

# **Confusing symptoms and infectiousness will not always disrupt forecasting and control of Ebola outbreaks**

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To The Editor—The devastating impact of the 2013-16 Ebola outbreak emphasizes the need for effective management of invading pathogens. Mathematical modeling is increasingly used to optimize interventions during outbreaks<sup>1-3</sup>. A recent review<sup>4</sup> demonstrated that the incubation and latent periods differ for Ebola, since dry symptoms precede wet symptoms that accompany infectiousness. The authors suggested that accounting for this difference is likely to have implications for models of Ebola intervention strategies.

We tested this assertion, and found that carefully differentiating between symptoms and infectiousness will not always change forecasts significantly. By fitting models to data collected during an outbreak, the estimated values of disease transmission parameters can compensate for errors driven by incorrect assumptions about the underlying epidemiology. In some cases, forecasts can be accurate even if “wrong” epidemiological models are used.

To demonstrate this principle, we considered two epidemiological models of Ebola (Fig 1A). In the first, symptoms and infectiousness coincided exactly (the commonly used SEIR model<sup>5,6,7</sup>), but in the second the symptoms/infectiousness mismatch was accounted for (SEUIR model<sup>5</sup>). A “dataset” for the start of a hypothetical outbreak was generated using the realistic SEUIR model, producing data on the daily numbers of symptomatic cases (Fig 1B). Then, these data were used to estimate the infection rate parameter of the models ( $\beta$ ), first using the SEIR model and then using the SEUIR model (see Supplementary Material). The estimated values of  $\beta$  were different using each model (Fig 1C left), driven by the incorrect assumption in the SEIR model case about the length of the infectious period. However, when these  $\beta$  values were included with the assumed infectious periods to provide estimates of the basic reproduction number ( $R_0$ ), which characterizes how widely the pathogen is likely to spread, we found that estimates were

approximately the same (Fig 1C right). Consequently, forecasts resulting from forward simulations (Fig 1D) might be unaffected if the incorrect assumption that symptoms and infectiousness always occur concurrently is made in the underlying model of spread. This remains true even when interventions such as vaccination<sup>8</sup> are included in the forward projections (Fig 1E). For further information about our analysis and additional discussion, see Supplementary Material.

For forecasting the effects of some interventions, such as those that reduce the time between symptom onset and isolation, it might be necessary to ensure that infectious periods and symptomatic periods are accurately represented by the epidemiological model. However, for predicting the impacts of vaccination campaigns during Ebola outbreaks, it may not be necessary to measure the lengths of these periods with absolute precision. Careful testing of model assumptions during outbreaks – as well as long-term engagement between clinicians, modellers, and policy-makers – will allow the development of public health policy to be optimized.

## Notes

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Figure 1. Forecasts are similar irrespective of whether or not symptoms and infectiousness are carefully distinguished between. (A) Schematic of the models used to characterize Ebola outbreaks: the oft-used SEIR model (top); and the more realistic SEUIR model (bottom) in which dry and wet symptoms are distinguished between. (B) The simulated “dataset” for the first three months of an Ebola outbreak, generated using the realistic SEUIR model. After three months, in total 48 symptomatic cases have occurred. (C) The value of the infection rate,  $\beta$ , is generated using likelihood estimation (see Supplementary Material) with the SEIR model (top left) and SEUIR model (bottom left). These are combined with the infectious periods for each model to give posterior estimates of  $R_0$  (right). In the right subpanel, vertical dotted lines show the true value of  $R_0$  (dotted blue) and the value of  $R_0$  that might naïvely be expected when the SEIR model is used to estimate  $R_0$  (dotted red – see Supplementary Material). (D) An example single forward simulation using the SEUIR model with no vaccination to project possible numbers of future cases. (E) The results of a large number of forward simulations can be used to estimate the expected final size of the outbreak under different numbers of individuals vaccinated after 3 months of the outbreak. Three quantities are compared: the expected final size with the value of  $R_0$  estimated using the SEUIR model (blue), the expected final size using the value of  $R_0$  that might naïvely be expected when the SEIR model is used (dotted red – see Supplementary Material), and the expected final size with the value of  $R_0$  estimated using the SEUIR model (red). In E, for each line, 1,000 simulations are run per value of the number of individuals vaccinated to calculate the expected values.

Figure 1.

