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]

We declare no competing interests.

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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