Ebolavirus and evidence-based speculations

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Dear Sirs,

Certain aspects of Ebolavirus disease (EVD) trigger speculations, which we attempt to substantiate with published evidence.

First, gastroenteritis symptoms (massive watery diarrhea, vomiting and abdominal pain) are highly prevalent in EVD, but pathogenesis remains poorly understood. T-cell immunoglobulin and mucin domain 1 (Tim-1) is the most important receptor for Zaire Ebolavirus (ZEBOV) and is highly expressed on T_h2 lymphocytes (Kondratowicz *et al.*, 2001). Survival from Ebola hemorrhagic fever is associated with early and well-regulated inflammatory responses (Baize *et al.*, 2002). Tim-1 stimulation induces polyclonal, antigen-independent activation of T_h2 lymphocytes. EVD non-survivors show signs of massive lymphocyte apoptosis and type 2 cytokine storm compared to survivors, suggesting that the virus acts as a superagonist for Tim-1.

Cytokine storm has also been reported after treatment with anti-CD28 superagonist monoclonal antibody. Even after approval, expensive investigational monoclonal antibodies for EVD treatment will likely remain affordable only to wealthy health systems, as is the case for therapeutic plasma exchange.

On the other hand, cheap and clinically safe immunosuppressants (i.e. high-dose methylprednisolone) have proven effective at controlling cytokine storm syndrome and could easily be added to initial supportive treatment in re-

source-poor settings. Steroids have been shown to be effective in the treatment of patients with multiorgan failure caused by Puumalavirus infection, a virus also characterized by hemorrhagic symptoms (Seitsonen *et al.*, 2006). A review of management of western repatriated cases, including steroid treatment, is in progress and additional information will be available soon.

Second, asymptomatic, replicative EVD was first described in nearly 50% of asymptomatic contacts of symptomatic patients during the 1996 outbreak in Gabon *et al*. A "Person Under Investigation" for EVD is defined by the CDC as *"A person who has both consistent signs or symptoms … AND … an epidemiologic risk factor within the 21 days before the onset of symptoms"*. The WHO also focused on contacts defined as *"Any person having been exposed to a suspect, probable or confirmed case of Ebola …. provided that this exposure has taken place less than 21 days before the identification as a contact by surveillance teams"*.

Excluding asymptomatic contacts of symptomatic patients from investigations implies that asymptomatic infections go entirely unreported. Lowering the number of cases in that way has two immediate consequences: overestimating mortality, and underestimating the basic reproductive number, the average number of secondary cases generated by an average primary case in an entirely susceptible population (Pandey *et al.*, 2014).

IgM testing and real-time PCR (impossible in the African context during a devastating outbreak) of contacts exposed to cases repatriated in Westernized countries should be implement-

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ed to better define the extent and mortality of the current outbreak.

We expect that immunization through asymptomatic infection could contribute to the declining incidence rate by herd effect.

Third, Schieffelin *et al.* and previous observations show that age >45 is a determinant of poor survival in ZEBOV disease. ZEBOV infection induces glycoprotein (GP)-specific antibodies that have the ability to enhance viral infectivity of certain cells *in vitro* (Takada *et al.,* 2003).

This mechanism, known as antibody-dependent enhancement (ADE) of viral infection, depends on either the cross-linking of virus-antibody complexes through interaction with cellular Fc receptors or complement protein C1q and C1q receptor.

Epitopes involved in ADE have been identified predominantly in the mucin-like region of the ZEBOV GP1 subunit.

Assuming ADE contributes to increased mortality in patients over 45 implies widespread circulation of ZEBOV or a genetically related filovirus before 1969.

The results of emergency vaccination recently published did not disclose major problems. Nevertheless, the ADE risk should be excluded before massive deployment of vaccines and therapeutic antibodies against ZEBOV disease, both of which target ZEBOV GP.

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