

The Liberia Men's Health Screening Program for Ebola virus: win-win-win for survivor, scientist, and public health



Among the most important findings to have emerged from the massive 2013–16 outbreak of Ebola virus disease in west Africa is the delayed clearance of virus from the semen of men who survived the disease^{1–4} and the consequent risk of sexual transmission of the virus, although this seems to be rare.⁵ In *The Lancet Global Health*, Moses J Soka and colleagues⁶ used data from the largest cohort (n=466) of male survivors reported so far from the Men's Health Screening Program in Liberia to further expand our understanding of this important issue. They found that of 38 participants with at least one semen specimen that tested positive for Ebola virus, 24 (63%) tested positive 12 months or longer after recovery from Ebola virus disease, and the longest interval between disease recovery and collection of a positive semen sample was 565 days. These findings essentially confirm those of previous reports,^{1–4} but extend the duration that Ebola virus RNA can be detected in the semen.

Although concerning with regard to risk of sexual transmission during recovery from Ebola virus disease, the results must be interpreted with caution since, as with most other studies of Ebola virus persistence, confirmatory virus isolation on cell culture was not done. This technique requires access to a biosafety level four laboratory, of which none exist in west Africa, and the logistical and regulatory obstacles of shipping samples internationally to suitable laboratories are formidable. Without confirmatory cell culture, we cannot know whether a positive RT-PCR result suggests the presence of infectious virus or just residual viral RNA of no concern for transmission. In the absence of cell culture data, RT-PCR cycle threshold, which is inversely associated with viral load, is often used to infer infectivity, although standards to reliably and consistently interpret these data across laboratories and sample types have not been established.⁷ Only Uyeky and colleagues,² in their study of five male Ebola virus disease survivors in the USA, were able to undertake cell culture on the semen samples, with the result being that, despite positive RT-PCR results in one man over 9 months after acute disease, all culture samples that tested positive were taken within 70 days and had cycle threshold values of 30 or less. Soka and colleagues' findings in Liberia⁶ show that almost all mean

cycle threshold values of men who tested positive for Ebola virus on RT-PCR were at least 36 after 3 months, suggesting that these men harbour only a small amount of infectious virus. Nevertheless, a documented case of sexual transmission in Liberia 6 months after acute Ebola virus disease,⁵ along with accumulating evidence of similar events,⁸ remind us that even low levels of virus can result in transmission. Until more data are available to clarify the risk, Ebola virus disease survivors should continue to follow WHO recommendations⁹ to remain abstinent or use condoms until RT-PCR semen testing, beginning at 3 months after disease onset, is repeatedly negative.

Many questions remain. To assess the relationship between RT-PCR results, infectivity, and risk of transmission we need to understand the mechanism of virus persistence. Persistent RT-PCR positivity, albeit at high cycle threshold values, would seem to imply ongoing viral replication, particularly for this RNA virus without any known mechanism for genome integration or latency. Findings from full genome sequencing of viruses related to transmission events suggests a reduced viral evolutionary rate in the setting of persistence,⁸ perhaps related to very-low-level viral replication. However, in what cellular compartment in the testis or other immune-privileged sites this occurs is unknown.

Importantly, Soka and colleagues⁶ provide the first suggestion so far of a host determinant of semen persistence, with men older than 40 years more likely than those aged 40 years or younger to have a positive RT-PCR after the first 3 months of recovery (p=0.0004). Although age might be a proxy for other risk factors, age-related changes in immune function or in semen composition could plausibly underlie this finding. Are there other risk factors that can help identify survivors at high risk for virus persistence, thus helping to target surveillance activities, while avoiding enhancing the stigma they so often encounter? High viraemia during acute infection has been postulated to result in deep seeding of the immunologically protected sites and delay virus clearance,¹⁰ as have HIV and other co-infections and immunosuppressive disorders, although these remain to be definitively shown. Unfortunately, Soka and colleagues⁶ did not have access to nadir cycle threshold

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values or data on illness severity of acute Ebola virus disease to explore relationships between these factors and semen persistence. Another important question is whether experimental antiviral drugs shown to have activity against Ebola virus, such as favipiravir¹¹ and Gilead-573^{4,12} can accelerate Ebola virus clearance from the semen and other immunologically protected sites. Studies are in their early phases.

Equally important to the scientific findings of Soka and colleagues' report⁶ is the context of the activities—established not as a research study but as a national programme oriented toward health service provision and risk reduction. The programme packaged semen testing with counselling for survivors to promote safer sex practices, including condom provision and instruction, and enabled referral for other health problems that survivors might encounter. A mobile team was established to expand programme access and to provide counselling for sexual partners. Although interpretation of the self-reported results and the potential for social desirability bias should be done with caution, the public health effects of the programme seemed to be substantial; participants reported increases in abstinence ($p < 0.0001$) and condom use ($p < 0.0001$), with 75% feeling “very confident” in correct condom use at programme graduation. These behavioural changes might have not only prevented sexual transmission of Ebola virus and potential re-ignition of the outbreak, but also other sexually transmitted diseases and unwanted pregnancies. 290 (97%) of 299 programme graduates reported that they would refer others to participate and 257 (86%) shared or planned to share their test results with their sexual partners. Soka and colleagues⁶ have graciously provided programmatic details in an online appendix to facilitate rapid establishment of similar programmes elsewhere.

Throughout the Ebola virus disease outbreak in west Africa, tension has existed between Ebola virus disease survivors as patients (ie, in need of clinical attention), as research participants (ie, in need of scientific attention), and as potential viral reservoirs (ie, in need of public health attention), each role requiring a portion of the scarce resources for care provision, scientific

investigation, and public health. Although meaningful, these divisions are of course false—all three roles are important, and must ideally be integrated as much as possible into existing routine health services, helping to streamline logistics and control costs. The Liberia Men's Health Screening Program represents important progress toward addressing these challenges in an integrated fashion, and will have broad importance and provides opportunity for strengthening health systems that must sufficiently attend to all three needs. We hope that this win-win-win approach becomes the norm.

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We declare no competing interests.

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