Dynamics and control of Ebola virus transmission in Montserrado, Liberia: a mathematical modelling analysis







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Summary

Background A substantial scale-up in public health response is needed to control the unprecedented Ebola virus disease (EVD) epidemic in west Africa. Current international commitments seek to expand intervention capacity in three areas: new EVD treatment centres, case ascertainment through contact tracing, and household protective kit allocation. We aimed to assess how these interventions could be applied individually and in combination to avert future EVD cases and deaths.

Methods We developed a transmission model of Ebola virus that we fitted to reported EVD cases and deaths in Montserrado County, Liberia. We used this model to assess the effectiveness of expanding EVD treatment centres, increasing case ascertainment, and allocating protective kits for controlling the outbreak in Montserrado. We varied the efficacy of protective kits from 10% to 50%. We compared intervention initiation on Oct 15, 2014, Oct 31, 2014, and Nov 15, 2014. The status quo intervention was defined in terms of case ascertainment and capacity of EVD treatment centres on Sept 23, 2014, and all behaviour and contact patterns relevant to transmission as they were occurring at that time. The primary outcome measure was the expected number of cases averted by Dec 15, 2014.

Findings We estimated the basic reproductive number for EVD in Montserrado to be $2\cdot49$ (95% CI $2\cdot38-2\cdot60$). We expect that allocating 4800 additional beds at EVD treatment centres and increasing case ascertainment fivefold in November, 2014, can avert 77 312 (95% CI $68\,400-85\,870$) cases of EVD relative to the status quo by Dec 15, 2014. Complementing these measures with protective kit allocation raises the expectation as high as 97 940 (90 096–105 606) EVD cases. If deployed by Oct 15, 2014, equivalent interventions would have been expected to avert 137 432 (129 736–145 874) cases of EVD. If delayed to Nov 15, 2014, we expect the interventions will at best avert 53 957 (46 963–60 490) EVD cases.

Interpretation The number of beds at EVD treatment centres needed to effectively control EVD in Montserrado substantially exceeds the 1700 pledged by the USA to west Africa. Accelerated case ascertainment is needed to maximise effectiveness of expanding the capacity of EVD treatment centres. Distributing protective kits can further augment prevention of EVD, but it is not an adequate stand-alone measure for controlling the outbreak. Our findings highlight the rapidly closing window of opportunity for controlling the outbreak and averting a catastrophic toll of EVD cases and deaths.

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Introduction

The scale of the Ebola virus disease (EVD) epidemic currently affecting west Africa is unprecedented.¹ As of Oct 8, 2014, WHO reported 4656 cases of EVD, with most cases occurring in Liberia,² where the epidemic is increasing most rapidly and is exacerbated by extraordinary socioeconomic disadvantage and health system inadequacies. Although west African countries are among the least-developed worldwide, the gross domestic product in Liberia is especially low at US\$454 per person, compared with \$809 in Sierra Leone and \$3010 in Nigeria.³ Before the EVD epidemic, Liberia had only 2.8 health-care workers per 10 000 people and 51 medical doctors serving its 4.29 million population.⁴⁵

Because Ebola virus spreads through contact with bodily fluids from infected people, overcrowded urban areas can present an exceptionally high risk for disease transmission. More than 1 million individuals and over

90% of residents of Montserrado County live in Monrovia, the capital of Liberia. Reducing transmission is especially challenging in Monrovia's West Point slum, where more than 75 000 people live without running water, making it impossible to implement WHO-recommended handwashing procedures when caring for sick household members.' The current outbreak poses a mounting threat internationally, as witnessed by infected individuals travelling from Monrovia to the USA and to Nigeria, causing an outbreak of at least 19 cases in Nigeria.^{8,9}

Containment of previous EVD epidemics in more remote areas has relied on identification and monitoring of contacts of patients for symptoms, and performing hygienic burials to prevent family and community members from being exposed during funerals. ^{10,11} So far, these approaches have not been successful in curtailing the current epidemic in cities such as Monrovia. Responses including *cordons sanitaires*, border closures

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and international flight cancellations, curfews, and bans on public gatherings have resulted in overwhelming losses for impoverished national economies^{11,12} and civil unrest.¹³

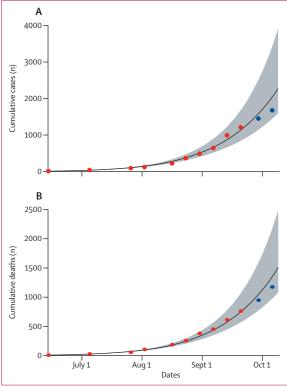


Figure 1: Model calibration

 (\bar{A}) Reported and model-predicted cases in 2014, with red points showing observed data used in model calibration, blue points showing observations outside the fitting period, and shaded areas showing 95% credible intervals around model predictions. (B) Reported deaths, as in (A). Credible intervals are calculated based on 5000 simulations. The superimposed line indicates median predicted cases and deaths.

See Online for appendix

1	Model parameter affected	Total change	Deployment schedule
	Ascertainment rate	0-400% increase	Remains at baseline (0); 12-5% per week over 4 weeks (1A); 25% per week over 2 weeks (1B); 25% per week over 4 weeks (2A); 50% per week over 2 weeks (2B); 50% per week over 4 weeks (3A); 100% per week over 2 weeks (3B); 100% per week over 4 weeks (4A); 200% per week over 2 weeks (4B)
Building ETCs	Number of beds	0-48 new ETCs (0-4800 new beds)	Three ETCs per week for 2 and 4 weeks (I); Six ETCs per week for 1, 2, and 4 weeks (II); 12 ETCs per week for 1, 2, 3, and 4 weeks (III)
household protective kits	Transmission rate for ascertained cases	10–50% reduction in transmission rate for ascertained cases that remain at home	N/A (implemented among all newly ascertained cases)
ETC=Ebola virus disease treatment centre. N/A=not applicable.			
Table: Interventions deployed			

WHO has appealed urgently to the international community to commit resources towards combating the EVD epidemic.^{10,14} On Sept 16, 2014, the USA announced the largest and most comprehensive response so far, which includes construction of 17 new EVD treatment centres to isolate and treat 1700 patients.^{15,16} However, the pace of epidemic growth brings into question whether the extent and timing of commitments will be sufficient to curtail the epidemic. After recommendations and provisions from the US Centers for Disease Control and Prevention (CDC), the Liberian Ministry of Health and Social Welfare has begun distributing home-based protective kits and instructional programmes to facilitate household-based isolation of infected individuals for whom beds are unavailable.

To assess the effect these various intervention strategies could have on controlling the spread of Ebola virus in Montserrado, we developed a mathematical model for transmission, fitted probabilistically to epidemiological data of reported cases and deaths. We used the model to evaluate the potential effect in Montserrado of expanding EVD treatment centres, increasing case ascertainment, and allocating protective kits.

Methods

Model outline

We developed a mathematical model to track susceptible, latently infected, infectious, and recovered individuals and infectious people who have died of the disease. We assumed that infected individuals are identified via presentation to EVD treatment centres or through active contact-tracing. We further assumed that admitted and other ascertained individuals who die receive sanitary burials, preventing transmission after death. By contrast, people with EVD who are not ascertained contribute to transmission until they are buried.

Calibration

We derived EVD parameters from epidemiological data for the current epidemic.¹ We propagated uncertainty in epidemiological parameters onto the model predictions by doing Bayesian Markov Chain Monte Carlo sampling for model calibration. We calibrated the model to reproduce cases and deaths reported in Montserrado for the period from June 14, 2014 (when the first cases were reported), to Sept 23, 2014 (figure 1).7 The appendix (pp 1–8) provides details of the model equations and calibration. Our model predictions under the status quo are based on the assumption of no change from Sept 23, 2014, in population behaviour and mixing patterns by Dec 15, 2014.

Interventions

We compared three interventions individually and in combination: acceleration of case ascertainment; expansion of EVD treatment centres; and distribution

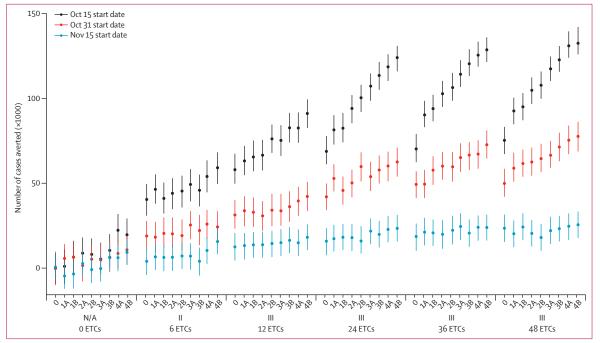


Figure 2: Effect of adding new EVD treatment centres and increasing case ascertainment
Intervention effects of programmes started on Oct 15, 2014, and Oct 31, 2014, and delayed until Nov 15, 2014, in which expansions in EVD treatment centres and case ascertainment are considered. Il and III represent construction of EVD treatment centres at the rate of six and 12 centres per week, respectively. The case-ascertainment rate is defined as follows: 0 represents the baseline rate, 1A is an increase of 12-5% per week over 4 weeks, 1B is an increase of 25% per week over 2 weeks, 2A is an increase of 25% per week over 4 weeks, 3B represents an increase of 50% a week over 4 weeks, 3B is an increase of 100% per week over 2 weeks, 4A represents an increase of 100% a week over 4 weeks, and 4B is an increase in case ascertainment of 200% a week over 4 weeks, and 4B is an increase in case ascertainment of 200% a week over 4 weeks, In the appendix (p 9), we have expanded this figure to show the effects under all modelled deployment schedules for EVD treatment centres. EVD=Ebola virus disease. ETC=EVD treatment centre. N/A=not applicable.

of protective kits to households of ascertained patients for whom EVD treatment centre beds are unavailable (table). In view of empirical uncertainty with respect to the effectiveness of protective kits at reducing household transmission, we varied the efficacy from 10% to 50%. We also compared intervention initiation on Oct 15, 2014, Oct 31, 2014, and Nov 15, 2014. The status quo intervention was defined in terms of case ascertainment and capacity of EVD treatment centres on Sept 23, 2014, and all behaviour and contact patterns relevant to transmission as they were occurring at that time.

Outcomes

Our primary outcome measure was the expected number of cases averted by Dec 15, 2014, around which we computed 95% credible intervals (95% CIs) via bootstrap resampling. As a secondary outcome measure, we calculated deaths averted by Dec 15, 2014.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For Montserrado, we estimated a basic reproductive number (R_0) for EVD of 2.49 (95% CI 2.38–2.60). This value defines the expected number of EVD cases caused by an individual infected with Ebola virus in an otherwise susceptible population without any public health or clinical interventions. As of Oct 5, 2014, we estimated that 7260 EVD cases (95% CI 5132-11560) and 2941 deaths (4070-6140) had occurred, of which we predicted 1975 (1390-3100) and 1315 (959-1984), respectively, would be reported. Data from the Liberian Ministry of Health and Social Welfare show that, in total, 1635 cases of EVD and 1081 deaths had been reported as of that time.7 Without expanded control efforts beyond levels on Sept 23, 2014, our model projects a total of 170 996 EVD cases (95% CI 81909-361793) and 90122 deaths (44734-194801) by Dec 15, 2014. Of these, we estimate 42 669 EVD cases (20 471-94 143) and 27 175 deaths (13498-59791) will have been reported.

We found that the effect of expanding the capacity of EVD treatment centres depends on concomitant acceleration of case ascertainment (figure 2). For example, for status quo case ascertainment, we estimate that the addition of 4800 beds over a period of 4 weeks would be expected to avert 49553 (95% CI 41720–58152) cases of EVD. Providing 2400 beds over a period of 2 weeks, while

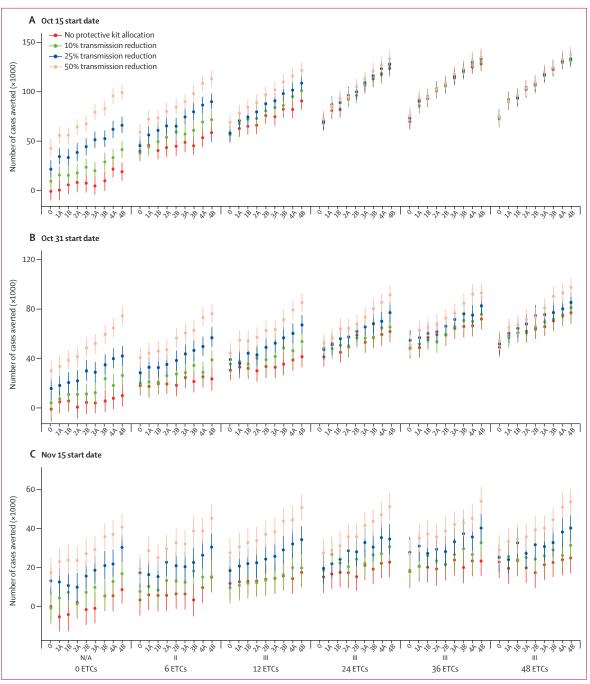


Figure 3: Effect of augmenting interventions with protective kit allocation

(A) Effectiveness of programmes beginning on Oct 15, 2014, (B) Oct 31, 2014, and (C) Nov 15, 2014, considering all possible expansions in EVD treatment centres and case ascertainment, and varying efficacy levels for protective kits. Il and Ill represent construction of EVD treatment centres at the rate of six and 12 centres per week, respectively. The case-ascertainment rate is defined as follows: 0 represents the baseline rate, 1A is an increase of 12-5% per week over 4 weeks, 1B is an increase of 25% per week over 2 weeks, 2B represents an increase in case ascertainment of 50% per week over 2 weeks, 3A represents an increase of 50% a week over 4 weeks, 3B is an increase of 100% per week over 2 weeks, 4A represents an increase of 100% a week over 4 weeks, and 4B is an increase in case ascertainment of 200% a week over 2 weeks. In the appendix (p 11), we have expanded the figure to show the effects under all modelled deployment schedules for EVD treatment centres. EVD=Ebola virus disease. ETC=EVD treatment centre. N/A=not applicable.

concurrently accelerating case ascertainment five-fold, would be expected to avert 62220 (53556–70654) EVD cases by Dec 15, 2014.

Protective kits might reduce transmission under scenarios in which the capacity of EVD treatment centres is exceeded. At status quo case ascertainment and

hospital capacity, distribution of kits to households of ascertained cases for whom no beds are available could be expected to avert between 4497 (95% CI –5153 to 13 524) and 30 557 (22 535–38 663) cases, corresponding to intervention efficacy ranging from 10% to 50% (figure 3). If case ascertainment were increased five-fold, we could expect to avert between 26746 (19 003–35 127) and 75 065 (67 330–82 994) cases of EVD.

In view of our projection that incidence of EVD in Montserrado will probably soon exceed capacity of EVD treatment centres under current international commitments, protective kits could supplement hospital-based case isolation (figure 3). For instance, if protective kits halve transmission, we expect that allocation of kits while increasing case ascertainment on Oct 31, 2014, would avert between 46123 (95% CI 37897–54295) and 78623 (71304–86442) EVD cases by Dec 15, 2014, if 600 new beds were allocated concurrently over a period of 2 weeks. With 4800 new beds delivered by mid-November, the number of cases of EVD averted rises to between 65228 (95% CI 57385–72705) and 97940 (90096–105606), compared with a range from 58529 (50557–67738) to 77312 (68400–85870) without protective kits.

For scenarios in which households of ascertained cases receive protective kits, rollout of programmes increasing case ascertainment within 2 weeks averts more EVD cases than do slower rollout alternatives (figure 3). However, we are unclear whether the timing of increased case ascertainment rollout affects the effectiveness of EVD treatment centre expansion when protective kits are not allocated (figure 2). However, rates at which EVD treatment centres are constructed substantially affect the expected number of EVD cases averted. For instance, we estimate that the number of averted cases of EVD escalates from 39314 (29664-48414) to 62222 (53556-70654) when 2400 new beds are constructed over a span of 4 weeks versus 2 weeks, even when both scenarios are complemented with five-fold acceleration of case ascertainment (figure 3).

Had more timely interventions been implemented, the expected number of EVD cases and deaths averted would have been much higher under all intervention scenarios (figures 2 and 3; appendix pp 9-12). Without protective kits, concurrent deployment of the maximum number of EVD treatment centres and case ascertainment interventions on Oct 31, 2014, would be expected to avert 77 312 (95% CI 68 400-85 870) cases by Dec 15, 2014. Augmenting these interventions with protective kits can increase the number of EVD cases averted to between 81627 (73536–89790) and 97940 (90096–105606), depending on kit efficacy. Starting all three interventions on Oct 15, 2014, would have averted up to 137432 (129736-145874) cases of EVD. In this last scenario, allocation of protective kits does not affect outcomes, showing the diminished importance of protective kits when adequate EVD treatment centres are available. If started on Nov 15, 2014, our projections suggest that these three interventions will avert between 31690 (95% CI 24506–39680) and 53957 (46963–60490) cases of EVD.

With our model, we predict a total of 27 378 (17 671–75 717) EVD cases and 18 606 (12 108–49 373) deaths will occur under a best-case scenario for timely intervention started on Oct 15, 2014, compared with 65 367 (28 991–204 523) cases and 41 754 (19 327–122 955) deaths if started on Oct 31, 2014, and 112 960 (50 589–291771) cases and 66 820 (31 556–171 299) deaths with a start date of Nov 15, 2014.

Discussion

Findings of our analysis suggest that the capacity of EVD treatment centres needed to reduce the severity of the current outbreak greatly exceeds current international commitments. Therefore, many more EVD treatment centres than have been pledged will be needed to avert substantial numbers of EVD cases and deaths. Our findings also show that the effectiveness of new EVD treatment centres can be maximised with concurrent acceleration of case ascertainment. Moreover, allocation of protective kits will further reduce EVD cases and deaths and augment control probability. Although the window of opportunity for timely control of the outbreak has passed, the risk for catastrophic devastation both in west Africa and beyond might have only just begun. We found that equivalent interventions would have had substantially greater effect if started 2 weeks earlier. Further delays in the provision of effective interventions will continue to undermine the likelihood of averting EVD cases and deaths, suggesting we must scale interventions to the continuously escalating need expeditiously, despite potential costs (panel).

The rapid growth in the EVD epidemic, exacerbated by the inadequate and delayed international response, has left many people with no other option but to care for sick relatives within their homes. As a stop-gap measure, protective kits have begun to be provided to households of infected individuals for whom hospital beds are not available, in an attempt to reduce household transmission.14,16,17 Although these kits do not facilitate treatment per se, they do include soap and bleach, personal protective equipment (eg, gloves and masks), and sanitary containers for disposal of contaminated materials. A previous model suggesting that these measures could be effective stand-alone interventions assumed that they achieve a 90% reduction in household transmission.18 However, substantial uncertainty surrounds the effectiveness of protective kits, as shown by estimates from previous outbreaks in the Democratic Republic of the Congo and Uganda, where efficacy of these kits was 12% (95% CI 0-78) and 88% (1-92), respectively.¹⁸ Considering a range in efficacy from 10% to 50%, our predictions suggest that although these protective kits can complement improvements in EVD treatment centre capacity and case isolation, they would

Panel: Research in context

Systematic review

We searched PubMed and Google Scholar with various terms: "Ebola transmission model", "Ebola control", "Ebola treatment centers", and "Ebola household protective kit". We restricted the search to reports in English and French. The last search was done on Oct 14, 2014. The search yielded no studies assessing the speed of intervention measures needed to curtail the ongoing Ebola virus disease (EVD) outbreak in west Africa.

Interpretation

Our study is the first to assess the effect of the speed of implementing non-pharmaceutical interventions to curb the 2014 EVD outbreak in Liberia. Substantial and prompt scaling up of interventions is needed urgently to avert a catastrophic disease burden. As such, our findings emphasise the inadequacy, both in timing and scale, of current US and international commitments to expand the capacity of isolation and case ascertainment.

alone remain insufficient to reverse the EVD outbreak in Montserrado.

Our analysis of the EVD outbreak within Montserrado complements recent models of the current west African EVD epidemic that have predominantly sought to replicate national-scale transmission dynamics. 1,9,17,19-21 Although the epidemic is unfolding across several countries, interventions must ultimately be implemented and scaled to specific community needs. 10,12 Furthermore, epidemic dynamics and reporting vary geographically because of inherent differences in health system capacity, timing of index cases, and unique local conditions that can exacerbate transmission.17 Focusing on Montserrado, where transmission rates seem highest,7 allows us to assess timing and scale of interventions needed in this most challenging of settings. Predicted intervention requirements in Montserrado are probably applicable, yet conservative, relative to those necessary in regions where transmission rates are lower.

EVD cases are typically identified and reported well after onset of symptoms.1 Thus, most infected patients reported every day probably became symptomatic days before, and they could have transmitted Ebola virus in the intervening time. The assumption that daily reported cases accurately represents the number of individuals entering the infectious class, without taking into account under-reporting or delays in reporting, could lead to underestimation of the actual epidemic. We addressed this challenge by fitting our model to estimate the delay between the beginning of the infectious period and time of ascertainment. Caveats with respect to our findings include the scarcity of empirical assessment of ascertainment rates and uncertainty in population mixing patterns, by which we assume that Ebola virus can continue to spread within the remaining susceptible

population. To address the limitation that status quo ascertainment is unknown, we used a Bayesian framework to propagate uncertainty about this parameter onto our model predictions, to ensure the robustness of our results. Because the extent to which unquantified factors (eg, human behaviour changes and population mixing) can reduce transmission is unclear, the conventional homogeneous mixing assumptions we used here allow for worst-case estimates of the attack rate and, thus, inform conservative response strategies. Within the range of current reported epidemiological observations, our projections might be slightly high because protective kits began to be distributed in late September and early October, 2014, which could contribute to an earlier deceleration in the epidemic than would be predicted under the status quo (figures 1 and 3).

Another limitation is our model assumption that all people infected with Ebola virus (both alive and dead) contribute to transmission at equal rates. Since viral load levels of Zaire ebolavirus vary during the course of infection in non-human primates, 22,23 people who are alive and those who have died might transmit Ebola virus differentially because of variations in viraemia and rates at which susceptible people contact them.²⁴ Because the interventions we considered mainly address isolation of infected people within either EVD treatment centres or their own homes, our outcomes are most useful for informing control of transmission from living patients with EVD. Additionally, we assumed that EVD cases arising in Montserrado from June 14, 2014, onwards were acquired within the county. Although this assumption might not strictly be true, the relative geographical isolation of early epidemic foci in Montserrado and Lofa counties suggest imported cases would not be an influential source for transmission in Montserrado. Lastly, we assumed that no transmission of Ebola virus happens during sanitary burials, because no data are available to set parameters for the relative risk of infection during such events. In the absence of concurrent interventions, the only effect offered by ascertainment is sanitary burial. We did not identify appreciable changes in cases or deaths averted from altering ascertainment rates when beds remain at their levels of Sept 23, 2014 (figure 2). Thus, allowing for risk of transmission during sanitary burials would probably have a small marginal effect on our results.

We have not considered the costs of intervention implementations. Although the costs of scaling up construction of new EVD treatment centres, acceleration of case ascertainment, and provision of household protective kits are important factors for measuring the feasibility of different intervention strategies, intervention needs and costs will rise if the Ebola outbreak continues to expand at its current rate. Further studies should integrate both speed and cost of intervention measures to assess the health and economic burdens of delaying scaling up of control measures in west Africa.

In addition to non-pharmaceutical interventions, several potential medicinal treatments and vaccines for EVD control are being developed and tested.^{25,26} Although these measures will probably not be available for large-scale distribution until much later in the epidemic, they have the potential to contribute significantly to reduction of disease burden and saving lives. Further studies should investigate the potential effect of combining pharmaceutical and non-pharmaceutical interventions.

Continued spread of Ebola virus threatens affected west African nations and the rest of the world, making outbreak containment a global health priority. Because vaccines to prevent EVD remain unavailable, we urge a rapid and immediate scaling up of currently available non-pharmaceutical intervention strategies to minimise the occurrence of new EVD cases and deaths. Perhaps most alarming is that, although we might still be within the midst of what will ultimately be viewed as the early phase of the current EVD outbreak, the window of opportunity for aversion of calamitous repercussions from an initially delayed and insufficient response is diminishing rapidly. Our predictions suggest that current commitments are grossly inadequate to provide beds for all infected individuals, even only considering near-term growth of the epidemic in Montserrado. Although transmission reduction afforded through provision of home protection kits could have a limited effect on mitigation of temporary bed shortages, our results suggest transmission of Ebola virus will not be curtailed without much greater commitment to improvement of all preventive measures that international aid is currently attempting to address.

Contributors

JAL contributed to the literature search, figures, study design, data analysis, interpretation of data, and writing of the report. MLNM contributed to study design, the literature search, data interpretation, and writing of the report. JAA-M contributed to the literature search, study design, data analysis, and writing of the report. FLA contributed to data interpretation and writing of the report. LB and TGN contributed to collection and interpretation of data. APG contributed to study design, data interpretation, and writing of the report.

Declaration of interests

We declare no competing interests.

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