



Accurate forecasts of the effectiveness of interventions against Ebola may require models that account for variations in symptoms during infection



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ABSTRACT

Epidemiological models are routinely used to predict the effects of interventions aimed at reducing the impacts of Ebola epidemics. Most models of interventions targeting symptomatic hosts, such as isolation or treatment, assume that all symptomatic hosts are equally likely to be detected. In other words, following an incubation period, the level of symptoms displayed by an individual host is assumed to remain constant throughout an infection. In reality, however, symptoms vary between different stages of infection. During an Ebola infection, individuals progress from initial non-specific symptoms through to more severe phases of infection. Here we compare predictions of a model in which a constant symptoms level is assumed to those generated by a more epidemiologically realistic model that accounts for varying symptoms during infection. Both models can reproduce observed epidemic data, as we show by fitting the models to data from the ongoing epidemic in the Democratic Republic of the Congo and the 2014–16 epidemic in Liberia. However, for both of these epidemics, when interventions are altered identically in the models with and without levels of symptoms that depend on the time since first infection, predictions from the models differ. Our work highlights the need to consider whether or not varying symptoms should be accounted for in models used by decision makers to assess the likely efficacy of Ebola interventions.

1. Introduction

Ebola epidemics have devastating consequences. The current epidemic in the Democratic Republic of the Congo is the second largest in history, with 2025 cases (1931 confirmed and 94 probable) having been recorded as of 4th June 2019 (World Health Organization, 2019a). Mathematical models are increasingly used for exploring the effects of different possible control interventions during Ebola epidemics (WHO Ebola Response Team, 2014; Camacho et al., 2015; Meakin et al., 2018). The values of model parameters are chosen so that the model output matches observed epidemic data (model fitting; Fig. 1A), and then interventions are introduced in the fitted model to predict how the course of the epidemic is altered by different possible control strategies (intervention testing; Fig. 1B).

A commonly used model for characterising epidemics of diseases including Ebola is the Susceptible-Exposed-Infectious-Recovered (SEIR) model (Chowell et al., 2004; Althaus, 2014; Chowell and Nishiura, 2014), and extensions to this basic model include explicit incorporation

of transmission from Ebola deceased hosts (Agusto et al., 2015; Barbarossa et al., 2015; Weitz and Dushoff, 2015) or accounting for mismatches between symptoms and infectiousness (Thompson et al., 2016; Thompson and Hart, 2018). Possible interventions include isolation of symptomatic hosts, which can be included in the SEIR model by removing individuals from the infectious class. All individuals in the infectious class are usually assumed to be symptomatic, with the level of symptoms being assumed constant and therefore independent of the stage of infection. As an example, Chowell et al. (2015) assume that symptomatic individuals are isolated at a constant rate, and Meakin et al. (2018) assume that symptomatic individuals are hospitalised at a constant rate.

However, in reality, it is not the case that all symptomatic hosts are equally symptomatic. During an Ebola infection, an infected host progresses through different stages (Beeching et al., 2014) – from initial non-specific symptoms (fever, headache and myalgia) to a gastrointestinal phase (diarrhoea, vomiting, abdominal symptoms and dehydration), and then either to a deterioration phase (collapse,

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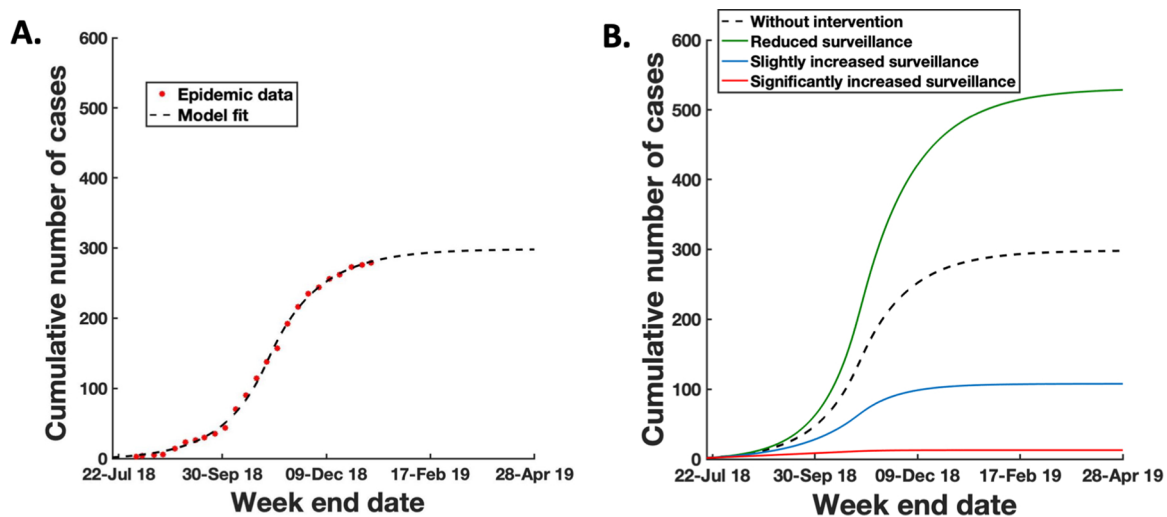


Fig. 1. Schematic showing how a model can be used to predict the effect of changing control interventions on epidemic dynamics. Here, an intensification of surveillance is assumed to lead to improved detection and control of infectious hosts, thereby reducing the total number of cases. A. Model fitting. Model parameters are chosen so that the model output (black dotted) approximates epidemic data (red dots). B. Intervention testing. A range of alternative control interventions are introduced into the fitted model, and predicted dynamics under these new control interventions can be observed – predictions of the effects of reduced surveillance (green), slightly intensified surveillance (blue) and significantly intensified surveillance (red).

neurological manifestations and bleeding) or recovery. Individuals with non-specific symptoms are less likely to be observed and treated/isolated than individuals who have progressed further through infection and have developed more specific and more serious symptoms.

Here, we investigate whether explicitly accounting for variations in symptom expression during the course of an Ebola infection leads to different epidemiological model dynamics compared to assuming a constant level of symptoms. To do this, we compare predictions derived from a model in which infectious hosts have a constant level of symptoms (the constant symptoms model – see Methods) with those from a model in which variable symptoms during infection are accounted for (the variable symptoms model). We parameterise our models using data from the ongoing Ebola epidemic in the Democratic Republic of the Congo. We find that both models can be fitted closely to data from the epidemic. However, when control interventions in the models are altered, for example to explore the effects of intensifying surveillance and control, forecasts generated by the models are very different. We find the same qualitative result when we instead parameterise our models using data from the largest Ebola epidemic in history: the 2014–16 epidemic in west Africa.

These analyses demonstrate that models with or without variable symptoms can reproduce observed disease incidence time series, but that predictions from the models are different when interventions are altered, even when the change in interventions is identical in both models. Our results highlight the need to consider whether variations in symptom expression during infection should be included in models of Ebola epidemics. Without accounting for variable symptoms, predictions of the possible effects of interventions may be incorrect.

2. Methods

2.1. Datasets

To show that our results are not conditioned on particular properties of data from a single epidemic, we conducted an analysis of simulated data (see Section S2 of the Supplementary Material) as well as two separate analyses in which we considered data from two different Ebola epidemics.

In the first analysis of real epidemic data, we used data on the numbers of cases in approximately weekly time intervals from the ongoing Ebola epidemic in the Democratic Republic of the Congo. It has recently been

suggested by Dr Peter Salama, Deputy Director-General of Emergency Preparedness and Response at the World Health Organization, that this epidemic comprises several distinct outbreaks in different affected areas (<https://web.archive.org/web/20190921181952/https://twitter.com/PeteSalama/status/1085265184162238465>). Indeed, disease incidence time series display distinct phases (large numbers of cases at the end of July/beginning of August 2018, followed by low numbers of cases in September, and then larger numbers of cases again thereafter), probably due to spatial effects of spread of the virus which are not captured by standard non-spatial compartmental models (Keeling and Rohani, 2008). For this reason, we focussed on data from the health zone of Beni, a city in the north-east of the Democratic Republic of the Congo, and the neighbouring health zone of Kalunguta. This region has been severely impacted by the current epidemic. These data were obtained from World Health Organization disease outbreak news reports from 4th August 2018 to 10th January 2019 (Data S1, see also World Health Organization, 2019b).

In the second analysis of real epidemic data, we considered data consisting of the numbers of cases in approximately weekly time intervals in Liberia during the 2014–16 Ebola epidemic, which were obtained from the World Health Organization (Data S2, see also World Health Organization, 2016).

2.2. Mathematical models

In the commonly used SEIR model, individuals are classified according to whether they are (S)usceptible to infection, (E)xposed, (I)nfected or (R)emoved and no longer infectious. We extended this model to account explicitly for case finding followed by isolation of infectious individuals. We also assumed that there were three distinct phases of infection, corresponding to different stages of an Ebola infection. This delivered the additional benefit that the infectious period (in the absence of control) was gamma distributed, rather than exponentially distributed – and gamma distributions have been found to characterise epidemiological periods accurately in a range of systems (Wearing et al., 2005; Cuniffe et al., 2012; Thompson et al., 2019a). This gave rise to the SEI₁I₂I₃RC model,

$$\frac{dS}{dt} = -\beta(t)S(I_1 + I_2 + I_3),$$

$$\frac{dE}{dt} = \beta(t)S(I_1 + I_2 + I_3) - \gamma E,$$

$$\frac{dI_1}{dt} = \gamma E - \mu I_1 - \delta_1 I_1,$$

$$\frac{dI_2}{dt} = \mu I_1 - \mu I_2 - \delta_2 I_2,$$

$$\frac{dI_3}{dt} = \mu I_2 - \mu I_3 - \delta_3 I_3,$$

$$\frac{dR}{dt} = \mu I_3,$$

$$\frac{dC}{dt} = \delta_1 I_1 + \delta_2 I_2 + \delta_3 I_3.$$

In this model, the C compartment represents the number of individuals that have ever been controlled (detected and isolated) until the current time. Since we wish to determine the impact on prediction of variable symptoms alone, in the baseline version of the model we assume that all infectious hosts are equally infectious – although we consider the effect of relaxing this assumption later.

In our analyses, we made the assumption widely used in Ebola models that the infection rate parameter in the model is temporally-varying (Meakin et al., 2018; Chowell et al., 2004), to reflect changes in transmissibility during the epidemic. This could, for example, indicate changes in behavioural responses or alterations to interventions (aside from detection and isolation, since we model that explicitly). In particular, we assumed that

$$\beta(t) = \begin{cases} \beta_0 & \text{for } t \leq T \text{ weeks,} \\ \beta_1 & \text{for } t > T \text{ weeks.} \end{cases}$$

We then considered two alternative versions of the model. In the first (the constant symptoms model – Fig. 2A), we assumed that all infectious individuals are successfully detected and isolated at the same average rate per week, so that $\delta_1 = \delta_2 = \delta_3 = \delta$, say. This assumption is common to any epidemiological model that includes interventions aimed at symptomatic hosts, unless differences in symptom expression are accounted for explicitly. The constant symptoms model is therefore similar to most epidemiological models that have been used to represent Ebola epidemics previously (e.g. Meakin et al., 2018; Chowell et al., 2015).

We also considered the more realistic case in which symptoms become more severe as infection progresses, so that $\delta_1 < \delta_2 < \delta_3$. We refer to the resulting model as the variable symptoms model (Fig. 2B). This model reflects the fact that, in reality, individuals with initial mild symptoms are less likely to be detected and isolated to prevent further transmission than individuals with more developed symptoms who are in the gastrointestinal or deterioration phases.

2.3. Model fitting and parameters

We considered the numerical solutions of the models described above in a host population of size $S + E + I_1 + I_2 + I_3 + R + C = N$ individuals and a basic reproduction number at the beginning of the epidemic and in the absence of surveillance given by $R_0 = \frac{\beta_0 N}{\mu}$.

The default parameter values used in our analyses of real epidemic data are given in Table 1 (for the Democratic Republic of the Congo in 2018–19) and Table 2 (for Liberia in 2014–16). However, as described in the Results, we also checked the robustness of our results to these particular parameter values. The values of the infection rates β_0 and β_1 , as well as the date on which the infection rate changes, T , were obtained by fitting the outputs of the models to the epidemic data. The start date of the epidemic, T_0 , was also estimated during the fitting procedure. Model fitting was performed using least squares estimation – i.e. choosing parameter values to minimise the sum of squares distance between the cumulative numbers of detected or removed hosts in the model under consideration ($C + R$) and the cumulative numbers of cases in the data, although we also considered fitting to non-cumulative data (see Discussion and Supplementary Material Section S7). Numerical solutions were generated starting with a single host in the E compartment at the start time of the epidemic, T_0 , with all other individuals susceptible.

The values of the parameters characterising the rate of Ebola detection and isolation, i.e. δ_1 , δ_2 and δ_3 , depend on the level of surveillance, which includes various passive and active case finding strategies. We did not model explicitly the wide range of different surveillance activities that take place during an Ebola response (see Discussion). However, to provide a concrete setting in which to illustrate that forecasts can be different under the constant symptoms and variable

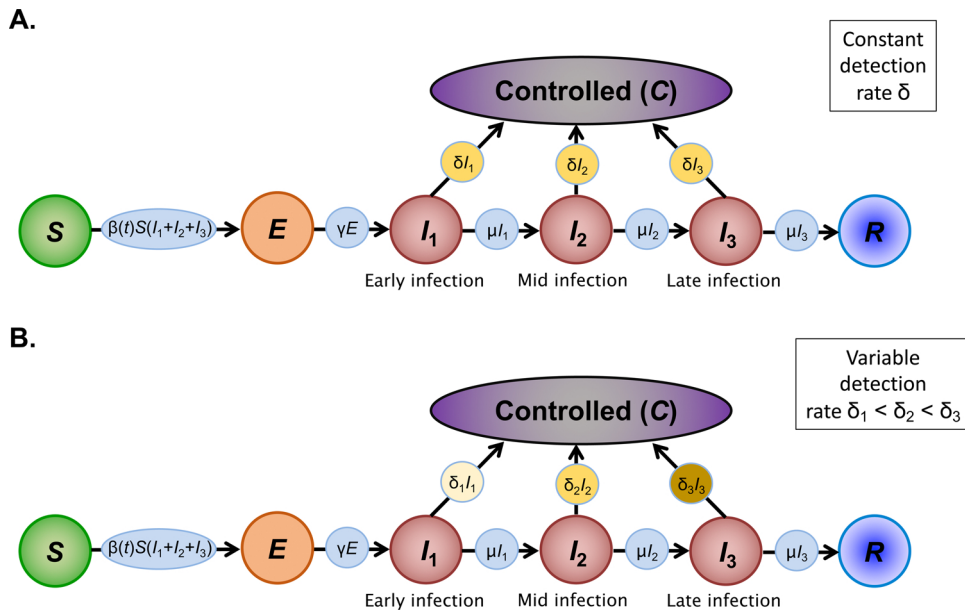


Fig. 2. Schematic of the different models that we considered. A. Constant symptoms model, in which individuals in each stage of infection are equally likely to be detected and isolated (so that the detection rate, δ , is equal for all three infectious classes); B. Variable symptoms model, in which symptoms are assumed to worsen during an Ebola infection (so that the detection rate is smaller for individuals in earlier infection compared to later infection, i.e. $\delta_1 < \delta_2 < \delta_3$). We also show how additional epidemiological complexity can be included in these models (see Section S6 of the Supplementary Material).

Table 1

Default parameter values used in our analysis of data from the ongoing Democratic Republic of the Congo epidemic.

Parameter	Definition	Default Value (except where stated)	Justification
N	Population size	230,000	ReliefWeb (2019)
β_0	Infection rate early in epidemic	$5.90 \times 10^{-6} \text{ week}^{-1}$ (constant symptoms model) or $5.67 \times 10^{-6} \text{ week}^{-1}$ (variable symptoms model)	Fitted to data
β_1	Infection rate late in epidemic	$2.57 \times 10^{-6} \text{ week}^{-1}$ (constant symptoms model) or $2.51 \times 10^{-6} \text{ week}^{-1}$ (variable symptoms model)	Fitted to data
T	Infection rate switch time	25 th October 2018 (constant symptoms model) or 24 th October 2018 (variable symptoms model)	Fitted to data
$1/\gamma$	Latent/incubation period	1 week	Meakin et al. (2018)
$3/\mu$	Infectious period	1.4 weeks	Meakin et al. (2018)
p_1	Detection probability in early infection	0.6 (constant symptoms model) or 0.1 (variable symptoms model)	Assumption (for analyses with different values, see Supplementary Material)
p_2	Detection probability in mid infection	0.6 (constant symptoms model) or 0.8 (variable symptoms model)	Assumption (for analyses with different values, see Supplementary Material)
p_3	Detection probability in late infection	0.6 (constant symptoms model) or 0.9 (variable symptoms model)	Assumption (for analyses with different values, see Supplementary Material)
Δ	Sampling frequency	3 weeks (weak surveillance) or 2 weeks (intensified surveillance)	Assumption (for analyses with different values, see Supplementary Material)
δ_1	Detection/isolation rate in early infection	$2.86 \times 10^{-1} \text{ week}^{-1}$ (constant symptoms model) or $3.51 \times 10^{-1} \text{ week}^{-1}$ (variable symptoms model)	Calculated using values of p_1 and Δ (see Methods)
δ_2	Detection/isolation rate in mid infection	$2.86 \times 10^{-1} \text{ week}^{-1}$ (constant symptoms model) or $4.44 \times 10^{-1} \text{ week}^{-1}$ (variable symptoms model)	Calculated using values of p_2 and Δ (see Methods)
δ_3	Detection/isolation rate in late infection	$2.86 \times 10^{-1} \text{ week}^{-1}$ (constant symptoms model) or $5.45 \times 10^{-1} \text{ week}^{-1}$ (variable symptoms model)	Calculated using values of p_3 and Δ (see Methods)
T_0	Start date of epidemic	25 th June 2018 (constant symptoms model and variable symptoms model)	Fitted to data

Table 2

Default parameter values used in our analysis of data from the 2014–16 epidemic in Liberia.

Parameter	Definition	Default Value (except where stated)	Justification
N	Population size	4,500,000	2015 estimate obtained from World Bank (2019)
β_0	Infection rate early in epidemic	$3.18 \times 10^{-7} \text{ week}^{-1}$ (constant symptoms model) or $3.03 \times 10^{-7} \text{ week}^{-1}$ (variable symptoms model)	Fitted to data
β_1	Infection rate late in epidemic	$1.32 \times 10^{-7} \text{ week}^{-1}$ (constant symptoms model) or $1.27 \times 10^{-7} \text{ week}^{-1}$ (variable symptoms model)	Fitted to data
T	Infection rate switch time	21 st September 2014 (constant symptoms model and variable symptoms model)	Fitted to data
$1/\gamma$	Latent/incubation period	1 week	Meakin et al. (2018)
$3/\mu$	Infectious period	1.4 weeks	Meakin et al. (2018)
p_1	Detection probability in early infection	0.6 (constant symptoms model) or 0.1 (variable symptoms model)	Assumption (for analyses with different values, see Supplementary Material)
p_2	Detection probability in mid infection	0.6 (constant symptoms model) or 0.8 (variable symptoms model)	Assumption (for analyses with different values, see Supplementary Material)
p_3	Detection probability in late infection	0.6 (constant symptoms model) or 0.9 (variable symptoms model)	Assumption (for analyses with different values, see Supplementary Material)
Δ	Sampling frequency	3 weeks (weak surveillance) or 2 weeks (intensified surveillance)	Assumption (for analyses with different values, see Supplementary Material)
δ_1	Detection/isolation rate in early infection	$2.86 \times 10^{-1} \text{ week}^{-1}$ (constant symptoms model) or $3.51 \times 10^{-2} \text{ week}^{-1}$ (variable symptoms model)	Calculated using values of p_1 and Δ (see Methods)
δ_2	Detection/isolation rate in mid infection	$2.86 \times 10^{-1} \text{ week}^{-1}$ (constant symptoms model) or $4.44 \times 10^{-1} \text{ week}^{-1}$ (variable symptoms model)	Calculated using values of p_2 and Δ (see Methods)
δ_3	Detection/isolation rate in late infection	$2.86 \times 10^{-1} \text{ week}^{-1}$ (constant symptoms model) or $5.45 \times 10^{-1} \text{ week}^{-1}$ (variable symptoms model)	Calculated using values of p_3 and Δ (see Methods)
T_0	Start date of epidemic	21 st March 2014 (constant symptoms model) or 19 th March 2014 (variable symptoms model)	Fitted to data

symptoms models, we instead considered a simplified scenario in which each host is checked for infection on average every Δ weeks. Each time monitoring occurs, there is a detection probability of p_i for individuals in class I_i (for $i = 1, 2$, or 3). As a result,

$$\delta_i = \frac{1}{\Delta \left(\frac{1}{p_i} - \frac{1}{2} \right)}.$$

This expression is derived in Section S1 of the Supplementary Material (for a similar approach, also see [Cunniffe et al., 2014](#)).

In most of our analyses (except where stated), we considered two different surveillance regimes. When the models were fitted, under

weak surveillance, we assumed that the default surveillance period was $\Delta = 3$ weeks. When the fitted models were then used to predict the impacts of intensified surveillance, the surveillance period was changed to $\Delta = 2$ weeks. We assumed that the detection probability in the constant symptoms model was $p_1 = p_2 = p_3 = 0.6$. When we accounted for the possibility that symptoms change as hosts progress through infection, we instead used default values of $p_1 = 0.1$, $p_2 = 0.8$ and $p_3 = 0.9$ so that the mean value of p_1 , p_2 and p_3 was equal to the value of these parameters in the constant symptoms model. In other words, conditional on not being detected previously, a host chosen at a random time in the infectious period was equally likely to be detected in both models.

3. Results

As described in the Introduction, fitted models are often used to test potential control interventions (Fig. 1). We therefore considered estimating the values of parameters of the constant symptoms and variable symptoms models using different epidemic datasets, and then using these models to predict the impacts of different interventions. Initially, we analysed simulated data to verify that our model fitting procedure could identify the values of the parameters used to generate the data. We then conducted a further investigation in which we fitted the models to data from two Ebola epidemics – first, the current Ebola epidemic in the Democratic Republic of the Congo, and second the Ebola epidemic in west Africa in 2014–16.

3.1. Simulation study

First, we generated synthetic data on the cumulative numbers of detected hosts during a simulated Ebola epidemic. To do this, we ran the more realistic variable symptoms model, and then assumed that the value of $C + R$ was observed each week for 52 weeks. In reality, there are often errors when recording data and so epidemic datasets are “messy”. To account for this, we also assumed normally distributed error on the recorded values in some of our analyses of simulated data (for details of the simulation study, see Section S2 of the Supplementary Material).

We then estimated the values of the parameters β_0 , β_1 , T and T_0 in the variable symptoms and constant symptoms models using least squares estimation, assuming that the values of other parameters are known exactly. We found that the estimated parameter values of the variable symptoms model matched those used to simulate the data (Figs. S1C and S1D and Table S2). However, we found that the constant symptoms model could also fit the data equally well (see e.g. Fig. S2A, in which the distance between the simulated data and the numerical solution of the fitted model is almost identical when the constant symptoms and variable symptoms models are used; see also the R^2 values reported in Table S3).

However, while both models can reproduce the simulated epidemic data equally well, when the models are used to predict the impacts of intensifying surveillance, the predictions from the models were entirely different (Fig. S2B). We tested the robustness of this result to the values of the parameters used to generate the synthetic dataset (Figs. S4–S6), as well as to different magnitudes of error in the data (Fig. S3). We found that, in each case, when surveillance is altered identically in the fitted models, the predictions of epidemiological dynamics generated by the models are different.

3.2. Application to Ebola data

To show that our main message – that accurate forecasts of the effects of interventions may require models that account for variations in symptoms during infection – is important for real world epidemics, we then repeated our analyses using data from two Ebola epidemics rather than using synthetic data.

We first considered data from the ongoing Ebola epidemic in the Democratic Republic of the Congo (Fig. 3A). We again fitted the constant symptoms model and variable symptoms model to this dataset in turn, and found that both of these models could replicate the observed dynamics of the epidemic (Fig. 3B). Interestingly, the fitted value of the basic reproduction number in the absence of interventions at the beginning of the outbreak (i.e. $R_0 = \frac{\beta_0 N}{\mu}$) was smaller for the variable symptoms model as opposed to the constant symptoms model ($R_0 = 1.83$ for the variable symptoms model compared to $R_0 = 1.90$ for the constant symptoms model), demonstrating the well-known fact that the choice of model structure affects estimates of important epidemiological quantities (Wearing et al., 2005; Lloyd, 2001a, 2009; Weitz and

Dushoff, 2015). We then used these fitted models to predict how the epidemic dynamics would have been altered under a different control intervention. In particular, we again increased the rate of detection in the fitted models, to represent predictions under an intensification of surveillance and control efforts (see Methods).

When surveillance was intensified, the prediction of the constant symptoms model differed substantially from that of the variable symptoms model (Fig. 3C). In particular, for the parameter values displayed here, the constant symptoms model predicted 24% fewer cases than the more epidemiologically realistic variable symptoms model (108 cases in the constant symptoms model as opposed to 142 cases in the variable symptoms model). Consequently, even though the observed dynamics of the models appear identical when fitted to data, they produce different predictions when control interventions are changed.

We then conducted the same analysis with data from the 2014–16 Ebola epidemic in west Africa (Fig. 3D–F). In this case, the constant symptoms model predicted 35% fewer cases than the variable symptoms model when surveillance was intensified (Fig. 3F). Since the total number of cases in this epidemic was so large, this corresponded to a difference of 641 cases between the forecasts of the two models.

We considered the robustness of our results to the values of the model parameters, including the level of surveillance assumed when fitting to data and the extent to which surveillance was changed in the fitted models (Figs. S7–S14). In addition, we considered different assumptions about the level of symptoms in each stage of an Ebola infection by considering different values of the detection probability whenever surveillance occurs (Figs. S15 and S16). In each case, we found qualitatively identical results – both the constant symptoms and variable symptoms models could reproduce epidemic time series data, but when interventions were changed in the models the predicted epidemic dynamics then differed. As well as considering an intensification of surveillance, we also examined cases in which surveillance was relaxed (e.g. two rightmost columns of Fig. S10). Whenever surveillance was intensified, the constant symptoms model underestimated the total number of cases compared to the more realistic variable symptoms model. However, when surveillance was instead reduced, the constant symptoms model led to overestimation of the total number of cases.

We also examined the effect of enhancing surveillance at different times during the epidemic. In particular, we considered increasing the surveillance level only once, after the epidemics had already been in progress until a certain date, for different possible dates of surveillance intensification. The earlier that surveillance was intensified, the larger the error when using the constant symptoms model rather than the more epidemiologically realistic variable symptoms model, since early surveillance intensification then allows more time for model predictions to differ (Figs. 4 and S17).

Until this point, so that we could isolate the effect of variable symptoms alone on the predicted outcomes of interventions, we assumed that at any time during an epidemic all infectious and uncontrolled hosts generated new infections at a constant rate. However, we also conducted an analysis in which the infection rate varied throughout the course of an Ebola infection, by considering cases in which infectiousness was either correlated with or correlated against the level of symptom expression (Fig. 5 and Section S5 of the Supplementary Material). In cases in which higher levels of symptoms were associated with reduced infectiousness – for example due to a lower level of mixing in the population compared to hosts with less serious symptoms – our result that predictions are different between the constant symptoms and variable symptoms models was enhanced (Fig. 5B and D).

4. Discussion

Epidemiological models that have been fitted to data are often used

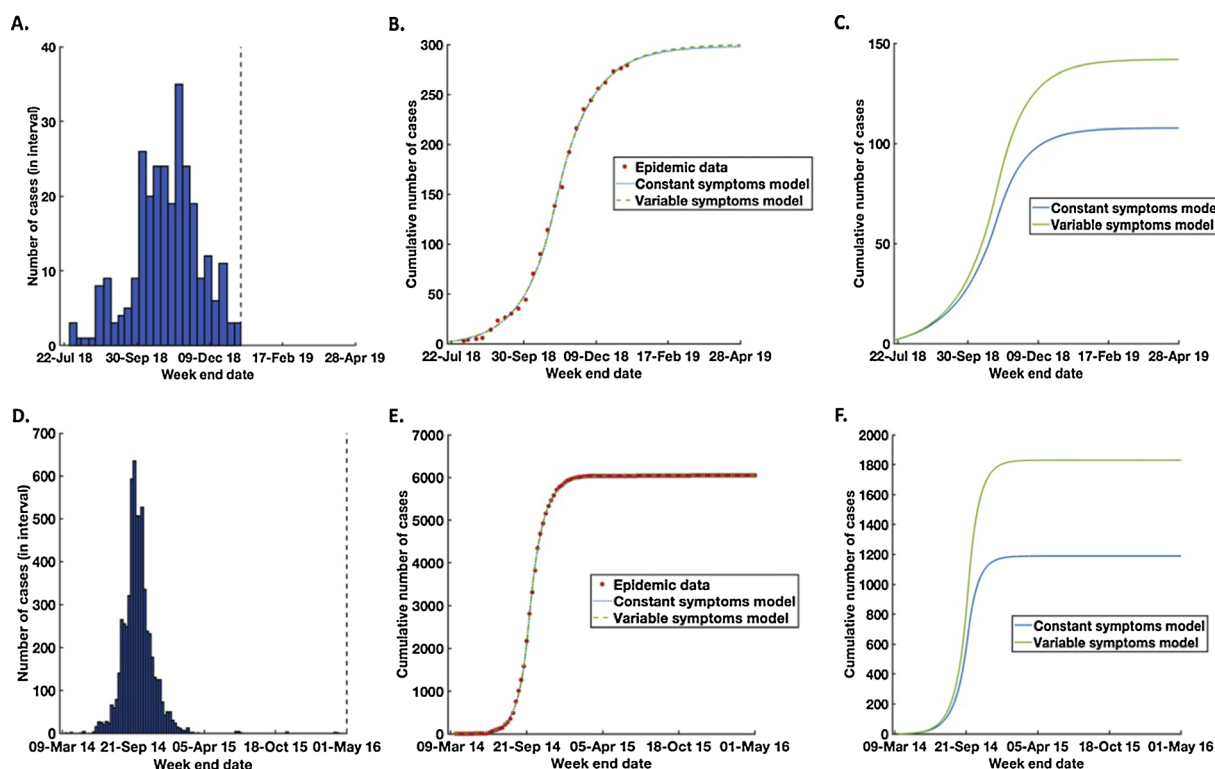


Fig. 3. Using the constant symptoms model and variable symptoms model to predict the effects of alternative interventions. A. Number of cases each week in Beni and Kalunguta health zones in the Democratic Republic of the Congo. The dotted black vertical line represents the time before which data were available. B. Model fits to the data (red dots), using the constant symptoms model (blue dotted) and variable symptoms model (green dash). C. Predictions of the effect of intensified surveillance, using the constant symptoms model (blue) and variable symptoms model (green). D–F. Equivalent figures to A–C, using the data from the 2014–16 Ebola epidemic in Liberia. For model parameters, see Methods and Tables 1 and 2. The quality of the model fits in panels B and E are explored in Section S8 of the Supplementary Material.

to predict the dynamics of an epidemic under different control interventions (Ferguson et al., 2001; Merler et al., 2014; Brooks-Pollock et al., 2014; Kucharski et al., 2015; Cuniffe et al., 2016). However, most models considering interventions targeted at symptomatic hosts assume that those hosts display a constant level of symptoms that does not change during the course of infection. For a number of infectious diseases, however – including Ebola virus disease – there are different stages of an infection, and in each of these stages the level of symptoms is likely to be different. Individuals in early infection tend to have milder symptoms than those in later infection. As a result, symptomatic hosts in early infection are less likely to have appeared in the surveillance data that are routinely collected during an epidemic than those in later infection, who not only have had a longer period during which to be detected but are also likely to have developed more severe and recognisable symptoms.

Here, we have considered Ebola virus disease as a case study, and used two models to explore the dynamics of epidemics under different surveillance levels. We assumed that increased surveillance leads to improved detection and control of symptomatic hosts. We compared the output of a model in which, if an individual is surveyed, the probability of detection is constant at each time during the infectious period (the constant symptoms model) to the equivalent predictions from a model in which the probability of detection increases throughout infection (the variable symptoms model). We found that both these models can be fitted closely to data from Ebola epidemics (Fig. 3B and E). However, when the level of surveillance in the models is increased, we found that the more epidemiologically realistic variable symptoms model predicted a larger number of cases (e.g. Fig. 3C and F). This is concerning, because it suggests that using the epidemiologically unrealistic constant symptoms model, which is of the type most likely to be used in practice, leads to an overestimation of the likely efficacy of

additional interventions. Thus, it might be important to use the more realistic model to predict the quantitative effects of interventions aimed at reducing the impacts of Ebola epidemics.

Variations in symptoms between different stages of infection, as well as the signature of such variable symptoms in those types of data that are collected during an epidemic, have to date received little attention. Until now, the impact of variable symptoms on predictions of models used for testing Ebola interventions has never been rigorously assessed. However, our approach of splitting the infectious and symptomatic period into different compartments was inspired by the so-called “method of stages” (Lloyd, 2001b; Wearing et al., 2005), a technique most often used to model gamma distributed epidemiological periods (Anderson and Watson, 1980; Ma and Earn, 2006; Thompson et al., 2016). Within that framework, varying infectiousness – rather than symptoms – over the course of infection has been considered previously. For example, Cuniffe et al. (2012) considered a model of plant disease epidemics in which the rate of sporulation (production of viable spores by each infected host) is a function of the time since infection, and implemented this in an SEIR model by splitting the *E* and *I* classes into subcompartments, then assigning different infection rates to hosts in the different *I* classes. A similar modelling framework could be adopted in our work, using a large number of compartments so that the level of symptoms is represented by a continuous curve (rather than being at constant levels within the different stages of infection). However, we do not pursue this here, since discrete changes in symptom expression in each symptomatic host are sufficient to make our underlying point that accurate forecasts of the effects of Ebola interventions may require models that account for variations in symptoms.

To conduct our analyses, we sought to develop a simple model in which the level of symptoms increases during infection, and to compare the results from this model to those from the analogous model in which

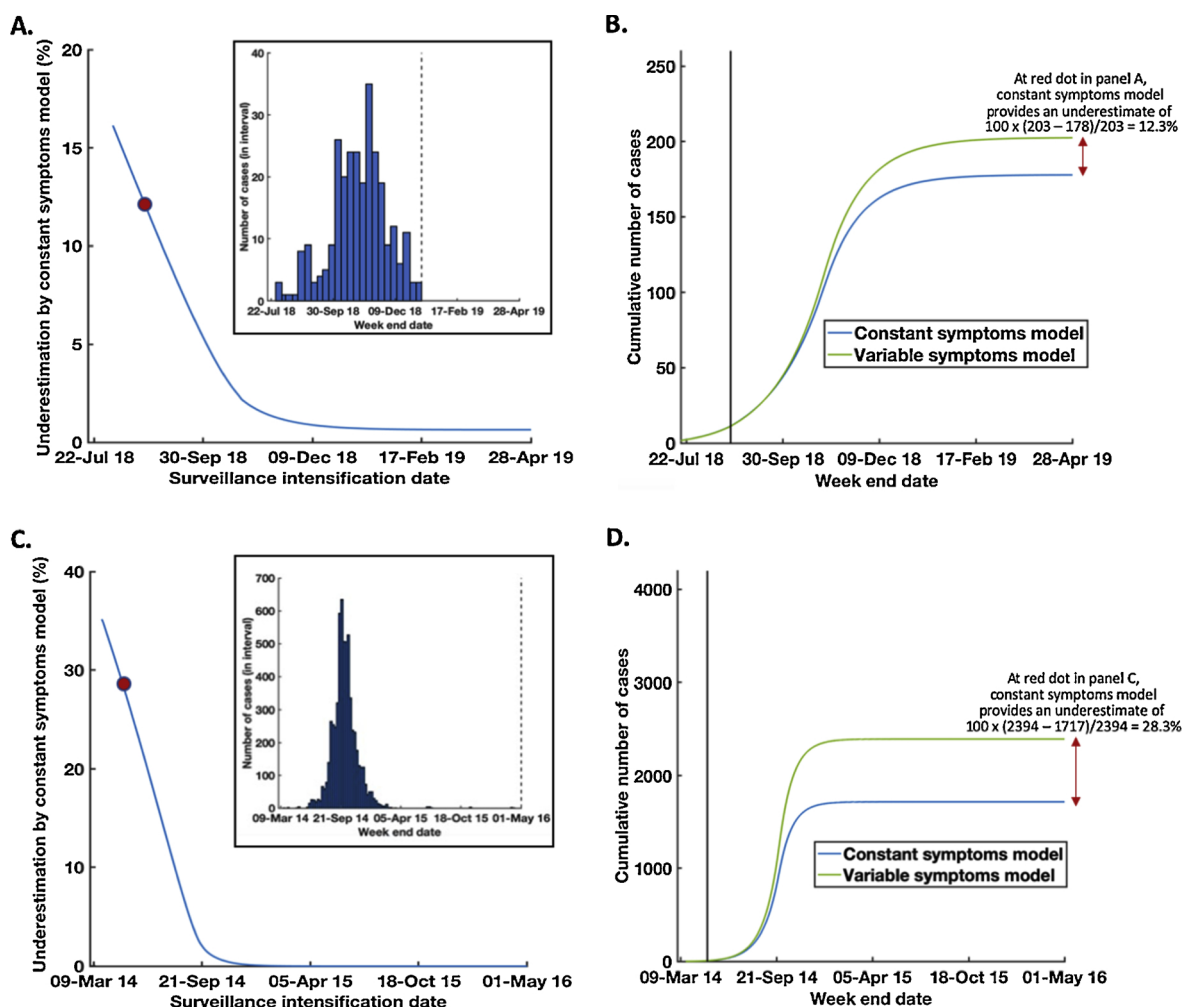


Fig. 4. Using the constant symptoms model and variable symptoms model to predict the effects of alternative interventions, for different times of surveillance intensification. **A.** Reduction in the total number of cases predicted by the constant symptoms model compared to the variable symptoms model, expressed as a percentage of the number of cases predicted by the variable symptoms model, for different times of surveillance intensification. The models were fitted to data from the ongoing epidemic in the Democratic Republic of the Congo. **B.** Illustration of how the values in panel A were calculated. In the graph shown, intensified surveillance began on 23rd August 2018 (black vertical line) in the models fitted to data from the ongoing epidemic in the Democratic Republic of the Congo. This corresponds to the time denoted by the red dot in panel A. **C–D.** Equivalent panels to A–B, for the 2014–16 Ebola epidemic in Liberia. In panel D, intensified surveillance began on 2nd May 2014 (black vertical line). In panels A and C, we only consider intensifying surveillance at or after the time that the first cases were observed (i.e. 3rd August 2018 for the ongoing epidemic in the Democratic Republic of the Congo, and 23rd March 2014 for the 2014–16 Liberia epidemic). The original epidemic datasets are shown as insets to panels A and C. For model parameters, see [Tables 1 and 2](#) and Section S4 of the Supplementary Material.

there is a constant level of symptoms during infection. Practical use of either model during an Ebola epidemic would require adjustment for the particular epidemic under consideration. For example, transmission in different settings could be included in a single model, such as spread in hospitals, community care centres, at funerals or in the wider community ([Camacho et al., 2015](#); [Meakin et al., 2018](#)). We modelled detection and isolation of symptomatic hosts here, but other interventions such as vaccination could be modelled explicitly ([Fisman and Tuite, 2014](#)). If an Ebola vaccine is not perfectly effective, as was suggested for the vaccine being used in the ongoing Ebola epidemic ([Metzger and Vivas-Martínez, 2018](#)), the possibility that vaccination might mask symptoms while not completely stopping infectiousness could be included in our approach. A model that includes spatial spread of the pathogen or transmission through social contact networks might be required to replicate observed data ([Kramer et al., 2016](#); [Kiskowski and Chowell, 2016](#)), or different geographical areas could be considered separately ([WHO Ebola Response Team, 2014](#); [Meakin et al., 2018](#)). To demonstrate that variable symptoms can affect predictions of the effects of interventions, we assumed that all infected individuals pass through three stages of an Ebola infection (from non-specific symptoms, to a

gastrointestinal phase and then to a deterioration phase), whereas in reality some hosts might recover rather than passing to the deterioration phase ([Beeching et al., 2014](#)). At the cost of an additional parameter value to be determined, it would be straightforward to include this in a compartmental epidemiological model (see a preliminary analysis in Section S6 of the Supplementary Material and Fig S18, in which some hosts recover rather than passing to the final stage of infection).

We also modelled surveillance in a simple fashion, by assuming that hosts are surveyed on average at periodic intervals and that there is a particular probability of detection whenever a host is surveyed. For forecasting, it would be necessary to consider the wide range of different surveillance approaches used in practice including contact tracing from known cases ([Pandey et al., 2014](#)) and rural village visitations to detect cases in locations where access to healthcare is limited ([Namukose et al., 2018](#)), as well as disruptions to surveillance caused by factors including armed conflict ([Gostin et al., 2018](#)).

We parameterised our models using the simplest possible approach – namely fitting the total numbers of detected or removed individuals in the relevant classes of the models to data on the cumulative numbers of

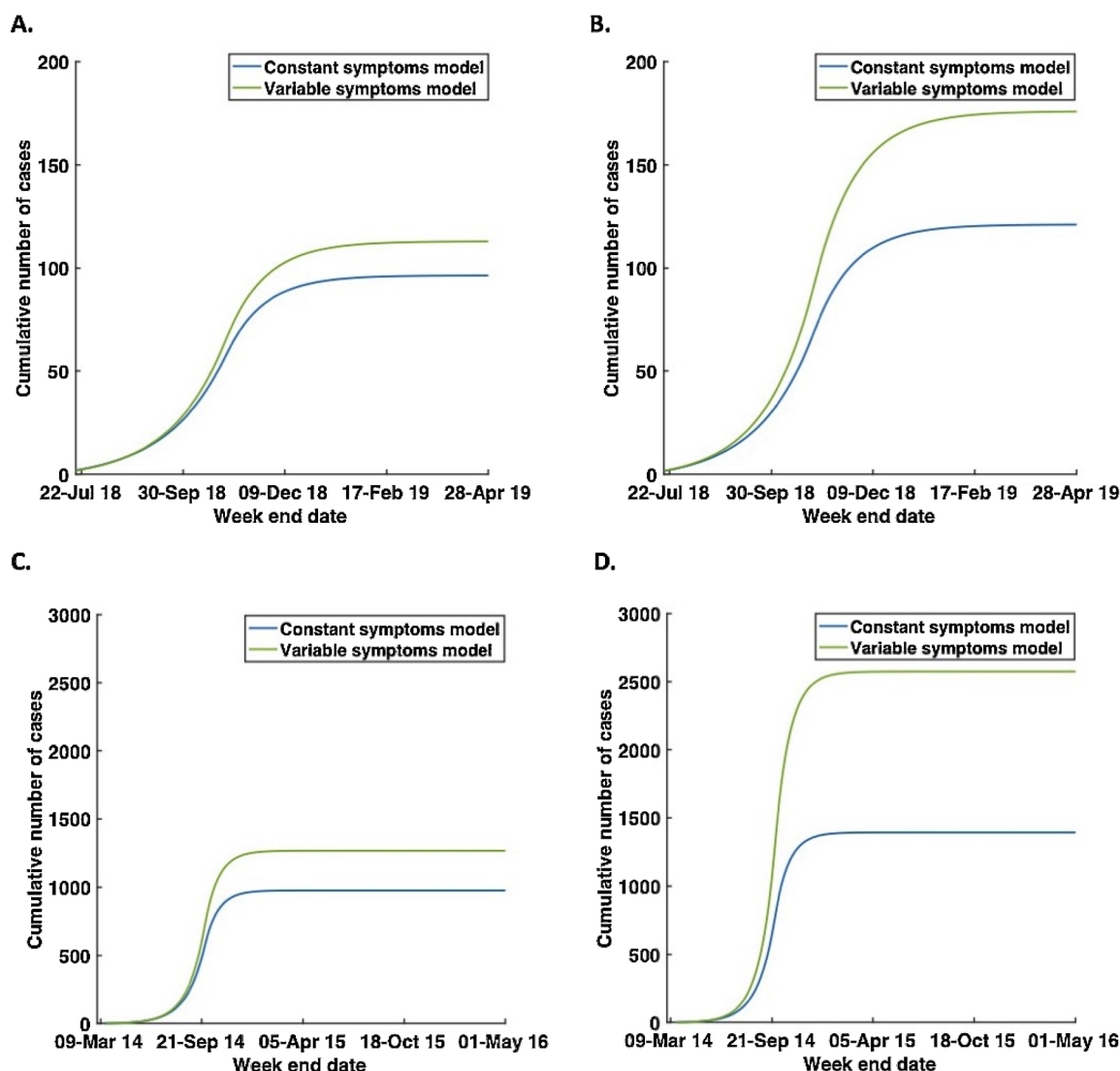


Fig. 5. Using the constant symptoms model and variable symptoms model to predict the effects of alternative interventions, if infectiousness is also assumed to depend on the stage of infection. A. Predictions of the effect of intensified surveillance using the constant symptoms model (blue) and variable symptoms model (green), fitted to data from the ongoing epidemic in the Democratic Republic of the Congo and assuming that infectiousness increases during an Ebola infection as described in Section S5 of the Supplementary Material. B. Predictions of the effect of intensified surveillance using the constant symptoms model (blue) and variable symptoms model (green), fitted to data from the ongoing epidemic in the Democratic Republic of the Congo and assuming that infectiousness decreases during an Ebola infection as described in Section S5 of the Supplementary Material. C–D. Equivalent figures to A–B but fitted to data from the 2014–16 Ebola epidemic in Liberia. The values of parameters other than the fitted parameters (the fitted parameters are: the infection rates β_0 and β_1 , the start times of the epidemics and the times at which the infection rates change) are identical to those in Tables 1 and 2. Surveillance intensification is assumed to occur at the beginning of the epidemic. Model fits are not shown, since they appear identical by eye to those in Fig. 3B and E.

symptomatic cases using least squares estimation – since the precise method of parameter inference was not central to our message. This type of approach has been used previously (Chowell et al., 2004; Chowell et al., 2014; Rivers et al., 2014; Shen et al., 2015; Webb et al., 2015), although we note that fitting stochastic models to non-cumulative incidence data is usually preferable (Grad et al., 2012; Towers et al., 2014; Ma et al., 2014; King et al., 2015), particularly when assessing uncertainty in parameter estimates and forward projections. However, we did not seek to quantify uncertainty in the estimated values of model parameters here. In fact, it has been shown that fitting deterministic models to cumulative incidence data often leads to very similar central parameter estimates compared to fitting stochastic models to raw disaggregated data, despite these approaches generating very different assessments of the uncertainty associated with those parameter estimates (King et al., 2015). As a consequence, we expect our main result, that it may be necessary to include variable symptoms

in models of Ebola interventions, to hold true whether the models are fitted to raw or cumulative data, irrespective of the method of parameter inference used. We demonstrated that this is the case by fitting the models to non-cumulative incidence data for the two Ebola epidemics we considered in the main text (see Supplementary Material Section S7), as well as showing that our model fitting procedure is able to recover parameter values used to generate synthetic datasets even when aggregated data are used (see Supplementary Material Section S2). As a result, fitting to cumulative data has not hindered estimation here. Extending our approach to a stochastic setting for practical applications, including quantification of uncertainty in parameter estimates and forecasts, is an area for future work. Different types and forms of noise in observations, driven by factors including stochasticity in the underlying epidemiological dynamics as well as errors in reporting, could also be considered. In our analyses of synthetic data, we added noise to the datasets by assuming that reporting errors followed a

normal distribution, however alternative error structures could be explored in future studies.

One advantage of the models that we used is that the surveillance level is assumed to impact on the epidemiological dynamics themselves, rather than simply the observed dynamics. This is not always the case in epidemiological models: a common method for accounting for under-reporting is simply to scale the incidence data up (Meltzer et al., 2015), thereby assuming a fixed percentage of infectious cases are detected with no impact on the numbers of cases generated by those individuals. Another approach is to assume that some individuals in the infectious class are unobserved (Thompson et al., 2019b). In reality, detected hosts have a lower probability of transmitting the pathogen than undetected hosts due to the higher chance that detected individuals are subject to interventions, and our models reflect this.

Here, we considered a control strategy of detection and isolation under different surveillance levels. The effects of including variable symptoms in models of other intervention strategies should be tested, to see whether it is always necessary to account for changing levels of symptoms throughout infection. We note that including additional epidemiological detail in forecasting models does not always improve predictions (Thompson and Hart, 2018). Simple models are easier to parameterise and interpret than more complex models, and so modellers should consider carefully, in each study, whether or not including variable symptoms will change model predictions. We also note that, in theory, it might be possible to deploy commonly used epidemiological models with altered parameter values as a proxy for explicit consideration of variable symptoms (Fraser et al., 2004). For example, if the chance of detection in early infection is low, then the period of early non-specific symptoms could be considered as part of the incubation period. In that case, care should be taken when “lifting” the values of model parameters directly from the clinical literature, to ensure that the definitions of parameters in the model match those in the original studies.

In summary, including different levels of symptoms at different stages of infection in epidemiological models can alter predictions of the effects of intervention strategies compared to assuming a fixed level of symptoms. If variations in symptoms during infection – and their impacts on detectability – can be characterised by epidemiologists and then included in predictive tools by modellers, decision makers will be able to make more informed choices as to which particular intervention, or combination of interventions, to pursue.

Authors' contributions

RNT conceived the research; All authors designed the study; RNT, LFRH and WSH carried out the research; RNT supervised the research; RNT and WSH drafted the manuscript; All authors revised the manuscript and gave final approval for publication.

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Data availability

The data used in our analyses are available in the supplementary files DataS1.csv and DataS2.csv. Analyses were performed in Matlab. Code is available for running the models, and is accessible at <https://github.com/will-s-hart/EbolaVariableSymptoms>.

Declaration of Competing Interest

We have no competing interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.epidem.2019.100371>.

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