Ebola control: effect of asymptomatic infection and acquired immunity

Evidence suggests that many Ebola infections are asymptomatic,[1,2] a factor overlooked by recent outbreak summaries and projections.[3] Particularly, results from one post-Ebola outbreak serosurvey[1] showed that 71% of seropositive individuals did not have the disease; another study[2] reported that 46% of asymptomatic close contacts of patients with Ebola were seropositive. Although asymptomatic infections are unlikely to be infectious,[2] they might confer protective immunity and thus have important epidemiological consequences.

Although a forceful response is needed, forecasts that ignore naturally acquired immunity from asymptomatic infections overestimate incidence late in epidemics. We illustrate this point by comparing the projections of two simple models based on the Ebola epidemic in Liberia, a model that does not account for asymptomatic infections, and another that assumes 50% of infections are asymptomatic and induce protective immunity. In both models, the basic reproduction number (R_0) is identical and based on published estimates.[3] The figure shows the projected cumulative incidence through time. Although the initial outbreaks are almost identical, by Jan 10, the model without asymptomatic infections projects 50% more cumulative symptomatic cases than the model that accounts for asymptomatic infection. This difference arises because asymptomatic infection contributes to herd immunity and thereby dampens epidemic spread.

Widespread asymptomatic immunity would likewise have implications for Ebola control measures and should be considered when planning intervention strategies. For instance, should a safe and effective vaccine become available, the vaccination coverage needed for elimination will depend on pre-existing immunity in the population (appendix). Immunity resulting from asymptomatic infections should reduce the intervention effort needed to interrupt transmission but might also complicate the design and interpretation of vaccine trials. Trials and interventions are likely to target exactly those high-risk populations most likely to have been asymptomatically immunised. Thus, for assessment of vaccines and other countermeasures, baseline serum should be collected to improve both estimates of intervention effectiveness and our understanding of asymptomatic immunity. Additionally, assessment of intervention measures should account for the contribution of asymptomatic immunity in curbing epidemic spread.

Asymptomatic infection could also potentially be directly harnessed to mitigate transmission. If individuals who have cleared asymptomatic infections could be identified reliably, and if they are indeed immune to symptomatic re-infection, they could potentially be recruited to serve as caregivers or to undertake other high-risk disease control tasks, providing a buffer akin to that of ring vaccination. Recruitment of such individuals might be preferable to enlistment of survivors of symptomatic Ebola disease because survivors might experience psychological trauma or stigmatisation and be fewer in number—in view of the asymptomatic proportions suggested in previous studies[1,2] and the low survival rate of symptomatic cases.[3] Health-care workers with natural immunity acquired from asymptomatic infection, if identified, could be allocated to care for acutely ill and infectious patients, minimising disease spread to susceptible health-care workers.

The conclusions above depend on whether asymptomatic infections are common, and protective against future infection. Further, strategies to leverage protective immunity will depend on the development and validation of assays that can reliably identify individuals who are effectively protected against re-infection. Previous studies have identified many asymptomatic infections using IgM and IgG antibody assays and PCR,[1,2] which, although indicative of infection, do not necessarily imply protective immunity.[4] Evidence for long-term protective immunity reported in (symptomatic) Ebola survivors is suggestive,[4] but the extent of protective immunity after asymptomatic infection and the identification of serological markers for protective immunity can only be definitively addressed in settings with ongoing transmission risk. As has been proposed for vaccination,[5] the epidemic therefore provides a unique opportunity to investigate asymptomatically acquired protective immunity to Ebola virus. Although resources are scarce, now is the

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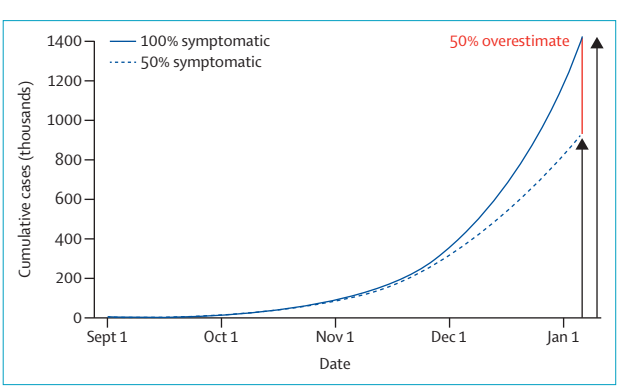

Figure: **Effects of immunising asymptomatic infections on Liberia outbreak projections**
Projected cumulative incidence including and excluding asymptomatic infection. If 50% of infections are asymptomatic, then models overlooking asymptomatic infection will overestimate disease incidence later in the epidemic, as individuals who were asymptomatically infected become immune and contribute to herd immunity. By Jan 10, 2015 (red vertical line) models ignoring asymptomatic immunity overestimate cumulative incidence by 50% (red). The code for models and calculations are from the Ebola code repository.

time for interventions protecting people at risk of contracting Ebola (ie, health-care workers and household caregivers) to incorporate serological assessments to ascertain asymptomatic infections—feasible with even introduced cases such as recently occurred in Dallas, Texas—and immunological correlates of protection—feasible only in settings with ongoing transmission.

A more direct investigation of asymptomatically acquired immunity might be possible by leveraging proposed trials to assess the efficacy of blood transfusions from Ebola survivors.[6] During the 1995 outbreak in DR Congo, a study reported increased survival rates in transfusion recipients but was potentially confounded by the superior supportive care afforded to the treated patients.[7] Burnouf and colleagues[6] have advocated for randomised controlled clinical trials comparing the treatment efficacy of transfusions from survivors with those from control donors. By including a third study group in which patients receive transfusions from asymptomatic seropositive individuals, this design could simultaneously assess the therapeutic value of these transfusions from asymptomatic individuals, and indicate whether such individuals have protective immunity.

We propose that launching of an immediate investigation of asymptomatic immunity, by coupling serological testing to ongoing intervention efforts in west Africa, is warranted and feasible, and might ultimately save lives.

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*Steve E Bellan, Juliet R C Pulliam, Jonathan Dushoff, Lauren Ancel Meyers
steve.bellan@gmail.com

Center for Computational Biology and Bioinformatics (SEB) and Department of Integrative Biology (LAM), The University of Texas at Austin, Austin, TX 78712, USA; Department of Biology and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA (JRCP); Fogarty International Center, National Institutes of Health, Bethesda, MD, USA (JRCP); Department of Biology and Institute of Infectious Disease Research, McMaster University, Hamilton, ON, Canada (JD); and Santa Fe Institute, Santa Fe, NM, USA (LAM)

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Conflict and drug-resistant tuberculosis in Ukraine

The UN released a report on Aug 29 about the worsening situation for human rights in the conflict region of Ukraine.[1] An average of 36 people are killed every day and at least 260 000 people have been displaced from this region.[1] Ed Holt in *The Lancet* (Aug 30, p 735)[2] reported about the threat to medical staff, equipment, and essential drugs, including for tuberculosis. Ukraine is one of the 27 countries in the world with a high burden of multidrug-resistant (MDR) tuberculosis and in 2012, there were an estimated 6800 new cases in the country.[3] In view of the large number of people displaced, the control of tuberculosis and MDR-tuberculosis in Ukraine and surrounding countries will not only depend on the provision of medicines and health-care services in the conflict zone, but also on effective measures for detection and care of internally displaced people (IDP) and refugees.

Migrants, particularly IDP and refugees, are populations susceptible to contracting or developing tuberculosis or MDR-tuberculosis.[4] Several factors increase this population's risk for transmission of disease, including poor underlying health and, often, overcrowded temporary living conditions. In the conflict areas of Ukraine, essential medicines are either in low supply or cannot be delivered because of continuing fighting,[1] placing patients with tuberculosis at risk of interrupted or inadequate treatment and subsequent drug resistance, treatment failure, or death. Furthermore, thousands of unregistered IDP do not have access to medical services.[1] With an estimated 3·9 million people living in areas directly affected by the conflict in Ukraine,[1] the number of IDP and refugees will probably continue to increase.

The tuberculosis situation in the conflict zone needs to be improved. However, since this change might not be feasible or safe for health and humanitarian workers until the conflict ends, the international community needs to be prepared to support detection of disease and care in people who have been displaced. Studies have suggest that transmission of tuberculosis is largely contained in migrant communities.[5] Therefore, now is a crucial time in Europe to ensure a minimum package for IDP and cross-border tuberculosis control and care, including a legal framework for tuberculosis cross-border collaboration.[6] Programmes to screen for latent and active tuberculosis should