Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Web appendix

S1. Model

We develop a differential equation model of Ebola virus transmission and public health interventions in Montserrado County, Liberia. We outline the model structure in the main text and present an illustration in this supplement (Figure S1).

Susceptible persons (\(S\)) are infected at a rate given by the force of infection (\(\lambda\), described below):

\[
\frac{d}{dt} S(t) = -\lambda(t) S(t).
\]

Upon infection, individuals enter a latent, non-infectious incubation period (\(L\)). Onset of initial symptoms and infectiousness occurs at the rate \(\gamma_L\):

\[
\frac{d}{dt} L(t) = \lambda(t) S(t) - \gamma_L L(t).
\]

A proportion (\(\delta\), as calculated among persons with known disease outcomes [1]) of infected individuals will ultimately die from their disease at the rate \(\gamma_D\); the remainder \((1 - \delta)\) will recover at the rate \(\gamma_R\). Individuals from the classes \(I_D\) and \(I_R\) become ascertained by the public health sector when they present to Ebola virus disease treatment centers (ETCs) or are identified under active case finding programs. Together, such ascertainment occurs at the rate \(\xi\):

\[
\frac{d}{dt} I_D(t) = \delta \gamma_L L(t) - (\xi + \gamma_D) I_D(t),
\]

\[
\frac{d}{dt} I_R(t) = (1 - \delta) \gamma_L L(t) - (\xi + \gamma_R) I_R(t).
\]

The near-equivalent mortality ratios reported in hospitalized and non-hospitalized cases during the current epidemic [1] suggest that hospitalization in ETCs primarily terminates community transmission rather than improves patient survival. Consequently we assume ascertained patients in the fatal subclass \((A_D)\) cannot transition into the survivorship subclass \((A_R)\):

\[
\frac{d}{dt} A_D(t) = \xi I_D(t) - \gamma_D A_D(t),
\]

\[
\frac{d}{dt} A_R(t) = \xi I_R(t) - \gamma_R A_R(t).
\]

We assume ascertained individuals in the community, who are routinely followed-up by public health workers, are removed from their homes and hygienically buried upon death, and likewise that susceptibles have no contact with cadavers of EVD victims who die in hospital. Individuals who are not ascertained and die in the community \((C)\) are tracked until their burial, which occurs the rate \(\gamma_C:\)

\[
\frac{d}{dt} C(t) = \gamma_D I_D(t) - \gamma_C C(t).
\]
Non-fatally infected persons recover into the $R$ class at the rate $\gamma_R$:

\[ \frac{d}{dt} R(t) = \gamma_R (I_R(t) + A_R(t)). \]

We assume deaths among ascertained persons under follow-up are reported, and that an additional proportion ($\alpha_1$) occurring among previously non-ascertained victims become reported as the victims’ cadavers are removed from their homes or communities for burial. Consequently the rate of change in cumulative reported deaths ($Z$) is:

\[ \frac{d}{dt} Z(t) = \gamma_D A_D(t) + \alpha_1 \gamma_C C(t). \]

We likewise assume cumulative cases ($Y$) are reported via two processes. The first occurs as individuals become ascertained during their infectious course. The second occurs among a proportion ($\alpha_2$) of the ascertained deaths, which become recorded posthumously into aggregate case reports when they are identified as Ebola victims:

\[ \frac{d}{dt} Y(t) = \xi (I_R(t) + I_D(t)) + \alpha_1 \alpha_2 \gamma_C C(t). \]

We assume infected and ascertained persons as well as infectious cadavers contribute to new cases in the community at the frequency-dependent rate $\beta$. We define $\kappa$ as the relative transmission rate for ascertained persons within households that have received kits, so that $\kappa = 1 - (\text{Kit Efficacy})$. To account for the fact that hospitalized patients occupying $B$ available ETC beds do not cause infections in the community, we define the number of ascertained patients contributing to new infections as $\max\{A_R(t) + A_D(t) - B(t), 0\}$:

\[ \lambda(t) = \beta (I_R(t) + I_D(t) + C(t)) + \kappa \max\{A_R(t) + A_D(t) - B(t), 0\}. \]

Whereas $Y(0) = 7$ suspected, probable, and confirmed cases were reported 14 June, the actual number of latent and symptomatic cases in the community at that time is uncertain. To propagate this uncertainty in our model, we initialize the system assuming the products $\frac{\chi}{\xi} Y(0)$ and $\frac{\chi}{\xi} Y(0)$ give the actual number of latent and infectious cases in the community as of that time, and calibrate the distribution of these values (Section ??). The system is initiated under the following conditions:

\begin{align*}
S(0) &= N_0 - (L(0) + I_R(0) + I_D(0) + A_R(0) + A_D(0)), \\
L(0) &= \frac{\chi}{\xi} Y(0), \\
I_R(0) &= \frac{\chi}{\xi} (1 - \delta) Y(0), \\
I_D(0) &= \frac{\chi}{\xi} \delta Y(0), \\
A_R(0) &= (1 - \delta) Y(0), \\
A_D(0) &= \delta Y(0).
\end{align*}

We list the parameters and their sources in Table ??.
S2. Estimation of the starting population

We use the population estimates from the Republic of Liberia 2008 Population and Housing Census [5] for the county of Montserrado between the years 1984 (491078) and 2008 (1118241) to calculate annual population growth for Montserrado. Using 2008 as a basis we then applied this annual growth for six years to obtain the population size for 2014 (1373668).

S3. Basic reproductive number ($R_0$) derivation

We derived the basic reproductive number ($R_0$) following van den Driessche and Watmough [6]. Considering a disease-free equilibrium, the rates of change in the infected compartments are

$$\dot{X} = \begin{pmatrix} \dot{L} \\ \dot{I}_R \\ \dot{I}_D \\ \dot{C} \end{pmatrix} = \mathcal{F}(X) - \mathcal{V}(X),$$

with new infections occurring at the rates $\mathcal{F} = (\lambda S 0 0 0)^T$, and all other transitions occurring at

$$\mathcal{V} = \begin{pmatrix} \gamma_L L \\ -(1-\delta)\gamma_L L + \gamma_R I_R \\ -\delta\gamma_L L + \gamma_D I_D \\ -\gamma_D I_D + \gamma_C C \end{pmatrix}.$$

Evaluating the Jacobians at the disease-free equilibrium $x = (0 0 0 0)^T$, we have

$$F = \frac{d\mathcal{F}_i}{dX_j} \bigg|_{x_i=0} = S \begin{pmatrix} 0 & \beta & \beta & \beta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \frac{d\mathcal{V}_i}{dX_j} \bigg|_{x_i=0} = \begin{pmatrix} \gamma_L & 0 & 0 & 0 \\ -(1-\delta)\gamma_L & \gamma_R & 0 & 0 \\ -\delta\gamma_L & 0 & \gamma_D & 0 \\ 0 & 0 & -\gamma_D & \gamma_C \end{pmatrix}.$$

Defining $R_0$ as the dominant eigenvalue of $FV^{-1}$,

$$R_0 = \beta \left( \frac{1-\delta}{\gamma_R} + \frac{(\gamma_D + \gamma_C)\delta}{\gamma_D \gamma_C} \right) N_0.$$
S4. Calibration to epidemic dynamics

We calibrate the model by fitting to cumulative cases and deaths reported by the Liberian Ministry of Health and Social Welfare [3]. We consider cumulative suspected, probable, and confirmed case reports aggregated once per week to reduce noise in the data from inconsistencies in daily reporting effort. We use reports aggregated on Mondays as this day had the fewest missing data points. Since our model does not incorporate nosocomial transmission, we subtract reported cases and deaths among healthcare workers from cumulative cases and deaths prior to fitting.

S4.1. Accounting for under-reporting

The number of cases and deaths occurring in the current epidemic is likely under-reported, but the extent of under-reporting is unknown. To assess the extent of under-reporting and hence the actual cases and fatalities in Monrovia, we fit the rates at which symptomatic individuals and fatalities are ascertained, respectively. The CDC has estimated that 60% of the total cases in treatment across all affected settings are not reported [7]. We assume this estimate provides an upper bound on ascertainment failure in Montserrado, because Liberia’s Ebola response services are concentrated in Monrovia, and here serve a densely-populated area with superior geographic access to ETCs, ambulances, and case-finding programs relative to rural areas, where geographic isolation and poor road conditions impede case ascertainment. Empirically, the Liberian Ministry of Health and Social Welfare reports accounted for 398 patients in treatment as of 23 September [3], corresponding to 93% of the county’s 430 total ETC beds as of that date, all of which were known to be occupied [4]. These factors suggest West African-wide under-reporting estimates can be interpreted as a worst-case under-reporting estimate for Montserrado County.

S4.2. Markov Chain Monte Carlo sampling

We model cumulative cases and mortality as a Poisson-distributed random variable. We calibrate the model by sampling from the posterior distribution of the parameter vector \( \theta | y, z = \{ \beta, \alpha_1, \alpha_2, \chi_L, \chi_I, \xi \} \) where the vectors \( y \) and \( z \) are derived from \( \frac{d}{dt}Y(t) \) and \( \frac{d}{dt}Z(t) \), respectively, via integrating the system of equations for randomly-sampled values of the parameters. We conduct sampling via Markov Chain Monte Carlo using a Metropolis-Hastings acceptance rule. The posterior density is

\[
f_\theta(y,z|\theta) = \prod_T \mathcal{L}(Y(t)|\theta) \mathcal{L}(Z(t)|\theta) f_\theta(\theta)
\]

We conduct 1,500,000 iterations and discard the first 200,000 samples as a burn-in period.

The prior density \( f_\theta(\theta) \) is the joint probability of several univariate priors. Of these, six are uninformative: we consider that \( \chi_L \) and \( \chi_I \) are strictly positive, that \( \beta, \alpha_1, \) and \( \alpha_2 \) are distributed according to \( \mathcal{U}(0,1) \), and that the total proportion of cases that do not become ascertained before death is \( (1 - \xi) \), where \( \xi \) is the assumed upper bound on the proportion of cases that never become reported as per [7].
We consider the informative prior that \( R_0 = g(\beta) \sim \Gamma(k, \theta) \) with mean 1.51 and 95% confidence intervals [1.41, 1.60], a previous estimate for the epidemic in Liberia as a whole [1]. We derived the hyperparameters \{k, \theta\} for the Gamma prior on \( R_0 \) reproducing the observed mean and confidence intervals in [1]. Because ETCs are known to have been occupied at full capacity throughout the epidemic, we reject parameter proposals for which the number of ascertained cases is below the number of beds on five or more days.

We accounted for uncertainty among remaining parameters by treating these as random variables. We assumed durations and probabilities as listed in Table ?? were distributed as \( \Gamma(k, \theta) \) and \( \text{Beta}(\alpha, \beta) \), respectively, among individuals who acquire Ebola. We derived distributions from observations during the present epidemic as reported by the WHO [1]. We inferred hyperparameters \{k, \theta\} from the reported information \{\mu, \sigma\} using the relation \( k = \frac{\mu^2}{\sigma^2} \) and \( \theta = \frac{\sigma^2}{\mu} \) for Gamma-distributed durations; for Beta-distributed probabilities, the \( \alpha \) and \( \beta \) hyperparameters were reported directly. We generated a value for each parameter \( p_i \) as the mean of \( N_i \) random draws from the parameter’s distribution, where \( N_i \) gave the number of observations in [1] informing the hyperparameter specification for \( p_i \). Since \( N_i \) was less than the size of the epidemic for all \( p_i \) parameters, this allowed us to account for statistical uncertainty in the central limits.

We inferred times at which the number of beds in ETCs increased from Liberian Ministry of Health reports [3] and from monitoring organizations [4] documenting when new ETCs were opened or existing ETCs expanded.

**S4.3. Parameter estimates**

Our estimated value for the frequency-dependent transmission rate \( \beta \) corresponds to an \( R_0 \) estimate of 2.49 [95% CI 2.38, 2.60] for a population of 1,373,668 susceptibles. This posterior distribution of \( R_0 \) is well above the mean and 95% credible intervals of the prior distribution (1.51 [1.41, 1.60]), suggesting the data were adequate for the likelihood to dominate the prior in our estimation procedure.

On the basis of our fitted distributions of \( \xi, \chi_L, \) and \( \chi_I \), we estimate that there were 47.5 [30.7, 62.7] latent cases and 8.3 [0.3, 18.3] non-ascertained infectious cases in Montserrado as of 14 June, when the first seven cases were notified.

Our estimated case ascertainment rate suggests that approximately one in twenty cases in the community becomes identified each day. Our estimate for this parameter converged to the vicinity of the assumed upper bound [7], in that our estimated rate corresponds to the circumstance where 59% [58%, 60%] of symptomatic cases ultimately remain non-ascertained. This suggests the actual under-reporting may be higher than we allow here, and consequently that our estimated size of the epidemic and future case projections are conservative. While ongoing data collection is needed to ultimately validate under-reporting estimates, accounting for potential under-reporting is essential to ensure adequate responses are mounted to avert future cases and deaths.
References


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value or Distribution</th>
<th>N</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_0$</td>
<td>Total population of Montserrado County</td>
<td>1373668</td>
<td>??</td>
<td></td>
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<tr>
<td>$\gamma^{-1}_{L}$</td>
<td>Incubation period</td>
<td>$\Gamma \left( k = \frac{3.4^2}{4\pi}, \theta = \frac{2a^2}{9} \right)$</td>
<td>500</td>
<td>[1]</td>
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<tr>
<td>$\delta$</td>
<td>Case fatality ratio (community)</td>
<td>Beta ($\alpha = 413, \beta = 171$)</td>
<td>584</td>
<td>[1]</td>
</tr>
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<td>$\gamma^{-1}_{R}$</td>
<td>Time to recovery (non-fatal cases)</td>
<td>$\Gamma \left( k = \frac{6.4^2}{5.5^2}, \theta = \frac{6.5^2}{1.6} \right)$</td>
<td>267</td>
<td>[1]</td>
</tr>
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<td>$\gamma^{-1}_{D}$</td>
<td>Time to death (fatal cases)</td>
<td>$\Gamma \left( k = \frac{2.5^2}{6.8^2}, \theta = \frac{4.8^2}{7.5} \right)$</td>
<td>594</td>
<td>[1]</td>
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<td>$\gamma^{-1}_{F}$</td>
<td>Time to burial</td>
<td>2d</td>
<td>[2]</td>
<td></td>
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<tr>
<td>$\beta_F$</td>
<td>Transmission parameter</td>
<td>Fitted</td>
<td>??</td>
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<tr>
<td>$\alpha_1$</td>
<td>Proportion of deceased Ebola virus disease victims ascertained at time of burial</td>
<td>Fitted</td>
<td>??</td>
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<tr>
<td>$\alpha_2$</td>
<td>Proportion of deceased Ebola virus disease victims reported as cases conditioned on ascertainment at burial</td>
<td>Fitted</td>
<td>??</td>
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<tr>
<td>$\xi$</td>
<td>Case ascertainment rate</td>
<td>(pre-intervention) Fitted</td>
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<tr>
<td></td>
<td></td>
<td>(intervention) Varied (1-5$\xi$ to 5$\xi$)</td>
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<tr>
<td>$B(t)$</td>
<td>Beds in Ebola Treatment Centers</td>
<td>(pre-intervention) Interpolated</td>
<td>[3, 4]</td>
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<td>(intervention) Varied (0 to 4800)</td>
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<td>$\kappa$</td>
<td>Relative transmission rate (HCI)</td>
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<td>[2]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(intervention) Varied (0-1 to 0-5)</td>
<td></td>
<td></td>
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<tr>
<td>$Y(0)$</td>
<td>Total ascertained cases as of 14 June</td>
<td>7</td>
<td>[3]</td>
<td></td>
</tr>
<tr>
<td>$Y(0)_{\chi L/\xi}$</td>
<td>Latently-infected population as of 14 June</td>
<td>Fitted</td>
<td>??</td>
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<tr>
<td>$Y(0)_{\chi I/\xi}$</td>
<td>Non-ascertained infected population as of 14 June</td>
<td>Fitted</td>
<td>??</td>
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Table S1: Model Parameters
<table>
<thead>
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<th>Variable</th>
<th>Prior</th>
<th>Mean [95% CI]</th>
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<tbody>
<tr>
<td>$\beta$</td>
<td>$U(0, 1)$</td>
<td>$1.57 \times 10^{-7} [1.54 \times 10^{-7}, 1.61 \times 10^{-7}]$</td>
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<tr>
<td>$\xi$</td>
<td>Section ??</td>
<td>$4.99 \times 10^{-2} [4.93 \times 10^{-2}, 5.17 \times 10^{-2}]$</td>
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<tr>
<td>$\chi_L$</td>
<td>$U(0, \infty)$</td>
<td>$3.39 \times 10^{-1} [2.19 \times 10^{-1}, 4.47 \times 10^{-1}]$</td>
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<tr>
<td>$\chi_I$</td>
<td>$U(0, \infty)$</td>
<td>$5.89 \times 10^{-1} [1.83 \times 10^{-2}, 1.30 \times 10^{-1}]$</td>
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<tr>
<td>$\alpha_1$</td>
<td>$U(0, 1)$</td>
<td>$1.16 \times 10^{-1} [9.51 \times 10^{-2}, 1.37 \times 10^{-1}]$</td>
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<tr>
<td>$\alpha_2$</td>
<td>$U(0, 1)$</td>
<td>$4.46 \times 10^{-2} [1.37 \times 10^{-3}, 1.47 \times 10^{-1}]$</td>
</tr>
</tbody>
</table>

$R_0 = g(\beta) \Gamma(1062.6562, 1.722 \times 10^{-3}) = 2.488 [2.378, 2.601]$  

Table S2: Calibrated parameters

Figure S1: Model diagram illustrating transitions through disease stages. White nodes are uninfected, pink nodes are infected, and grey nodes are fatalities. Red-bordered nodes are infectious. Individuals progress from susceptibility to latent infection ($L$), and upon symptom onset enter a trajectory ending with death ($I_D, C$) or recovery ($I_R, R$) with probabilities $\delta$ and $(1 - \delta)$, respectively. Infections in the community enter the ascertained classes ($A_R, A_D$), of whom $B(t)$ are isolated in ETCs at any time and do not contribute to community transmission.
Figure S2: Effects of ETC expansion and increasing case ascertainment (expanded from Figure 2, Main Text) for programs initiated 31 October, 15 October, and 15 November. Small tick marks correspond to ascertainment interventions in the order 0, 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B (as defined in Table 1). Roman numerals I, II, and III describe ETC construction at the rates of 3, 6, and 12 ETCs per week, respectively.
Figure S3: Deaths averted under ETC expansion and increased case ascertainment. We illustrate intervention effects for programs initiated 31 October, 15 October, and 15 November. Small tick marks correspond to ascertainment interventions in the order 0, 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B (as defined in Table 1). Roman numerals I, II, and III describe ETC construction at the rates of 3, 6, and 12 ETCs per week, respectively.
Figure S4: Effects of augmenting interventions with protective kit allocation (expanded from Figure 3). We illustrate intervention effects for programs initiated on 31 October, 15 October, or 15 November, varying efficacy for protective kits. Small tick marks correspond to ascertainment interventions in the order 0, 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B (as defined in Table 1). Roman numerals I, II, and III describe ETC construction at the rates of 3, 6, and 12 ETCs per week, respectively.
Figure S5: Deaths averted under differing interventions. We illustrate intervention effects for programs beginning 31 October, 15 October and 15 November, varying efficacy for protective kits. Small tick marks correspond to ascertainment interventions in the order 0, 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B (as defined in Table 1). Roman numerals I, II, and III describe ETC construction at the rates of 3, 6, and 12 ETCs per week, respectively.