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

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

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

22 They demonstrated increased seropositivity in contacts who reported any symptom associated with  
23 EVD (8.33%; 95% CI: 5.01% to 12.80%, described as paucisymptomatic contacts) compared to EVI in  
24 asymptomatic contacts (3.32%; 95% CI: 2.37% to 4.51%,  $p=0.0002$ ). Participation in burial rituals and  
25 contact with blood or vomit were independent significant risk factors for EVI in asymptomatic  
26 contacts in multivariate analysis, whilst older age and participation in burial practices were risk  
27 factors in paucisymptomatic cases. Their findings concur with a recent meta-analysis of  
28 seroprevalence surveys <sup>3</sup> and the results of a study in Sierra Leone of 486 household members of  
29 EVD survivors, which identified EVI in 12% (95% CI: 6.1–20.4) of those with symptoms compared to  
30 2.6% (95% CI: 1.2–4.8) of asymptomatic household members<sup>4</sup>. The same study also demonstrated  
31 that burial contact and older age were risk factors for EVI<sup>5</sup>.

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

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

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

58 TF and HB declare no competing interests

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