What is the standard of care for Viral Haemorrhagic Fevers (VHFs)?: a systematic review of clinical management guidelines for high priority VHFs

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ABSTRACT

Background: Viral haemorrhagic fevers (VHFs) continue to cause regular outbreaks with high morbidity and mortality. Supportive care is the mainstay treatment for most VHFs; however, consensus is limited on what this supportive care constitutes. This systematic review aims to explore the availability, scope and inclusivity of clinical management guidelines for VHFs globally.

Methods: Six databases were searched (Ovid Medline, Ovid Embase, Ovid Global Health, Scopus, Web of Science, WHO Global Index Medicus), complemented by a grey literature search until March 2022. Ebola virus disease (EVD), Crimean-Congo Haemorrhagic Fever (CCHF), Lassa Fever, Marburg virus disease (MVD), and Rift Valley Fever (RVF) guidelines were included. Two reviewers extracted data and assessed quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool.

Results: Thirty-one guidelines (EVD (48%, 15/31), CCHF (13%, 4/31), Lassa fever (6%, 2/31), MVD (6%, 2/31), RVF (3%, 1/31), multiple VHFs (23%)) were identified. Most (84%, 26/31) were of low quality (median (range): 2 (1-7)); many lacked supporting evidence and were not recently updated. Guidance on supportive care and therapeutics was lacking in detail and, at times, contradictory. Ribavirin was recommended for Lassa fever and CCHF, but with contradictory advise for children and pregnant women. The EVD guidelines provided more complex guidance on supportive care, but only the most recent ones discussed monoclonal antibodies. There were limited guidelines for patients with RVF and MVD, and no empirical treatment recommendations.

Conclusion: Our data highlight a lack of up-to-date, evidence-based VHF clinical management guidelines for different populations globally. There were concerning lack of standardisation in recommendations between guidelines and many were of low quality. Our data shows an urgent need for investment into well-designed clinical studies to identify optimal supportive care and effective VHF treatments, with evidence incorporated into standardised, accessible guidelines to facilitate access to best available evidence-based care recommendations to benefit patient care and outcomes.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42020167361.

Keywords: Viral Haemorrhagic fevers, Ebola, clinical management guidelines, clinical guidance, AGREE II tool, Inclusivity

What is already known on this topic:

- VHFs are responsible for outbreaks predominantly affecting resource-constrained settings, with risks of nosocomial outbreaks and high morbidity and mortality.
- While specific disease-modifying treatments (such as monoclonal antibodies) are now available for some VHFs, the cornerstone of patient management is consistent, high-quality supportive care, supported by haemodynamic monitoring.
- Guidelines are key tools for guiding clinical decision-making and standardising care across settings. Even when the evidence-base is limited, guidelines provide a role in setting parameters for care and in preventing administration of treatments without an evidence base.

What this study adds:

- This review has identified a concerning lack of high-quality clinical management guidelines for high consequence VHFs globally. This deficiency poses a risk to patient care and outcomes, variations between recommendations observed can also be a barrier for implementation of trials into therapeutics.
- The scope of the identified guidelines was limited; when available, supportive care and treatment recommendations were often made without supporting evidence and at times contradictory.
- Ribavirin was recommended by all guidelines focused on Lassa fever and CCHF, despite a limited evidence-base and with concerning contradictory advice on treatment in children and pregnant women with CCHF. There were limited guidelines identified for MVD and RVF, and there were no antiviral or other therapeutic recommendations provided.
- The EVD guidelines provided more complex recommendations, but only the most recently updated provided recommendation on new treatments to consider, highlighting the need for guidelines to be regularly reviewed and updated.

Implications:

- Our data show an urgent need for investment into well-designed clinical studies to identify optimal supportive care and effective therapeutics for different at-risk populations and innovations to support delivery of critical care in resource-variable settings.
- Existing guidelines need to be reviewed and updated. An updated living guideline framework is recommended to improve quality, inclusivity, and standardisation of recommendations to improve access to evidence-based recommendations to benefit patient care and outcomes.

INTRODUCTION

Despite the high morbidity and mortality risk associated with several viral haemorrhagic fevers (VHFs) our understanding of how to treat these diseases is still limited. The World Health Organisation (WHO) has designated Ebola and Marburg virus disease (EVD, MVD), Lassa Fever, Crimean-Congo Haemorrhagic fever (CCHF) and Rift Valley Fever (RVF) as high priority VHFs for research and development. (cite)

The majority of these VHFs predominantly affect populations in outbreak-prone regions of sub-Saharan Africa. (cite here) CCHF is also widespread in regions in the Middle East, and Asia. (cite studies) Fuelled by climate change, increased global travel, trade and changes in human activity that lead to disruption of ecosystems, there has been an increase in VHF outbreaks in previously unaffected areas in recent years.(cite) Consequently, as recently illustrated by a Lassa fever fatality in the UK, clinicians globally need to be astute about the risk of travel imported cases.(CITE study) Early identification of cases is critical for reducing the risk of nosocomial and community transmission. Early treatment, supportive care and management of complications are also key for improving outcomes. This was illustrated during the EVD outbreak in West Africa (2013-2016), where mortality among patients evacuated to well-resourced high-income countries for treatment were considerably lower compared to in patients who were treated in West Africa (18.5 % versus 40 to 70%%). (cite study) This difference was likely influenced by the provision of critical care (such as invasive ventilation, renal replacement therapy, intensive nursing). (Cite study) (cite study)

A high proportion of patients treated in high income settings also received experimental therapies, generally unavailable to patients in West Africa.

Variation in case fatality ratios between high-resource and resource-constrained settings has also been observed for MVD and Lassa fever. (Cite study) Yet there is still a paucity of evidence that helps to specify which aspects of optimal supportive care have the most impact on improving survival. Further understanding of optimal care strategies may not only improve patient outcomes but also direct targeted use of resources.

Clinical management guidelines are key tools for guiding clinical decision making, and standardising care, to benefit patient outcomes. (Cite WHO) Even when the evidence base is limited, guidelines provide a role in supporting clinicians by informing decision making and discouraging use of treatments that lack an evidence base. Standardisation of care across sites can also facilitate implementation of interventional trials. In 2018-2019, the Pamoja Tulinde Maisha (PALM) EVD

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https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/viral-hemorrhagic-fevers

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Of the 27 patients with EVD who received treatment in the United States or Europe, only 5 died, corresponding to a case fatality ratio, expressed as a percentage, of 18.5% — substantially lower than the case fatality ratio of 40 to 70% reported in West Africa - https://www.nejm.org/doi/full/10.1056/NEJMp1817070

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treatment trial conducted in the Democratic Republic of Congo (DRC) demonstrated that variation in access and delivery of standard of care across sites posed a key challenge in design, implementation, and analysis of the trial. (Cite) The aim of this review is to explore the availability of evidence-based clinical guidelines for high priority VHFs (cite here) and explore consensus on evidence-based supportive care and treatment recommendations for different at-risk populations globally.

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METHODS

This is a systematic review of the availability, inclusivity, scope, and quality of guidelines for high priority VHFs. (CITE). This study is nested within a series of systematic reviews of clinical management guidelines for high consequence infectious diseases. It is registered with the international prospective register of systematic reviews (PROSPERO) (CRD42020167361) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines on the conduct of systematic reviews (supplementary material). (cite PRISMA)

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Eligibility criteria

We defined guidelines as documents that provide recommendations on supportive care (e.g., fluid resuscitation; oxygen delivery) and empirical treatments following the World Health Organisation (WHO) definition (cite WHO) and contain recommendations to guide practice, provide statements designed to help end-users make informed decisions regarding clinical interventions with the aim of achieving the best possible individual health outcomes. Guidelines providing supportive care or empirical treatment recommendations, focused on EVD, Lassa Fever, MVD, CCHF, RVF or generic VHFs were included. We excluded local hospital standard operating procedures and public health or microbiology guidelines if they did not provide any treatment guidance. There were no language limitations. Only the latest version of a guideline was included.

Search strategy

We searched Ovid Medline, Ovid Embase, Ovid Global Health, Scopus, Web of Science Core Collection, and WHO Global Index Medicus from inception to 14th February 2021. We validated the search strategy by testing the terms before finalising the search strategy **(supplemental file).** Recognising that most clinical guidelines were not published in peer-reviewed journals, we complemented this with a grey literature search until March 2022. We requested clinical management guidelines from the Ministry of Health of each G20 nation when none were available on their respective websites. Additionally, we sent a brief survey to members of the International

Severe Acute Respiratory and Emerging Infections Consortium (ISARIC), an international clinical infectious disease research network, and contacted VHF experts in the field requesting available clinical management guidelines. Database search strategies applied the Canadian Agency for Drugs and Technology in Health (CADTH) search filter, with no limits applied to search results. The grey literature searches were conducted in Arabic, English, Mandarin, Russian, and Spanish. (Supplementary file x). A full search strategy is available in the supplemental file.

Screening

After deduplication, two reviewers screened the search results for inclusion (title and abstract, followed by full text), using Rayyan QCRI software. (cite) Any conflicts were resolved through consensus or by a third reviewer. For non-English records, the documents were translated using Google Translate for rapid translate of the full document, then screened, data extracted and critically appraised by a reviewer with good to excellent knowledge of the language.

Data extraction

The data were extracted using the methodological guide by *Johnston et al.* Data extraction was extracted by one reviewer performed using a standardised form, which was previously piloted before being finalised (supplementary file x). (cite study) Data on source, year issued, inclusivity (children, pregnant women, adults, older adults, people living with HIV), scope (empirical treatment and supportive care recommendations) were extracted by one reviewer and checked by a second reviewer. Any conflicts were resolved through consensus or by a third reviewer. We extracted and categorised data on the methods used to formulate the recommendations made by clinical guidelines (i.e., systematic, expert consensus, a combination of methods or based on other guidelines).

Quality assessment

Two reviewers independently assessed the quality using the Appraisal of Guidelines for Research & Evaluation (AGREE) II tool [cite]. 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) and two global rating items (cite). The assessment scoring for each item was completed by two assessors using a seven-point scale from 1 (strongly disagree) to 7 (strongly agree). A score of 100% is achieved if each reviewer scored the top score of 7 for all items in a domain and 0% if each reviewer scored 1 for all items in the domain. [cite] If there was limited information

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presented regarding the methodology of the guideline, efforts were made to search for any additional information via associated websites.

Overall domain scores were calculated as per the AGREE II tool user manual, converting the sum of individual scores from each reviewer into a standardised percentage for each domain. The clinical guidelines were considered of high quality if they scored more than 60% in domain three (rigour of development; as this is considered a high-quality indicator), and 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 clinical management guideline did not reach any of these criteria, it was assessed as being low quality.

Data analysis

The synthesis sought to identify areas of congruence and incongruence between guidelines. The availability of clinical management guidelines was determined based on 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 (children, adults, pregnant women, older people > 65 years, or people living with HIV/immunosuppression). Descriptive statistical analysis was done in R language version 4.0.2 [cite] and graphics were produced with the ggplot2 library and Tableau. [cite]

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Patient public involvement

There was no patient public involvement in this project due to the ongoing pandemic constraints.

RESULTS

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Of the 4,033 documents screened, 31 guidelines met the inclusion criteria and were included in the review. (Figure 1). Most were produced in English (81%, 25/31) (cite studies), followed by French (6%, 2/31) (cite studies), Russian (6%, 2/31) (cite studies), Chinese (3%, 1/31) (cite studies), and Japanese (3%, 1/31) (cite studies).

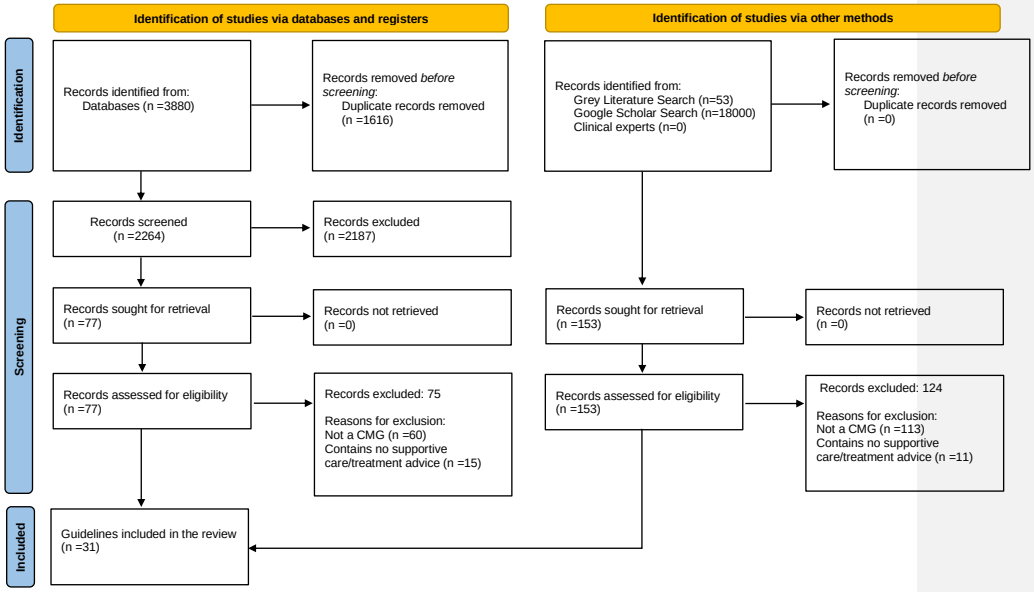

Figure 1: PRISMA flowchart

Availability

Almost half of the clinical guidelines focused on the management of EVD (48%, 15/31) (cite), of which 53% (8/15) (cite) were produced during the 2013-2016 West African EVD epidemic. The remaining focused on CCHF (13%, 4/31) (cite), Lassa Fever (6%, 2/31) (cite) MVD (6%, 2/31) (cite) and RVF (3%, 1/31) (cite); 23% (7/31) covered more than one VHF (Cite). Only 29% were updated within the last three years (cite) (Table 1). The guidelines were produced for use in North America (26%, 8/31), Europe and Central Asia (16%, 5/31), Sub-Saharan Africa (13%, 4/31), East Asia & Pacific (10%, 3/31), South Asia (6%, 2/31), or for global use (29%, 9/31) (Figure 2, Table 1). Most were produced by national (68%, 21/31); and 32% (10/31) by international organisations (Table 2).

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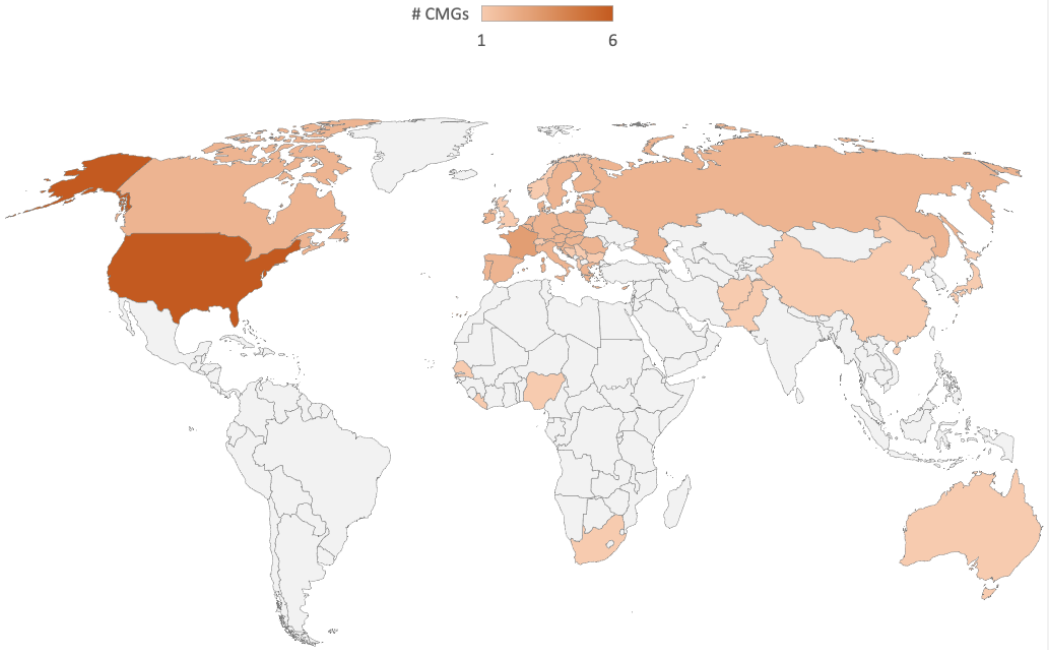

Figure 2: Availability of VHF guidelines

The map shows where the identified guidelines were produced. The shading represents the number of identified guidelines and the country they were produced in. In addition, there were nine guidelines aimed at regional or global settings (CITE)

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Table 1: Guidelines identified by type of VHF and the regions they were aimed for

Region	CCHF	EVD	LF	MVD	RVF	Generic/Multiple VHFs*	Total
East Asia & Pacific	-	3	-	-	-	-	3
Europe & Central Asia	1	2	-	-	-	2	5
Latin America & Caribbean	-	-	-	-	-	-	0
Middle East & North Africa	-	-	-	-	-	-	0
North Americas	1	3	1	1	1	1	8
South Asia	2	-	-	-	-	-	2
Sub-Saharan Africa	-	2	1	-	-	1	4
Global	-	5	-	1	-	3	9
Total	4	15	2	2	1	7	31

Abbreviations: CCHF: Crimean-Congo Haemorrhagic Fever, EVD: Ebola Virus Disease, LF: Lassa Fever, MVD: Marburg Virus Disease, RVF: Rift Valley Fever, VHF: Viral Haemorrhagic Fever
*These guidelines focused on more than one type of VHFs

Table 2: Characteristics, inclusivity, and quality of the VHF guidelines

Disease	Authorising Organisation	Country/region*	Year	Inclusivity	Quality
CCHF	NIH, WHO	Pakistan	2018	A	Low
CCHF	MoH Russia	Russia	2014	C, A, P	High
CCHF	US CDC	North America	2013	N.S	Low
CCHF	MoPH Afghanistan, WHO, et al.	Afghanistan	2012	C, A, P	Low
EVD	US CDC	United States of America	2021	C, A, P	Low
EVD	Uptodate	Global	2021	A, P	Low
EVD	WHO	Global	2020	I, A, P	High
EVD	Mission COREB nationale	France	2019	C, A	Low
EVD	WHO	Global	2019	C, A, P	Low
EVD	Lamontagne, F. et al.,	Global	2018	C, A	High
EVD	MoHSA	Senegal	2015	C, A, P	Low
EVD	SCC and WFPICCS	North America	2015	I, C, A,	Low
EVD	SOG Canada	Canada	2015	A, P	Low
EVD	Japan MoHLW	Japan	2015	A	Low
EVD	MoH Russia & SSMU	Russia	2014	C, A, P	Low
EVD	Queensland Health, Queensland Government	Australia	2014	C, A, P	Low
EVD	Canadian CCS	Canada	2014	C, A,	Low
EVD	MoHSW	Liberia	2014	C, A, P, H	High
EVD	NHC China	China	2008	A	Low
FHF	MSF	Global	2008	C, A, P	Low
LF	Nigeria CDC	Nigeria	2018	C, A, P	Low
LF	US CDC	North America	2014	N.S	Low
MVD	Uptodate	Global	2021	N.S	Low
MVD	US CDC	North America	2021	N.S	Low
RVF	US CDC	North America	2020	N.S	Low
VHF (CCHF, EVD, MVD, LF, RVF)	MSF	Global	2021	C, A	Low
VHF (CCHF, EVD, MVD, LF)	WHO	Global	2016	C, A, P	Low
VHF (CCHF, EVD, MVD, LF, RVF)	DoH South Africa	South Africa	2015	C, A	Low
VHF (CCHF, EVD, MVD, LF, RVF)	San Francisco DoPH	United States of America	2008	C, A, P	Low
VHF (EVD, MVD, LF, RVF)	TFBCAT	Luxembourg	2004	A, P	Low
VHF (CCHF, EVD, MVD, LF, RVF)	ENIVD	Europe	2001	A	Low

A: Adults, C: Children, H: People living with HIV/immunocompromised, I: Infants, P: Pregnant Women
* Country/region guidelines were produced
Abbreviations: BICHAT: Biological and Chemical Agent Threats, CCCS: Canadian Critical Care Society,

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CDC: Centers for Disease Control and Prevention, CCHF: Crimean-Congo Haemorrhagic fever, DoH: Department of Health, DoPH: Department of Public Health, EVD: Ebola Virus Disease, ENIVD: European Network for Diagnostics of Imported Viral Diseases, FHF: Filovirus haemorrhagic fever, IMC: International Medical Corps, LF: Lassa Fever, MVD: Marburg Virus Disease, MSF: Médecins Sans Frontières, MoH: Ministry of Health, MoHLW: Ministry of Health Labour & Welfare, MoHSA: Ministry of Health and Social Action, MoHSW: Ministry of Health and Social Welfare, MoPH: Ministry of Public Health, NHC: National Health Commission, NIH: National Institute of Health, PCCM: Paediatric Critical Care Medicine, RRT: Renal Replacement Therapy, RVF: Rift Valley Fever, SCC and WFPICCS: Society of Critical Care Medicine and World Federation of Paediatric Intensive and Critical Care Societies, SCOG: Society of Obstetricians and Gynaecologists of Canada, SSMU: Smolensk State Medical University, TFBCAT: Task Force on Biological and Chemical Agent Threats, VHF: Viral Haemorrhagic fevers, WHO: World Health Organisation

Quality

Most clinical guidelines (74%, 26/31) were assessed as low quality (overall score ≤3); only 13% (5/31) as high quality (Table 2, Figure 3). The median overall quality score was 2 (range: 1-7) (Supplementary file x). There were wide variations across the individual domain scores. The highest scoring domains were clarity of presentation (median (IQR): 61% (42-67)) and scope and purpose (median (IQR): 53% (28-67)). There were particular deficits in the domains for rigour of development (median (IQR): 17% (9-35)), applicability (median (IQR): 21% (15-30)), stakeholder involvement (median (IQR): 22% (6-36)) and editorial independence (median (IQR): 0% (0-17)) (Figure 3). The low scores for editorial independence may be partly attributed to the limited information provided regarding competing interest. Many lacked information about the methodology used to develop the guidelines and lacked links to evidence supporting the recommendations. About one in five guidelines (19%, 6/31) (cite) specified the use of systematic methods to search for evidence; 23% (7/31) (cite) used expert consensus to inform the recommendations. The remaining 58% (18/31) (cite) did not disclose the methodology used for developing the guideline. Four guidelines used GRADE for assessing the strength of the evidence alone or in combination with expert consensus, (cite) ten (32%, 10/31) (cite) were peer-reviewed prior to publication and 11 (35%) stated plans for regular updates (cite), but only one outlined clear criteria or timeframe (cite).

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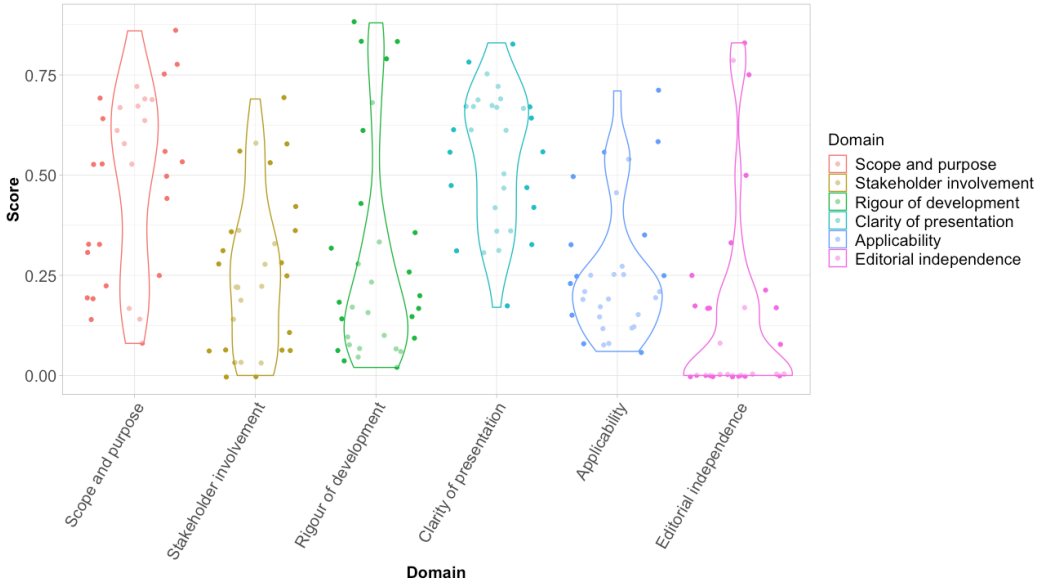

Figure 3 AGREE II domain scores

The violin plot depicts the individual scores of the guidelines in each domain. Each dot represents a guideline's proportional score per domain. The width of each curve represents the frequency of guideline scoring in each region.

Inclusivity

Although some guidelines made specific recommendations for different at-risk populations, including pregnant women (52%, 16/31) (cite) and children (61%, 19/31) (cite), none provided specific guidance for older adults and only one provided specific guidance for people living with HIV. (cite) (Table 2)

Supportive care and treatment

There were some examples of more comprehensive guidance, especially in more recent EVD guidelines, but the supportive care and treatment guidance were limited in general. The guidance provided is summarised below (Table 3).

Table 3: Overview of type of supportive care and treatments recommended

VHFs		Arenavirus	Bunyaviridae		Filoviruses			Generic
Interventions		Lassa fever (N=2)	CCHF (N=4)	RVF (N=1)	EVD (N=15)	EVD/MVD (N=1)	MVD (N=2)	Multiple VHFs (N=6)
Basic supportive Care	**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)

(% (n))	**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
Treatments (% (n))	**Antimalarial**	-	-	-	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 (
Advanced supportive care (% (n))	**Invasive monitoring**	50 (1)	25 (1)	-	26 (4)	100 (1)	50 (1)	-
	RRT	50 (1)	-	-	60 (9)	-	50 (1)	17 (1
	Vasopressors & Inotropes	50 (1)	25 (1)	-	53 (8)	-	50 (1)	17 (1

Abbreviations: CCHF: Crimean-Congo Haemorrhagic fever, EVD: Ebola Virus Disease, Lassa: Lassa Fever, MVD: Marburg Virus Disease, RRT: Renal replacement therapy, RVF: Rift Valley Fever, VHF: Viral Haemorrhagic fevers

Physiological support

Patients with VHF can experience fluid loss from pyrexia, haemorrhage, or gastrointestinal losses (cite). Whilst there was broad consensus on the need for intravenous fluid replacement in patients with VHF and that the fluid resuscitation largely depends on patients' clinical condition, specific guidance was heterogeneous and vague, with a considerable variation on the ideal fluid resuscitation strategy (Table 3). Some (29%, 9/31) advocated for fluid resuscitation using crystalloids (e.g., normal saline or Ringer's lactate). (cite studies) (cite) Three clinical guidelines advised the use of human albumin solution in persistently hypovolaemic patients. (cite) Some (10%, 3/31) recommended fluid resuscitation with bolus infusions as part of a 'fluid challenge' approach, especially for patients in shock. (cite) One of the guidelines advocated for initial 20ml/kg fluid boluses, followed by repeated administration of 250-500ml boluses every thirty minutes for adults. (cite) Another specified that hypotensive patients be administered initial boluses of Ringer's lactate at 20ml/kg, to be repeated until symptoms of hypotension are no longer apparent. (cite) Others recommended liberal fluid resuscitation, (Cite) although the appropriateness of such a strategy has been challenged by fluid resuscitation trials involving patients hospitalised with sepsis in sub-Saharan Africa. (cite trial) Furthermore, the guidelines recommendations were vague about the endpoint of fluid resuscitation. Only one guideline made it explicit that total fluid volume is not to exceed 60ml/kg in the first two hours and advocated for continuing fluid resuscitation until systolic blood pressure (SBP) is >90 and monitoring of target parameters (e.g., heart rate (HR) <100, urinary output (UO) >30ml/h, capillary refill time (CRT) <3 sec, absence of skin mottling, easily palpable pulses, and improved mentation) (Cite). Two guidelines advocated for a goal of targeting an SBP of >90, absence of skin mottling and normal CRT (cite). Others incorporated HR, blood pressure and 'parameters of end-organ perfusion.' (cite) It was rare for guidelines to make any specific mention of resource barriers to fluid resuscitation.

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Only 14% (3/22) advised central line access; two of these were produced for higher resourced settings. (cite) One of these stated that central line access will likely benefit pregnant women with EVD. (WHO EVD) (cite) (2)

Similarly, there was limited consensus on administration of inotropes and vasopressors. Twelve guidelines advocated for the use of inotropes or vasopressors if clinically appropriate (3) (4). **(Cite)** One (3%) specified an indication (when fluid resuscitation has failed despite administration of 30ml/kg fluid in the first three hours or signs and symptoms of fluid overload). (cite) Two guidelines recommended norepinephrine when hypotension persisted (cite); another recommended adrenaline and dopamine (when adrenaline is not available). (cite) Another detailed that norepinephrine infusion should be used to target a mean arterial pressure of 65-70mmHg (cite), with adrenaline as a second-line agent and to avoid dopamine due to its association with increased rates of cardiac arrhythmias and mortality. (cite)

Eleven guidelines (cite) provided guidance on the role of renal replacement therapy (RRT), with four (13%) (cite) advising that its use is resource dependent. For instance, the Canadian Critical Care Society (CCCS) guidelines advised that haemodialysis can be safely used in a high resourced setting. (**cite)**

Blood products

Recommendations on the use of blood products were similarly heterogeneous and limited. Whilst there was a recognition that VHF patients are at risk of anaemia, different target thresholds for transfusion were set (7g/dl (4, 11, 15), 8g/dl (17) and 5g/dl (21)).**(cite studies)** There was no agreement on the use of plasma or platelets. One guideline advocated for using plasma to obtain an international normalized ratio (INR) <1.5 and platelets >50 X 10^9/L (cite). Two guidelines suggested treatment with fresh frozen plasma 'as required' (cite) (cite) but without further guidance. Another guideline recommended vitamin K and tranexamic acid for people suffering from active haemorrhage (cite).

Symptom management

Symptom management recommendations were provided, including four guidelines recommending benzodiazepines for anxiety (cite) and six recommending ondansetron for nausea (cite). Analgesics (e.g., paracetamol and opioids) were recommended for pain relief in 14 guidelines (cite), while ten (32%) advised against aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). (cite)

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COREB, Japan, Australia

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It's still 3 that recommend central line access (CCCS 2014, French COREB, WHO EVD).
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denominator of 22 when counting all global CMG & high income country CMGs
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Physiological monitoring

There was little agreement on the 'gold standard' of patient monitoring. Twelve guidelines (39%) recommended repeated physical observations (cite), but there was no consensus on which observations to take, a baseline acceptable rate or frequency of vital sign observations (cite) (cite). Many guidelines (42%, 13/31) only provided vague advice to monitor fluid balance, with no further details (CITE). Five (16%) provided more detailed guidance (cite) with one advising to examine fluid status on admission and daily weights for monitoring urine balance in children [cite]. There were disagreements about the role of urinary catheterisation, with one guideline (cite) opposing and another advocating for its use to monitor urine output in critically ill patients (cite). Most (68%, 21/31) made no mention of the role of invasive physiological monitoring. One clinical guideline recommended to avoid invasive procedures when possible (cite), and another that they should only be carried out in adequately safe conditions (cite).

There was also a lack of agreement on optimal biochemical investigations. Ten guidelines (32%) recommended monitoring of biochemistry (cite), electrolytes and renal functioning (cite). Of these, five suggested daily monitoring of urea and electrolytes, ideally using point-of-care-testing (Cite), whilst one suggested laboratory monitoring every five days (cite). The guideline on Lassa fever emphasised liver function monitoring (Cite). Some guidelines stressed the importance of haemoglobin monitoring, at least on admission, alongside a coagulation test (4, 11, 13, 15, 17, 18).(cite).

Antimicrobials and investigational therapies

Forty-two percent of guidelines (13/31) provided guidance on antiviral use (Table 3). All Lassa fever-focused guidelines recommended ribavirin for adults (cite), but only one explicitly stated the target population. (Table 4). (cite) Additionally, ribavirin was also recommended by all CCHF guidelines, despite its limited evidence base for use in both CHHF and Lassa fever (**cite**). Of these, two specifically advised the use in children and one in pregnancy.(cite) In contrast, one CCHF CMG stated that ribavirin was contraindicated in children (cite) and three that pregnancy was a contraindication. (Cite) (Table 4). For EVD, one (7%, 1/15) CMG (2019) recommended Zmapp (a combination of three monoclonal antibodies) alone or in combination with remdesivir as first-line therapy. (cite) Favipiravir was recommended as an alternative if these were unavailable. (Cite France Coreb) None of the guidelines focused on MVD or RVF recommended antivirals. Twelve guidelines (39%) suggested empirical use of antibiotics (4, 11, 16-20) (cite), whereas six (19%) did not recommend it empirically (cite) (Table 3).

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CCS 2014 recommends the use of foley catheter

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Nine guidelines discussed convalescent plasma; one recommended its use for EVD patients 'when necessary', (cite) whereas others highlighted that convalescent plasma therapy is experimental (26%, 8/31) (cite), one stating that it should only be used in a controlled trial (cite). Three (9%) discussed monoclonal antibodies (e.g., mAb114, REGN-3) to be considered against *Zaire ebolavirus* (EBOV) in addition to supportive care.**(cite)** One of these recommended these therapeutics to be considered specifically for pregnant women in the context of research. (cite) REGN-3 is a combination of three human monoclonal antibodies (atoltivimab (REGN3470), maftivimab (REGN3479) and odesivimab (REGN3471)) that target EBOV glycoprotein. Ansuvimab (mAb114) a single monoclonal antibody that binds to the core receptor binding domain of the EBOV surface protein, prevents the virus from infecting human cells. Both REGN-3 and mAb114 have been approved by the US Food and Drug Administration for EVD based on the results of the PALM trial in 2018 (Cite).

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Table 4: Ribavirin recommendations for CCHF and Lassa Fever

Guideline Population	CCHF NIH, WHO	CCHF MoPH Afghanistan	CCHF MOH Russia	CCHF, Lassa fever ENIVD	Lassa fever Nigeria CDC
Children	N.S	**Oral:** 30mg/kg loading dose; then 15mg/kg (IV) x 4 for 4 days; 7mg/kg x4 for another 6 days (Total 10 days)	**IV**: 30 mg/kg loading dose then 15 mg/kg x 2 (total 10 days)	N.S	**IV:** 33mg/kg loading dose, then, 16mg/kg x4 for 4 days; and 8mg/kg x 3 for 6 days (Total 10 days)
Adults	**Oral**: Loading dose of 2 gm, then 4 gm x 4/day for 6 days, gm x 4/ day for another 6 days. (Total 12 days)	**Oral:** 2000mg loading, then 1000mg x 4 for 4 days, 500mg x 4 for another 6 days **IV**: 30 mg/kg loading dose, then 15 mg/kg x 4 for 4 days, 7.5 mg/kg x 3 for another 6 days. (Total 10 days)	**Adults, incl. in pregnancy** **Oral**: 2000 mg loading dose, then 1200 mg /day (>75kg), or 1000mg (<75kg) x 2 (total 10 days.) **IV**: 30 mg/kg loading dose (max. 2g), then, 16 mg / kg x 4 for 4 days, t, 8 mg / kg x 3 for 6 days. (Total 10 days.)	**IV**: loading dose 30 mg/kg then, 16 mg/kg x4 for 4 days; 8 mg/kg x 3 for 6 days. (Total 10 days)	**If an ongoing outbreak?** **IV:** 33mg/kg loading, then, 16mg/kg x4 / 4 days; 8mg/kg x 3 / 6 days. (Total 10 days) If no outbreak? **IV**: 100mg/kg loading dose x 2 Then, 25mg/kg x1 for 7 days; 12.5 mg/kg (single dose) for 3 days. (Total 10 days) **Pregnant women**: IV: 100mg/kg loading dose x2. Then, 16mg/kg x4 for 4 days; 8mg/kg x3 for 5 days. (Total 10 days)

Abbreviations: CMG- Clinical management guidelines, VHF- Viral Haemorrhagic fevers, CCHF- Crimean-Congo Haemorrhagic fever, NCDC- Nigeria Center for Disease Control, ENVID- European Network for Diagnostics of Imported Viral Diseases

DISCUSSION

Our findings demonstrate limited availability, scope, and standardisation of clinical management guidelines for high priority VHFs globally. Most guidelines identified were focused on the management of EVD. There were few clinical guidelines providing guidance on management of CCHF, Lassa fever, MVD and RVF identified. Of those available, many were of limited quality, inclusivity and scope and produced in non-endemic countries.

There were a few examples of high-quality guidelines which were developed using systematic methods including grading of the evidence. (cite) Many of the guidelines failed to provide details of the methodology used to formulate recommendations. Further, we observed a pattern of guidelines being rapidly developed in emergencies and rarely revisited and updated.

Our results highlight a lack of consensus on disease-modifying treatments. Ribavirin was recommended by all guidelines focused on CCHF, (Cite) (cite) (cite) despite a recent Cochrane review concluding that there is insufficient reliable evidence on the effectiveness of ribavirin for CCHF. (CITE Johnson et al) Likewise, ribavirin was recommended by all Lassa fever clinical management guidelines, despite limited evidence of effectiveness and studies indicating that it increases mortality risk in patients without elevated aspartate aminotransferase. (cite) The variations in treatment recommendations for children and pregnant women is another cause for concern illustrated by the conflicting guidance on ribavirin for CCHF, with some guidelines recommending it in these groups while others stating it is contraindicated. (cite)

Our findings indicate a need to review and update existing clinical management guidelines and for the future, develop an improved guideline development framework that includes mechanism for regular reviews and updates. Moreover, a system where outdated guidelines are retracted from public domains, to protect patients. Although there were several treatment trials set up during the 2013-2016 EVD outbreak most did not manage to include sufficient participants to generate conclusive results. **(CITE)** A more recent trial of four investigational treatments for EVD set in DRC in 2018 concluded that mAb114 and REGN-3 were superior to standard care and ZMapp in reducing mortality rate. (cite) However, only three EVD guidelines identified in our review had been updated recently to incorporate these recent findings. (CITE)

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Ebola up to date
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US CDC Ebola
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Although there was a consensus on administering fluids, there was no clear consensus regarding strategies on how best to resuscitate a VHF patient in shock). While the volume, rate, and composition of resuscitation fluids in general remains an active topic of research globally, there are reasons that extrapolation of large trials for other conditions may be unfounded for patients with VHFs, since the pathology, as well as demographics, and comorbidity profiles of patients may differ. The first saline-like solution was administered to humans with cholera in 1832 and has since been a mainstay of critical supportive care, but, as with all treatments, comes at a cost and with risks. The recent FEAST trial (set in multiple countries in Africa) reported an increased 48-hour mortality in critically ill children with febrile illness and impaired perfusion compared to controls. (cite) Although there are trials into different types of fluids, there are few evaluating the benefit of fluids compared to no fluids. It is likely that the optimal ratio of resuscitative fluids is different within VHFs, and even within a certain disease, the pathogenesis of shock may change as the disease progresses. With improvement in the delivery of advanced levels of care for VHFs demonstrated in several settings (e.g., intensive care units in HICs during the 2013-2016 West Africa EVD outbreak; introduction of biosecure emergency care units during the 2018-19 DRC EVD outbreak) (Cite), investigating fluid, antibiotic, antimalarial and anti-inflammatory choices in high-quality clinical trials should be prioritised particularly given that these strategies are not dependent on lengthy and expensive drug pipelines.

This review is not without limitations. Despite searches in different languages, we may have missed national clinical guidelines which were not readily accessible. Additionally, due to the COVID-19 pandemic constraints, we received very few responses from the members of the clinical infectious disease network and VHF experts. Although there were no exclusions on language, some nuances may have been lost in the translation of those identified. However, through our searches including searching national databases in different languages and contacting topic experts, several guidelines were identified from different regions.

Even when the evidence base is limited, clinical management guidelines play a role in guiding diagnostics and care and, also in discouraging inappropriate treatments. As was observed during the COVID-19 pandemic, there can be a tendency to recommend any drugs in dire emergency situations. **(cite)** Guidelines, can play a key role in providing evidence-based information for this context, if they are regularly updated and easily accessible by frontline clinicians.

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However, other factors that impact on implementation also need to be considered. For example, few guidelines in our analysis discuss how frequently monitoring should occur for a patient, which may partly reflect the scarcity of clinical resources early during the West Africa EVD outbreak. Likewise, few included recommendation on interventions for organ support (such as mechanical ventilation and renal replacement therapy).

The number of clinical management guidelines providing recommendations that are not evidence-based is high and need to be addressed, particularly from a patient risk perspective where there are potential side-effects and excess mortality associated with the use of experimental treatments, but also in terms of resource implications, especially of relevance to lower resourced settings where utility costs have to be considered. The high proportion recommending empiric antibiotics to all patients with VHFs, poses additional risks with regards to antimicrobial resistance, another global health threat. 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 when scarce, as well as patient outcomes.

Conclusion

Our data highlights a concerning lack of up-to-date clinical management guidelines for high priority VHFs globally. The limited and at times conflicting recommendations identified, together with the emergence of VHFs in new regions in recent years, highlights an urgency to invest in research to identify optimal treatment strategies for VHF priority pathogens inclusive of the whole population. . Investments in healthcare systems and innovation to strengthen capacity for critical care interventions in lower-resourced settings are also needed. It is imperative that existing VHF guidelines are reviewed and updated. We recommend a 'living' evidence-based guideline framework for individual guidelines to improve the quality, inclusivity, and standardisation of evidence-based recommendations to benefit patient care and outcomes globally.

Author's contributions

PH, STJ, LB, LS, VC, AD, HG, EH, PH and PWH conceptualised the study. AD, SL, VC, LS, EH, IR, and MM developed the study protocol. IR, MM, AD and LS lead on writing the manuscript with input from all co-authors. EH and AD carried out the database search. IR, MM, AO, RJ, EC, DD and AD conducted the grey literature searches, and screened the articles. MM, IR, VB, AO, EW and AD extracted the data and completed the risk of bias analyses. MM, IR, SL, VC, AD, DD, AR, and LS led on the data analysis,

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

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Competing interest

All authors have completed the ICMJE uniform disclosure form. Peter Hart is a senior research advisor and Helen Groves is a research manager at the Wellcome Trust, which provided part of the funding for this work, but, neither had a role in data collection, analysis, or interpretation of the findings. The funders had a role in writing the report but do not stand to materially benefit from the work. Wellcome supports a range of research funding activities including awards made to ISARIC.

Ethical approval

None required.

Data sharing

All data generated or analysed during this study are available on reasonable requests from the corresponding author.

Transparency statement

The lead authors (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

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List of abbreviations:

AGREE- Appraisal of Guidelines for Research and Evaluation

CADTH- The Canadian Agency for Drugs and Technologies

CCHF- Crimean-Congo haemorrhagic fever

CFR- Case Fatality Rate

CMG- Clinical Management Guideline

DRC- Democratic Republic of Congo

EVD- Ebola Virus Disease

FBC- Full Blood Count

INR- international normalized ratio

ISARIC- International Severe Acute Respiratory and emerging Infection Consortium

LF: Lassa fever

NSAID- non-steroidal anti-inflammatory drugs

PALM- The PAmoja TuLinde Maisha Trial

POCT- Point-of-care- testing

PROSPERO- The International Prospective Register of Systematic Reviews

RRT- Renal Replacement Therapy

SOP- Standard Operating Procedure

VHF- Viral Haemorrhagic Fever

WHO- World Health Organisation

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Commented [LS138]: To be updated

Supplement 4: Supplementary tables

Table S4.1: Characteristics of included studies

Author	Year published	Authorising Organisation	VHF type	Language	Country	Income-level	Region	Produced for a specific resourced setting?	Organisational classification	Vulnerable population covered	Quality
Nigeria CDC	2018	Nigeria CDC	Lassa Fever	English	Nigeria	Middle-Income	Africa	Produced in a LMIC	National	Pregnant patients, Children	Low-quality
DoH South Africa	2015	DoH South Africa	VHF	English	South Africa	Middle-Income	Africa	Produced in a LMIC	National	Children	Low-quality
WHO	2019	WHO	Ebola	English	N/A	N/A	Global	Global CMG	International	Pregnant patients, Children	Low-quality
WHO	2016	WHO	VHF (Focuses on Ebola and Lassa)	English	N/A	N/A	Global	Global CMG	International	Pregnant patients, Children	Low-quality
François Lamontagne, et al.,	2018	Not specified	Ebola	English	None stated	N/A	Global	Global CMG	International	Children	High-quality
Canadian CCS	2014	Canadian CCS	Ebola	English	Canada	High	North America	Produced in a HIC	National	Children	Low-quality
Deborah Money et al.,	2015	SOG Canada	Ebola	English	Canada	High	North America	Produced in a HIC	National	Pregnant patients	Low-quality
Matthias Borchert, et al.,	2008	MSF	FHF	English	N/A	N/A	Global	Global CMG	International	Pregnant patients, Children	Low-quality

NHC China	2008	NHC China	Ebola	Chinese	China	Middle-Income	China	Produced in a LMIC	National	Adults only/Generic	Low-quality
MoHSW	2014	MoHSW	Ebola	English	Liberia	Low-Income	Africa	Produced in a LMIC	National	Children, Pregnant patients, HIV/Immunocompromised	High-quality
C Chidiac, et al.,	2019	Mission COREB nationale	Ebola	French	France	High	Europe	Produced in a HIC	National	Children	Low-quality
Japan MoHLW	2015	Japan MoHLW	Ebola	Japanese	Japan	High	Asia	Produced in a HIC	National	Adults only/Generic	Low-quality
MoHSA	2015	MoHSA	Ebola	French	Senegal	Middle-Income	Africa	Produced in a LMIC	National	Children, Pregnant patients	Low-quality
NIH and WHO	2018	NIH and WHO	CCHF	English	Pakistan	Middle-Income	Asia	Produced in a LMIC	National	Adults only/Generic	Low-quality
MoH Russia & SSMU	2014	MoH Russia & SSMU	Ebola	Russian	Russia	Middle-Income	Europe	Produced in a LMIC	National	Children, Pregnant patients	Low-quality
MoPH Afghanistan, WHO, and other collaborative partners	2012	MoPH Afghanistan, WHO, and other collaborative partners	Crimean Congo Haemorrhagic fever	English	Afghanistan	Low-Income	Asia	Produced in a LMIC	National	Children, Pregnant patients	Low-quality
US CDC	2021	US CDC	Ebola	English	United States of America	High	North America	Produced in a HIC	National	Children, Pregnant patients	Low-quality
MSF	2021	MSF	VHFs	English	MSF	N/A	Global	Global CMG	International	Children	Low-quality
Queensland Health, Queensland Governement	2014	Queensland Health, Queensland Governement	Ebola	English	Australia	High	Australasia	Produced in a HIC	National	Children, Pregnant patients	Low-quality
MoH Russia	2014	MoH Russia	Crimean Congo Haemorrhagic fever	Russian	Russia	Middle-Income	Europe	Produced in a LMIC	National	Children, Pregnant patients	High-quality
ENDIVD	2001	ENDIVD	VHF	English	Europe	N/A	Europe	Global CMG	International	Adults only/Generic	Low-quality
San Francisco DoPH	2008	San Francisco DoPH	VHF	English	United States of America	High	North America	Produced in a HIC	National	Children, Pregnant patients	Low-quality

P Bossi, et al.,	2004	TFBCAT	VHF	English	Luxembourg	High	Europe	Produced in a HIC	National	Pregnant patients	Low-quality
Mike Bray, et al.,		2021 Uptodate	Marburg	English	N/A	N/A	Global	Global CMG	International	Generic	Low-quality
Daniel S Chertow, et al.,		2021 Uptodate	Ebola	English	N/A	N/A	Global	Global CMG	International	Pregnancy,	Low-quality
WHO		2020 WHO	Ebola	English	N/A	N/A	Global	Global CMG	International	Pregnancy, infants	High-quality
Carl O Eriksson, et al.,		2015 SCC and WFPICCS	Ebola	English	North America	High	Global - Rich resourced setting	Global CMG	International	Infants, children	Low-quality
US CDC		2013 US CDC	CCHF	English	North America	High	North America	Produced in a HIC	National	Not specified	Low-quality
US CDC		2014 US CDC	Lassa	English	North America	High	North America	Produced in a HIC	National	Not specified	Low-quality
US CDC		2021 US CDC	Marburg	English	North America	High	North America	Produced in a HIC	National	Not specified	Low-quality
US CDC		2020 US CDC	RVF	English	North America	High	North America	Produced in a HIC	National	Not specified	Low-quality

Table legend: Abbreviations

Table S4.2: Supportive care and treatment recommendations for each guideline. The tick indicates the CMGs that provided guidance for the topic.

				Basic supportive Care				Antimicrobials			Advanced supportive care		
Disease	**Year**	**Country/ Region**	**Produced by**	**Fluid resuscitation**	**Supplemental oxygen**	**Blood products**	**Symptom control**	**Antimalarials**	**Antibiotics**	**Antivirals**	**Invasive monitoring**	**RRT**	**Vasopressors & inotropes**
CCHF	2018	Pakistan	NIH, Islamabad, WHO	-	-	-	-	-	-	✓	✓	-	-
CCHF	2013	USA	US CDC	✓	✓	-	-	-	-	✓	-	✓	-
CCHF	2014	Russia	MoH	✓	✓	✓	✓	-	✓	✓	-	-	✓
CCHF	2012	Afghanistan	MoPH, WHO & Collaborators	-	-	✓	-	-	-	-	-	-	-
EVD	2021	Global	Uptodate	✓	✓	✓	✓	-	✓	-	✓	✓	✓
EVD	2021	USA	US CDC	✓	-	-	✓	-	✓	-	-	✓	✓
EVD	2020	Global	WHO	✓	-	-	-	-	-	-	-	✓	✓
EVD	2019	Global	WHO	✓	-	✓	✓	✓	✓	-	✓	-	✓
EVD	2019	France	COREB	✓	-	✓	-	✓	✓	✓	✓	✓	-
EVD	2018	Global	Lamontagne et al.,	✓	-	-	✓	-	✓	-	-	-	-
EVD	2015	Canada	SCOG	✓	-	-	-	-	✓	-	-	-	-
EVD	2015	Japan	MoHLW	✓	-	✓	✓	✓	✓	-	✓	✓	✓
EVD	2015	Senegal	MoHSA	✓	-	-	✓	✓	✓	-	-	-	-
EVD	2014	Liberia	MoHSW	✓	-	✓	✓	✓	✓	-	-	-	-
EVD	2014	Canada	CCCS	✓	-	✓	✓	✓	-	-	✓	✓	✓
EVD	2014	Russia	MoH	-	-	-	✓	-	✓	✓	-	✓	-
EVD	2015	Global	PCCM, WFPI, CCS	✓	✓	✓	✓	-	✓	-	-	-	✓
EVD	2014	Australia	Queensland DoH	✓	-	✓	✓	-	-	-	-	✓	✓
EVD	2008	China	NHC	✓	-	✓	✓	-	-	-	-	-	-
EVD/MVD	2008	Global	MSF	✓	-	-	✓	✓	✓	-	✓	-	-

Lassa	2014	USA	US CDC	✓	✓	-	-	-	-	✓	-	-	-
Lassa	2018	Nigeria	Nigeria CDC	✓	-	✓	-	✓	✓	✓	✓	-	✓
MVD	2021	USA	US CDC	✓	✓	✓	-	-	-	-	-	-	-
MVD	2021	Global	Uptodate	✓	✓	-	✓	-	✓	-	✓	✓	✓
RVF	2020	USA	US CDC	-	-	-		-	-	-	-	-	-
VHF	2021	Global	MSF	✓	-	-	✓	-	-	✓	-	-	-
VHF	2016	Global	WHO	✓	-	✓	✓	-	✓	✓	-	-	-
VHF	2015	South Africa	MoH	✓	-	✓	-	-	✓	✓	-	-	-
VHF	2008	USA	San Francisco DoPH	-	-	-	-	-	-	✓	-	✓	-
VHF	2004	Europe	BICHAT	-	-	-	-	-	-	✓	-	-	-
VHF	2001	Europe	ENVID	-	-	-	-	✓	-	✓	-	-	-

Abbreviations: VHF- Viral Haemorrhagic fevers, CCHF- Crimean-Congo Haemorrhagic fever, WHO- World Health Organisation, MoH- Ministry of Health, CDC- Center for Disease Control and Prevention, MoHLW- Ministry of Health Labour & Welfare, ENIVD- European Network for Diagnostics of Imported Viral Diseases, MSF- Médecins Sans Frontières, DoH- Department of Health, DoPH- Department of Public Health, MoPH- Ministry of Public Health, NIH- National Institute of Health, CCCS- Canadian Critical Care Society, IMC- International Medical Corps, MoHSA- Ministry of Health and Social Action, MoHSW- Ministry of Health & Social Welfare, RRT- Renal Replacement Therapy, SCOG-Society of Obstetricians and Gynaecologists of Canada; DHOSA- Department of Health, South Africa, BICHAT- Biological and Chemical Agent Threats, PCCM- Paediatric Critical Care Medicine, EVD- Ebola Virus Disease