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# New filovirus disease classification and nomenclature

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The recent large outbreak of Ebola virus disease (EVD) in Western Africa resulted in greatly increased accumulation of human genotypic, phenotypic and clinical data, and improved our understanding of the spectrum of clinical manifestations. As a result, the WHO disease classification of EVD underwent major revision.

## [H1] Former filovirus disease names

Filoviruses, the members of the family *Filoviridae*, are currently classified into one proposed and five established genera (Supplementary Table 1). Of the twelve described filoviruses, six have been identified as etiological agents of naturally occurring human disease outbreaks.

The International Classification of Diseases (ICD; Supplementary Box 1) is primarily a statistical tabulation. Consequently, frequently observed diseases with large patient cohorts are more likely to have their own disease names, codes and subcategories of disease manifestations than uncommonly occurring diseases because larger cohorts ensure statistical reliability of disease descriptions. Given the past low number of filovirus disease outbreaks and overall case-numbers (34 disease outbreaks until 2013, involving 2,872 infections and 1,968 deaths), it is not surprising that the diseases caused by filoviruses were not captured by early ICD iterations. In ICD-9, the only code defining filovirus diseases was “078.89 Other specified diseases due to viruses.” Consequently, various unofficial filovirus disease names have been used in the scientific literature (Supplementary Tables 2 and 3).

The currently used ICD-10 recognizes filovirus diseases specifically via entries “A98.4 Ebola virus disease (EVD)” and “A98.3 Marburg virus disease (MVD)” (<https://icd.who.int/browse10/2016/en>) since 1994. However, the ICD-10 does not specify which filoviruses are considered to cause which of the two diseases, offer disease definitions, or account for unusual disease manifestations (for example, subclinical or persistent infections).

## [H1] A need for new filovirus disease names

In 2014, Ebola virus (EBOV) was identified as the etiological agent of an EVD outbreak in Western Africa in 2013–2016 that would ultimately cause at least 28,652 human infections and 11,325 deaths. This single outbreak involved almost ten times the combined number of patients from all previous filovirus disease outbreaks. Consequently, the clinical presentation of EVD could be refined using statistical measures, and subclinical EBOV infections leading to sexual transmission or disease relapse were substantiated through clinical observations. In addition, often-debilitating sequelae in EVD survivors were observed longitudinally for the first time. As clinical research data on EVD accumulated, the coverage of filovirus disease in ICD-10 was inadequate

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to cover complex clinical presentations of filovirus disease.

### **[H1] Discussion framework**

[H2] *Expert panel and method.* Responding to the WHO's public call for input in the development of the ICD-11, we assembled a large group of experts (the authors) who have treated filovirus-infected patients or were heavily involved in organizing the treatment of patients to develop ICD-11's entries on filovirus disease. Consensus was obtained by step-wise, simple-majority, semi-blind voting. The participants represented a wide spectrum of scientists and health workers of both sexes and from numerous countries, including African nations most affected by human filovirus infections.

[H2] *Main issues.* The ICD-10 recognizes two filovirus diseases: EVD and MVD; however, four ebolaviruses (members of the genus *Ebolavirus*) cause disease, with EBOV only being one of them, and two marburgviruses (members of the genus *Marburgvirus*) cause disease, with Marburg virus (MARV) being one of them (Table 1). The terms 'Ebola virus disease' and 'Marburg virus disease' are therefore ambiguous: either the ICD-10 does not capture diseases caused by ebolaviruses and marburgviruses other than EBOV and MARV or EVD and MVD are cover terms for diseases caused by all ebolaviruses and marburgviruses (MARV and Ravn virus (RAVV)), requiring authors to specify which ebolavirus or marburgvirus caused a particular EVD or MVD outbreak. These ambiguities cause major confusion in communication among researchers and copy editors who are not necessarily familiar with the differences between 'Ebola virus' and 'ebolavirus' or 'Ebola virus disease due to Ebola virus infection' versus 'Ebola virus disease due to Bundibugyo virus infection'<sup>1</sup>. Consequently, the expert panel debated whether the EVD and MVD entries in ICD-10 should be merged into a single entry, whether the two terms should be split into several entries based on etiologic agents, or whether a hierarchical scheme should be adopted to cover both possibilities.

Although official virus taxonomy may change annually through decisions made by the International Committee on Taxonomy of Viruses (ICTV), ICD updates and revisions are released at much longer intervals. Hence, the ICD cannot keep pace with taxonomic developments. Independence of ICD-11 filovirus disease names from virus taxonomy considerations was therefore thought to be imperative.

### **[H1] Results of expert panel discussions**

A single umbrella term for the disease(s) caused by filoviruses is urgently needed as differentiation between ICD-10's EVD and MVD on clinical grounds alone is impossible. Following the publication of the 'WHO Best Practices for the Naming of New Human Infectious Diseases' this parent disease name should not contain any geographic locations; people's names; species or class of animal or food; cultural,

population, industry or occupational references; or components that incite undue fear<sup>2,3</sup>. Furthermore, the panel almost unanimously discouraged the use of 'hemorrhagic fever' for any filovirus-associated disease name because 'hemorrhagic fever' is not unambiguously defined, and the majority of filovirus-infected individuals do not develop overt hemorrhage. Consequently, healthcare workers could misdiagnose filovirus diseases or potentially infected individuals may not seek admittance to a treatment unit based on the absence of hemorrhage. After thorough consideration, 'Filovirus disease (FVD)' was chosen as the ICD-11 parent disease term. Because filoviruses comprise a distinct and monophyletic group of viruses, the expert panel felt that the prefix 'filo-' was unlikely to disappear in the near future if taxonomic changes to the virus family would be required. Additional subcategories should be established to codify diseases caused by filovirus that have not yet been associated with filovirus disease or yet-to-be-discovered novel filoviruses; diseases very likely caused by filoviruses without final agent confirmation; and filovirus diseases with 'unusual' clinical presentation(s).

The panel advocated for two subcategories to the filovirus parent entry for ebolavirus and marburgvirus diseases and recommended, if necessary, further subcategorization. The classical distinction of ICD-10's EVD and MVD was felt to be important for traditional and familiarity reasons. Furthermore, molecular evidence is accumulating that ebolaviruses and marburgviruses behave differently *in vitro* and *in vivo*, suggesting that differences in clinical presentation of infections with ebolaviruses or marburgviruses will become evident in the future. 'Ebola disease (EBOD)' and 'Marburg disease (MARD)' were chosen for the major FVD subcategories (Table 1); FVD due to ebolavirus and marburgvirus infections, respectively. The WHO naming guidelines were not applied in coining these terms because both 'Ebola' and 'Marburg' have been components of filovirus disease names since the 1970s and 1960s, respectively. The absence of the word 'virus' in the two disease names makes them taxonomically independent and therefore stable.

The panel then reintroduced the ICD-10 names 'Ebola virus disease (EVD)' and 'Marburg virus disease (MVD)' as EBOD and MARD subcategories because of their familiarity to the filovirus research community but restricted the use of EVD and MVD to diseases caused by agents belonging to only one species: EBOV (species *Zaire ebolavirus*), and MARV and RAVV (both species *Marburg marburgvirus*), respectively. Two additional EBOD subcategory disease terms were added to cover the remaining pathogenic filoviruses that have caused more than one registered human infection: Bundibugyo virus disease (BVD) and Sudan virus disease (SVD). Three additional subcategories for both EBOD and MARD were proposed: 'Atypical Ebola/Marburg disease' for EBOD or MARD patients with unusual clinical presentation(s); 'Other specified Ebola/Marburg

disease' for EBOD or MARD patients infected with ebolaviruses/marburgviruses not covered by BDV, EVD and SVD or MVD (for example, disease due to Tai Forest virus infection); and 'Ebola/Marburg disease, virus unspecified' for patients who are suspected to be infected with an ebolavirus or marburgvirus in absence of virus identification.

The expert panel did not establish a separate category for filovirus-induced sequelae in filovirus disease survivors (for example, 'post-Ebola syndrome') as the ICD-11 allows combinatorial coding (for example, 'Atypical Ebola disease' plus 'Arthritis').

### [H1] New official filovirus disease names

The panel submitted a proposal containing the proposed filovirus disease classification and nomenclature to the WHO's ICD-11 Proposal Platform in April of 2018. After peer review and appropriate revisions, the new filovirus disease classification and nomenclature (Table 1, Supplementary Table 4) were accepted in May of 2018 and subsequently incorporated into the ICD-11 framework (<https://icd.who.int/browse11/l-m/en>). The panel recommends that the new filovirus disease names and abbreviations be used immediately in forthcoming filovirus publications to ensure a seamless transition once the ICD-11 is adopted by United Nations member states.

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#### Supplementary information

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#### Competing interests

The authors declare no competing interests.

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	disease, virus unspecified	
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<sup>a</sup>Caused by Bundibugyo virus (BDBV); <sup>b</sup>caused by Ebola virus (EBOV); <sup>c</sup>caused by Sudan virus (SUDV); <sup>d</sup>caused by, for instance, Tai Forest virus (TAFV); <sup>e</sup>caused by Marburg virus (MARV) or Ravn virus (RAVV). ICD-11; The International [Statistical] Classification of Diseases [and Related Health Problems] Revision 11.

**Table 1. Recommended new human filovirus disease classification and nomenclature as accepted by the WHO.**

Main disease category.	First disease subcategory.	Second disease subcategory.
<b>ICD-11 code and disease name</b>		
1D60 Filovirus disease (FVD)		
	1D60.0 Ebola disease (EBOD)	
		1D60.00 Bundibugyo virus disease (BVD) <sup>a</sup>
		1D60.01 Ebola virus disease (EVD) <sup>b</sup>
		1D60.02 Sudan virus disease (SVD) <sup>c</sup>
		1D60.03 Atypical Ebola disease
		1D60.0Y Other specified Ebola disease <sup>d</sup>
		1D60.0Z Ebola disease, virus unspecified
	1D60.1 Marburg disease (MARD)	
		1D60.10 Marburg virus disease (MVD) <sup>e</sup>
		1D60.11 Atypical Marburg disease
		1D60.1Y Other specified Marburg disease
		1D60.1Z Marburg disease, virus unspecified
	1D60.Y Other specified filovirus disease	
	1D60.Z Filovirus	