Title: Unrecognised Ebola virus infection in contacts: what can we learn from it?

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The epidemic of Ebola virus disease (EVD) in West Africa in 2014-2016 was the largest and most complicated the world has ever seen. The four pillars of Ebola response include: case management; case finding and contact tracing; safe and dignified burial; and social mobilisation and community engagement. These are being implemented in the current outbreak in the Democratic Republic of Congo (DRC), that is further complicated by its location in a conflict zone[1]. Increased understanding of disease pathogenesis and the evaluation of novel therapeutics and vaccine candidates has informed current control measures, whilst access to survivors and their contacts in West Africa also provides a unique opportunity to research Filovirus transmission.

In their article published in The Lancet Infectious Diseases, Diallo and colleagues (ref) report data from a large cross-sectional study of contacts of an established survivor cohort in Guinea. They aimed to estimate the frequency of unrecognised Ebola virus infection (EVI) in contacts, after excluding those that were vaccinated, and to identify risk factors for infection. Utilising a novel and previously validated Luminex assay [2] on dried blood spots, and detailed retrospective exposure histories they identified 57 EVIs among 1390 contacts (4.1%).

They demonstrated increased seropositivity in contacts who reported any symptom associated with EVD (8·33%; 95% CI: 5·01% to 12·80%, described as paucisymptomatic contacts) compared to EVI in asymptomatic contacts (3.32%; 95% CI: 2·37% to 4·51%, p=0.0002). Participation in burial rituals and contact with blood or vomit were independent significant risk factors for EVI in asymptomatic contacts in multivariate analysis, whilst older age and participation in burial practices were risk factors in paucisymptomatic cases. Their findings concur with a recent meta-analysis of seroprevalence surveys [3] and the results of a study in Sierra Leone of 486 household members of EVD survivors, which identified EVI in 12% (95% CI: 6·1–20·4) of those with symptoms compared to 2·6% (95% CI: 1·2–4·8) of asymptomatic household members[4]. The same study also demonstrated that burial contact and older age were risk factors for EVI[5].

The conclusions drawn by Diallo et al reaffirm the challenges/failures in case finding and contact tracing highlighted by others in Guinea[6]. This is evidenced by the 73% of paucisymptomatic contacts who, in reporting a history of fever, met the WHO definitions for suspect cases that required isolation and further evaluation[7,8]. Furthermore, they highlight that 30/216 paucisymptomatic contacts met the EVD suspect case definition without contact but were not diagnosed acutely, of whom 20% were seropositive. These results are timely as in the DRC, as of 23 October, 5723 contacts remain under surveillance, with follow-up rates ranging from 85-97% [9]. The data from Diallo et al highlights the varying spectrum of EVD severity, consistent with early clinical reports in West Africa[10], and again challenges our perceptions of the roles and balance of viral infective dose and host immune response in clinical phenotypes. Studies like this may be unique, and impossible to replicate, because of the scale of the West African outbreak and the now-established practice of ring vaccination.

Care must also be taken in the interpretation and extrapolation of these results. As the authors acknowledge, there is risk of recall bias: it is challenging to remember clinical symptoms, exposure and exact timing over two years after the event. The key 'question' is whether these unidentified EVI contacts had any role in transmission chains. This issue was recently highlighted by Dokubo et al [11], who reported a familial cluster occurring in Liberia one year after an undiagnosed EVI in a female contact, due to viral persistence. This potential transmission risk must be balanced against the risk of further stigmatisation of both survivors and household contacts.

This study reinforces the importance of robust and detailed contact tracing as a control measure and highlights the high risk posed by burial practices and direct contact with infected fluids. What is also notable is how few contacts (>90%) who reported high-risk exposures were infected. Greater understanding is needed about the mechanisms of Ebola virus transmission in order to improve the targeting of interventions as part of a coordinated response. Epidemics of Ebola virus disease remain a major risk to healthcare workers and populations in endemic regions, as well as a global threat to health security.

TF and HB declare no competing interests

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