Essential information: Uncertainty and optimal control of Ebola outbreaks

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Early resolution of uncertainty during an epidemic outbreak can lead to rapid and efficient decision-making, provided the uncertainty affects prioritization of actions. The wide range in caseload projections for the 2014 Ebola outbreak caused great concern and debate about the utility of models. By coding and running 37 published Ebola models with five candidate interventions, we found that, despite this large variation in caseload projection, the ranking of management options was relatively consistent. Reducing funeral and community transmission were generally ranked as the two best options. Value of Information (VoI) analyses show that caseloads could be reduced by 11% by resolving all model-specific uncertainties, with information about model structure accounting for 82% of this reduction, and uncertainty about caseload only accounting for 12%. Our study demonstrates that the uncertainty that is of most interest epidemiologically may not be the same as the uncertainty that is most relevant for management. If the goal is to improve management outcomes, then the focus of study should be to identify and resolve those uncertainties that most hinder the choice of an optimal intervention. Our study further demonstrates that simplifying multiple alternative models into a smaller number of relevant groups (here, with shared structure) could streamline the decision-making process, and may allow for a better integration of epidemiological modeling and decision-making for policy.

Value of Information (VoI) | Epidemiological outbreak management; | Decision making

Introduction

The devastating 2014 Ebola outbreak in West Africa is the largest ever recorded (1, 2). It resulted in 28646 cases and 11323 deaths by March 27, 2016 (WHO report; http://apps.who.int/ebola/ebola-situation-reports), and engendered an outpouring of concern for those affected. A large number of epidemiological models were developed and published (2-4). To date we have identified 55 published Ebola models. Most of these models (50/55) projected caseloads as the preferred way to predict epidemic trajectory. However, caseload projections varied widely between models, drawing a great deal of attention, and causing intense debate (5, 6).

Caseload projection is critical for predicting the size of an epidemic and for planning management efforts, and it can vary from model to model for several reasons, such as differences in model structure, parameterization, and other assumptions. Despite this, a critical question for decision-making is whether different models lead to different management recommendations, or different rankings of alternative management actions. If all models agree on the optimal management, then differences in projections are not a critical concern for decision-making. Otherwise, if models disagree with respect to the ranking of management recommendations, then the optimal intervention is model specific, which means policy-makers face the question of which model(s) to rely on to make management decisions; a closer examination of the source of the disagreement is then warranted.

Here, with the objective of minimizing the Ebola caseload, we explored the management recommendations of a large set of published Ebola models. We considered 37 published compartmental Ebola models that varied widely in model structure, parameterization, or both (Table S1). Among them, the *SEIR* compartment model is the most commonly adopted model framework, where individuals progress through susceptible (S) to exposed (E), infectious (I) and then removed (R) compartments through either recovery or death. Since hospital settings and funerals have been identified as critical transmission sources and targets for intervention, some models explicitly include a hospital (H) or a funeral (F) compartment. Based on model structure, we classified the 37 models into four categories: models with both H and F explicitly represented (referred to as *SEIHFR*), models with only H explicitly represented (*SEIHR*), models with only F explicitly represented (*SEIFR*), and models with neither H nor F compartments (*SEIR*). To ensure consistency, we recoded all the models within the same stochastic environment by simulating the epidemic birth-and-death processes using the Gillespie algorithm with a tau-leaping approximation (3, 7). We then identified five management actions that are broadly applied to control Ebola: reducing community transmission, reducing hospital transmission, reducing funeral transmission, increasing hospitalization, and reducing case fatality ratio (2, 3, 8, 9). We projected the caseload under the five management interventions and identified the optimum management for each model. We then used Value of Information (VoI; 10, 11) analyses to quantify the potential improvement in caseload outcomes achieved by resolving model-

Significance

The 2014 Ebola outbreak illustrates the complexities of decision-making in the face of explosive epidemics; management interventions must be enacted despite imperfect or missing information. The wide range in projected caseload generated attention as a source of uncertainty, but debate did not address whether this uncertainty affected the choice of action. By re-evaluating 37 published models, we show that the majority of models concur that reducing funeral and community transmission are robust and effective management actions to minimize projected caseload. While models disagreed about absolute caseload, this has little relevance for evaluating candidate interventions. Our study highlights the importance of projecting the impact of interventions, and is applicable to the management of other epidemic outbreaks where rapid decision-making is critical.

Reserved for Publication Footnotes

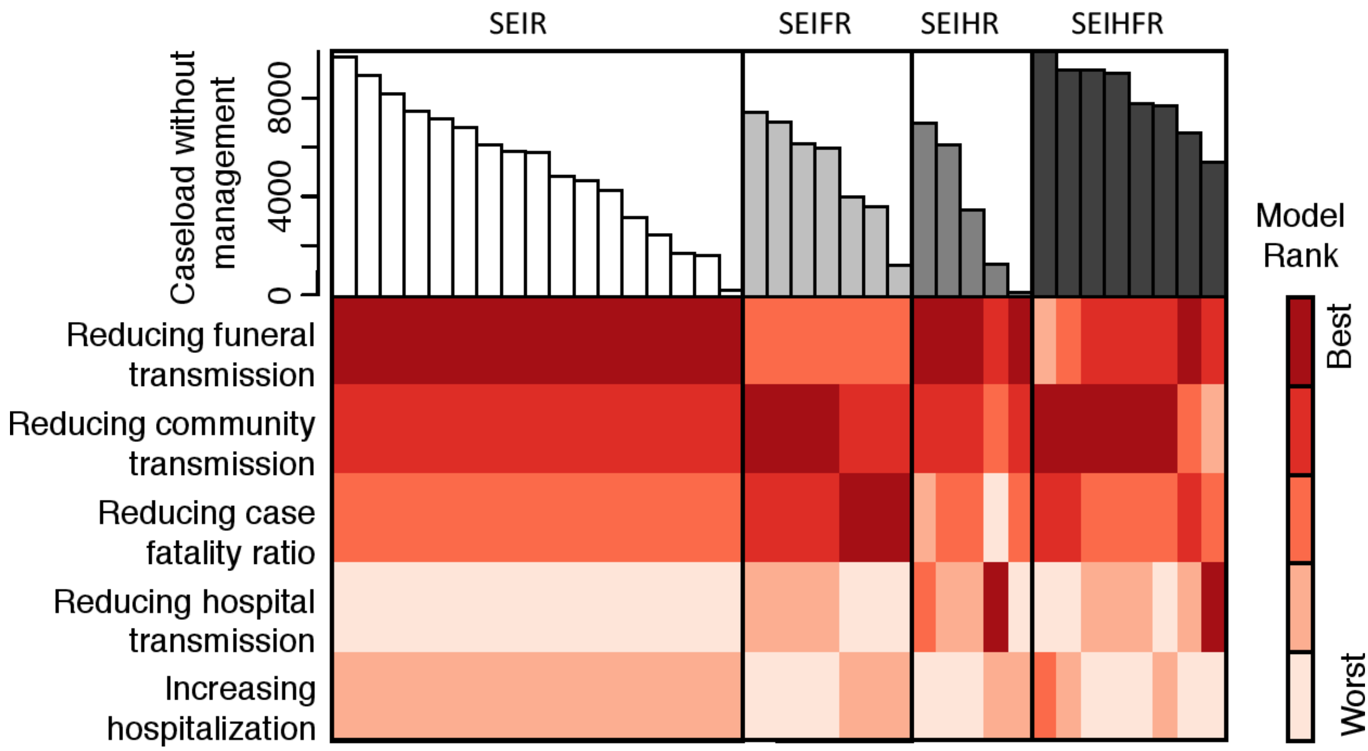

Fig. 1. Unconstrained caseload projections (above) and ranks of five management actions (below) under 37 published compartmental Ebola models with *SEIHFR* (representing susceptible, exposed, infectious, hospitalized and funeral compartments), *SEIHR*, *SEIFR* or *SEIR* structures. For each model, the five management actions were ranked from the worst (with highest caseload projection) as shown in light red to the best (with lowest caseload projection) as shown in dark red. Simulated population size is 10000 people, and the effectiveness is 30% for each management action.

specific uncertainty and to identify the key uncertainties to resolve in order to achieve that improvement.

The Ebola outbreak highlighted the challenges and opportunities that arise when multiple modeling groups contribute models and projections to help inform decision-making. The VoI framework allows us to study the robustness of conclusions in the face of multiple alternative models and to discover important model sensitivities with respect to the ranking of interventions. By studying an ensemble of models, we can identify actions that are robust in the face of uncertainty, as well as sources of uncertainty that warrant immediate study.

Results

In our simulations, starting with 10 infectious cases in a population of 10000 individuals, the mean projected caseload was 5615 ± 2705 (sd), ranging from 184 to 9887 cases (Fig. 1). Despite this difference in caseload projections, the majority of the models suggested similar management recommendations (Fig. 1).

We define the effect of an intervention as the percentage change compared to a no-intervention baseline. The effect of an intervention on underlying rates (e.g. transmission, hospitalization) is unlikely to be known *a priori*; therefore we first projected caseload assuming each intervention resulted in a 30% change in affected parameters. Given a 30% change for each intervention, the majority (22/37) of the models recommended reducing funeral transmission as the optimal action, and 29/37 or 36/37 models ranked it as among the top two or three, respectively. Reducing community transmission was optimal for 10/37 models, and 33/37 models ranked it in the top two. Reducing the case fatality ratio was optimal for 3/37 models, and reducing hospital transmission was optimal for 2/37 models, while increasing hospitalization was not optimal in any model (Fig. 1). The optimal management recommendation was closely associated with model structure, for example all *SEIR* and the majority (4/5) of *SEIHR* models recommended reducing funeral transmission as the optimal action, while the majority (6/8) of *SEIHFR* models recommended reducing community transmission (Fig. 1).

The final epidemic size (i.e., the total caseload) is linked to the basic reproductive ratio, R_0, in *SEIR*-like compartmental models such as those analyzed here (12). To provide a deeper mathematical understanding of our individual model results, we therefore conducted elasticity (proportional sensitivity) analyses of R_0 to the parameters associated with the five interventions in the full *SEIHFR* models (in which all parameters could be explicitly perturbed). This analysis revealed that the ranking of the elasticities was the same as that of the associated interventions (Table S2, Fig. 1); if we only have a single model, alternative interventions can be ranked by their effect on R_0.

To illustrate the sensitivity of the optimal intervention to the intervention effect size we also compared caseload projections under a particular intervention over a gradient of changes ranging from 10%-100% in increments of 10% to projections under the rest of the four interventions with the baseline change of 30%. These analyses highlight that whether an intervention is ranked as optimal depends on its effect size. Reducing funeral transmission is optimal in 22/37 models if the effect is over 30%, and optimal in 31/37 models if interventions associated with burials lead to an 80% reduction. Reducing community transmission is rarely optimal when the effect size is less than 30%, but it is recommended as the best intervention in 32/37 models if it can be reduced by 50%. Interventions aimed at reducing the case fatality ratio must achieve a reduction of 60% in order to be optimal in 26/37 of the models (Fig. 2, Fig. S1). Notably, increasing hospitalization or reducing hospital transmission were rarely optimal interventions, even at 100% effectiveness.

We calculated the Expected Value of Perfect Information (EVPI; 10, 11), which quantifies the maximum achievable improvement in management that could be obtained by identifying

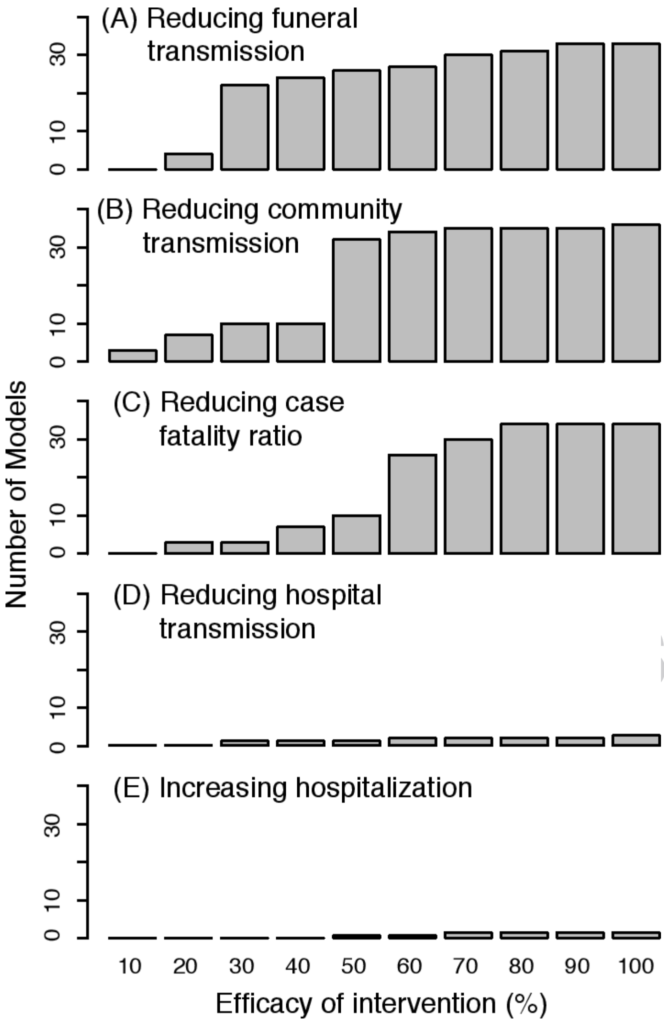

Fig. 2. The number of models that are recommended as optimal for the interventions of (A) reducing funeral transmission, (B) reducing community transmission, (C) reducing case fatality ratio, (D) reducing hospital transmission, and (E) increasing hospitalization. Evaluation was based on comparisons of caseload projections under each specific management action over a gradient of changes ranging from 10% to 100% against all of the other management actions with a baseline intensity of 30%.

a single model as "best" prior to the implementation of specific decisions (see Materials and Methods for formal definition). The EVPI analysis showed that the expected improvement in management outcomes due to resolving all model specific uncertainties is an 11% reduction in caseload. We further conducted an analysis of the Expected Value of Partial Information (EVPXI; 10), which quantifies the expected improvement in management performance by resolving a subset of uncertainties. In particular, we quantified the relative contribution of uncertainty about model structure (*SEIR*, *SEIHR*, *SEIFR*, or *SEIHFR*) and caseload projection (models that projected low, low intermediate, high intermediate, or high case burden) to expected management outcomes. The EVPXI analysis illustrates that targeting the uncertainties in model structure could improve management (i.e. reduction in caseload) by 9% (82% of total EVPI), but targeting uncertainties in caseload projection could only achieve 1% improvement of management (12% of total EVPI). Thus, the two most important take home messages from our analyses are that while differences in caseload projections from the various models dominated much of the public discussion, (i) intervention rankings are not affected by this issue, and (ii) resolving uncertainty in model structure is important for identifying optimal response strategies.

Discussion

Identifying the uncertainties that affect the choice of management intervention is critical for focusing scientific inquiry on questions that will improve the management of an epidemic. Conditional on a single model, a conventional approach is to evaluate the sensitivity of outcomes and management recommendations to parametric uncertainty. However, it is increasingly common that there are multiple, independent models that can contribute to the evaluation of candidate interventions and policy development (2, 3, 8, 9). Thus, we present a framework for integrating model output to identify actions that are robust to the parametric, structural and other uncertainty reflected in an ensemble of models. Our study showed that, despite large differences in caseload projections, management recommendations are broadly consistent across 37 published Ebola models; reducing funeral and community transmission are generally ranked as the top two best management options, while hospital-associated actions are rarely the best. Focusing on individual *SEIHFR* models, the same rank order was found for the proportional sensitivity of R_0 to the parameters associated with each of the five interventions. This aligns with classical theory (12): if we only have a single model, interventions that most affect the basic reproductive ratio are the best. Both funeral transmission (*2*, *9*) and community transmission (*9*, *13*) were identified as critical transmission sources and therefore targets for intervention against Ebola in previous studies. Despite the broad consensus among model recommendations, our EVPI analysis showed that resolving model uncertainties could improve management by 11%. Considering the 2014 Ebola outbreak, which had a caseload of 28646 and a case fatality ratio of over 50%, this would represent a reduction of 3266 cases and 1633 deaths averted. By conducting model-class-specific analyses of EVPXI, we found that the value of information for model structure was far higher than for caseload projections. Thus, the ranking of interventions was not strongly correlated with caseload projections, though expected caseload does provide information on how much effort will be required to halt the epidemic. The ranking of interventions differed more between than within model structures. This result could be a reflection of the inherent differences in the dynamics of different model structures, or due to differences between explicit and implicit representation of interventions within the same model structure. When the target compartments for specific interventions were not explicitly represented in the originally published models, then implementing interventions involved more subtle decisions. While we tried to achieve the best standardization, our choices (detailed in the Supplementary Information) may hamper fair comparisons. An obvious solution is to focus on models that consistently and explicitly represent both compartments and interventions (implying an important role for the integration of operations research and epidemic modeling, to ensure that modeled interventions are realistic and reflect real-world constraints). However, we garnered important new insights by studying all 37 models rather than restricting our analysis to the eight parameterized *SEIHFR* models.

Our study chose a 30% change to illustrate the management ranking based on caseload; we did not specifically consider the operational cost or constraints inherent in achieving that level of effect with each intervention. In practice, the same percentage change in one intervention might be harder or more expensive to achieve than another. Therefore, it is also important to consider operational and economic constraints (14, 15). Our analysis showed that some interventions, like reducing funeral transmission, can be ranked highly even if they only achieve low effectiveness, but others, such as reducing community transmission and reducing the case fatality ratio, are only ranked high if highly effective. In contrast, interventions targeting hospitalization rate and hospital transmission were rarely optimal, even at 100% effectiveness. Thus, while additional operational or behavioral information may be necessary to evaluate the potential effect of these interventions (e.g. because of interactions with social and cultural processes; *16*), the framework we have presented can be used to estimate minimal levels of effectiveness necessary to consider different classes of interventions. It also needs to be noted that, for purposes of illustration, we evaluated each management action separately in the current study. However, management interventions are not mutually exclusive and combined interventions should be studied. The VoI decision-theoretic approach can easily extend to this situation.

In the current study, we focused on minimizing cases as our objective, as most of the published models projected caseload. However, recommended interventions may differ when considering different objectives, such as minimizing mortality or epidemic duration (17). In the case of the 2014 Ebola outbreak, intervention recommendations for the objective of minimizing deaths were the same as for minimizing caseload because the case fatality ratio was quite similar for different compartments in the published models.

Overall, our study demonstrates that, while differences in Ebola caseload projections were a subject of concern, identification and resolution of uncertainties that hinder management (here, model structure) are more relevant to the selection of optimal response strategies. Our work adds to a growing body of literature on uncertainty in disease dynamics from the standpoint of the decision maker, and emphasizes that the uncertainty that is of interest epidemiologically (here, final epidemic size) may not be the same as the uncertainty that is most relevant to management (ranking of candidate interventions).

Our work used VoI to quantify the expected benefit of resolving uncertainty in a decision-making context, conditional on model-specific projections. For the published Ebola models, we showed that achieving scientific resolution on model structure achieves 82% of the expected benefit of reducing all uncertainty considered. Scientific understanding (legitimate scientific differences of opinion/data) is frequently described in multiple competing models. Previous methods have assessed potential interventions conditional on individual models, or used ensemble prediction (*18*). Instead, we propose the use of VoI to identify which scientific differences of opinion lead to different management recommendations; research should then prioritize learning about these operationally relevant uncertainties. Thus, our analysis is explicitly not focused on selecting a "best" model (as is commonly done). Rather we use all models to identify actions that are robust and uncertainties that are important across the suite of candidate models. For Ebola, simplifying a large set of models into a smaller number of relevant classes (at the level of model structure) may allow for better integration of epidemiological modeling and decision-making for policy. In other outbreak situations, resolution of other sources of uncertainty may be more important. More generally, our study demonstrates how VoI analysis may provide "rules of thumb" to guide the decision-making process for other epidemics, such as Zika or avian influenza, where significant uncertainty about individual models remains, but timely decision-making is required.

Materials and Methods

Literature survey of published Ebola models

We conducted a literature survey for any published Ebola models on the Institute for Scientific Information (ISI) Web of Knowledge and through the Google search engine, using the search terms "Ebola" and "model". We identified a total of 55 mathematical models in 35 publications and one online final report. The majority (37/55) of the models were compartmental models, while the rest (18/55) adopted one or more of a variety of modeling approaches, such as branching process models (*19*), and spatial models (*20*). Our study focused on the 37 compartment models (see list in supplementary Table S1); this was the most widely-used modelling approach for Ebola epidemic projection and management evaluation (*2*, *3*, *9*). The consistent framework of compartmental models allows for a general comparison of projected epidemic dynamics among models. Additionally, the widely proposed interventions in practice are either explicitly or implicitly applicable to these models and therefore the effectiveness of different interventions can be compared within and among models.

Compartment models

In an Ebola compartment model, individuals in a population are classified into different states, as represented by different model compartments, based on their health status. All individuals remain in the susceptible (*S*) compartment until they contract the virus through contact with infectious individuals; they then enter the exposed (*E*) compartment, where they are infected but not yet infectious. Exposed individuals move to the infectious (*I*) compartment after a certain latent period, at which point they start to show symptoms and become infectious to other individuals. Infectious individuals will either remain in the community or be hospitalized; both are removed (*R*) from the chain of transmission through either recovery or death. Deceased individuals may infect others until they are buried.

Compartment models may incorporate different subsets of compartments to explore different transmission mechanisms or to evaluate the effectiveness of different interventions. Hospital settings and transmission during funeral practices have been identified as critical transmission sources of Ebola. A number of published Ebola compartment models have addressed these transmission mechanisms by explicitly including a hospitalized (*H*) compartment and a funeral (*F*) compartment (3, 8, 9, 13). Based on the model structure, we classified the 37 models into four categories: models with both *H* and *F* explicitly represented (8 models; referred to as *SEIHFR*), models with only *H* explicitly represented (5 models; referred to as *SEIHR*), models with only *F* explicitly represented (7 models; referred to as *SEIFR*), and models with neither *H* nor *F* compartments, i.e. these mechanisms of transmission were implicitly incorporated in overall transmission (17 models; referred to as *SEIR* models). To ensure consistency, we recoded all the 37 models within the same stochastic environment (epidemic birth-and-death processes simulated using the Gillespie algorithm with a tau-leaping approximation; see details below; 3, 7) using R 3.2.1 (21). A figure of the global model, within which all the 37 models can be represented as sub-models, is presented in supplementary Fig. S2. Parameters for the 37 models are listed in supplementary Table S3. Additionally, to ensure correct representation of the published models, we recalculated the basic reproductive number (R_0; see Table S3) using the next generation framework (22). Code to run all the models is available in the supplementary information files: "Parameters.R", "Functions.R", and "Running models.R".

Management actions

By surveying the literature, we selected five interventions that were broadly applied to control Ebola outbreaks: reducing community transmission, increasing hospitalization, reducing hospital transmission, reducing case fatality ratio, and reducing funeral transmission (2, 3, 8). Reducing community transmission (i.e. transmission in the community) is a general intervention that is achieved in a variety of ways, such as by providing household sanitation kits, improving contact tracing, improving self-quarantine of sick individuals in the community, reducing individual mobility and border crossing, and increasing community awareness through educational campaigns (2, 3, 8). Hospitalization increase can be realized by improving contact tracing and intensifying campaigns to identify and isolate patients, building more Ebola Treatment Centers (ETC), increasing the number of beds, and increasing necessary supplies and public support (3, 9). A reduction in hospital transmission can be achieved by encouraging the use of personal protective equipment (PPE) for healthcare personnel treating infected cases and reducing hospital visits (8). Hydration of infected individuals has proved to be an important way to reduce mortality of Ebola cases, and various other new pharmaceutical approaches are being explored for future outbreaks. Funeral transmission (i.e. transmission at funerals) reduction can be achieved through improved funeral practices to increase safe burial by reducing risky behavior (2, 8).

Intervention implementation

Interventions can be modeled by changing the parameters thought to be influenced by the corresponding management actions. A reduction in transmission in the community, in hospitals, or at funerals can be modeled by reducing the transmission coefficients associated with these classes. Increasing hospitalization can be simulated by increasing the hospitalization ratio, and reducing mortality can be modeled by decreasing the case fatality ratio. Each intervention was assessed in each model in terms of the objective to minimize the Ebola caseload; for each model, we projected caseload under the five interventions, and then ranked the interventions from the best (lowest caseload) to the worst (highest caseload). All the five interventions can be explicitly implemented in the full *SEIHFR* models; for the other models with some compartments unspecified, the corresponding interventions need to be simulated implicitly. For example, reducing hospital transmission can only be explicitly applied to the *SEIHFR* and *SEIHR* models in which the *H* compartment is explicitly represented, but not in the *SEIFR* or *SEIR* models where the *H* compartment is unspecified. To be able to evaluate management options and conduct Value of Information (VoI) analysis across all the published models, including those that do not explicitly represent all infectious compartments, we calculated the implicit effect of an intervention via the average proportional contribution of the target transmission to the overall transmission based on the full *SEIHFR* models. For example, a proportional reduction of ΔH in hospital transmission can be explicitly simulated by multiplying the coefficient of hospital transmission by 1 - ΔH in the *SEIHFR* and *SEIHR* models. But, for the *SEIFR* or *SEIR* models where the *H* compartment is unspecified, an implicit simulation method needs to be applied. If P_H is the proportional contribution of hospital transmission to the overall transmission, then a reduction of ΔH in hospital transmission can be implicitly simulated via multiplying the coefficient of overall transmission by the factor 1 - ΔHP_H. Detailed description of the implicit simulation of the other interventions is provided in the supplementary information. The parameters used for the implicit management simulations were all based on the mean of the parameters across all the published *SEIHFR* full models as shown in the supplementary Table S4.

The effect of an intervention, which we define as the percentage change compared to baseline, may not be known *a priori*. For illustration, we first projected caseload considering a 30% change for each of the five interventions. Based on the caseload projection, we evaluated the five interventions as well as the outcomes expected without any intervention for each of the 37 models. We ranked them from the best (lowest caseload) to the worst (highest caseload). To illustrate how to identify at what effect size a particular intervention shifts to be best, we also compared caseload projections under a particular intervention over a gradient of changes ranging from 10%-100% (with an interval of 10%) against the projections under the rest of the four interventions with the baseline change of 30%. For example, to assess the intervention of reducing community transmission, we did caseload projections by reducing community transmission from 10% to 100% for all 37 models, and then compared each projection under each level of change against the other four interventions with a change of 30%, and then ranked the intervention.

We implemented stochastic simulations for all models using Gillespie's algorithm with a tau-leaping approximation (3, 7) to capture the random nature of epidemic birth and death processes (23). We performed 100 stochastic simulations for each management intervention-model combination, with 10 initial infectious individuals in a population of 10000 individuals. When the parameters in the original publication were time-dependent, we fixed baseline parameters at values used at the start of the epidemic, and/or set them to the no-intervention baseline. To be able to conduct this broad comparison across all models, hospitalization capacity was not modeled, as only a few models considered this factor. Code to assess all interventions in all the models in the current study is given in supplementary information files named "Parameters.R", "Functions.R", and "Running models.R". Additionally, to examine how sensitive R_0 is to parameters associated with the five interventions, we conducted an elasticity (proportional sensitivity) analysis (supplementary Table S2). We calculated R_0 using the next generation framework and estimated derivatives numerically by the method of difference. We limited this analysis to the full *SEIHFR* models, in which all associated parameters were explicitly represented, thus allowing a perturbation of the full set of associated parameters. We then compared the rank of the elasticity of the parameters to the rank of the associated interventions.

Value of Information (VoI) analysis

We calculated Expected Value of Perfect Information (EVPI), which quantifies the maximum achievable improvement in management that could be obtained by resolving uncertainties prior to the implementation of specific decisions (10, 11). It is quantified as:

$$EVPI = \sum_{j=1}^{n} p_j\left(opt_a C_{a,j}\right) - opt_a \sum_{j=1}^{n} p_j C_{a,j} \qquad (1)$$

Where n is the total number of models, $C_{a,j}$ represents management performance (i.e. caseload in the current study) associated with taking intervention *a* under model *j*, p_j is the weight associated with model *j* (i.e. the belief that model *j* is the true model; subject to the constraint that the p_j sum to 1), and opt_a indicates the optimum over all interventions (10, 11). In this initial analysis we weighed the models equally.

EVPI describes the benefit of resolving all sources of uncertainty. In practice, due to limited time and resources, it may not be possible to collect all the required information. In this case, it is more realistic to prioritize a subset of uncertainties to resolve to maximize management improvement. Analysis of the Expected Value of Partial Information (EVPXI) quantifies how much management performance could be improved by resolving a subset of uncertainties, and therefore provides a useful tool to identify which subset of uncertainties should be given priority if time and resources are limited (10). EVPXI is calculated as:

$$EVPXI = \sum_{i=1}^{q} opt_a \sum_{j \in s_i} p_j C_{a,j} - opt_a \sum_{j=1}^{n} p_j C_{a,j} \qquad (2)$$

where *n* models are grouped into $i = 1 \ldots q$ mutually exclusive and exhaustive sets, set s_i has n_i models in it, p_j is the weight associated with model *j*, and $C_{a,j}$ is the management performance under model *j* and intervention *a* . Therefore, EVPXI quantifies the improvement in management performance by resolving the uncertainty associated with s_i (10). We conducted EVPXI analyses for four subsets of models with different types of structures (*SEIHFR*, *SEIHR*, *SEIFR* and *SEIR*) and also for four subsets of models with different ranges of caseload projections (<2500, 2500-5000, 5000-7500 and >7500 cases) to evaluate the improvement in management by resolving uncertainties in model structure and the range of caseload projections.

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