MAJOR ARTICLE

Factors Associated with Marburg Hemorrhagic Fever: Analysis of Patient Data from Uige, Angola

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Background. Reliable on-site polymerase chain reaction (PCR) testing for Marburg hemorrhagic fever (MHF) is not always available. Therefore, clinicians triage patients on the basis of presenting symptoms and contact history. Using patient data collected in Uige, Angola, in 2005, we assessed the sensitivity and specificity of these factors to evaluate the validity of World Health Organization (WHO)–recommended case definitions for MHF.

Methods. Multivariable logistic regression was used to identify independent predictors of PCR confirmation of MHF. A data-derived algorithm was developed to obtain new MHF case definitions with improved sensitivity and specificity.

Results. A MHF case definition comprising (1) an epidemiological link or (2) the combination of myalgia or arthralgia and any hemorrhage could potentially serve as an alternative to current case definitions. Our data-derived case definitions maintained the sensitivity and improved the specificity of current WHO-recommended case definitions.

Conclusions. Continued efforts to improve clinical documentation during filovirus outbreaks would aid in the refinement of case definitions and facilitate outbreak control.

Marburg hemorrhagic fever (MHF) was first described in 1967 in an outbreak in Germany and the former Yugoslavia that was linked to contact with monkeys imported from Uganda [1]. The causative agent of MHF is *Lake Victoria marburgvirus* (MARV), a filovirus similar to Ebola virus [2]. Disease onset is sudden, with fever, chills, headache, and myalgia. Approximately 5 days after disease onset, a nonpruritic rash may appear, followed by nausea, vomiting, diarrhea, bone pain, and abdominal pain. Symptoms may become increasingly severe and lead to massive hemorrhaging and multiorgan dysfunction [3]. Most deaths occur during the second week of illness [4]. Person-to-person transmission occurs through direct contact with symptomatic patients with MHF, their body fluids, or their remains [4]. The natural reservoir of the virus remains unknown, although bats have been implicated [5, 6].

Since 1967, sporadic cases of MHF [7–12] and 2 large outbreaks have been recorded [3, 13]. The 1998–2000 outbreak occurred in the Durba and Watsa region of the Democratic Republic of the Congo, resulting in 154 cases and 125 deaths (case–fatality rate [CFR], 83%) [14, 15]. The 2005 outbreak occurred in Uige, Angola, with 374 putative cases (including 158 laboratory-confirmed cases) and 329 deaths (CFR, 88%) [16]. The relatively low number of recognized infections and the poor quality of their clinical documentation [17] have hampered the assessment of clinical MHF characteristics in humans.

Diagnostic tests for MHF include reverse-transcriptase polymerase chain reaction (PCR) assays to identify viral nucleic acids [18]. However, the usefulness of these assays is limited during the first few days of illness because of low concentrations of circulating virus [19,

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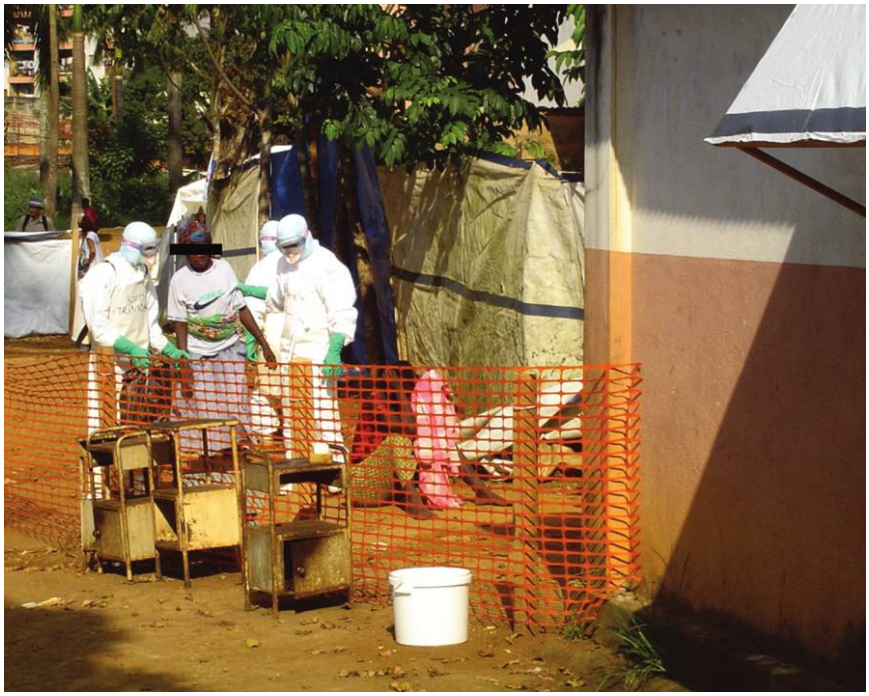

Figure 1. Uige Provincial Hospital's Marburg ward receiving a triaged patient with Marburg hemorrhagic fever–compatible symptoms.

20] and, at times, the nonavailability of on-site testing. Clinical case definitions for MHF determine whether clinicians take a sample for diagnostic testing and influence triage decisions.

Clinical case definitions were developed by the World Health Organization (WHO) during the Durba and Watsa outbreak that were based on the Ebola hemorrhagic fever (EHF) case definition. To fulfil the WHO-recommended definition, which was adapted during the outbreak, a patient must have either (1) an epidemiological link to an individual potentially infected with MARV and at least 3 of the following general symptoms: asthenia, anorexia, myalgia or arthralgia, diarrhea, abdominal pain, nausea, vomiting, headache, dysphagia, dyspnea, conjunctivitis, jaundice, and hiccups; or (2) fever plus at least 3 general symptoms; or (3) fever plus unexplained hemorrhage [21]. A highly sensitive clinical case definition ensures that patients with true MHF are isolated and prevented from transmitting MARV to community members; a highly specific case definition ensures that uninfected patients are not placed at risk of nosocomial infection in the Marburg ward. Until the Uige outbreak, there were limited opportunities to test the validity of individual patient characteristics, symptomology, and contact history as diagnostic criteria of MHF.

The Uige outbreak is the largest recorded outbreak of MHF to date. Most cases originated from Uige City, a municipality of ~180,000 inhabitants. The initial investigation, confirmation, and notification of the outbreak are described elsewhere [3, 22–24]. During the outbreak, Uige Provincial Hospital's Marburg ward received patients with MHF-compatible symptoms identified by surveillance teams operating in the community, health care workers operating a triage system elsewhere in the hospital, and patient self-referral (Figure 1). On presentation at the hospital, patients with suspected MHF were examined by a clinician and had blood specimens taken for onsite laboratory testing by the National Microbiology Laboratory–Public Health Agency of Canada, who provided results within 4–6 h. A laboratory in Luanda, Angola, operated by the US Centers for Disease Control and Prevention, subsequently confirmed all Marburg-related laboratory results.

Patients with positive PCR results were classified as confirmed cases and admitted to the Marburg ward. Patients with negative PCR results who had a blood sample obtained more than 2–3 days after the onset of symptoms were classified as having non-MHF cases and were reexamined for an alternative illness. If a patient with negative PCR results had samples obtained 2–3 days or less after symptom onset, an additional sample was obtained for testing 24–48 h later. Patients with a positive result were admitted to the Marburg ward, and those with a second negative PCR result were classified as not having MHF.

The objectives of this study were to: (1) evaluate the diagnostic validity of individual patient clinical and epidemiological characteristics and WHO-recommended case definitions for MHF and (2) develop a data-derived diagnostic algorithm for MHF that improves the WHO-recommended definitions. Analysis of the patient data was approved by the Ethical Review Boards of Médecins Sans Frontières, London School of Hygiene

and Tropical Medicine, and by representatives of the Angolan Ministry of Health and the Angolan Armed Forces in Uige.

METHODS

Study population and variables. Patients with suspected MHF who presented at the Uige Provincial Hospital from March through July 2005 and who had MARV PCR results were included in this study. Data were collected on patient demographic characteristics, contact history, clinical symptoms at hospital admission, and MARV PCR results. Demographic variables included sex, age, residence, ethnicity, and occupation. Contact history with an individual potentially infected with MARV (defined as a person, alive or deceased, who met the criteria for an MHF operational case definition) was restricted to contact 2–21 days before symptom onset, which is the putative incubation period for MHF. Contact was categorized into 3 groups: (1) indirect contact comprised sleeping in the same household as an individual potentially infected with MARV or touching objects used by the individual (eg, cutlery); (2) direct contact comprised contact with the body or body fluids (including breast milk) of an individual potentially infected with MARV; (3) contact during funeral practices included direct contact with the corpse of an individual potentially infected with MARV, the corpse's body fluids, or potentially contaminated objects (eg, soiled clothing or mattresses). Funeral contact was categorized separately, because the intensity and duration of contact may have differed from that for contact with live patients. Because contact categories were not mutually exclusive, patients were categorized according to their highest level of contact. For example, patients with direct and indirect contact were classified as having direct contact; those with funeral and other contact were assigned to funeral contact. Individuals with direct or funeral contact were defined as having an epidemiological link.

The outcome variable was MHF confirmation by PCR. Confirmation was obtained by 1-step reverse-transcriptase PCR assay targeting the polymerase, glycoprotein, and nucleoprotein genes of the MARV genome. Amplification was run on a SmartCycler (Cepheid) using SYBR Green incorporation and subsequent melt curve analysis [25, 26; A. Grolla and H. Feldmann, unpublished data]. A sample was considered to be positive when at least 2 assays resulted in positive amplification. When possible, PCR products were sequence-confirmed at the National Microbiology Laboratory–Public Health Agency of Canada.

Data analysis. Data were entered into Microsoft Excel and analyzed with Stata, version 9 (StataCorp). Clinical and contact characteristics were cross-tabulated against PCR results to obtain their sensitivity and specificity. Each element of the WHO-recommended clinical case definition was assessed, together with 2 overall WHO definitions: (1) individuals who had any of the 3 elements of the case definition (including an epidemiological link) or (2) individuals with either of the 2 clinical definitions (fever plus at least 3 general symptoms or fever plus unexplained hemorrhage). The latter definition was assessed because it may be employed when information about epidemiological contact is unavailable.

Based on clinical and contact characteristics and using the method of Quigley et al [27], alternative diagnostic algorithms for MHF were identified using logistic regression. Using PCR results as the outcome, univariable odds ratios (ORs) were obtained for each characteristic. Variables with an OR of $\geqslant 1.5$ or $\leqslant 0.75$ and a P value of $<.2$ on univariable analysis were added sequentially to a multivariable logistic model starting with the variable with the strongest association and were retained if they maintained a P value of $<.1$. Two separate multivariable models were created; the first was based on symptoms only, whereas the second included symptoms and contact variables, thus simulating a situation where a surveillance system delivers this information.

The log ORs for the characteristics in the final models were used to assign an overall score for each individual by summing the values of the log ORs for each characteristic that the individual possessed. A range of score cutoffs were assessed to identify the cutoff that maximized sensitivity and specificity of the diagnosis by best dividing individuals with a PCR-positive result (score greater than or equal to the cutoff value) from those with a PCR-negative result (score less than the cutoff value) [27]. New case definitions were constructed using these cutoff values.

RESULTS

Description of study population. Table 1 shows the demographic characteristics of the 102 patients with suspected MHF who presented at the Uige Provincial Hospital from March through July 2005. An MHF diagnosis was confirmed by PCR in 41 patients. Three-quarters of patients with confirmed cases were female, nearly one-third were housewives, 14.6% were children <5 years of age, and 13.2% were health care workers. The majority of patients with confirmed MHF came from Uige urban or suburban residential areas.

Univariable analyses. Table 2 shows the sensitivity, specificity, and univariable OR of contact history, clinical symptoms, and WHO-recommended case definitions for a valid PCR-positive diagnosis. Compared with patients without a reported contact history, the odds of having positive PCR results were 6.88 times greater for patients with indirect contact with an individual with a suspected case of MHF, 11 times greater for patients with direct contact, and 38.5 times greater for patients with funeral contact. Having an epidemiological link (direct or funeral contact) had moderate sensitivity (67%) and high specificity (86%) for a PCR-positive diagnosis.

Table 1. Demographic Characteristics of Patients with Suspected Marburg Hemorrhagic Fever who Presented at the Uige Provincial Hospital (Uige, Angola), March–July 2005, by Polymerase Chain Reaction (PCR) Result.

Variable	No. (%) of patients, by PCR results	
	Positive (n = 41)	Negative (n = 61)
Sex		
Male	10 (24.4)	27 (44.3)
Female	31 (75.6)	34 (55.7)
Age		
<5 Years	6 (14.6)	17 (27.9)
5–14 Years	2 (4.9)	4 (6.6)
15–29 Years	12 (29.3)	13 (21.3)
30–39 Years	13 (31.7)	15 (24.6)
⩾ 40 Years	8 (19.5)	12 (19.7)
Ethnicity[a]		
Other	3/34 (8.8)	12/49 (24.5)
Kikongo	31/34 (91.2)	37/49 (75.5)
Occupation[a]		
Student	12/38 (31.6)	20/55 (36.4)
Housewife	12/38 (31.6)	15/55 (27.3)
Other adult worker	9/38 (23.7)	15/55 (27.3)
Health care worker	5/38 (13.2)	5/55 (9.1)
Residence[a]		
Urban/suburban	34/39 (87.2)	50/56 (89.3)
Rural	5/39 (12.8)	6/56 (10.7)

[a] Data missing for some individuals

Of the general symptoms at hospital admission, myalgia or arthralgia had the strongest association with PCR confirmation, with a sensitivity and specificity of 63% and 66%, respectively. Conjunctivitis, hiccups, and jaundice had high specificity (⩾90%) but poor sensitivity. Conversely, fever and asthenia had high sensitivity but poor specificity. Among the hemorrhagic symptoms, bleeding at the injection site was most strongly associated with PCR confirmation, with high specificity (97%) but low sensitivity (12%).

The WHO-recommended case definition requiring an epidemiological link and ⩾3 general symptoms had high specificity (93%) but low sensitivity (54%); decreasing the number of required general symptoms to 2 failed to improve sensitivity (Table 2). The WHO-recommended case definition that was based on clinical criteria alone had lower specificity (43%), compared with that of definitions requiring an epidemiological link, but higher sensitivity (73%). Combining all elements of the WHO-recommended case definition (epidemiological link plus at least 3 general symptoms, fever plus 3 general symptoms, or fever plus hemorrhage), as practiced during the outbreak, yielded a sensitivity of 79% and a specificity of 39% for correctly identifying patients with PCR-confirmed MHF.

Multivariable analyses. Variables eligible for the multivariable models were myalgia or arthralgia, anorexia, asthenia, any hemorrhage, bleeding at an injection site, bloody gingivitis and, for model 2, an epidemiological link. In the first model, comprising only clinical characteristics (n = 102), no variables remained associated with a PCR-positive result at the $P < .1$ level after adjusting for other variables (data not shown). Table 3 shows the results for the model that included the epidemiological link variable for the 95 patients with available data. Because bleeding at an injection site and bloody gingivitis were components of any form of hemorrhage, all 3 variables could not be used in the same model. Therefore, 2 separate submodels were built: Model 2a assessed any form of hemorrhage, and Model 2b assessed the 2 individual hemorrhage variables.

In both Models 2a and 2b, an epidemiological link was most strongly associated with a PCR-positive result (adjusted ORs of 14.29 and 13.47, respectively; $P < .001$), and myalgia or arthralgia remained a predictor for a valid MHF diagnosis, with adjusted ORs of 2.66 and 2.81, respectively. Also retained in the final models were any hemorrhage in Model 2a (OR, 2.59; $P = .09$) and bleeding at injection site in Model 2b (OR, 6.7; $P = .05$).

The log ORs, listed in Table 3, were used to derive individuals' scores. After examining a range of score cutoff values (Table 4), we identified a cutoff value of 1.93 for Model 2a, which produced a diagnostic algorithm with equivalent sensitivity (79%) and appreciably higher specificity than all combinations of WHO-recommended case definitions (73% vs 39%; $P < .001$, by exact McNemar test). Using this cutoff value, an individual who presented at the hospital would be considered to have MHF if he or she had either (1) an epidemiological link or (2) both myalgia or arthralgia and any hemorrhage. Model 2b gave a sensitivity of 74% (95% confidence interval [CI], 58%–87%) and specificity of 86% (95% CI, 74%–94%) when a cutoff of 2.60 was used. This resulted in a case definition similar to that in Model 2a, whereby an individual required either (1) an epidemiological link or (2) both myalgia or arthralgia and bleeding from the injection site (data not shown).

Because indirect contact with a case of suspected MHF was also associated with increased odds of positive PCR results, we conducted a sensitivity analysis that recreated the epidemiological link variable to include all contact categories (direct, funeral, and indirect) and assessed this new variable in the diagnostic algorithm. Both the sensitivity and the specificity of this new variable were 79% on univariable analysis. The log OR of the new variable in Model 2a was 3.64, and the optimum balance of sensitivity and specificity was obtained using a cutoff value just below this value (data not shown). This gave a case definition whereby an individual was considered to have MHF if he or she had any contact (direct, funeral, or indirect) with a suspected case, irrespective of any other clinical symptoms

or signs (sensitivity, 79% [95% CI, 64%–91%]; specificity, 79% [95% CI, 66%–88%]).

DISCUSSION

We used patient epidemiological and clinical data on presentation to the hospital during the 2005 Uige MHF outbreak and MARV-PCR results to assess the sensitivity and specificity of epidemiological and clinical indicators and WHO-recommended case definitions. Our findings indicate that, for individuals who presented at the hospital, a history of contact with an individual potentially infected with MARV was highly predictive of MHF, whereas much of the clinical data were less helpful. The disease hallmark, fever in combination with ⩾3 general symptoms or with hemorrhage, was only weakly associated with PCR confirmation of MHF. Of the generalized symptoms, myalgia or arthralgia was the strongest predictor of MHF but had intermediate sensitivity and specificity. The usefulness of this symptom as an MHF predictor is limited by its subjectivity and the difficulty in assessing it in young children.

The frequency of clinical manifestations experienced by individuals with confirmed MHF at admission to the Marburg ward in Uige corresponds to those documented during the Durba and Watsa outbreak [17]. Because our data only captured MHF clinical manifestations at hospital admission, symptoms that typically manifest later in the course of disease (eg, nausea and vomiting, abdominal pain, and diarrhea) were reported relatively infrequently (in <50% of cases), and late-onset symptoms (eg, hiccups, jaundice, and conjunctivitis) were observed in <20% of patients.

In filovirus hemorrhagic fever (FHF), hemorrhagic symptoms typically develop late in the course of disease [17, 28]. Only one-half of the patients who were later confirmed to have MHF presented with hemorrhagic symptoms at hospital admission. Epistaxis and hematemesis were observed in <10% of patients with confirmed MHF and bleeding from gums or bloody diarrhea in <20%. Bleeding from an injection site had high specificity; its low sensitivity may be explained by its dependence on having received an injection. Although hemorrhage from natural orifices can be caused by local and systemic disturbances, bleeding from an injection site is rare without a systemic coagulation disorder, as may occur with FHF [29] but not, typically, in certain diseases for which FHF can be mistaken (eg, typhoid and shigellosis). The high specificity of this characteristic suggests that a bedside clotting test could help to differentiate late-stage FHF from other diseases that cause bleeding when specific on-site virological tests are unavailable. Because in vitro coagulopathy may precede spontaneous bleeding, a bedside clotting test could also help to diagnose FHF before hemorrhage manifests. Further study is warranted.

The WHO-recommended case definition integrating information on prior contact and general clinical symptoms had a sensitivity of 54%, thus failing to identify many MHF-infected individuals. Notably, sensitivity was not improved by reducing the number of required general symptoms from 3 to 2. The combination of WHO-recommended case definitions incorporating epidemiological criteria and clinical data on fever, general symptoms, and hemorrhage achieved reasonable sensitivity (79%) but low specificity (39%).

We explored alternative diagnostic algorithms for MHF that might improve sensitivity and/or specificity, compared with the WHO-recommended case definitions. Our findings suggest that a case definition that is based on the presence of an epidemiological link or the combination of myalgia or arthralgia and any hemorrhage could potentially serve as a reasonable alternative to currently recommended MHF case definitions when assessing patients who present to the hospital. In our study population, this new case definition maintained the sensitivity of the all-combined WHO case definition (79%) but had increased specificity (73% vs 39%). This underlines the importance of a community surveillance system that provides epidemiological data on prior patient contacts and of integrating epidemiological data into the clinical assessment when deciding on isolation or PCR testing. Sensitivity analyses suggested that a higher specificity (79%) could be obtained by incorporating all contact (including indirect contact) into the epidemiological link variable and using this variable alone for an operational MHF case definition. This may be attributable to misclassification of direct contact as indirect contact.

We found that the age and sex distribution of our study population differed from that reported in the only other major MHF outbreak. The Durba and Watsa outbreak was driven by repeated primary transmission to adult male mining workers [15], whereas the Uige outbreak was fuelled by nosocomial and secondary transmission to caregivers in the community [30]. Caregiving is traditionally a female role in sub-Saharan Africa, which may explain the dominance of females among patients with confirmed MHF (75.6%). A similar pattern was found for EHF in Kikwit, Democratic Republic of the Congo [28, 31]. Children <5 years of age accounted for 15% of patients with confirmed MHF in Uige, which contrasts with previous reports of infrequent FHF in young children [32, 33]. The children in Uige were possibly infected while using health services during the early stages of the outbreak [34]. Without a detailed epidemiological description of the outbreak, it is difficult to interpret the sex and age distribution.

One limitation of this study is its small sample size. We could not fully replicate Quigley's approach, which involves dividing the database into two subsets, using one subset for developing the case definition and the other for its validation. The sample size also limited statistical power to detect associations between many variables and PCR results positive for MARV and yielded large confidence intervals for sensitivity and specificity

Table 2. Sensitivity, Specificity, and Crude Odds Ratios (ORs) for Contact History, Clinical Symptoms and World Health Organization (WHO)–Recommended Case Definitions of Marburg Hemorrhagic Fever (MHF) among Polymerase Chain Reaction (PCR)–Positive and PCR-Negative Patients with Suspected MHF who Presented at the Uige Provincial Hospital (Uige, Angola), March–July 2005.

Variable	No. (%) of patients, by PCR results		Sensitivity, % (95% CI)	Specificity, % (95% CI)	OR (95% CI)	*P*
	Positive (n = 41)	Negative (n = 61)				
Contact history[a]						
None	8/39 (20.5)	44/56 (78.6)			1.00	
Indirect	5/39 (12.8)	4/56 (7.1)	…	…	6.88 (1.35–35.08)	.007
Direct	12/39 (30.8)	6/56 (10.7)			11.00 (2.62–46.15)	<.001
Funeral	14/39 (35.9)	2/56 (3.6)			38.50 (4.2–352.1)	<.001
Contact history/epidemiological link [a,b]						
Yes	26/39 (66.7)	8/56 (14.3)	67 (50–81)	86 (74–94)	12.00 (3.64–39.61)	<.001
No	13/39 (33.3)	48/56 (85.7)			1.00	
Fever						
Yes	35 (85.4)	49 (80.3)	85 (71–94)	20 (11–32)	1.43 (0.49–4.20)	.51
No	6 (14.6)	12 (19.7)			1.00	
Asthenia						
Yes	34 (82.9)	41 (67.2)	83 (68–93)	33 (21–46)	2.37 (0.88–6.40)	
No	7 (17.1)	20 (32.8)			1.00	.08
Anorexia						
Yes	27 (65.9)	29 (47.5)	66 (49–80)	53 (39–65)	2.13 (0.92–4.91)	.07
No	14 (34.2)	32 (52.5)			1.00	
Myalgia or arthralgia						
Yes	26 (63.4)	21 (34.4)	63 (47–78)	66 (52–77)	3.30 (1.39–7.85)	.004
No	15 (36.6)	40 (65.6)			1.00	
Diarrhea						
Yes	19 (46.3)	24 (39.3)	46 (31–63)	61 (47–73)	1.33 (0.59–2.98)	.49
No	22 (53.7)	37 (60.7)			1.00	
Abdominal pain						
Yes	15 (36.6)	22 (36.1)	37 (22–53)	64 (51–76)	1.02 (0.45–2.34)	.96
No	26 (63.4)	39 (63.9)			1.00	
Nausea and vomiting						
Yes	14 (34.2)	20 (32.8)	34 (20–51)	67 (54–79)	1.06 (0.46–2.47)	.89
No	27 (65.9)	41 (67.2)			1.00	
Headache						
Yes	13 (31.7)	21 (34.4)	32 (18–48)	66 (52–77)	0.88 (0.38–2.07)	.78
No	28 (68.3)	40 (65.6)			1.00	
Dysphagia						
Yes	11 (26.8)	13 (21.3)	27 (14–43)	79 (66–88)	1.35 (0.53–3.43)	.52
No	30 (73.2)	48 (78.7)			1.00	
Conjunctivitis						
Yes	7 (17.1)	6 (9.8)	17 (7–32)	90 (80–96)	1.89 (0.58–6.17)	.28
No	34 (82.9)	55 (90.2)			1.00	
Dyspnea						
Yes	5 (12.2)	13 (21.3)	12 (4–26)	79 (66–88)	0.51 (0.17–1.59)	.24
No	36 (87.8)	48 (78.7)			1.00	
Hiccups						
Yes	2 (4.9)	3 (4.9)	5 (1–17)	95 (86–99)	0.99 (0.16–6.27)	.99
No	39 (95.1)	58 (95.1)			1.00	
Jaundice						
Yes	1 (2.4)	4 (6.6)	2 (0–13)	93 (84–98)	0.36 (0.04–3.38)	.35
No	40 (97.6)	57 (93.4)			1.00	
Any hemorrhage						
Yes	21 (51.2)	22 (36.1)	51 (35–67)	64 (51–76)	1.86 (0.82–4.22)	.13
No	20 (48.8)	39 (63.9)			1.00	
Nonmenstrual vaginal bleed[c]						
Yes	6 (20.0)	3 (9.4)	20 (8–39)	91 (75–98)	2.42 (0.53–11.0)	.24

Table 2. ***(Continued.)***

Variable	No. (%) of patients, by PCR results		Sensitivity, % (95% CI)	Specificity, % (95% CI)	OR (95% CI)	*P*
	Positive (n = 41)	Negative (n = 61)				
No	24 (80.0)	29 (90.6)			1.00	
Bloody gingivitis						
Yes	7 (17.1)	4 (6.6)	17 (7–32)	93 (84–98)	2.93 (0.78–11.0)	.09
No	34 (82.9)	57 (93.4)			1.00	
Bloody diarrhea						
Yes	7 (17.1)	14 (22.9)	17 (7–32)	77 (65–87)	0.69 (0.25–1.91)	.47
No	34 (82.9)	47 (77.1)			1.00	
Bleeding at injection site						
Yes	5 (12.2)	2 (3.3)	12 (4–26)	97 (89–100)	4.10 (0.73–23.0)	.08
No	36 (87.8)	59 (96.7)			1.00	
Hematemesis						
Yes	3 (7.3)	7 (11.5)	7 (2–20)	89 (78–95)	0.61 (0.15–2.53)	.49
No	38 (92.7)	54 (88.5)			1.00	
Epistaxis						
Yes	2 (4.9)	1 (1.6)	5 (1–17)	98 (91–100)	3.08 (0.26–35.9)	.34
No	39 (95.1)	60 (98.4)			1.00	
Hemoptysis						
Yes	0 (0.0)	1 (1.6)	0 (0–9)	98 (91–100)	…	…
No	41 (100.0)	60 (98.4)				
Definition 1: epidemiological link and ⩾3 general symptoms[a]						
Yes	21/39 (53.9)	4/56 (7.1)	54 (37–70)	93 (83–98)	15.2 (3.7–62.1)	<.001
No	18/39 (46.2)	52/56 (92.9)			1.00	
Definition 2: epidemiological link and ⩾2 general symptoms[a]						
Yes	21/39 (53.9)	5/56 (8.9)	54 (37–70)	91 (80–97)	11.9 (3.3–43.2)	<.001
No	18/39 (46.2)	51/56 (91.1)			1.00	
Definition 3: fever ⩾3 symptoms						
Yes	28 (68.3)	33 (54.1)	68 (52–82)	46 (33–59)	1.83 (0.79–4.24)	.15
No	13 (31.7)	28 (45.9)			1.00	
Definition 4: Fever and hemorrhage						
Yes	18 (43.9)	17 (27.9)	44 (28–60)	72 (59–83)	2.03 (0.87–4.73)	.10
No	23 (56.1)	44 (72.1)			1.00	
Any WHO case definition[d] (clinical criteria only)						
Yes	30 (73.2)	35 (57.4)	73 (57–86)	43 (30–56)	2.03 (0.85–4.85)	.11
No	11 (26.8)	26 (42.6)			1.00	
Any WHO case definition[a,e] (all elements included)						
Yes	31/39 (79.5)	34/56 (60.7)	79 (64–91)	39 (26–53)	2.5 (0.95–6.61)	.05
No	8/39 (20.5)	22/56 (39.3)			1.00	

NOTE. CI, confidence interval.

[a] Data missing for some individuals

[b] Epidemiological link was defined as direct contact with an individual potentially infected with MHF or his or her body fluids or direct contact during funeral practices.

[c] Nonmenstrual vaginal bleeding includes females only (n = 62).

[d] Defined as corresponding to WHO definition 3 or 4.

[e] Defined as corresponding to WHO definition 1, 3, or 4.

Table 3. Adjusted Odds Ratios (ORs) for Characteristics Associated with Marburg Hemorrhagic Fever Confirmation in 95 Patients at Uige Provincial Hospital for Whom Epidemiological Data were Available

Variable	Adjusted OR[a] (95% confidence interval)	*P*	Log OR
Model 2a			
Epilink			
Yes	14.29 (4.62–44.16)	<.001	2.66
No	1.00		
Myalgia or arthralgia			
Yes	2.66 (0.96–7.41)	.06	0.98
No	1.00		
Any hemorrhage			
Yes	2.59 (0.87–7.71)	.09	0.95
No	1.00		
Model 2b			
Epilink			
Yes	13.47 (4.60–39.46)	<.001	2.60
No	1.00		
Myalgia or arthralgia			
Yes	2.81 (1.00–7.85)	.05	1.03
No	1.00		
Bleeding at injection site			
Yes	6.70 (0.97–46.00)	.05	1.90
No	1.00		

[a] Adjusted for other variables in the model.

estimates. Because Uige was a major outbreak, this limitation can possibly only be overcome by pooling data across comparable outbreaks and/or testing our diagnostic algorithm in future outbreaks.

Predominant transmission routes vary among outbreaks, which makes it difficult to develop a universal FHF case definition. Our proposed case definition, which was developed using data from an outbreak fueled by secondary transmission, may be less sensitive during an epidemic that is driven by multiple primary introductions. However, a case definition that emphasizes the role of epidemiological contact is likely to be relevant for most FHF outbreaks, because those that are fuelled by primary transmission are infrequent.

Detailed data were not available for all of the MHF cases that were declared to have occurred by the WHO and the Angolan Ministry of Health. The hospital-based data collection may have influenced the sex and age distribution, frequency of symptoms observed, and the generalizability of our findings. Many ill individuals avoided seeking hospital care because of reports of numerous deaths occurring at the hospital. Individuals with more-serious symptoms that necessitated hospitalization may be overrepresented in our study.

In contrast to the Durba and Watsa outbreak, in which the onset, duration, and symptom patterns that developed during hospitalization were collected, only presenting symptoms were recorded in Uige patients. This is regrettable, because a hospital is an ideal location for collecting clinical data. As in previous FHF outbreaks, the clinical picture of hospitalized patients with MHF in Uige, including any response to treatment, is incomplete because of poor clinical documentation. This highlights the need for (1) collection of high-quality clinical data on these poorly understood diseases by the organizations that provide clinical care to patients with FHF and (2) agreement, together with the WHO, whose mandate it is to set standards, on standardized clinical data forms and their implementation in future outbreaks. In the meantime, we suggest using the clinical data form proposed by Colebunders et al [17].

CONCLUSIONS

During an epidemic of a highly lethal disease, such as MHF, care of severely ill individuals often takes precedence over clinical data collection efforts. Despite the challenges, organizations

Table 4. Possible Combinations of Predictors of Marburg Hemorrhagic Fever Retained in Final Logistic Regression Model 2a (Epidemiological Link, Myalgia or Arthralgia, Any Hemorrhage): Sums of Log Odds Ratios (ORs), Cutoff Values, Sensitivity, and Specificity

Variable	Epi link	Epi link plus any hemorrhage	Epi link plus myalgia or arthralgia	Epi link plus myalgia or arthralgia plus any hemorrhage	Myalgia or arthralgia plus any hemorrhage	Myalgia or arthralgia	Any hemorrhage	Sensitivity (95% CI)	Specificity (95% CI)
Sum of log ORs	2.66	3.61	3.64	4.59	1.93	0.98	0.95		
Cutoff value									
⩾4.59	…	…	…	X	…	…	…	31 (17–48)	98 (90–100)
⩾3.64	…	…	X	X	…	…	…	46 (30–63)	95 (85–99)
⩾3.61	…	X	X	X	…	…	…	49 (32–65)	95 (85–99)
⩾2.66	X	X	X	X	…	…	…	67 (50–81)	86 (74–94)
⩾1.93	X	X	X	X	X	…	…	79 (64–91)	73 (60–84)
⩾0.98	X	X	X	X	X	X	…	87 (73–96)	54 (40–67)
⩾0.95	X	X	X	X	X	X	X	95 (83–99)	29 (17–42)

NOTE. CI, confidence interval; Epi, epidemiological; X, possible combination.

that respond to an FHF outbreak must work collaboratively to collect high-quality clinical and epidemiological data. The current MHF case definitions recommended by the WHO were useful for clinicians who responded to the Uige outbreak but could possibly be improved. During the outbreak, FHF-experienced clinicians encountered some potentially infected individuals whose presenting criteria did not match a WHO-recommended case definition, and those clinicians decided to proceed with a diagnostic test or assess the individual for an alternative illness. We believe that clinicians should continue to use their discretion in these circumstances.

This article suggests possible alternatives to the current MHF case definitions when deciding on isolation or PCR testing and highlights the necessity of collecting high-quality clinical and epidemiological data during outbreaks. Improved data on patient characteristics, symptoms, and contact history would further our knowledge about FHF epidemiological patterns and may help to refine WHO-recommended FHF case definitions. This, together with treatment modality data, will improve outbreak response.

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