The Quantification and Management of Uncertainty in Smallpox Intervention Models

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1 Introduction

Uncertainty is an issue present throughout the field of modeling and simulation. Due to uncertainty, modelers must make assumptions which affect simulation output. The user must possess knowledge about how and to what extent each assumption affects results in order to gain useful insights from the model. This knowledge is often, however, not present.

To address this problem, we implement and evaluate a framework for quantified representation and propagation of uncertainty. This framework allows for incorporation of uncertainty in model input and produces an uncertainty range in model output through use of imprecise probability theory. Combined with a sensitivity analysis, the quantifiable effect of each assumption is obtainable. Our work provides users with insights into model validity and enables effective comparison between models.

To measure success, the framework is applied to smallpox intervention models. Due to the high level of uncertainty in smallpox models and the high-risk decisions they influence, smallpox models serve as an appropriate case study. Focusing on two commonly-cited smallpox models and a range of subject matter expert parameter sets, we demonstrate that insights can be gained from the application of the framework which are not attainable from the model output itself. This outcome serves as a validation of the framework and as a significant contribution to the field of computational epidemiology.

1.1 Significance of Smallpox

Funding for the study of smallpox spread and intervention has increased in the past decade due to social and political factors. Despite eradication of smallpox in 1980, U.S. intelligence has uncovered at least five countries, including the U.S., which possess samples of the smallpox virus (Kemper, 2003). In light of the events of September 11th and the subsequent anthrax attacks, potential malicious use of these samples is a concern.

In order to protect the public, policy officials seek to devise an intervention strategy to minimize deaths in the event of an outbreak. The smallpox vaccination carries high risk of adverse effects, making the solution more complex than requiring mass public vaccination. As experimental studies of intervention effectiveness are not possible short of intentionally infecting the public, policy officials have turned to computational methods.

Numerous groups have created models to aid in determining an optimal intervention strategy. These models, however, give conflicting results and recommendations due to varying model assumptions. Figure 1 depicts the estimated total smallpox cases from a single model when run with different parameter sets assumed by four subject matter experts. The predicted number of total cases differs by orders of magnitude.

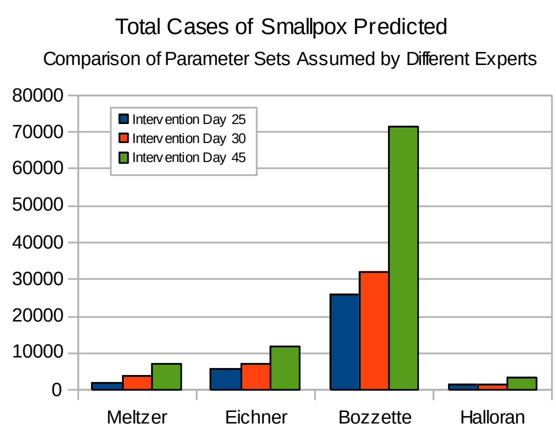


Figure 1. Comparison of Model Output When Assuming Various Parameter Sets. Implementation of Meltzer model used to obtain data (Meltzer, 2001). (Carson).

The issue of conflicting results due to uncertainty has been acknowledged by epidemiologists. Ferguson (2003) argues that a detailed understanding of model sensitivity to assumptions is essential. He warns that if such analysis is not performed, incorrect policy decisions could be made, increasing the death toll of a smallpox outbreak. This work seeks to address the concerns of Ferguson, enabling policy officials to understand the effect of uncertainty when using model results as a basis for high-risk decisions.

1.2 OBJECTIVES

The objectives defining the scope of this work include:

1. Implementation of a framework for the quantification and propagation of uncertainty, including:
   a. Enumeration of values and distributions for a set of assumptions common to the specified area of modeling
   b. Calculation of imprecise probability structures, aggregating values and distributions from a variety of subject matter expert opinions
   c. Implementation of models and ability to sample from uncertainty structures
2. Application of this framework to smallpox intervention models
3. Analysis of insights that can be obtained and benefits provided by use of this framework to serve as validation of effectiveness

2 BACKGROUND

To preface this study, we present an overview of commonly-cited smallpox intervention models and methods in imprecise probability theory.

2.1 SMALLPOX INTERVENTION MODELS

Multiple groups have built models to simulate smallpox spread and intervention techniques. These models are based on the accepted SEIR compartmental model to describe disease spread, in which an individual goes through Susceptible, Exposed, Infected, and Removed stages. Progression to the next stage is determined by a probability distribution.

The Center for Disease Control and Prevention in Atlanta, Georgia published a model in 2001 (Meltzer, 2001). The authors consider vaccination, quarantine, and a combination technique in halting disease spread. Their results led to the recommendation of a combination of quarantine and vaccination in the event of an outbreak.

In 2002, an intervention model was published in *Science* (Halloran, 2002). This group considers different vaccination strategies, modeling targeted vaccination as well as mass vaccination before and after the epidemic. The resulting policy recommendation is highly dependent on whether there exists residual immunity from vaccinations up until 1972. When residual immunity is assumed, this group found that targeted vaccination is optimal under all scenarios.

A third model, from the University of Tubingen in Germany, focuses on case isolation, contact tracing, and vaccination of contacts as intervention methods (Eichner, 2003). The author claims that a smallpox outbreak could be extinguished in less than half a year with no more than 550 cases per 100 index cases.

A model created by the RAND Center for Domestic and International Health Security goes a step further, simulating a variety of attack scenarios (Bozzette, 2003). The study focuses solely on strategies involving vaccination, including mass vaccination, ring vaccination, and prophylactic vaccination. Potentially adverse effects of vaccination are considered when determining an optimal policy. The authors conclude that prior vaccination of health care workers is preferable, but depending on the scenario, mass vaccination could cause more deaths than the disease itself.

Elderd et al (2006) addresses the call for recognition and analysis of smallpox model uncertainties. They study a model with vaccination strategies incorporated and focus on four key epidemic parameters. Their results quantitatively demonstrate the risks associated with ignoring uncertainty in these four parameters. However, only uncertainty in disease spread is taken into account and uncertainty estimates are based on historical outbreak data rather than current subject matter expert estimates. Furthermore, the methodology used is only applicable to analytic models, whereas a large portion of smallpox models are agent-based. Their results therefore do not go far enough in aiding a policy official to evaluate and support an intervention strategy.

2.2 IMPRECISE PROBABILITY THEORY

Imprecise probability theory is useful in capturing uncertainty in parameters and distributions, enabling the representation of both partial knowledge and conflicting knowledge. The simplest approach employs traditional probability theory, allowing computation of expected value and upper and lower bounds. However, traditional probability theory falls short in the representation of epistemic uncertainty, uncertainty due to a lack of knowledge. The use of probability boxes improves upon the shortcomings of traditional probability theory. Probability boxes allow epistemic and aleatory uncertainty, uncertainty due to inherent variability, to be represented differently through upper and lower bounds of possible values.

Dempster-Shafer theory goes a step further and allows multiple, contradictory intervals, and employs “belief” and “plausibility” functions as upper and lower bounds (Spiegel, 2007). Belief is used to quantify the extent to which evidence exists to imply something *is* true, and plausibility captures the extent to which evidence implies that something *might* be true. Dempster-Shafer theory is useful because it allows for the incorporation of only partial information and allows results to be derived despite conflicting evidence. Due to the conflicting and partial information present in smallpox data and subject matter expert opinions, we have selected Dempster-Shafer theory for use in this study.

The framework employed here for uncertainty representation and propagation was implemented based on methods proposed in Spiegel (2007). Spiegel outlines a plan for a new programming language, RiskModelica, which will enable specification of uncertainty. The success of the work presented here establishes the viability and utility of RiskModelica.

3 METHODOLOGY

Two commonly-cited smallpox intervention models were selected for use in this study: Meltzer (2001) and Eichner (2003). Our framework’s methodology involves model implementation and validation, generation of Dempster-Shafer imprecise probability structures, and propagation of uncertainty through the simulation.

Although smallpox is employed as a case study, we suspect that our study can benefit other fields which use modeling and simulation for decision-making purposes. A generalized approach is as follows:

1. In-depth analysis of relevant models and enumeration of both implicit and explicit assumptions made in each
2. Identification of uncertain quantities or methods associated with each assumption
3. Collection of a variety of subject matter expert opinions and data sets to support various estimates of uncertain quantities
4. Quantification of uncertainty using imprecise probability theory
5. Modification of models to sample from imprecise probability structures
6. Analysis of the extent to which each uncertain quantity enlarges this range

3.1 MODEL IMPLEMENTATION AND VALIDATION

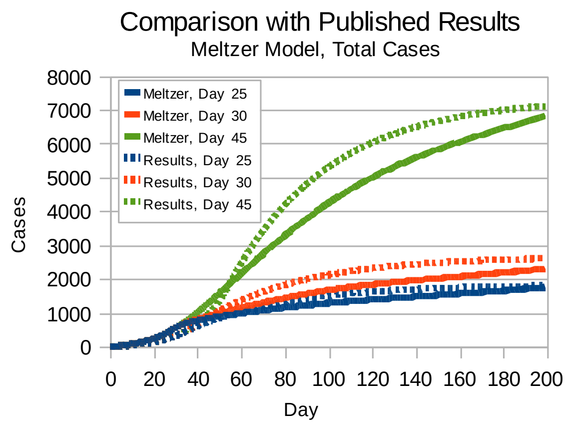
Models presented by Meltzer (2001) and Eichner (2003), herein referred to as the Meltzer model and the Eichner model, were selected for use based on ease of implementation and their prominence in the literature. The Meltzer model simulates a smallpox outbreak with 100 index cases and a transmission rate of 3.0, with an infinite population of susceptible individuals. The model assumes that contagion begins during the prodromal period. Quarantine, vaccination, and a combination strategy are considered, although our implementation is restricted to quarantine for simplification. Meltzer reports that an outbreak can be controlled if 50% of infected individuals are quarantined per day, considering intervention starting on day 25, 30, and 45.

Based on the published algorithm and parameter descriptions, the Meltzer model was implemented in Java. A comparison between published results and our implementation is given in Figure 2. Although our implementation and published results do not correspond precisely, results are on the same order of magnitude and general trends are preserved. Because the general order of magnitude of predicted cases is the important result, we consider the implemented model valid.

The Eichner model focuses on contact tracing as a method to stop disease outbreak. Eichner assumes 100 initially infected, with a transmission rate of 5 people. Time to detect a case starts at 7 days and exponentially decays over time to 3 days. Detected cases are immediately isolated and 5 close contacts are kept under surveillance. Code for the Eichner simulation was provided by the author, and thus the model used here is identical to the model used to obtain published results. Therefore, validation experiments were not necessary.

3.2 Generation of Imprecise Probability Structures

Our study focuses on five uncertain quantities: distributions for incubation time, prodromal time, and symptomatic time, as well as single-valued parameters for number of initial cases and transmission rate. These quantities were selected based on commonality in smallpox intervention models.



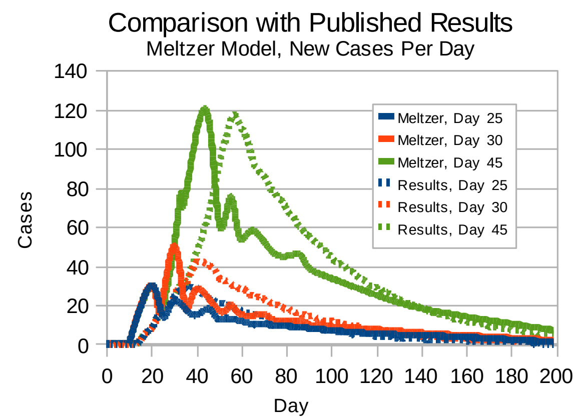


Figure 2. Comparison of Meltzer Implementation to Published Results. Data is given for simulations with intervention starting on day 25, 30, and 45. Results are presented for total cases and new cases per day. (Carson).

Subject matter expert opinions were collected and organized for use in generating uncertainty structures. Data for transmission rate is displayed in Table 1, while ranges for the remaining uncertain parameters and distributions are listed in Appendix A. Dempster-Shafer theory was used for quantification of uncertainty and the aggregation of various subject matter expert opinions. The MatLab Imprecise Probability Toolbox was used to calculate cumulative distribution functions for each disease stage distribution. For transmission rate and index case parameters, the calculation was performed by hand. The resulting Plausibility and Belief distributions for Incubation length are displayed in Figure 3. Remaining distributions can be found in Appendix B.

Range/Value	Source
3-6	(Kretzschmar, 2004)
5	(Eichner, 2003)
5.23	(Kretzschmar, 2004)
3	(LeGrand, 2003)
3.2	(Halloran, 2002)
10-20	(Kretzschmar, 2004)
5	(Porco, 2004)
3	(Kaplan, 2002)
3.5-6	(Kaplan, 2002)
1.5-20	(LeGrand, 2003)
4.52-10.1	(Eichner, 2003)
3	(Meltzer, 2001)

Table 1. Ranges of Subject Matter Expert Opinions for Transmission Rate Value. (Carson).

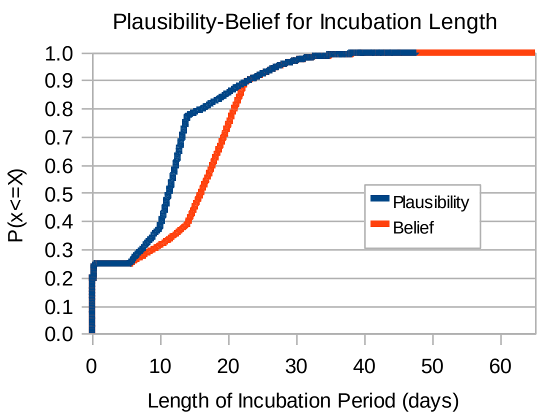


Figure 3. Plausibility Belief Graph for Incubation Length Distribution. (Carson).

3.3 Uncertainty Propagation

Plausibility and Belief functions portray a static view of uncertainty in model structure and parameters. For the purpose of obtaining uncertainty in model output using these structures, the uncertainty must be propagated over time through simulation. Sampling from a Plausibility-Belief distribution involves sampling from points both on and in between the two cumulative distribution functions.

We implemented this sampling method by creating a mesh across the graph and then selecting points on and in between the distributions. The mesh size was calculated based on the smallest distance between consecutive x and y values obtained for the plausibility and belief functions. To sample from the array of selected points, a random index was selected using the random number generator available in Java's Math package.

Each simulation was run for 1000 experiments, sampling from the Plausibility-Belief functions to obtain individual incubation length, prodromal length, and infection length, and to obtain a global transmission rate and number initially infected. The results of the experiments serve to create upper and lower bounds enveloping the range of output uncertainty.

4 Experimental Results and Analysis

Experiments were run for both the Meltzer model and the Eichner model, sampling from the generated uncertainty structures for the five selected uncertain quantities. In order to obtain a view of how different subject matter expert opinions align within the uncertainty envelope, the Meltzer model and the Eichner model were also run substituting in parameter sets used by various subject matter experts. Table 2 displays the parameters and distributions used.

To portray the quantifiable impact of each specific assumption, sensitivity analyses were performed for each of the five uncertain quantities for the Meltzer model. A similar exercise can be performed for the Eichner model.

4.1 Meltzer Model Uncertainty Results

Results were obtained for the Meltzer model for intervention starting on days 25, 30, and 45. Simulation output is organized to portray both cumulative total cases and the number of new cases per day. This format was selected to mirror the results reported by Meltzer (2001). Figure 4 shows simulation

	Meltzer	Eichner	Halloran	Bozzette
Incubation Length (days)	5-18 (Derived from inverse CDF in (Meltzer, 2003))	Gamma (μ=11.6, σ=1.90)	Uniform (10,14)	Uniform (5.5,22.5)
Prodromal Length (days)	Uniform (1,3)	Gamma (μ=2.49, σ=.88)	Uniform (3, 5)	Uniform (1.5,4.5)
Symptomatic Length (days)	Uniform (10,15)	Gamma (μ=16, σ=2.83)	Uniform (14, 17)	Uniform (9,25)
Transmission Rate	3	5	3.2	3.4
Index Cases	100	100	5	350

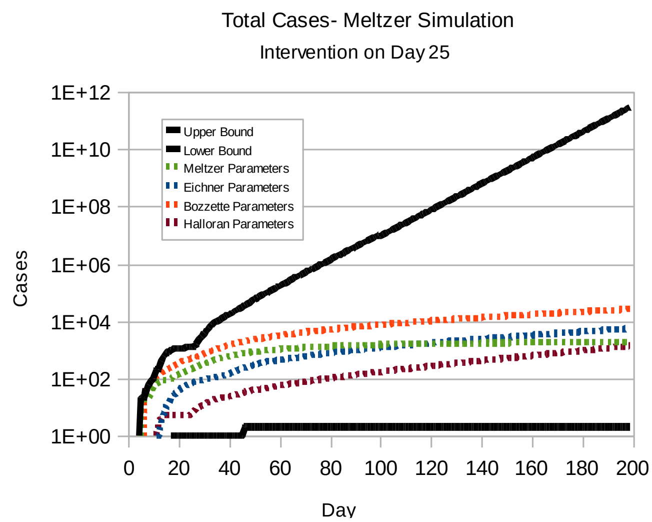
Table 2. Parameter Sets for Uncertain Quantities from Four Subject Matter Experts. Parameter set for Bozzette is from "building attack" scenario, chosen to most closely match attack scenario in other models. (Carson).

output for intervention starting on day 25, plotted on a log scale. Graphs for the remaining simulations are located in Appendix C. Dashed lines correspond to simulation results when run with a parameter set from a certain subject matter expert, while solid lines represent upper and lower bounds obtained by sampling from the uncertainty structures. Plotting model results using parameter sets advocated by different subject matter experts allows comparison of these estimates. It should be noted that the four parameter sets tested were only a subset of the values used to generate the uncertainty distributions.

When uncertainty is taken into account, the Meltzer model predicts a broad range of possible outcomes. The upper bound indicates exponential growth despite quarantine intervention, while the lower bound indicates that intervention methods successfully stopped spread of disease.

From the results, conclusions can be drawn which aid in understanding the impact of model assumptions. Analysis of new cases per day indicates that of the four parameter sets, the parameters chosen by Meltzer were the only set to result in control of the outbreak. This information indicates that success of the quarantine algorithm advocated by Meltzer depends highly on assumptions made by Meltzer. This serves as a warning to health officials when using the Meltzer model to support a quarantine policy.

Such insights provide valuable information to the user. When assumptions



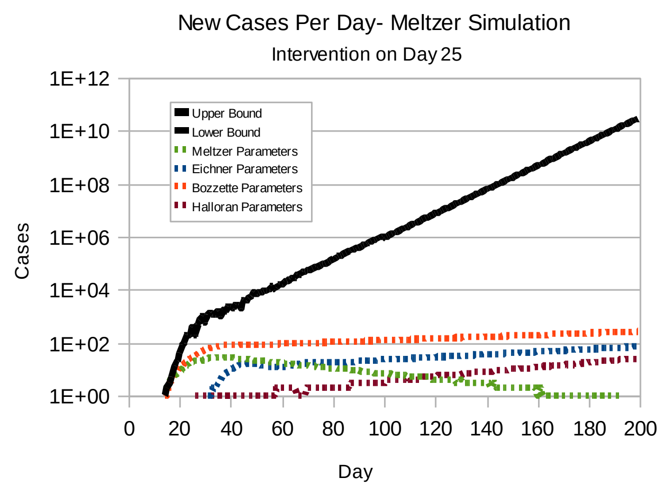


Figure 4. Total Cases and New Cases Per Day for Meltzer Model Uncertainty Analysis. Dependent variable axis is log scale. Lower bound for New Cases Per Day is constantly 0, and thus not visible on the log scale. (Carson).

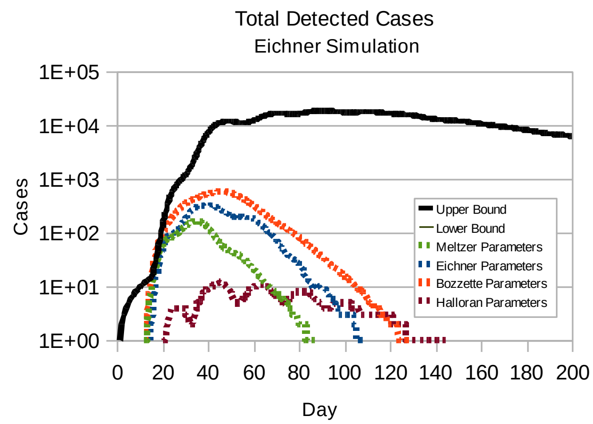
made in the model are accounted for through uncertainty analysis, it is apparent that Meltzer's intervention policy will not necessarily be successful. Additionally, use of the framework demonstrates that Meltzer's assumed parameter values produce results inconsistent with three other subject matter experts.

4.2 Eichner Model Uncertainty Results

The Eichner model implements contact tracing with surveillance as an intervention strategy. Uncertainty analysis was performed for five contacts traced per detected case. Simulation output, in Figure 5, is depicted in terms of total cases per day and the number of cases that go undetected per day in order to mirror the results published by Eichner (2003). The graph of total detected cases per day is plotted on a logarithmic scale. Again, dashed lines correspond to the parameter sets used by Meltzer, Eichner, Bozzette, and Halloran. These parameter sets are only a subset of the information used to generate the uncertainty structures.

Simulation results when taking uncertainty into account provide valuable insight in analysis of the Eichner model. The quarantine method of contact tracing and surveillance in the Eichner model proves to stop epidemic spread with as many as 1000 initial index cases and a high transmission rate of 20 individuals infected per infective case. The upper bound, obtained by sampling from Plausibility-Belief distributions for each uncertain parameter, indicates that spread of disease is decreasing after 200 days. From this data, the policy official can conclude that, based on the uncertain parameters analyzed, a variety of subject matter expert opinions and historical outbreak datasets agree*: the intervention strategy used in the Eichner model will successfully stop a smallpox outbreak*.

Of course, one can not draw the definitive conclusion that such a strategy will stop disease spread in all cases. A broader range of historical data incorporated into uncertainty structures and analysis of other parameters in the model may help, but this still fails to



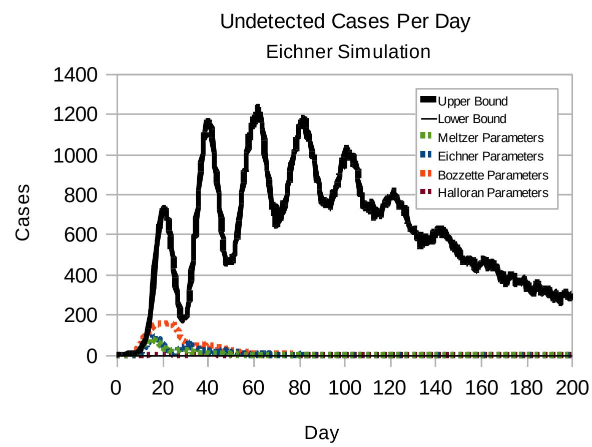


Figure 5. Total Detected Cases Per Day and Undetected Cases Per Day for Eichner Uncertainty Analysis. Total Detected Cases plotted on log scale. (Carson).

provide indication that the future will be dependent on the past. Caution must be exercised.

4. 3 Analysis of Parameter Sensitivity

A sensitivity analysis was performed for the Meltzer model to assess the extent to which each uncertain parameter contributes to the inability to control disease spread. Results are presented for the cumulative number of infectious cases. For all experiments, parameters and distributions in the original Meltzer model were kept constant except the quantity in question. Figure 6 displays the simulation results for sensitivity of the incubation length distribution and the prodromal length distribution. Results for the remaining parameters are listed in Appendix C.

Results indicate that the model is slightly sensitive to the incubation distribution selected. The total number of cases ranges from 500 to around 2500 at day 200, but the trend is decreasing in all cases. Results are similar for the symptomatic period distribution.

The selection of the prodromal period length, however, produces a wide range of results. Both Meltzer and Eichner parameter sets predict the end of disease spread, while others result in no control by intervention. Halloran's distribution for prodromal length produces the highest values for stage duration of all four parameter sets.

An analysis of model structure indicates that this behavior is attributable to structural choices made in the model. Meltzer assumes that an individual becomes contagious and can spread disease during the prodromal period, but due to a lack of physically evident symptoms of smallpox during this stage, only those in the symptomatic stage are eligible for quarantine. Thus, the longer the prodromal period, the more time an individual can spread infection without intervention.

For single-valued transmission rate and index case parameters, model sensitivity varies significantly as well. Selection of the number of initially infected individuals scales the resulting number of cases, but does not cause disease spread to grow exponentially despite intervention. The number of infected individuals, however, is exponential with respect to the transmission rate.

The user gains valuable insights through use of the uncertainty framework in sensitivity analysis. It can be concluded that a high transmission rate is the primary cause of large estimates of total cases in the results, preventing quarantine efforts from controlling smallpox spread. It is also evident that the structural assumptions in the Meltzer model necessitate careful choice of prodromal distribution. One can also make quantifiable comparisons between the effects of different subject matter expert assumptions.

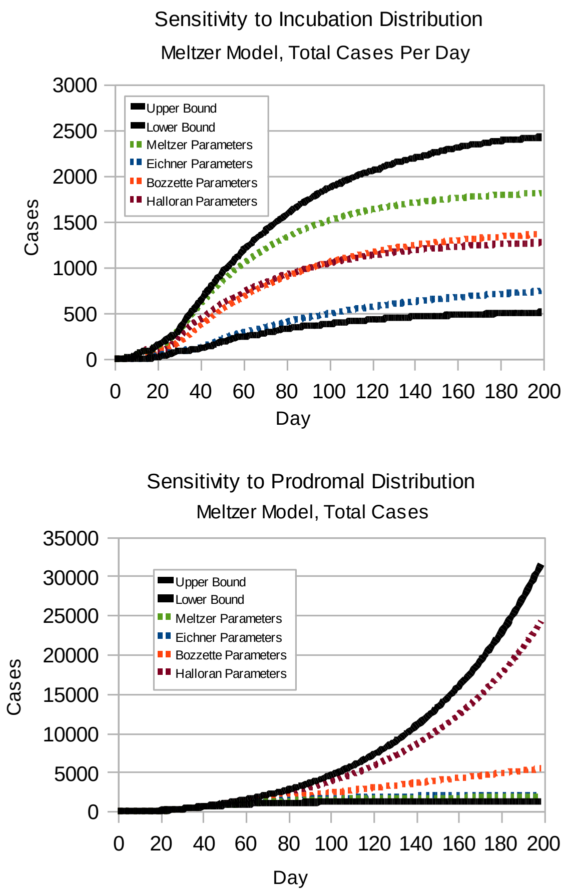


Figure 6. Sensitivity Analysis for Incubation Distribution and Prodromal Distribution. (Carson).

5 CONCLUSION

This work has large implications for use in evaluating and analyzing models to support decision-making. By recognizing model assumptions and quantifying uncertainty in corresponding model parameters, uncertainty in model output can be obtained. Sensitivity analysis can provide further insight into which parameters have the greatest effect on increasing the bounds of the uncertainty envelope. Through use of a case study, we have demonstrated how application of this framework can increase understanding of model assumptions and provide benefits to the end user of the model.

5.1 SUMMARY

The quantification and proper management of uncertainty is necessary where models are used to support high-risk decisions. Differences in model output and corresponding policy recommendations can be attributed to a number of assumptions, reflecting underlying uncertainty. To aid policy officials in interpreting and analyzing these conflicting results in terms of assumptions, a framework for uncertainty analysis has been implemented. This framework, which employs imprecise probability theory, has been applied to smallpox intervention models to demonstrate benefits of its use.

Due to high variability in predictions of smallpox spread and intervention strategy recommendations from different models, uncertainty analysis is necessary in order for such models to be useful in decision-making (N.M. Ferguson, 2003). The quantification and propagation of uncertainty in two smallpox intervention models for five uncertain quantities has been performed. Experimental results show that the Meltzer model and the Eichner model vary significantly even when uncertainty in these parameters is accounted for. A sensitivity analysis performed with uncertainty estimates provides insight into which assumptions have the greatest effect on model results. This, in turn, aids the policy official in assessment of the two different intervention strategies used, as well as in comparison between models and subject matter expert opinions.

5.2 INTERPRETATION

The results of the case study demonstrate that the Meltzer model and corresponding intervention strategy are more sensitive to assumptions than the Eichner model. Results of uncertainty propagation show that under certain sets of assumptions considered valid by subject matter experts, the Meltzer model predicts total number of smallpox cases in the trillions, despite attempted quarantine rate of 50% per day. In contrast, the uncertainty range for total cases predicted by the Eichner model, for the four parameter sets differs by only three orders of magnitude. Furthermore, of the four parameter sets assumed by four subject matter experts, the Meltzer model results show that Meltzer's assumptions were the only parameter set to result in end of the outbreak. Such results provide a caution to individuals using this model to support high-risk decisions.

A sensitivity analysis for each of the five uncertain quantities tested in the Meltzer model provides further information about which parameters must be considered most carefully. The choice of transmission rate and the distribution for the length of the prodromal period can result in predicted exponential growth of the epidemic, despite intervention. The number of index cases and distributions for the length of the incubation period and symptomatic period, although scaling the number infected in some cases, did not change the predicted end of epidemic spread after 200 days.

Due to high levels of uncertainty, various smallpox intervention models provide significantly different results. Application of our framework for uncertainty quantification has enabled insights into the effect of model assumptions not otherwise possible. We conclude that application of this framework is not merely beneficial to the user, but essential for models used in high-risk decision-making.

5.3 RECOMMENDATIONS FOR FUTURE WORK

To continue the study of uncertainty in smallpox intervention models, it is recommended that other assumptions and uncertainty be incorporated in order to paint a broader picture of the effects of uncertainty on output for these two models. Such assumptions may include existing residual immunity and structural changes such as vaccination policy. In order to analyze uncertainty when dealing with structural changes, a combinatorial method must be used to test uncertainty in place of imprecise probability theory.

Results of such a study will become increasingly robust as more information is incorporated into imprecise probability analysis. Data and distributions used here were extracted from various published work on smallpox models. Information calculated directly from historical outbreak documents, available from the World Health Organization database, could prove to be useful.

We highly recommend that this framework for uncertainty management be applied to other areas of study. Both modelers and model users can benefit from an increased understanding of how assumptions affect model behavior. This understanding enables informed decision-making when the user faces conflicting evidence.

It is necessary, however, that the user understands the limitations of modeling and simulation in general. Model results should not be viewed as definitive or absolutely correct, or be used as the single source in making predictions and high-risk decisions. No matter the amount of assumptions and data that are taken into account in uncertainty analysis, one can not conclude that the past will be an indication of the future. Although models can not solely provide definitive answers, they are useful tools for gaining insight and understanding which can help a user make decisions.

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