DYNAMIC INFECTIOUS DISEASE RESPONSE UNDER DEEP UNCERTAINTY

EPA 1361: Model – Based Decision Making

30 June 2017

Erin Bartholomew – 4627237

Patrick Steinmann – 4623991

Stefan Wigman – 4016246

Introduction

Several severe cases of contagious disease outbreaks have occurred over the last few years: Ebola in West-Africa, H1N1 in India, Zika in South and North America, and yellow fever in Angola. These disease outbreaks have in common that their character is highly unknown, and the severity of this kind of diseases proves hard to assess in the early stages of an outbreak. For this reason, policy-makers tend to struggle in terms of strategy, and often over- or underreact in their response to a disease outbreak.

With that in mind, this report will address the emergence of such an unknown infectious disease, of which all the parameters are characterized by a high uncertainty range. By using a variety of modeling techniques, an effective strategy will be designed and tested over a range of scenarios. The main challenge here is that the developed strategy should be proportional to the severity of the disease. This is extremely difficult in this case, as it has many of the characteristics of a wicked problem (Rittel and Webber, 1973). There is little room for mistakes in this case, and the policy strategy needs to be robust for each possible disease. A combination of exploratory modeling, policy development, and optimization can lead to a dynamic adaptive policy which meets these criteria.

The report will first discuss the method used to determine an effective policy plan, followed by a brief description of the results from each stage of analysis. Then, we will present a recommended adaptive policy plan and discuss the effect of that plan on the original model. Finally, we will conclude with some recommended next steps in this analysis.

Additional Materials

This report provides an overview of the results found over several steps of analysis. The details and results of each step can be found on Github, here:

https://github.com/eebart/EPA1361_20162017_PoliciesForInfectiousDisease

The report reference results found in several Jupyter Notebook files, all of which can be found in the root of that repository.

Method

Our analysis follows the approach for developing Dynamic Adaptive Policy Pathways (DAPP) described in Kwakkel et al. (2016) to develop a policy that has transformative adaptivity - it changes system functioning based on sequences of actions and monitoring using adaptation tipping points. Following the DAPP approach allows us to examine a situation with deep uncertainty and develop a plan that targets the immediate situation and guarantees flexibility to handle future changes. The procedure involves a cycle of 7 steps:

1. Analyzing objectives and describing uncertainties
2. Identify adaptation tipping points and develop scenarios
3. Identify and evaluate actions
4. Develop and evaluate policy pathways
5. Select preferred short- and long-term policy options
6. Implement the preferred policy plan

7. Monitor and adjust

This process is iterative, with reassessment required where necessary to adjust to weaknesses in policy decisions and new information. This report will focus on steps 1 through 5 of the analysis, where the end result will be an adaptive policy plan that includes a set of actions that are implemented based on specified adaptation tipping points.

Results

Objectives and Uncertainties

The first step focuses on determining objectives and analyzing the uncertainty space of the model. This generally involves stakeholder analysis to determine policy objectives and the uncertainty space. For this analysis uncertainties and an initial model description were provided for the characteristics of an unknown infectious disease, for which details can be found in Appendix A: Model Specification. Based on the provided information and other infectious disease model studies, such as Auping et al. (2016), we determined the initial objectives to be minimizing both the infectious and deceased populations.

Open Exploration

Open exploration focuses on determining proper sampling methods and examining the entire output space related to provided uncertainties for magnitude and behavior patterns. During open exploration, we first determined proper settings for sampling and for the SIR/SEIR switch (see the model description in Appendix A). Our analysis indicated that examining SIR and SEIR runs separately does not have a significant impact on the objective output spaces in this model, so data will include both versions. Further, we concluded that the Latin Hypercube sampling method provides the most even distribution of data among the uncertainty space, providing us with the best exploration of the entire space. Details of this analysis can be found in the jupyter notebook file 01_Open_Exploration.ipynb. This information was used together with the uncertainty space and the EMA-Workbench python library (Kwakkel, 2017) to generate a large data set for use in both scenario discovery and sensitivity analysis, described below.

Scenario Discovery: PRIM and CART

The purpose of scenario discovery is to determine which combination of inputs have the largest impact on causing a scenario to fail to meet a specified goal. Scenario discovery helps to determine which of the input uncertainties contribute the most to both the Infectious population and Deceased population exceeding specified target. This process is known as scenario selection. For this iteration, we selected cases that infected more than 20% of the population at any point in time, cases that resulted in death of at least 10% of the population, and the combination of both elements (Bryant, Lempert, 2010).

PRIM analysis concluded that for the relevant targets, Case fatality rate and Basic reproduction number, provide the driving force behind missing the established targets when Deceased population is considered and when both Infectious and Deceased population is considered together. When only Infectious population is considered, Basic reproduction number is the driving force. The analysis was able to obtain 80% coverage in while maintaining

high density in each of the final boxes. More information about the specific results can be found in the Jupyter notebook file 02_Scenario_Discovery.ipynb.

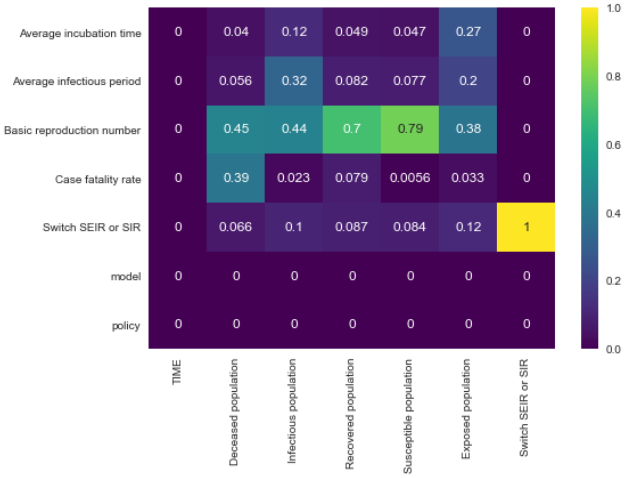
Sensitivity Analysis: Sobol Indices and Random Forests

The analysis of Sobol indices is a global variance-based sensitivity analysis used to determine the relationships between uncertain model inputs and outputs (see Saltelli et al., 2010).

	S1	S1_conf	ST	ST_conf
SwitchInput	0.057035	0.097399	0.995600	0.071341
Case fatality rate	0.046507	0.098749	0.989935	0.080614
Basic reproduction number	0.043061	0.095372	1.016037	0.072226
Average infectious period	0.017251	0.086576	0.970711	0.080070
Average incubation time	-0.016654	0.097919	0.985586	0.078190

The Sobol analysis assigns multiple indices to every uncertain input. Broadly speaking, high first-order effects (S1) mark inputs with significant sensitivity for the outcome of interest, while low total effects (ST) mark inputs with little effect on the model. While the outcomes here seem to show a high importance for the SEIR/SIR switch, we feel this must be treated with caution. We believe a modification of the original model to accommodate the Sobol analysis has artificially inflated the switch's sensitivity. Therefore, we consider the next two inputs, the Case fatality rate and the Basic reproduction number, the most sensitive inputs in relation to the outcome of interest (number of deaths).

To cross-check these conclusions, we also performed a Random Forests analysis (Breiman, 2001), which uses machine learning to assess the relevance of input variables for outcomes of interest. It can clearly be seen that Basic reproduction number has significant influence across all outcomes of interest, while the Case fatality rate is especially relevant for the Deceased population outcome.



Overall, both the sensitivity analysis methods and the scenario discovery tools congruently indicate that the Case fatality rate and the Basic reproduction number are the most important uncertain inputs for our outcomes of interest. This indicates that any potential policies to tackle this infectious disease should attack those two factors, as they show the greatest sensitivity.

For more information on performing and assessing the scenario discovery and sensitivity analysis methods, please see the associated notebooks: 03_Sobol_Analysis.ipynb and 04_Random_Forests_Analysis.ipynb.

Scenario and Adaptation Tipping Point Development

The next step of the analysis is to develop adaptation tipping points, or the points at which the model begins to behave unacceptably and requires additional policy intervention. We developed adaptation tipping points based on the two targeted inputs, 'Case fatality rate' and Basic reproduction number, to create four scenario 'buckets' that we will use to help

determine the proper action to take. The figure below provides an overview of the tipping points for each bucket.

However, the two inputs cannot be observed directly when policy implementers are determining when to adapt the current plan. Therefore, we also developed thresholds that indicate a high likelihood of reaching those tipping points using the stocks and flows of the model structure. This resulted in the following final set of monitorable tipping points:

Stock Thresholds

Total infected population	25 percent of Total population
Deceased population	12 percent of Total population

Rate Thresholds

Infecting / Susceptible population

Slow Infectious Rate	rate < 0.04
High Infectious Rate	0.04 < rate < 0.19
Super High Infectious Rate	0.19 < rate

Dying / Infectious population

Low Fatality Rate	rate < 0.015
High Fatality Rate	0.015 < rate < 0.045
Super High Fatality Rate	0.045 < rate

The stock thresholds provide an indication of which bucket the infectious disease is in, while the acceleration thresholds provide an early warning system that indicates how quickly we

are likely to pass the stock thresholds. This early warning system allows policy makers to have some lead time for implementing desired actions.

The Jupyter Notebook 06_Tipping_Point_Analysis.ipynb provides details about how these tipping points were determined.

Action Identification and Evaluation

There are several actions that decision-makers can consider when dealing with the spread of contagious diseases. This section will discuss the most prevailing ones and link them to the parameters in the model. There are two distinguishable principal strategies regarding disease control (Gosting and Berkman, 2007): therapeutic countermeasures (e.g. vaccines and antiviral medications) and public health interventions (e.g. infection control, social distancing, and the more severe quarantine). For the purpose of this study, we have selected the twelve most prevailing actions (see Appendix B).

Partly based on the literature research and partly based on logical reasoning, a numerical uncertainty range regarding the effectiveness, time to enact, societal impact, and required effort was estimated for each action. The effectiveness of an action is subdivided into its effect on the Basic reproduction number and on the Case fatality rate (Kwadijk et al., 2010). It was a deliberate choice not to use meaningful values such as cost or man-hours, since the high uncertainty and many unknowns make it impossible to give any reasonable estimate. Rather, we look at the differences in magnitude between actions, which are assumed to be representative enough for the purpose of this study.

Basic Policy Structure Evaluation

The implementation of the influence of actions (i.e. movement restrictions, quarantine, and vaccinations) on the Basic reproduction number (R0) and the Case fatality rate, is based on the mathematical methodologies described by Ferguson et al. (2003), and McLean (2013). Each action is assumed to reduce these variables by a multiplier effect.

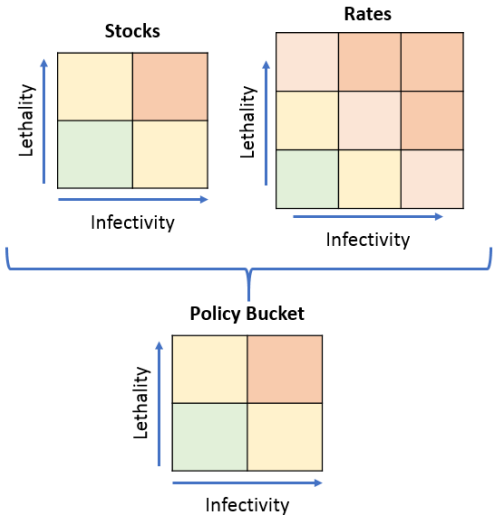
This structure was then subjected to multiobjective optimization to determine a pareto optimal set of solutions over the model uncertainty space that would both minimize infections and fatalities, and also minimize the number of policy actions required (via multiplier size). Details of this analysis can be found in the Jupyter notebook 06_Multiobjective_Optimization.ipynb in the project repository. The conclusions found indicated that by increasing the effect of each multiplier on their respective model property, there is in fact a linear relationship with the values of Deceased population and Infectious population. This indicates that by implementing policies that determine the multiplier value, we will be able to impact the target objectives. Additionally, the analysis revealed that a larger multiplier effect is required for the contact rate coefficient than for the treatment rate coefficient in the pareto optimal solution set.

The next step is to evaluate the actions themselves, and use that information to develop policy pathways. This is discussed in the next section.

Develop and Evaluate Policy Pathways

Based on the recognition of Basic reproduction number and Case fatality rate as the two sensitive uncertainties and the corresponding development of policies to affect them, we developed a two-step classification method for disease severity using the bucket thresholds described earlier. Over the entire simulation run, a disease instantiation is placed in one stocks bucket and one rates bucket, which may change over the simulation time horizon. Together, the stocks and rates buckets determine a policy bucket for each disease, which also changes over the model run. We use the rates as early warning mechanisms to be able to enact drastic policies as early as possible in case of severe diseases (super high infectivity, lethality or both).

Pathway Development



Each policy bucket is associated with a policy, itself consisting of multiple actions. These action sets were assigned to policy buckets by analyzing the outputs of multiobjective optimization experiments run only within the input-based infection and fatality ranges (see figure to the right). These experiments returned the action combinations most suitable for each bucket. The analysis demonstrated the rate at which actions were included in the non-dominated set of experiments. We use this information, in combination with likelihoods that actions will be activated together, to develop an initial idea of which actions belong to which policy. It transpired that certain policies were always activated, while some were never activated. We believe this is because these policies have especially (un-)favorable combinations of "cost", expressed through societal stress and effort, and "benefit", expressed through impact on infectivity and lethality. This represents a weak point in our model - the coefficients for each action were chosen through assumption and guesswork, and these values greatly influenced whether an action was implemented in policies or not. Also of interest is that the action sets separated clearly into low- and high-infectivity pairs, where the only difference within both pairs was the activation of a Facemasks/Personal Hygiene Equipment action. We consider this reasonable - for highly infectious diseases, this would be a useful addition to a policy.

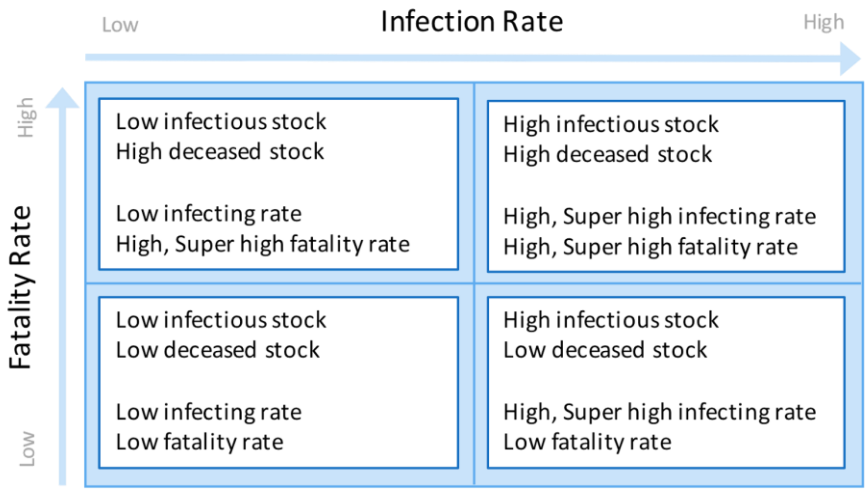
The results of the multiobjective optimization on the action-enabled model can be seen in the Jupyter notebook 07_Multiobjective_Optimization_WithActions.ipynb, which can be found in the project repository.

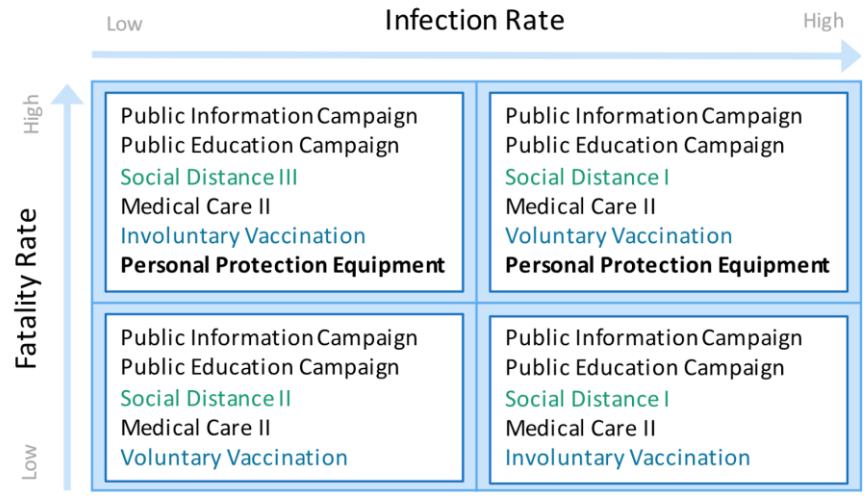
Pathway Evaluation

Once the policy pathways were developed, they was implemented into the Vensim model using the policy bucket thresholds to determine when to activate policies. This implementation can be found in the model *04_SEIR_SIR_FullPolicy.mdl*. A new set of experiment results were generated with this model, which were then analyzed using scenario discovery to examine the impact of the pathways on the targeted outputs. These results can be found in the Jupyter notebook 08_Scenario_Discovery_WithPolicies.ipynb. The general conclusion is that our policy does reduce the effect of Basic reproduction number and Case

fatality rate on the targeted output space. However, these parameters are still considered significant in determining infections and fatalities above thresholds at the higher ends of their uncertainty spectrums. Furthermore, there is a significant reduction in the number of cases that fall over the thresholds. This demonstrates that our policy is effective at reducing Infectious population and Deceased population, but also that there is significant room for improvement, both in reducing the number of cases above the thresholds and in reducing the impact of our target inputs, Basic reproduction number and Case fatality rate.

Conclusion and Advised Strategy

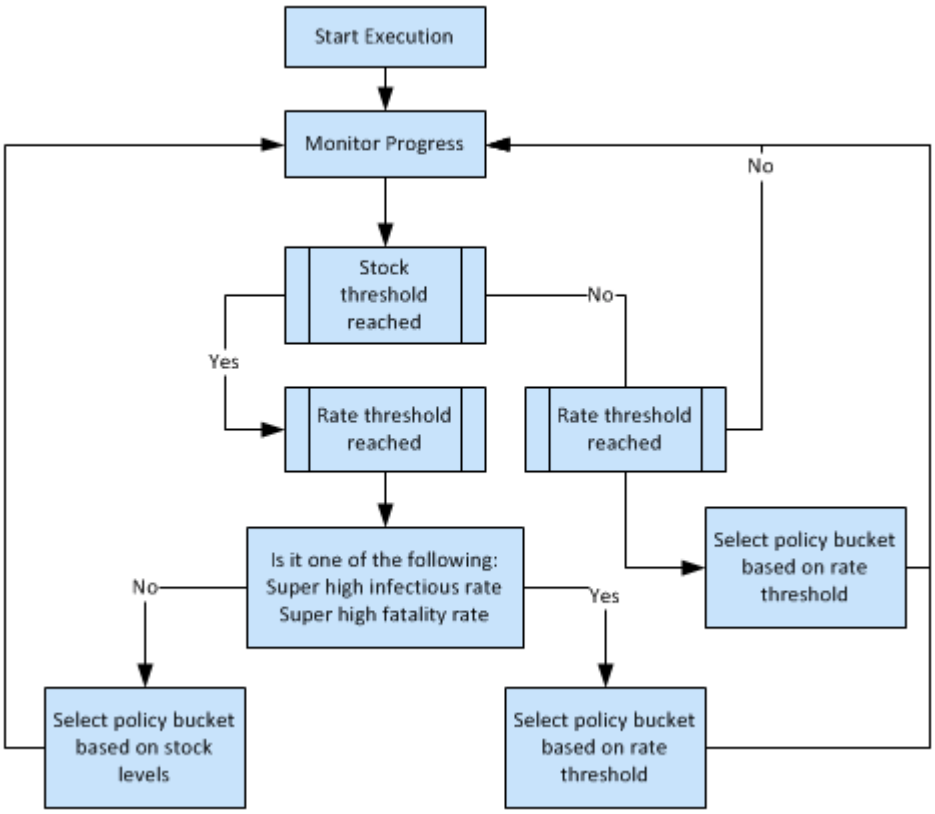




Our policy recommendation is shown below. The figure on the left shows the determining factors for each policy bucket. It includes the actions associated with each policy bucket. These two sets of information are then applied to a decision tree, shown on the following page, which determines how the active policy is selected.

The differences in actions for each policy are highlighted. The largest difference is the introduction of the Personal Protection Equipment policy, which involves distributing personal protection equipment like face masks and hand sanitizer to the public when there is an infectious disease outbreak. The other main difference refers to the magnitude of two policy categories: Social Distance and Vaccination. There is at least one element of both categories in each policy, with the category increasing as the severity of the outbreak increases. Highly infectious diseases, whether deadly or not, both indicate a mandatory vaccination policy. This is likely due to the mandatory vaccination process leading to a more rapid vaccination of the population, making the increased societal stress impact and effort worthwhile. The public education and information campaigns are also included in each policy. These two elements have little societal stress impact, and are relatively low effort to implement.

Of note, two policy actions were rarely included in the non-dominated experiment results: tracing and Medical Care I, which involves improving diagnostics. Based on the results analyzed, it is likely that the significant required effort associated with tracing, along with a smaller impact on the contact rate coefficient, scored that action out of most non-dominated experiment results. Similar reasoning scores Medical Care I out as well.



This adaptive policy plan was implemented and evaluated using two methods of scenario discovery, which indicated that the plan does have a positive impact on reducing Infectious and Deceased population. That analysis also indicated that there is room to improve the policy to reduce the impact of two key inputs Basic reproduction number and Case fatality rate. This iteration is the next step in the Dynamic Adaptive Policy Pathways approach, which involves iterating over a combination of scenarios and recommended pathways to both develop stronger policy responses and to ensure that policy responses reflect the most current knowledge about the problem at hand.

Future Work and Research

Based on the work presented in this strategy report, we see multiple possible directions both for improvement of the presented policy and more fundamental methodological advances in the field of policy analysis.

One of the shortcomings of our modelling efforts was that due to the large number and size of action uncertainties and policy options, our MORDM results were partially inconclusive and therefore did not fully specify our action combinations. A more extensive and well-defined MORDM, with a special focus on more precisely defined and relevant objectives, could create more useful and specific action combinations for the policy adaptations.

Properties of a model and of potential policy actions are a fundamental part of developing adaptive policy recommendations. It is important, therefore, to keep the sources of action properties in mind when analyzing the results of multiobjective analysis and post-policy scenario discovery. Because the properties in this project were largely developed based on literature research and assumptions, rather than in-depth stakeholder and data analysis, there is a high potential for under- or overestimation that could have a significant impact on the effect actions have on the SEIR-SIR model. When developing an official policy plan for recommendation, it is imperative to ensure that all model inputs and policy properties accurately reflect reality.

Methodologically, we believe the use of not only stock thresholds, but also flow thresholds as signposts and trigger points for adaptive policies holds potential and should be investigated further, especially in the context of early-warning mechanisms. Even flow rate of change thresholds could be examined, as they could for example inform whether a disease is already naturally dying out. We see a potential connection to machine control functions, where derivatives of varying order are used to control systems and keep them within specified parameters.

Appendix A: Model Specification

The disease model used for the purpose of this report is a SIR/SEIR model, based on the mathematical model by Kermack and McKendrick (1927). The stock-flow structure for Susceptible (S), Exposed (E), Infectious (I), and Recovered (R) population, is expanded with an Immune (Im) stock for vaccinated individuals. It is assumed that this model is sufficiently elaborate with respect to real contagious disease behavior for the purposes of this analysis, and so the basic stock-flow structure is not significantly altered throughout. The model represents a closed population of 100000, where 1 person is infectious at the start of a run. The most important parameters that determine the behavior of the model are Basic reproduction number, Average infectious period, Case fatality rate, and in the case of SEIR Average Incubation time. Assuming that the model structure does not change, policies can only influence the model by affecting these parameters. The original model can be found in the repository for this report as models/01_SEIR_SIR_Original.mdl. Below are the initial values and uncertainty ranges for the important variables in the model:

Uncertainty	Range	Default Value
Average incubation time	0.5 – 14	2
Average infectious period	7 – 21	14
Basic reproduction number	0.5 – 5	2
Case fatality rate	0.01 – 0.005	0.01
Switch SEIR or SIR	[1, 0]	0

Constant	Value
Initial deceased population	0
Initial exposed population	0
Initial infectious population	1
Initial recovered population	0
Initial susceptible population	100,000

Appendix B: Policy Actions

#	Action	Source
1	Public information campaign - e.g. hygiene, situational awareness	Gostin and Berkman (2007)
2	Public education campaign - inform about disease	Gostin and Berkman (2007)
3	Distribution of facemasks/PPE	Gostin and Berkman (2007)
4	Social distancing I: no public gathering	Gostin and Berkman (2007), Ferguson et al. (2003)
5	Social distancing II: closing public transport	Ferguson et al. (2003)
6	Social distancing III: quarantine/curfew	Gostin and Berkman (2007), Cetron and Landwirth (2005), Ferguson et al. (2003)
7	Case isolation	Gostin and Berkman (2007), Cetron and Landwirth (2005)
8	Vaccination I: voluntary (150)	Gostin and Berkman (2007)
9	Vaccination II: involuntary (200)	Assumed to be an option in severe disease outbreaks.
10	Improve medical care capacity I: minor increase (diagnostics)	Gostin and Berkman (2007)
11	Improve medical care capacity II: major increase (care)	Gostin and Berkman (2007)
12	Tracing of contacts	Cetron and Landwirth (2005)

	Action	Transmission Coefficient	Lethality Coefficient	Disruption Daily Life	Required Effort	Implementation Time	Duration Time
	Unit, Range	dmnl 0-1	dmnl 0-1	dmnl 0-1	dmnl 1-10	days	days
1	Public information campaign	0.97-099	1	0.01-0.1	1-2	2-5	7-28
2	Public education campaign	0.97-099	1	0.01-0.1	1-2	2-5	7-28
3	Distribution of facemasks/PPE	0.93-0.97	1	0.1-0.15	2-3	5-10	7-28
4	Social distancing I	0.92-0.97	1	0.2-0.3	2-3	1-3	7-90
5	Social distancing II	0.89-0.96	1	0.3-0.8	3-6	1-3	5-21
6	Social distancing III	0.7-0.8	1	0.5-0.9	4-8	2-4	5-21
7	Case isolation	0.73-0.87	0.92-0.97	0.3-0.6	5-9	14-28	14-60
8	Vaccination I	150/day	(other)	0.1-0.3	2-6	30-180	14-60
9	Vaccination II	200/day	(other)	0.5-0.8	5-10	30-180	7-14
10	Improve medical care capacity I	0.9-0.97	0.97-1	0.05-0.1	1-4	5-20	14-60
11	Improve medical care capacity II	0.83-0.9	0.7-0.98	0.05-0.1	4-8	20-40	14-60
12	Tracing of contacts	0.87-0.93	1	0.1-0.3	3-7	2-10	7-42

References

Auping, W.L., Pruyt, E., Kwakkel, J.H. (2016): Simulating endogenous dynamics of intervention-capacity deployment: Ebola outbreak in Liberia. International Journal of Systems Science: Operations & Logistics.

Breiman, L.. (2001). Random Forests. Machine Learning, Volume 45.

Bryant, B. P., & Lempert, R. J.. (2010). Thinking Inside the Box: a participatory computer-assisted approach to scenario discovery. Technological Forecasting and Social Change, 77(1).

Cetron, M., Landwirth J.. (2005). Public Health and Ethical Considerations in Planning for Quarantine. Yale Journal of Biology and Medicine.

Ferguson, N.M. et al.. (2003). Planning for smallpox outbreaks. Nature, Volume 425.

Fraser, C. et al.. (2004). Factors that make an infectious disease outbreak controllable. PNAS, Volume 101.

Gostin, L.O., Berkman B.E.. (2007). Preparing for Pandemic Influenza: Legal and Ethical Challenges. Administrative Law Review.

Haran, M.. (2009). An introduction to models for disease dynamics. Spatial Epidemiology.

Horoba, C., Neumann, F.. (2008). Benefits and drawbacks for the use of epsilon-dominance in evolutionary multi-objective optimization. Proceedings of the 10th annual conference on Genetic and Evolutionary Computation.

Kermack, W. O., McKendrick, A. G.. (1927). A Contribution to the Mathematical Theory of Epidemics. Proceedings of the Royal Society of London, Volume 115.

Kwadijk, J.C.J. et al.. (2010). Using adaptive tipping points to prepare for climate change and sea level rise: a case study in the Netherlands. WIREs Climate Change, Volume 1.

Kwakkel, J.H. et al.. (2016). Comparing Robust Decision-Making and Dynamic Adaptive Policy Pathways for model-based decision support under deep uncertainty. Environmental Modelling & Software, Volume 86.

Kwakkel, J.H.. (2017) EMA Workbench [Python Package] Retrieved from https://github.com/quaquel/EMAworkbench

McLean, A.R.. (2012). Infectious Disease Modeling. Infectious Diseases, Chapter 5.

Rittel, H.W.J., Webber, M.M.. (1973). Dilemmas in a General Theory of Planning. Policy Sciences, Volume 4.

Saltelli, A., & Annoni, P.. (2010). How to avoid a perfunctory sensitivity analysis. Environmental Modelling & Software.