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Evaluating case definitions for Ebola virus disease

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In *The Lancet Infectious Diseases*, Grazia Caleo and colleagues[1] report on the diagnostic usefulness of the WHO case definition for Ebola virus disease. Rapid identification of individuals potentially carrying an infection is among the most important concerns in the event of a major outbreak of an infectious disease. A valid case definition is key for the outbreak response, guiding diagnostic testing of individuals, based on which adequate medical management and transmission control measures are implemented. Any case definition has to be easily applicable by health-care workers, sufficiently discriminative, and acceptable for the affected communities. It needs to strike a delicate balance between high sensitivity (not to miss individuals requiring treatment and potentially spreading the disease) and high specificity (not to overburden health-care systems and the limited laboratory capacity needed to confirm a clinical suspicion). This task is challenging given that case definitions rely solely on clinical signs and risk factors reported by individuals.

The west African Ebola virus disease epidemic and the latest outbreak in the Democratic Republic of the Congo have demonstrated the potential devastating consequences of the disease for affected societies. WHO has played a central part in responding to these epidemics and has advocated for the use of the WHO case definition for identifying patients with suspected, probable, or confirmed Ebola virus disease.[2] Although Ebola virus disease is a viral haemorrhagic fever, only a small proportion of patients presents with bleeding. To emphasise this fact, WHO has included the term Ebola virus disease in the 10th edition of the International Classification of Diseases, whereas the use of the misleading term Ebola haemorrhagic fever was discouraged. Major clinical signs and symptoms of Ebola virus disease are also observed in a wide range of infectious diseases in Africa, including malaria and typhoid. Therefore, it might take weeks before an Ebola virus disease epidemic in Africa is recognised. The features that raised the alarm have rarely been symptoms, but mainly epidemiological peculiarities such as high case fatality rate, transmission of the disease to family members and caregivers, and nosocomial spread associated with death of health-care workers.[3] In light of these challenges, it is important to evaluate and, if possible, improve the accuracy of the WHO case definition to detect patients with Ebola virus disease.

Caleo and colleagues have undertaken a systematic review and meta-analysis of the diagnostic accuracy of the WHO case definition, which includes both clinical and epidemiological criteria, against molecular diagnosis of Ebola virus disease as the reference standard.[1] This analysis indicates that the case definition—applied on patients in Ebola treatment centres and to deaths in the community—has an estimated sensitivity of 81·5% (95% CI 74·1–87·2) and a specificity of 35·7% (28·5–43·6) to correctly identify patients with Ebola virus disease.

A main issue is the low specificity: 36% specificity means that the majority (64%) of people with suspected disease waiting a day or more in isolation for laboratory confirmation have other diseases. They are exposed to patients with Ebola virus disease and their diagnostic work-up is delayed. Clinical workflows have to ensure that the low specificity of the case definition does not lead to collateral deaths resulting from delayed diagnostic work-up and treatment of other infectious diseases. By contrast, 36% specificity of a clinical and epidemiological diagnosis is comparably high, implying that every third suspect is confirmed by laboratory testing. This proportion is probably higher than in the current COVID-19 pandemic. The 36% estimate is consistent with our own experience during the west African outbreak of Ebola virus disease: early during the epidemic in Guéckédou, Guinea, we confirmed Ebola virus disease by RT-PCR testing in 57% of 2178 patients with suspected disease and 50% of 563 individuals who died in communities; at a late stage of the epidemic in Coyah, Guinea, we confirmed 35% of 813 patients and 2% of 3823 community deaths.[4,5] Just these two studies underline that the performance of the case definition depends on a number of variables, including the transmission dynamics of an outbreak, the incidence of other infectious diseases with similar clinical characteristics as Ebola virus disease, such as malaria, typhoid, or arboviral infections, and its discriminative power in important subgroups, such as paediatric patients and pregnant women. The estimates of Caleo and colleagues represent an average for an Ebola virus

disease outbreak in Africa and are primarily valid in this setting.

Notably, the study also reveals that the WHO case definition does not show 100% sensitivity.[1] About 18% of patients with suspected disease who did not fulfil the case definition were confirmed to have the disease by laboratory testing. Unfortunately, the study does not disclose the clinical or epidemiological characteristics of these patients, although the sensitivity increased when fever was not a mandatory criterion. Health-care workers who have seen many patients with Ebola virus disease probably have a better chance of suspecting the infection than a list of criteria.

Furthermore, the authors assessed permutations of combinations of symptoms as revised case definitions for their diagnostic accuracy. Importantly, detailed analysis of predictors for Ebola virus disease identified intense fatigue and history of contact with a patient with Ebola virus disease as important variables to further improve the diagnostic accuracy of a refined case definition.[1]

Fortunately, we now have the opportunities to test patients using a range of molecular assays and we rely on these tools.[6,7] In the early days, outbreaks of Ebola virus disease were contained even though these tools were not yet available—essentially based on case definitions. The work of Caleo and colleagues has refocused our attention on this important clinical and epidemiological tool, with the ultimate goal of using resources more efficiently and containing Ebola virus disease outbreaks faster.

SG is a member of the WHO's Scientific Advisory Group of the R&D Blueprint. MR declares no competing interests.

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