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Randomisation addresses perhaps the biggest challenge in causal inference: confounding. Gumisiriza and colleagues described other possible causes of epilepsy (neurocysticercosis, malaria, HIV infection, antenatal or perinatal brain lesions, and genetics) and explain why these are unlikely to have affected epilepsy incidences between the two survey dates. A true confounder is not just an alternative explanation for an outcome, it is a common cause of both the exposure (onchocerciasis) and the outcome (epilepsy). Other parasitic diseases known to cause epilepsy are good candidates as confounders because exposure to multiple parasites is common, possibly due to inter-relatedness among lifecycles. However, other possible confounders remain elusive and might be affecting the results of the study when considering the migratory and sociodemographic differences between the two survey samples.

Confounding aside, one is left wondering what other evidence is needed to establish a causal relationship between onchocerciasis and epilepsy? Sir Austin Bradford Hill’s criteria for causation provide some insight into the evidence gaps. Biological explanations for associations in observational studies can help establish plausibility. For example, the biological explanation of how onchocerciasis causes blindness is well characterised, whereas the underlying mechanism of how onchocerciasis causes seizures, let alone epilepsy, remains unknown. The absence of O volvulus microfilariae and DNA (and the DNA of the endosymbiotic bacterium wolbachia) in the cerebrospinal fluid suggests that seizures are not caused by direct invasion of the CNS. Other mechanisms, either direct (eg, substances secreted by O volvulus crossing the blood–brain barrier) or indirect (eg, autoimmune), remain to be established.

Although generating research that helps us understand the underlying biological mechanism is very important, it should not stop us from taking appropriate public health action. According to Bradford Hill himself, establishing biological plausibility is helpful, but not essential, and ultimately “what is biologically plausible depends upon the biological knowledge of the day”. The study by Gumisiriza and colleagues, in addition to the collective evidence, shows that eliminating onchocerciasis might reduce epilepsy incidence. In sub-Saharan Africa, where people with epilepsy have limited access to treatment and are subject to devastating social consequences, preventing new cases of epilepsy could have a profound effect on morbidity. Therefore, reducing epilepsy incidence should be a reason to strengthen efforts to eliminate onchocerciasis, especially in endemic regions of sub-Saharan Africa with a high incidence of epilepsy.

I declare no competing interests.

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Evaluating case definitions for Ebola virus disease

In The Lancet Infectious Diseases, Grazia Caleo and colleagues 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. 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. 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. 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. 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. 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.2–5 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.

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Uncovering the burden of loiasis: first estimates from Gabon

Historically, clinicians have been at the forefront of describing diseases and subsequently identifying the causes. Assessing the extent of the disease, in terms of size of the affected population, severity, and associated morbidity, requires substantial investment. Without that investment, advances on the knowledge of the disease, and therefore advances on disease perception, would likely be small, and unlikely to facilitate the possible recognition of the disease as a public health problem.

Loiasis, the parasitic infection caused by the round worm Loa loa is a perfect example of a disease overdue for consideration as an important public health problem. Exclusively found in Africa, the burden of loiasis spreads from southeast Benin to South Sudan, and from Chad to Angola. Because of the bioecology of its arthropod vectors, loiasis is primarily found in forested rural areas, affecting poor populations.

Though this filariasis has been documented for more than two centuries, the international scientific community has considered that loiasis causes only benign manifestations, such as the migration of the worm under the conjunctiva, known as eyeborns, and transient instances of angioedema, known as Calabar swellings. Thanks to thorough literature reviews on loiasis,6–8 the clinical spectrum of loiasis signs and symptoms has recently been extended beyond swellings and eyeborns. For example, nearly half of patients in a series of 329 loiasis case reports showed atypical clinical signs including nervous system-based, cardiovascular, renal, and respiratory conditions.1 One of the striking features of the various literature reviews is that almost, if not all, scientific articles describing the clinical aspects of this infection are case reports of patients seen in non-endemic countries, mostly from European countries that have a former colonial history with central Africa. Therefore, these reviews are probably of little use to handle the extent of the problem in the endemic countries.

Luzia Veletzky and colleagues7 provide the results of the first clinical epidemiology survey conducted in a country where loiasis is highly endemic: Gabon. Based on the presence of L loa microfilaraemia or self-reported history of eyeborn, they found that loiasis was present throughout both of their two selected