015. https://www.medbox.org/document/protocoles-operationnels-normalises-ebola#GO (accessed June 29, 2022; in French).

53 Bray M, Chertow DS. Marburg virus. 2022. https://www.uptodate.com/contents/marburg-virus?search=marburg&source=search_result&selectedTitle=2~18&usage_type=default&display_rank=2 (accessed Sept 29, 2022).

54 WHO. Optimized supportive care for Ebola virus disease: clinical management standard operating procedures. 2019. https://apps.who.int/iris/handle/10665/325000 (accessed June 29, 2022).

55 WHO. Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease. 2020. https://www.who.int/publications-detail-redirect/9789240001381 (accessed June 29, 2022).

56 Médecins Sans Frontières. Viral haemorrhagic fevers. 2021. https://medicalguidelines.msf.org/en/viewport/CG/english/viral-haemorrhagic-fevers-16690024.html (accessed June 29, 2022).

57 Centers for Disease Control and Prevention. Lassa fever—treatment. 2014. https://www.cdc.gov/vhf/lassa/treatment/index.html (accessed June 29, 2022).

58 Money D, Yudin MH, Allen V, et al. SOGC committee opinion on the management of a pregnant woman exposed to or infected with Ebola virus disease in Canada. *J Obstet Gynaecol Can* 2015; **37:** 182–89.

59 Eriksson CO, Uyeki TM, Christian MD, et al. Care of the child with Ebola virus disease. *Pediatr Crit Care Med* 2015; **16:** 97–103.

60 State of Queensland. Interim guidelines for managing Ebola virus disease patients in Queensland. 2014. https://www.health.qld.gov.au/__data/assets/pdf_file/0027/444483/guidelines-managing-evd-patients.pdf (accessed June 29, 2022).

61 Japan Ministry of Health, Labour, and Welfare. About the treatment of patients with Ebola hemorrhagic fever. 2015. https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000076266.pdf (accessed June 29, 2022; in Japanese).

62 Lamontagne F, Fowler RA, Adhikari NK, et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. *Lancet* 2018; **391:** 700–08.

63 Centers for Disease Control and Prevention. Crimean–Congo hemorrhagic fever—treatment. 2013. https://www.cdc.gov/vhf/crimean-congo/treatment/index.html (accessed June 29, 2022).

64 Canadian Critical Care Society, Canadian Association of Emergency Physicians, Association of Medical Microbiology and Infectious Diseases Canada. Ebola clinical care guidelines: a guide for clinicians in Canada. 2014. https://caep.ca/wp-content/uploads/2016/03/ebola_clinical_care_guideline_english_201505.pdf (accessed June 29, 2022).

65 Rojek AM, Salam A, Ragotte RJ, et al. A systematic review and meta-analysis of patient data from the West Africa (2013–16) Ebola virus disease epidemic. *Clin Microbiol Infect* 2019; **25:** 1307–14.

66 Markham A. REGN-EB3: first approval. *Drugs* 2021; **81:** 175–78.

67 Gaudinski MR, Coates EE, Novik L, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study. *Lancet* 2019; **393:** 889–98.

68 National Institute of Allergy and Infectious Diseases. Investigational monoclonal antibody to treat Ebola is safe in adults. 2019. https://www.niaid.nih.gov/news-events/investigational-monoclonal-antibody-treat-ebola-safe-adults (accessed Aug 21, 2022).

69 Johnson S, Henschke N, Maayan N, et al. Ribavirin for treating Crimean–Congo haemorrhagic fever. *Cochrane Database Syst Rev* 2018; **6:** CD012713.

70 McCormick JB, King IJ, Webb PA, et al. Lassa fever. Effective therapy with ribavirin. *N Engl J Med* 1986; **314:** 20–26.

71 Hansen F, Jarvis MA, Feldmann H, Rosenke K. Lassa virus treatment options. *Microorganisms* 2021; **9:** 772.

72 Salam AP, Cheng V, Edwards T, Olliaro P, Sterne J, Horby P. Time to reconsider the role of ribavirin in Lassa fever. *PLoS Negl Trop Dis* 2021; **15:** e0009522.

73 Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; **364:** 2483–95.

74 Andrews B, Semler MW, Muchemwa L, et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial. *JAMA* 2017; **318:** 1233–40.

75 WHO. Rift valley fever. https://www.who.int/health-topics/rift-valley-fever (accessed Oct 25, 2022).
76 Ahmed A, Ali Y, Salim B, Dietrich I, Zinsstag J. Epidemics of Crimean–Congo hemorrhagic fever (CCHF) in Sudan between 2010 and 2020. *Microorganisms* 2022; **10:** 928.
77 Lipworth S, Rigby I, Cheng V, et al. From severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) to coronavirus disease 2019 (COVID-19): a systematic review of the quality and responsiveness of clinical management guidelines in outbreak settings. *Wellcome Open Res* 2021; **6:** 170.
78 Schünemann HJ, Mustafa R, Brozek J, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol* 2016; **76:** 89–98.