The OVIVA trial

We thank Markus Zeitlinger for his Comment[1] on the OVIVA trial.[2] It is correct we justified the choice of a pragmatic open-label trial design with ethical concerns. In addition, we also wanted a trial design that was applicable to a strategy of antibiotic use rather than to use of individual drugs, for which pragmatic trials are well suited.[3]

Zeitlinger suggested that we should have used a double-dummy design and noted low adherence to the oral strategy in the first 7 days. Blinding with placebo infusions is feasible when randomising to predefined drugs in short courses (ie, 5–10 days) as in Zeitlinger's references. However, it is not feasible where randomisation is to strategy (ie, oral *vs* intravenous) with hundreds of potential doses and antibiotic combinations in each strategy, administered over a 6-week course. The apparent low adherence to the oral strategy in the first 7 days is consistent with the trial design. We considered there was little benefit in comparing oral with intravenous in the first 7 days because oral antibiotics might not be tolerated acutely or after an operation, microbiology results to select an oral course are pending, and during the early inpatient stay intravenous antibiotics are convenient.

Zeitlinger stated that "treatment failure was strongly affected by investigators subjective visual inspection of the infection site (clinical findings were relevant in 83 [59%] of 141 outcomes)"[1] and suggested that "photographic documentation would have removed this bias".[1] However, we disagree. The independent endpoint committee reviewed a wide range of relevant clinical variables, including history, radiology, surgical findings, and laboratory tests. Visual inspection comprised a fraction of the information available. Zeitlinger cited an unblinded trial with masked assessors who determined the primary endpoint using reported clinical data, with no mention of photos (ie, the protocol was similar to our OVIVA trial).

Zeitlinger argued that the higher than expected failure rate on intravenous therapy in our trial was due to under-dosing. The 5% failure rate had been estimated on short-term follow-up. Rates were higher on longer term follow-up. Dosing was done by specialist clinicians and pharmacists in different hospitals, with subgroup analysis by hospital showing consistent non-inferiority of oral antibiotics.

In his Comment Zeitlinger suggested that the OVIVA trial had been a comparison of oral combination therapy versus intravenous monotherapy because "52% of patients in the oral group were provided with rifampicin versus 15% in the intravenous group".[1] However, these differences are the result of standard clinical practice among infectious disease specialists. A supplementary analysis based on intention to use rifampicin found consistent non-inferiority by subgroup.[2]

Finally, Zeitlinger argued that "widespread use of oral therapy for bone and joint infection appears premature".[1] We reported results from a large (n=1054) multicentre pragmatic trial suggesting non-inferiority of oral treatment.[2] We agree that further explanatory trials to test narrow hypotheses could be justified; however, at present there is insufficient evidence in support of intravenous antibiotic use in bone and joint infection and in other infections.[4,5] Intravenous antibiotics are life-saving in certain situations, but unsupported preferences for intravenous treatment could lead to harm.[6]

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Sustained transmission of Ebola in new locations: more likely than previously thought

A recent Editorial in *The Lancet* called for the international community to unify to contain the ongoing Ebola virus disease epidemic in the Democratic Republic of the Congo.[1] This epidemic has caused 2892 confirmed and 105 probable cases with 1998 deaths, including six cases in South Kivu's Mwenga Health Zone and three cases in the country of Uganda. The recent Newsdesk in *The Lancet Infectious Diseases* emphasised the high risk of spillover into neighbouring countries.[2]

When Ebola virus disease arrives in a new location, the standard estimate for the probability of a major outbreak starting from a single imported case is $1-(1/R)$, in which R is the reproduction number at that time. R represents the transmission potential of the virus, accounting for any public health measures. This

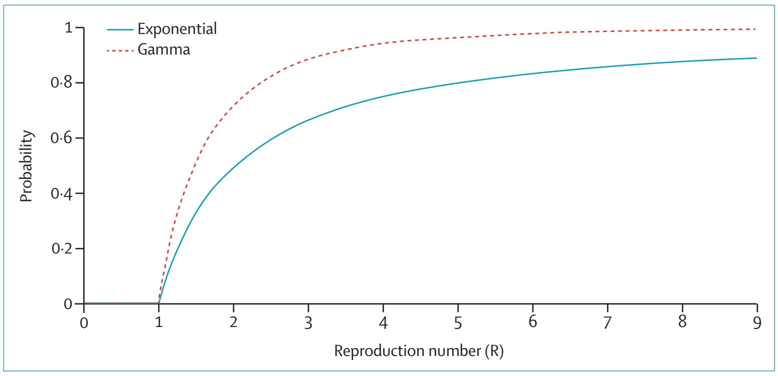

***Figure*: Probability of a major outbreak of Ebola virus disease from a single imported infectious host**
Assuming the infectious period follows an exponential or gamma distribution. Parameter values used are consistent with data from the 2014–16 Ebola epidemic in west Africa (appendix p 3). The x-axis range is set to 0–9 to reflect the wide variation in estimated values of reproduction numbers for Ebola outbreaks in different settings.

formula was used to assess the risk of sustained outbreaks in different countries during the 2014–16 west Africa epidemic,[3] and was considered in the context of vaccination.[4] In that epidemic, R ranged from 1·51 to 2·53 in Guinea, Liberia, and Sierra Leone, leading to major outbreak probabilities of 0·34–0·60 in those locations, with a higher value of R (9·01) estimated for Nigeria.[3]

However, implicit in these estimates is the common assumption that the infectious period follows an exponential distribution (appendix p 3).[5] For many pathogens, infectious periods are less dispersed than exponential distributions suggest, and gamma distributions characterise epidemiological periods more accurately (appendix p 3).[6] The standard estimate for the major outbreak probability must be altered to account for this difference (more detailed calculations and discussion are in the appendix [pp 1–3]). With this amendment, the risk is larger than the formula $1 - (1/R)$ suggests. Consequently, in the west African epidemic, the major outbreak probability in Guinea, Liberia, and Sierra Leone would have been 0·52–0·83. In the figure, we show this discrepancy between the standard and more realistic estimates using parameters consistent with Ebola virus transmission.[2] Our main qualitative result is robust to interventions used during Ebola virus disease epidemics (including vaccination, which has an important role currently); when R is greater than 1, the assumption of an exponentially distributed infectious period leads to the underestimation of risk.

Control of the ongoing epidemic is being hindered by factors including recurrent violent attacks on health workers and distrust of the government and outside organisations. Our results underline the importance of public health measures, including surveillance and outbreak preparedness in regions without observed cases and fast responses whenever newly imported cases are identified. These measures are vital to minimise the risk of sustained trasnmission after import of people with Ebola virus disease, and this risk is higher than previously estimated.

We declare no competing interests.

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Treating Ebola in eastern DRC

Ebola virus has infected more than 3000 people in the Democratic Republic of the Congo (DRC),[1] more than 200 000 people have received an investigational vaccine, and several new treatments are being tested. Nonetheless, the case fatality rate (>65%) remains high. Pierre Rollin notes that Ebola could become endemic in eastern DRC and only "immediate changes...[in]... leadership and coordination...will be able to reverse this trend", adding that helping health-care providers to "regain the population's confidence is crucial".[2]

See **Online** for appendix

Confidence could be regained by improving survival of patients with Ebola virus disease. News reports have announced that monoclonal antibody treatment improves survival in patients with low viral loads,[3] but these agents are unlikely to alter the trajectory of the outbreak. Another way to regain people's confidence might be to treat patients with drugs that target the host response, not the virus. Ebola is associated with endothelial dysfunction and breakdown of vascular barrier integrity.[4] In Sierra Leone, treatment with a statin–angiotensin receptor