Case definition for Ebola and Marburg haemorrhagic fevers: a complex challenge for epidemiologists and clinicians

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---- SUMMARY ----

Viral haemorrhagic fevers (VHFs) represent a challenge for public health because of their epidemic potential, and their possible use as bioterrorism agents poses particular concern. In 1999 the World Health Organization (WHO) proposed a case definition for VHFs, subsequently adopted by other international institutions with the aim of early detection of initial cases/outbreaks in western countries. We applied this case definition to reports of Ebola and Marburg virus infections to estimate its sensitivity to detect cases of the disease. We analyzed clinical descriptions of 795 reported cases of Ebola haemorrhagic fever: only 58.5% of patients met the proposed case definition. A similar figure was obtained reviewing 169 cases of Marburg diseases, of which only 64.5% were in accordance with the case definition. In conclusion, the WHO case definition for hemorrhagic fevers is too specific and has poor sensitivity both for case finding during Ebola or Marburg outbreaks, and for early detection of suspected cases in western countries. It can lead to a hazardous number of false negatives and its use should be discouraged for early detection of cases.

KEY WORDS: Viral haemorrhagic fevers, Ebola and Marburg virus outbreaks, Case definition

INTRODUCTION

Emerging and re-emerging life-threatening infections and the increasing concern about a possible bioterrorist attack highlight the urgent need for establishing effective surveillance and response systems that can rapidly detect the appearance of outbreaks.

These systems are in place in many western countries and are especially targeted to the early recognition and notification of epidemics due to bioterrorism-related agents, such as those listed by the Centers for Disease Control and prevention (CDC) as category A (CDC, 2006). These approaches can also be used to support physicians in western countries to detect imported or naturally occurring cases of diseases likely to cause large and severe epidemics, such as viral haemorrhagic fevers (VHFs).

Recent social and ecological global changes, such as the greater than ever proximity of human populations to wildlife, the increase in global travel, as well as global warming, facilitate the emerging of new zoonoses and the rapid spreading of communicable diseases (Chomel, 2007; Jones, 2008). All of the above factors make the occurrence of some diseases unpredictable, as suggested by the first appearance of an autochthonous Chikungunya fever outbreak sustained by *Aedes* mosquitoes in Europe (Rezza, 2007).

VHFs cause a severe clinical syndrome and represent a challenge for international public health. Although relatively rare, factors which increase concern surrounding VHFs are their epidemic potential, the often high case-fatality rate, and

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unusual difficulties in their treatment and prevention. Under the terms of the international health regulations (IHRs), acute haemorrhagic fever syndromes warrant immediate notification to the World Health Organization (WHO) before the causal agent is identified (WHO, 2005-1; WHO, 2008). In particular, agents of VHFs belonging to Filoviridae family (Ebola and Marburg viruses) are among the most lethal pathogens known to infect humans: the sudden onset, dramatic course, and lack of specific efficacious treatments are cause of great concern. Filoviruses are also included in the CDC's category A list of biological agents that have the potential to cause serious harm if used as biological weapons (CDC, 2006).

Although Ebola and Marburg are not transmitted by mosquitoes, there is the concrete possibility of imported cases in western countries, due to the increase in the international movement of humans, animals and goods, and prompt notification of an outbreak is essential to avoid international spread of the disease.

The key factor for outbreak control is thought to be the early detection and notification of the first cases, even before identification of the causal agent. The use of an adequate case definition, if feasible, should be adopted to ensure accurate reporting in each hospital likely to admit a possible case.

In 2002 Borio *et al.,* for the Working Group on Civilian Biodefense of the Johns Hopkins Center, Baltimore, developed consensus-based recommendations for medical and public health management of VHFs (Borio, 2002). They suggested using the following clinical criteria for case definition of VHF:

- body temperature ≥101°F (38.3°C) of <3 weeks' duration;
- severe illness, and no predisposing factors for haemorrhagic manifestations;
- and at least 2 of the following haemorrhagic symptoms: haemorrhagic or purple rash, epistaxis, haematemesis, haemoptysis, blood in stools, or other haemorrhagic signs;
- and no established alternative diagnosis.

This case definition is taken from the Recommended Surveillance Standards, 1999, Second edition, of the WHO (WHO, 1999). According to WHO, this case definition should be used for surveillance, and immediate case-based reporting of acute haemorrhagic fever syndrome, whether occurring singly or in clusters, should be rapidly notified to ensure prompt investigation and laboratory confirmation. Other institutions/panels of experts have adopted this case definition with the aim of early identification and notification of cases.

The Center for Infectious Disease Research and Policy (CIDRAP), University of Minnesota, recommends using the same case definition for the surveillance of VHFs (CIDRAP, 2002), as do the Seattle & King County Public Health Office (Department of Public Health, Seattle and King County, 2006), the Department of Public Health of San Francisco (Department of Public Health, San Francisco, 2005), and the Virginia Department of Health (Virginia Department of Health, 2003), although the two latter institutions did not include "no established alternative diagnosis".

This case definition refers to VHFs in general, and includes the presence of haemorrhages; for this reason, it should be considered appropriate mainly for Ebola and Marburg fevers, which are those with the higher occurrence of haemorrhagic signs among VHFs (WHO, 2007-1; WHO, 2005-2). In order to evaluate its sensitivity in the detection of initial cases/outbreaks in western countries, we applied this case definition to all Ebola and Marburg case reports as described in literature.

METHODS

Literature search

We identified published clinical descriptions of Ebola and Marburg virus disease by searching the English and French literature available in PubMed until March 2008. We used the MeSH Database for ("Haemorrhagic Fever, Ebola"[major] OR "Marburg Virus Disease"[Major]) AND ("Disease Outbreaks"[Major] OR "Case Reports "[Publication Type]) AND ("french"[lang] OR "english"[lang]) AND "humans"[MeSH Terms]. Moreover, we consulted web sites such as http://www.who.int, and http://www.cdc.gov, and reviewed the bibliographies of articles obtained through the search in PubMed, to identify other potentially interesting papers not previously detected.
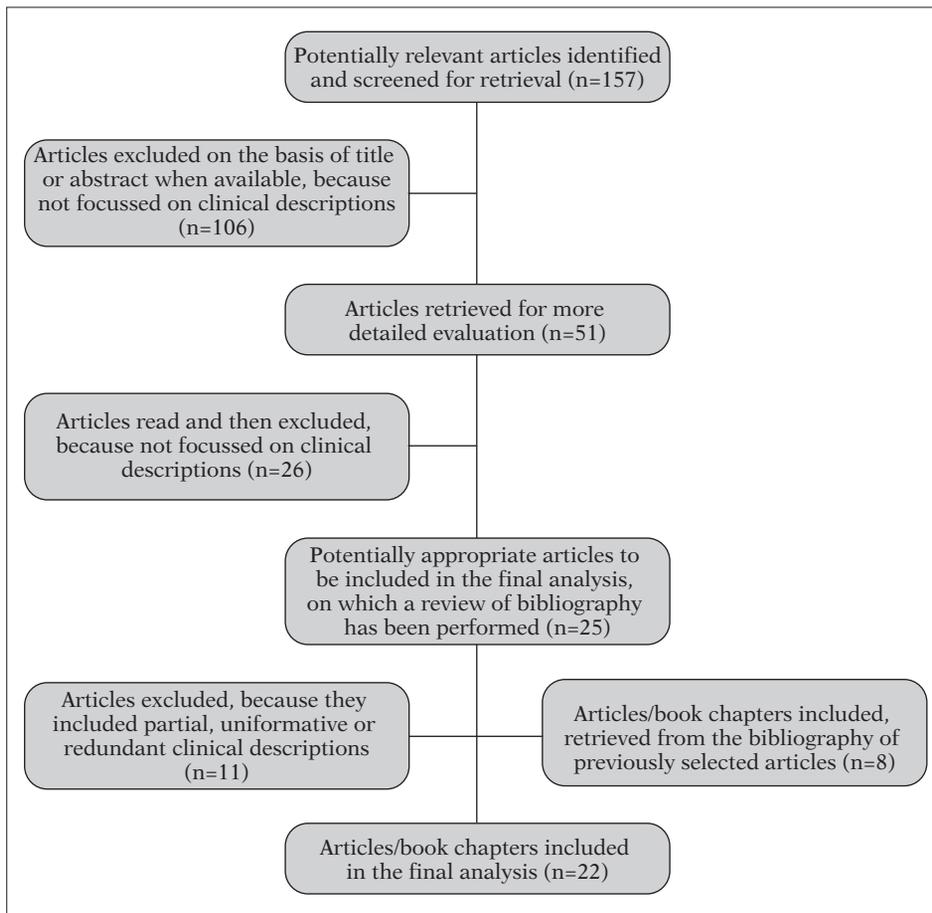
The flow diagram illustrating the process of retrieval and selection of the articles was developed according to QUOROM statement (Moher, 1999) (Fig. 1).

Selection of articles and data extraction
Among articles reporting clinical descriptions, we included only those referring to human beings and reporting at least information on body temperature and haemorrhagic signs.
Because of the study limits, described in the discussion, we simplified the WHO case definition, assuming that:
1) no predisposing factors for haemorrhagic manifestations and no established alternative diagnosis were present, when not specifically indicated;
2) the case definition was met when bleeding was reported in addition to fever (also without specification of number and sites of haemorrhagic signs).

Using this simplified case-definition, 22 articles/book chapters were included in our final analysis (WHO, 1978-1; WHO, 1978-2; Emond, 1977; Heymann, 1980, Baron, 1983; Formenty, 1999; Khan, 1999; Georges, 1999; Mupere, 2001; WHO, 2001; Nkoghe, 2005; WHO, 2003; Boumandouki, 2005; WHO, 2005-3; Martini, 1968; Martini, 1971; Gear, 1975; Smith, 1982; Johnson, 1996; Bausch, 2006; Jeffs, 2007; WHO, 2007-2). Two co-authors (SP and SL) independently extracted the relevant data from the original selected reports.

RESULTS

Approximately 2,270 cases including over 1,500 deaths have been documented since the Ebola virus was discovered (WHO, 2007-1; Ascenzi, 2008; International Society for Infectious Diseases, 2007).

TABLE 1 - *Summary of clinical descriptions available for Ebola patients.*

	Cases (n)	Cases for whom clinical description is available	Fever (%)	Bleeding, any (%)	References
Zaire (now DRC), 1976	318	231	98	78*	WHO, 1976-1
Sudan, 1976	284	183	100	71	WHO, 1976-2
United Kingdom^, 1976	1	0	100	0	Emond, 1977
Zaire (now DRC), 1977	1	1	100	100	Heymann, 1980
Sudan, 1979	34	34	100	74	Baron, 1983
Ivory Coast, 1994	1	1	100	0	Formenty, 1999
Gabon, 1994-1995	52	0	/	/	/
DRC, 1995	315	219	100	37	Khan, 1999
Gabon, 1996-97#	91	15°	100	/ °	Georges, 1999
Uganda, 2000-2001	425	62	100	16-20	Mupere, 2001; WHO, 2001
Republic of Congo and Gabon, 2001-2002	124	31	97	52	Nkoghe, 2005; WHO, 2003
Republic of Congo, 2002-2003	143	0	/	/	/
Republic of Congo, 2003	35	16	100	63	Boumandouki, 2005
Sudan, 2004	17	17	100	56	WHO, 2005-3
Republic of Congo, 2005	12	0	/	/	/
DRC, 2007	264	0	/	/	/

*Out of 223 patients; ^laboratory needle-stick injury; #two different outbreaks; °only total incidence of symptoms available. Total percentage of patients with bleeding could not be calculated. DRC: Democratic Republic of Congo.

Our simplified case definition can be applied to 796 Ebola fever cases for which clinical information is available (Table 1). 460 patients out of 796 are reported to have had haemorrhagic features, meaning that only 58% of patients met the simplified case definition.

For Marburg virus disease, 568 human cases have been reported to date, including 469 deaths (WHO, 2005-2; WHO, 2007-2; Ascenzi, 2008). Among the 169 cases that were clinically described, 60 (35.5%) did not show haemorrhagic features, and did not meet the simplified case definition (Table 2).

DISCUSSION

The attempt to apply the case definition adapted from WHO standards by Borio *et al.* to detect single episodes or clusters of Ebola or Marburg virus infections showed some limitations related both to the characteristics of the diseases and to the limited information available in the literature. Information on clinical pictures are limited and derived from the relatively rare, naturally occurring outbreaks.

Outbreaks often occur in areas with poor medical resources; recognition is therefore often de-

TABLE 2 - *Summary of clinical descriptions available for Marburg patients.*

	Cases (n)	*Cases for whom clinical description is available*	*Fever (%)*	*Bleeding, any (%)*	*References*
Germany (Marburg), 1967	23	23	100	31	Martini, 1968; Martini, 1971
Germany (Frankfurt), 1967	6	6	100	83	Martini, 1971
Yugoslavia, 1967	2	2	100	100	Martini, 1971
South Africa, 1975	3	3	100	67	Gear, 1975
Kenya, 1980	2	2	100	100	Smith, 1982
Kenya, 1987	1	1	100	100	Johnson, 1996
DRC, 1998-2000	154	129	93	69	Bausch, 2006
Angola, 2004-2005	374	/	/	42[§]	Jeffs, 2007
Uganda, 2007	3	3	100	33	WHO, 2007-2

[§]In hospitalized cases only. Total number of hospitalized cases not available; DRC: Democratic Republic of Congo.

layed, and technical difficulties in the field hamper a comprehensive epidemiological analysis of the outbreak.

Clinical descriptions are often available for hospitalized cases only, which presumably present the more serious signs and symptoms. Information collected is largely retrospective. For example, in the first recognition of Ebola outbreaks (Zaire and Sudan, 1976), well documented observations are reported for few patients, while only the symptoms and signs frequency – retrospectively collected - is reported for 231 out of 318 patients of the Zairean outbreak, and for 183 out of 284 total Sudanese cases. In these cases, fever was always present, while bleeding was reported for 78% and 71% of them respectively. A minor frequency of haemorrhagic signs (48%) was reported for patients who recovered in the Sudanese outbreak. Retrospective clinical data collection may be hampered by the fear of stigmatization.

Moreover, survivors may have suffered from mild or asymptomatic disease and these cases may easily have passed unnoticed if the case definition is limited to cases with haemorrhage (Borchert, 2002). In the available clinical descriptions, early symptoms are not distinguished from late manifestations: early in the epidemics, physicians probably will not suspect VHF until more specific signs develop and it becomes clear that the patient is unresponsive to recommended treatments for other illnesses.

The haemorrhagic signs usually appear between days 5 and 7 for Marburg virus disease, and as Ebola disease progresses.

Despite these limitations, we applied the simplified WHO case definition to available clinical descriptions of Ebola and Marburg cases, and we found that more than 30% of Ebola and Marburg cases could be missed because they do not meet the case definition.

Ours was an academic exercise, which suggests some reflections. The strict application of the WHO case definition can lead to a hazardous number of false negatives.

The inclusion of haemorrhagic manifestations makes the definition too specific, and not sensitive enough for case detection. On the other hand, a more sensitive case definition would likely introduce false alarms, with foreseeable consequences. According to WHO, "a *case definition is a set of diagnostic criteria that must be fulfilled for an individual to be regarded as a case of a particular disease for surveillance and outbreak investi-*

TABLE 3 - *Case Definitions used on the field in some Ebola outbreaks.*

	Field Case Definition	*References*
Sudan, 1976	Anyone 1. having fever and headache lasting for at least 2 days with diarrhoea or vomiting or chest pain; or 2. diagnosed by a physician in a hospital	WHO, 1978-2
Zaire (now DRC), 1976	PROBABLE: a person living in the epidemic area who died after one or more days with two or more of the following symptoms and signs: headache, fever, abdominal pain, nausea and/or vomiting, and bleeding; and who had, within the 3 previous weeks, received an injection or had contact with a probable or proven case; and in whom no other illness was diagnosed. CONFIRMED: virus isolation or electron microscopy demonstration or IFA>1:64 within 3 weeks after onset of symptoms	WHO, 1978-1
DRC, 1995	[Initial case definition]: SUSPECTED: a person who has been in contact with a case and who meets the clinical criteria (not specified): suspected cases were categorized into either PROBABLE or CLINICAL cases on the basis of the presence of hemorrhage. [Following case definition]: PROBABLE: someone who had: 1. an unexplained fever and contact with another case-patient; 2. unexplained fever plus [3] 3 of 10 symptoms (abdominal pain, anorexia, asthenia, diarrhoea, dysphagia, dyspnea, headache, hiccups, myalgia or arthralgia, and nausea or vomiting); 3. unexplained acute haemorrhagic signs or symptoms	Khan, 1999
Uganda, 2000-2001	ALERT: any case of sudden onset of high fever OR sudden death Or any form of bleeding (restricted to community use for notification to peripheral health units or mobile teams). SUSPECTED: all persons, living or deceased, with: history of contact with a case and fever OR fever plus ≥3 of the following symptoms (headache, vomiting, loss of appetite, diarrhoea, weakness, abdominal pain, body aches or joint pains, dysphagia, dyspnea, hiccups). PROBABLE: same as above, but the assessment was done by a clinician. CONFIRMED: any patient who met the clinical case definition, confirmed by Antigen, IgG, or PCR-positive laboratory results.	WHO, 2001

DRC: Democratic Republic of Congo; IFA: ImmunoFluorescence Antibody; Ig: Immunoglobulin; PCR: Polymerase Chain Reaction.

gation purposes" (WHO, 1999). A good case definition is a compromise between the need for detection of all the cases and capacity to describe the disease specifically: the lack of sensitivity may lead to a lack of control of person-to-person transmission, while the lack of specificity may overburden the health services (Borchert, 2002).

It is very difficult to propose an alternative case definition for VHFs, because early signs and symptoms (acute fever, abdominal pain, vomiting, arthralgias, headache, etc.) are not specific, very common, and shared with many other bacterial and viral diseases.

Therefore, the case definitions used during outbreaks are prepared *ad hoc*, on the field, and based on the specific characteristics of the epidemic in question. Exhaustive examples of literature descriptions for Ebola haemorrhagic fever show the main difficulties encountered in the field during an outbreak, and case definitions used in some Ebola outbreaks are reported in Table 3. In the comprehensive reports of the WHO/International Study Team on the two first large outbreaks of Ebola haemorrhagic fever in 1976 (WHO, 1978-1; WHO, 1978-2), the authors underline that, although there was a wide range in severity from mild to rapidly fatal, the presentation of the large majority of cases was clinically unique: the 284 cases notified in Sudan were all detected using a field case definition based on clinical signs, or just on the hospital physician's judgment.

The case of Kikwit, former-Zaire, in 1995, can explain the results and the difficulties of the surveillance system set up on the field (Khan, 1999). The initial on-the-field definition of suspected cases required both clinical (fever and other symptoms) and epidemiological (contact with a

case) criteria. The need for a more sensitive measure, able to identify individuals previously not contacted or who have not had a clear history of contact with a case, led to modifying the definition, not including any epidemiological links or limits of time and space, in order to assess the size of the outbreak. On the basis of this definition 315 cases were reported. Finally, individuals with negative laboratory results - who otherwise satisfied the field case definition - were later excluded, while patients with laboratory markers of acute or recent Ebola infection were included if they had history of an acute illness but insufficient criteria to meet the field case definition.

In conclusion, the WHO case definition for VHFs is rightly specific, developed for public health and epidemiological purposes, and not for clinical screening of cases. In the field, multiple case definitions are used and they are usually modified according to the situation of a particular outbreak. Because signs and symptoms are not specific, it is very difficult to propose an alternative case definition for VHFs.

Given the difficulty of detecting a case of VHF early, whether it is a sporadic episode or an epidemic, a high degree of suspicion is the only measure for the control of the disease. The suspicion can be raised by an awareness of the possibility of a VHF and a good knowledge of the specific diseases by health care workers, in particular European and North American physicians who have insufficient clinical experience of viral haemorrhagic syndromes.

We simply recommend, in accordance with the International Team that cooperated in the control of the first Ebola outbreak in Sudan, that *"any hospital in the tropics, or any hospital receiving patients from the tropics, should be on constant alert for haemorrhagic signs in febrile patients"* [WHO, 1978-2]. Only a high degree of suspicion makes it possible to apply the appropriate clinical and epidemiological measures for the international alert and the effective control of VHF.

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