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Simulating endogenous dynamics of intervention-capacity deployment: Ebola outbreak in Liberia

Willem L. Auping[a,b], Erik Pruyt[b] and Jan H. Kwakkel[b]

[a]The Hague Centre for Strategic Studies, The Hague, The Netherlands; [b]Department of Multi-Actor Systems, Faculty of Technology, Policy and Management, Delft University of Technology, Delft, The Netherlands

ABSTRACT

During the first months, the 2014 outbreak of the Ebola virus (EBOV) in West Africa was characterised by inadequate intervention capacities. In this paper, we investigate (1) the influence of limited but dynamic intervention capacities and their effect on the effective reproduction number, and (2) the effects of proactive versus reactive intervention approaches. We use a transmission model extended with dynamical intervention capacities. Taking into account a bandwidth for potential over- and under-reporting in reported Ebola virus disease cases, the model is used to generate ensembles of plausible scenarios. Next, it is used for testing the effectiveness of more proactive approaches in extending intervention capacities across these scenarios. We show that reactive approaches in extending intervention capacities can lead to continued under-capacity, and, consequently, to an increase of the effective reproduction number and to accelerated EBOV transmission. Proactive approaches, which take deployment delays, doubling times of diseases, and potential under-reporting of the number of cases into account, help in limiting the total number of cases and deaths if the effective reproduction number in isolation is lower than the effective reproduction number outside of isolation. If the effective reproduction number in isolation is higher, proactive intervention policies still outperform reactive intervention policies.

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Ebola virus disease; intervention capacity; reproduction number; system dynamics; scenario discovery

1. Introduction

The 2014 outbreak of the Ebola virus (EBOV) and, consequently, Ebola virus disease (EVD) in Liberia, Sierra Leone, Guinea, Senegal, Mali, Nigeria, Spain, and the United States of America (CDC, 2014; Gire et al., 2014) was by far the largest observed to date (WHO Ebola Response Team, 2014). The number of cases and deaths outnumbered the sum of all previous outbreaks. Where earlier outbreaks took place in rural or otherwise sparsely populated areas (Amblard et al., 1997; Borchert et al., 2011; Bwaka et al., 1999; Okware et al., 2002; Pattyn, 1977; Roddy et al., 2012; Shoemaker et al., 2012; WHO, 1978a, 1978b), the 2014 outbreak distinguished itself by occurring in densely populated urban areas (WHO Ebola Response Team, 2014).

Dynamic transmission models can be used for intervention capacity planning for epidemics like the 2014 EVD outbreak. During the 2014 outbreak, dynamic transmission models have been used for estimating the basic reproduction number of Ebola, and for projecting the future development of the epidemic (Chowell, Hengartner, Castillo-Chavez, Fenimore, & Hyman, 2004; Lekone & Finkenstädt, 2006; WHO Ebola Response Team, 2014). However, projecting the dynamics of EBOV was, especially during the first few months, complicated by uncertainty about many input factors (Butler, 2014). Examples of uncertain factors include the case fatality ratio (Kucharski & Edmunds, 2014), and the basic reproduction number R_0 (Althaus, 2014; Fisman, Khoo, & Tuite, 2014; WHO Ebola Response Team, 2014). Further, the actual number of cases during the outbreak in West Africa was believed to be considerably higher than the reported number of cases (Meltzer et al., 2014), since the infrastructure to diagnose new cases and identify contamination epicentres was insufficient. The insufficiency of the infrastructure to identify new cases and epicentres of contamination, and the resulting underestimation of the problem, contributed to the continued spreading of the disease (WHO Ebola Response Team, 2014).

With the continued EBOV spreading, capacities like medical staff, hospitals, isolation facilities, and tracing officers were being scaled up dynamically to curb the outbreak. Simultaneously, efforts were initiated to speed up the development and provision of Ebola medication and vaccines. That is, the extent of these capabilities in the region changed significantly over time. These intervention capacities, and their dynamics, therefore, need to be

CONTACT Erik Pruyt e.pruyt@tudelft.nl

incorporated inside transmission models aimed at projecting the future development of the epidemic. This is not new. For example, Bachinsky and Nizolenko (2013) combined a SEIR model (i.e. a model with separate compartments for Susceptible (S), Exposed (E), Infectious (I), and Recovered (R) populations) with constant isolation bed capacities. Studies on influenza also often include the influence of anti-viral medication and vaccination programs (Kenah, Chao, Matrajt, Halloran, & Longini, 2011; Klepac, Bjørnstad, Metcalf, & Grenfell, 2012; Luz, Vanni, Medlock, & Galvani, 2011; McCaw & McVernon, 2007; Moss, McCaw, & McVernon, 2011). However, none of the early Ebola studies made use of detailed dynamic sub-models of endogenous intervention capacity development for a broad range of intervention capacities.

In this paper, we present an extended SEIR model for EBOV propagation that includes intervention capacities endogenously. The model was developed and used early September 2014 to assess capability deployment needs in West Africa. The model presented here is parameterised for Liberia only. The uncertainty by which the EVD outbreak in West Africa was characterised is incorporated by means of large uncertainty ranges. This enables us to evaluate the influence of dynamic limits on EVD interventions on the effective reproduction number. That is, the effective reproduction number is modelled as the result of a SEIR model extended with endogenous intervention capacities. The effective reproduction number, as it is used here, therefore, relates to the average number of infections per single infection given the dynamics of the population immunity level and the dynamics of the intervention level.

We explore the dynamics of the model under uncertainty in order to explain how epidemic risk and intervention capacities interact, what the consequences may be of their interaction, and how the use of dynamic transmission models with integrated dynamic intervention capacities can inform planning of intervention capacities during future outbreaks.

The set-up of this paper is as follows. First, we present the SEIR model extended with model structures with limiting intervention capacities (i.e. isolation, health workers, tracing officers, and eventually vaccines), and the experimental set-up. Second, we discuss the results of our analysis for the cumulative number of cases, the effective reproduction number, and doubling time. Third, we discuss our findings and provide concluding remarks.

2. Methods

We developed a model combining a SEIR core with possible interventions aimed at curbing the Ebola epidemic in West Africa. The model was developed using the system dynamics (SD) method (Forrester, 1961; Pruyt, 2013; Sterman, 2000) and was used for exploratory purposes (Bryant & Lempert, 2010). SD is a method for modelling and simulating dynamically complex systems or issues characterised by causal relations, feedback loops, accumulations, and delays. SD models are essentially systems of differential equations or integral equations (Lane, 2000). Simulating the dynamic behaviour of the modelled system through numeric integration of these equations results in a simulation run displaying the behaviour of the modelled system over time. Simulation runs can be used to analyse problems related to the system, and to evaluate the effects of policy interventions in these systems. SD is regularly used to study disease dynamics and health policy (Sterman, 2000; Thompson & Duintjer Tebbens, 2009). In this particular case, we used it to explore the consequences of the different combinations of uncertainties on the dynamics of the epidemic, and test the effects of different intervention strategies.

2.1. Model description

We started with the traditional SEIR model. The central structure of the model contains state variables, aka stock variables, for the susceptible, exposed, infectious, and recovered sub-populations (Figure 1). Mathematically speaking, these stock variables are integral equations. We made several changes to this basic SEIR structure. We divided the infectious population in a critical phase (*infectious population*) and a recovery phase for survivors of the critical phase, where patients may either recover or die. The recovering patients are still infectious. Therefore, they were modelled using a second stock variable, the *infectious survived population*, who are recovering and will survive. We applied this subdivision to both the infectious population in isolation (*isolated infectious population* and *isolated survived population* in Figure 1) and the infectious population outside of isolation and treatment centres (*infectious population* and *infectious survived population*).

Further, we subdivided (i.e. vectorised or subscripted) these population stocks in order to take potential self-quarantining behaviour of the population into account. The S, E, and I stocks outside isolation (i.e. *susceptible population*, *exposed population*, *infectious population*, and *infectious survived population*), and the flows between these stocks, contain this subdivision. In Figure 1, these stock variables have a bold border. Introducing this structure is important, as a successful societal response to an outbreak leads to a significant decrease in the necessary intervention capacities like treatment and isolation capacity (Pruyt, Auping, & Kwakkel, 2015).

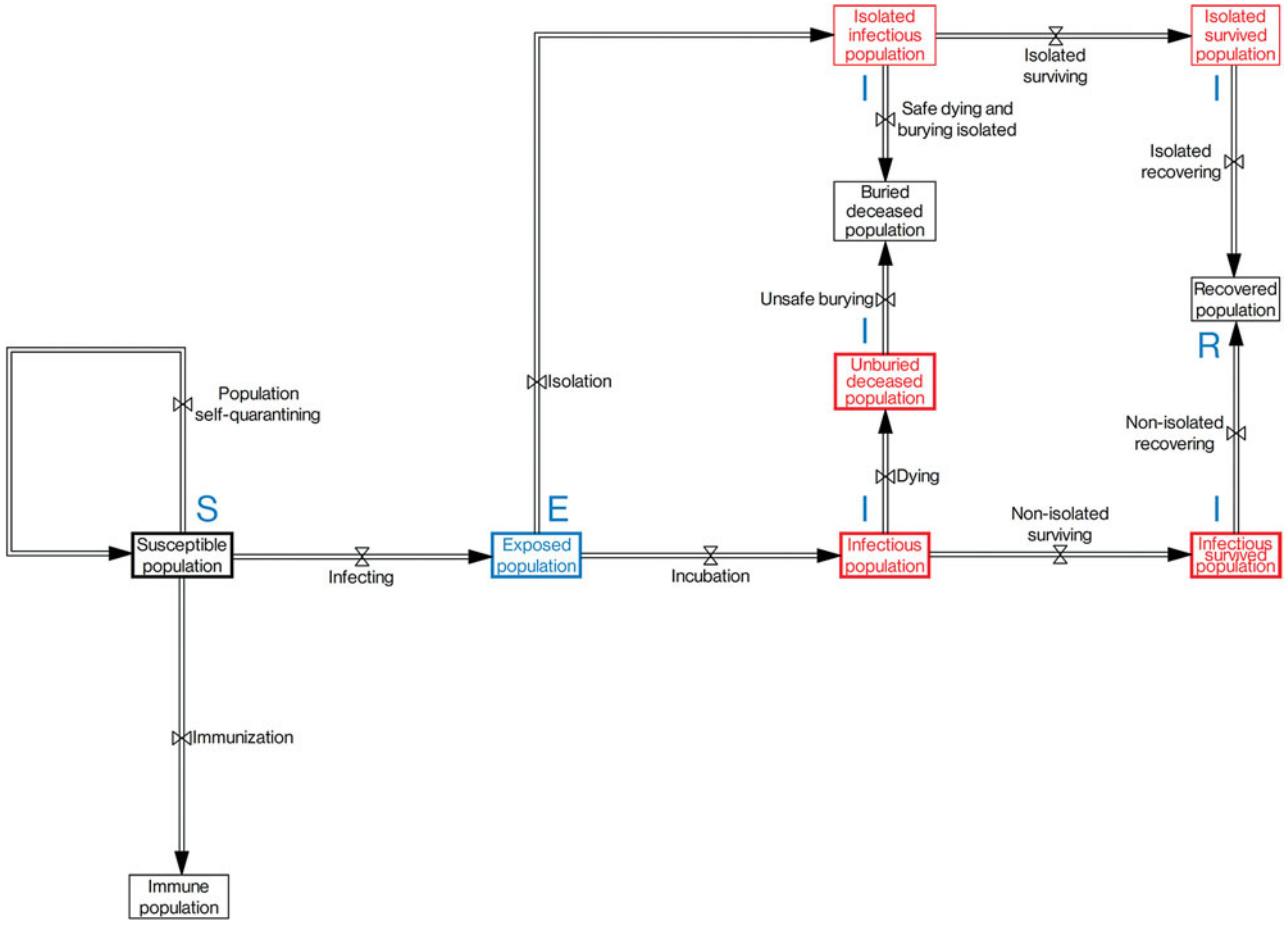

Figure 1. Stock–flow structure of the extended (other factors and causal relations are not shown) SEIR model containing isolated population stocks, and the immune population due to vaccination. Subscripted stocks have a bold border, infectious population stocks are marked with an 'I', and the exposed population stock is marked with an 'E'.

Treatment and isolation capacity refers here to Ebola Treatment Centres (ETCs) and to Community Care Centres (CCCs). ETCs provide care to suspected and confirmed cases while attempting to prevent infection of healthcare workers and members of the community. Small CCCs ensure that patients are isolated in areas with insufficient ETC bed capacity or in remote areas without access to ETCs.

The basic SEIR model was further extended with treatment and isolation capacity, not distinguishing between ETCs and CCCs. In our model, this extension consists of two stock variables: one for the critical *infectious population* and one for the *infectious survived population*. We further included a stock variable for the *unburied deceased population*. Finally, we included a stock variable for *immune population*, which contains the population that would be vaccinated after vaccines would have become available. This *immune population*, and the *recovered population*, are assumed to be no longer susceptible to EBOV.

In our model, intervention capacities are restricted and, unless specified differently, reactive. That is, we included the endogenous dynamic development of the availability of beds in treatment and isolation capacity, health workers, tracing officers, and vaccines. They are adapted to the needs, albeit delayed. This way, the numbers of health workers, tracing officers, and available vaccines increase in response to the dynamics of the epidemic. Scaling up of intervention capacities is delayed. That is why we added stocks for the preparation of intervention capacity and the available intervention capacity, and time delays between these stocks that slow the response to the epidemic (Fraser, Riley, Anderson, & Ferguson, 2004).

For health workers, the possibility of getting infected by EBOV and consequentially dying of EVD (Hewlett & Hewlett, 2005) is taken into consideration, thus reducing their availability. We assume that fully recovered healthcare workers will try to continue their efforts after an extensive recovery time. Further, health care workers may

be recruited domestically or from outside the region. All additional physicians needed are nevertheless assumed to be foreign for it was assumed that the very small group of domestic physicians were already working full time.[1] Only a small portion of the susceptible population in West Africa is considered suitable for nursing since they are not trained to protect themselves properly, but a larger part of the recovered population is suitable for nursing, since they are immune. If the medical staff capacity is not sufficient to provide for the necessary isolation capacity, the isolation capacity is limited by the available staff. This corresponds to closing down EVD treatment centres due to lack of staff.

Finally, the effective reproduction number is also included endogenously in the model (i.e. the effective reproduction number is dynamic). The effective reproduction number is calculated here as the daily rate of infections caused by the total infectious population in and outside isolation, multiplied by the average period during which infectious individuals are infectious. The effective reproduction number is thus, the weighted average of the basic reproduction numbers in and outside isolation, calculated at each moment in time. It can go down if measures are sufficient, but it can also go up if, over time, intervention measures prove to be insufficient. The effective reproduction number is approximated the model by the 'reproduction ratio' which is calculated as the product of the sum of all infections and the sum of the average recovery time of survivors and the average period critical condition, divided by the sum of all infectious patients. The doubling time of the number of cases is approximated by $ln2$ divided by the fractional growth rate of the number of cumulative cases. The latter variable is calculated as the increase in the number of cases divided by the total cumulative exposed cases. The increase in the number of cases is calculated as the exposed population divided by the incubation period. Three detailed stock-flow diagrams of the model are provided in the Appendix.

2.2. Experimental set-up

The model was implemented in the Vensim modelling software (Ventana Systems, 2010) and was parameterised for the Liberian situation. The model contains 161 variables, of which 20 were subdivided for hygienic and normal behaving population, and 35 parameters were considered uncertain. We simulated the model for 400 days, with a time step of 0.25 days using the Runge–Kutta 4 auto numerical integration method. For the 35 uncertain parameters, we used a Latin Hypercube sampling approach, based on uniform distributions with the ranges displayed in Table 1. The parameter ranges are specified in function of the model structure and in relation to other parameter ranges. In this model, the variable 'vaccinations' depends, for example, on six variables, one of which is the 'Vaccination speed'. A vaccination speed of 240 vaccines per person per day means that, if vaccines are available, 240 people can be vaccinated per medical worker per day.

Some 'soft' variables and parameters are included to account for uncertain but plausible effects. For example, the 'effect of self-quarantining behavior' represents the effect through which more hygienic behaviour causes the infectivity to decrease.

We generated 10,000 samples simulating this model using the open source EMA workbench (EMA Group, 2011) from https://github.com/quaquel/EMAworkbench. The model documentation and model are available as online supplementary materials on https://github.com/ep77/Ebola-Model-with-Endogenous-Response. The model equations are also available as online supplemental data. Visualisations and analyses are provided in an IPython notebook on http://nbviewer.ipython.org/gist/ep77/796491369b0e6fe84b4d.

3. Results

3.1. Scenario selection

The initial ensemble of 10,000 simulations contained a wide range of plausible evolutions of the epidemic. Only a subset of these evolutions was consistent with the outbreak observed in Liberia, as SEIR models can produce simulations of both very lethal and very non-lethal outbreaks. Due to the non-linear nature of these models, outputs of simulations could even fall outside of plausible ranges for combinations of input uncertainties within ranges that are known to be plausible. Therefore, we post-processed the ensemble by selecting only those simulations, where the cumulative number of Ebola cases fell within a range of 80%–250% of the WHO data on the total cumulative number of Ebola cases on 3 September 2014 (WHO, 2014b). Although we have used this model at later moments in time, we present our simulation results calibrated to the WHO data of 3 September 2014, because this ensemble of simulations provides a good illustration of the uncertainty we were facing at the time, as well as the potentially devastating impact of an outbreak without additional policies and changes in behaviour. The broad uncertainty range (of 80%–250%) was used at the time, because it was argued that the WHO data significantly under-reported the actual number of EVD cases (Meltzer et al., 2014), although some over-reporting could not be ruled out either. Following this method, we selected 3041 scenarios out of the total of 10,000 simulation runs. This

Table 1. Model inputs considered to be uncertain. Factors for which no references exist, are indicated as assumptions.

Variable name	Unit	Min	Max	References
Average contact rate infectious population	1/day	0.3	0.9	(Althaus, 2014; WHO, 2014b; WHO Ebola Response Team, 2014)
Average development time isolation facilities	Day	4.2	18.8	Derived from reports like Camacho et al. (2014)
Average extra recovery time survivors	Day	0.5	4.66	(WHO Ebola Response Team, 2014); Assumption (based on own analysis)
Average time staff active	Day	185	341	Assumption (based on own analysis)
Average time until burial	Day	0.5	2	(WHO, 2014b)
Average time until return diseased health workers	Day	21	60	Assumption
Average period critical condition	Day	4	9	(WHO Ebola Response Team, 2014)
Case fatality rate in isolation relative to outside isolation	Dimensionless	0.43	0.73	Broad bandwidth around data from WHO Ebola Response Team (2014); Assumption (based on own analysis)
Case fatality rate outside isolation	Dimensionless	0.45	0.86	(WHO Ebola Response Team, 2014)
Contact rate before funeral	1/day	0.32	0.97	Derived from (Camacho et al., 2014; WHO Ebola Response Team, 2014)
Contacts to be traced per quarantined patient	Contact/person	5.47	40	(Bachinsky & Nizolenko, 2013)
Contacts traceable per tracer per day	Contact/(person∗day)	10	40	(Bachinsky & Nizolenko, 2013)
Delay time development new vaccines	Day	250	350	Assuming that vaccines will be available in first or second quarter of 2015
Doctors per nurse	Dimensionless	0.12	0.46	Assumption (based on own analysis) (
Effect of self-quarantining behaviour	Dimensionless	2.28	20	Assumption
Fraction recovered population useful as medical staff	Dimensionless	0.000458	0.043	Assumption (based on own analysis)
Fraction susceptible population useful as medical staff	Dimensionless	1.86E-06	0.000189	Assumption (based on own analysis)
Incubation period	Day	7	15	WHO Ebola Response Team (2014)
Initial exposed population	Person	50	100	WHO (2014b)
Initial isolation capacity	Person	120	600	WHO (2014b)
Initial relative susceptible hygienic population	Dimensionless	0.01	0.2	Assumption
Initial tracing personnel	Person	5	30	Assumption
Initial vaccines in preparation	Vaccine	4	20	Assumption
Lifetime isolation capacity	Day	180	360	Assumption (based on own analysis)
Medical staff creating awareness	1/day	5	100	Assumption
Medical staff per new case	1/day	0.2	0.5	WHO (2014b)
Preparing time foreign staff	Day	14	60	Assumption (based on own analysis)
Recognition rate diseased	Dimensionless	0.2	0.95	Broad bandwidth around WHO (2014b)
Relative reduction in infectivity due to isolation	Dimensionless	0.7	5	Assumption
Training time new staff	Day	3	10	Assumption
Vaccination speed	Vaccine/(person∗day)	50	240	Assumption (estimated)

process is depicted in Figure 2. More visualisations of the initial ensemble, the screening, and subsequent analyses are provided in the online IPython notebook.

The ensemble (in shaded grey) and a randomly selected set of 30 out of the ensemble of 3041 scenarios are displayed in Figure 3(a) and 3(b) (these figures differ only in terms of the scales of the y-axes). The ensemble consists of different plausible projections of the simulated number of 'Actual cases' (i.e. the total 'Cumulative exposed cases' in the model) that were consistent with the WHO data on 3 September 2014. The runs start on 22 June 2014 ($t = 0$), after the WHO reported the first 51 cases in Liberia. In the best-case scenarios, the under-reporting of cases is limited due to sufficient tracing capacity.

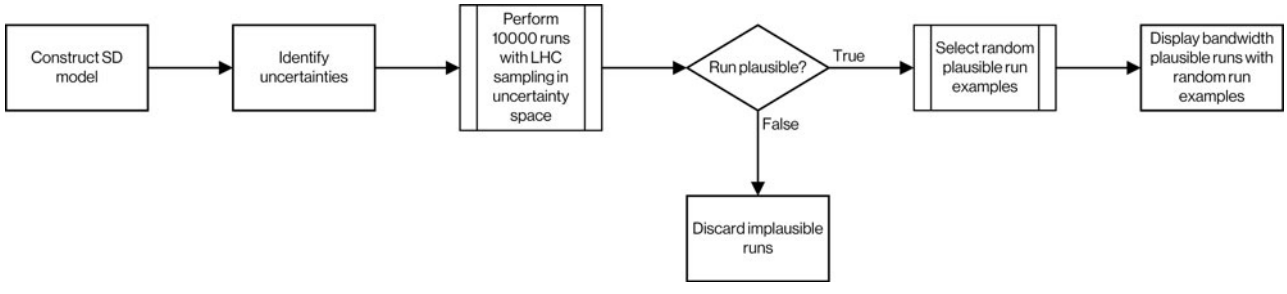

Figure 2. Flowchart of the experimental set-up and post-processing of the ensembles of scenarios.

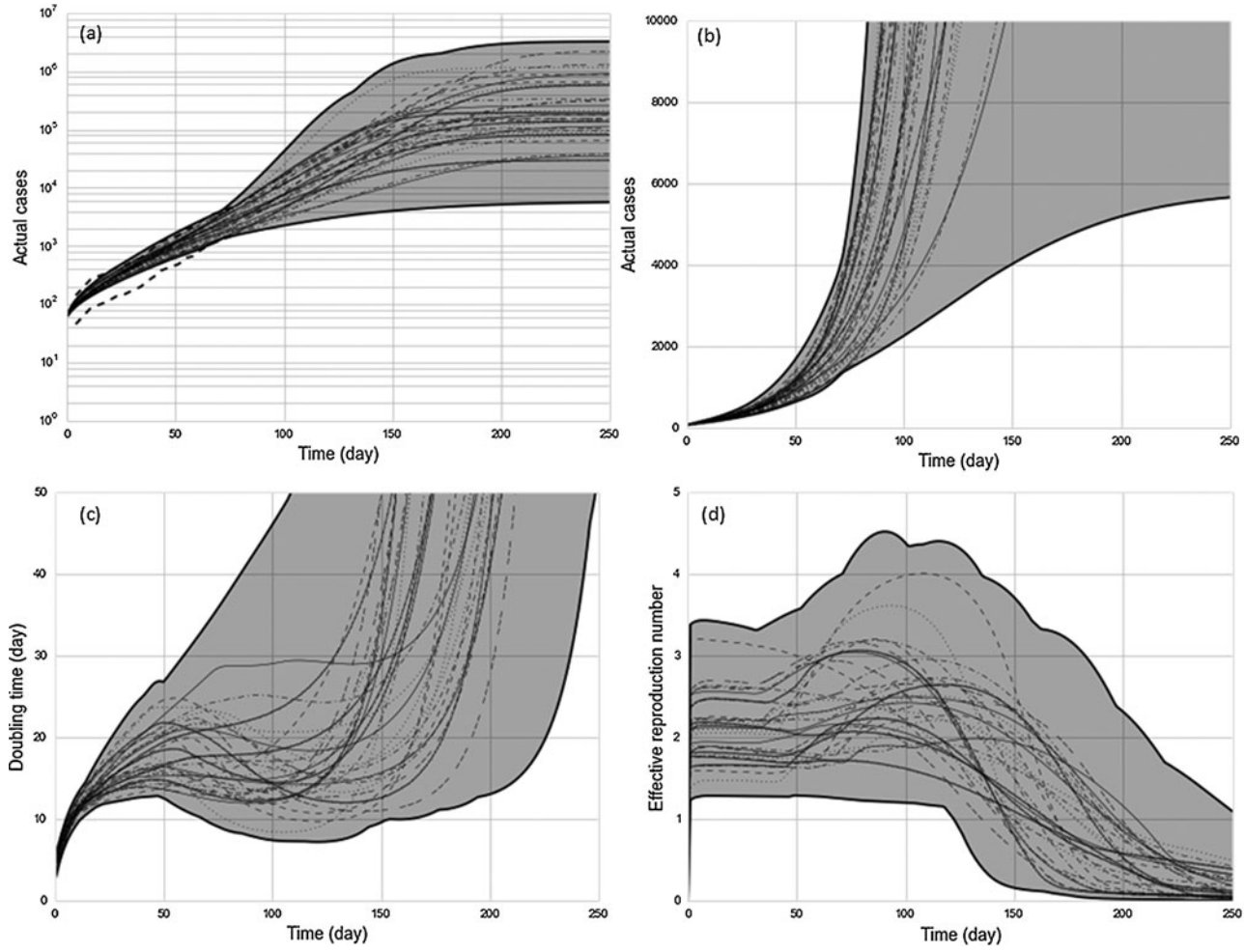

Figure 3. Dynamics of 30 randomly selected runs and the ensembles for: (a) the cumulative number of cases (i.e. the total 'Cumulative exposed cases') on a logarithmic *y*-axis (with bounds around the historic WHO data displayed with dashed lines), (b) the same cumulative number of cases on a non-logarithmic *y*-axis, (c) the effective reproduction number, and (d) the doubling time of cases.

In these scenarios, the effective reproduction number gradually declines as the intervention becomes more effective.

In other scenarios, the tracing capacity is inadequate, which leads to inadequate developments of isolation capacity and medical staff. In these cases, the development of the intervention capacity is overly delayed. The non-isolated population consequently peaks considerably earlier than the isolated population. This results in an order of magnitude difference between the maximum non-isolated infectious and the maximum isolated infectious. The required isolation and treatment capacities are not available in these worst-case scenarios, even if changes in population behaviour would be effective (e.g. when part of the diseased actively seek help at treatment centres, even if they were not traced).

Limits in the EBOV intervention capability influence the speed with which the virus is transmitted. That is, starting from a situation in which there is a lack of intervention capacity, an increasing lack of intervention capacity may even result in an increase in the speed of virus propagation. However, so do ineffective measures, or a rise in ineffectiveness of measures. That is, the speed of virus transmission may also increase if individuals with EVD who end up in isolation and treatment centres infect more individuals than individuals with EVD who do not end up in isolation and treatment centres. This may, for example, happen if EVD cases are not recognised as such, if many individuals with similar symptoms – some of whom have EVD and most of whom do not have EVD at first – spend a relatively long time at the same centre, if insufficient or ineffective protective measures are taken by non-infected individuals in isolation and treatment centres (e.g. health workers and patients with other diseases with similar symptoms), or if the trip to these centres results in many new infections.

Many problematic scenarios are characterised by at least one of two virus accelerating effects: (1) failure to isolate the large majority of EVD cases which leads to an increase in the reproduction rate of the disease, causing an increase in the effective reproduction number, and (2) successful isolation but with higher infectivity rates in isolation than outside of isolation which may lead to an increase in the effective reproduction rate of the disease, causing an increase in the effective reproduction number. The results of both accelerating effects are visible in Figure 3(c), which shows how the endogenously modelled effective reproduction number develops in 30 randomly selected scenarios out of the ensemble of 3041 scenarios as well as the ensemble itself. As a consequence, the doubling time of the number of cases declines (Figure 3(d)). Finally, when EBOV transmission has peaked, the doubling time of cases rises quickly as the effective reproduction number falls below 1.

It is important to realise that there may be two reasons why scenarios show increased effective reproduction numbers. First, the effective reproduction number is the result of infectious people having contact with their surroundings (e.g. with family members, or with deceased during unsafe burials). If the relative share of the infectious population that cannot be isolated increases, due to limitations in either available beds or available trained and well-equipped staff, then the effective reproduction number could be expected to increase too. Second, many studies estimating the base reproduction number of EBOV or similar diseases assume that intervention capability is not available at the beginning of the epidemic, while its adequacy increases over time (e.g. Chowell et al., 2004; Chowell & Nishiura, 2014). However, that assumption may be wrong. In the case of the 2014 EBOV epidemic in West Africa, for example, it looks as though the adequacy of the intervention capability was first deteriorating over time (which can be inferred from the data in WHO (2014b)), resulting in dynamics similar to those simulated here.

3.2. Effect of a more proactive approach

Responses to unforeseen outbreaks involving increases of intervention capabilities are mostly delayed. As a result, when new capacities become available they often fall short of the capacity that is actually required, especially when insufficient capacity further increases the speed with which the virus propagates. This is, for example, the case if a lack of tracing officers results in underestimation and under-reporting of the speed with which the virus is propagating. Therefore, increasing intervention capacities requires a more proactive approach, for example, by trying to anticipate future increases in cases, while taking irreducible delays in the development of new capacities, into account. We, therefore, introduce the following formula (Equation (1)), which is one way to capture proactive planning:

$$C_{t+1} = c_u * C_{t,\mathrm{des}} * \left(1 + \left(\frac{\tau_C}{\tau_2}\right)\right) - C_t, \qquad (1)$$

where

C_{t+1} is the capacity to develop;

c_u is the expected underestimation factor of the number of EVD cases;

$C_{t,\mathrm{des}}$ is the presently desired capacity;

τ_C is the delay on capacity development;

τ_2 is the doubling time for the number of EVD cases; and

C_t is the current available capacity.

This formula expresses that while preparing new intervention capacities, one should be prepared for those EVD cases that will arise during the preparation time, as well as the exposed population that will become infectious after the deployment of capacity additions. If the preparation time is relatively short compared to the doubling time, the necessary extra capacity is, therefore, smaller. Existing capacity may be subtracted from the capacity to develop. It should be noted, however, that in the case of underestimation of the number of cases, the desired capacity at that time should also be multiplied with the expected underestimation factor. The potential underestimation factor may be assessed by experts in the field, organisations like Médecins Sans Frontières (MSF) or the WHO, or from the literature (WHO Ebola Response Team, 2014).

Figure 4 shows the effects of a reactive response policy a proactive policy from day 110 on and a proactive policy from day 72 on on the selected 3041 scenarios, as well as 30 randomly selected scenarios.

Figure 4(a) shows that early post-processing under severe uncertainty (i.e. on 3 September 2014) results in rather similar ensembles in terms of the log-scaled cumulative number of Ebola cases. The underlying reason for this surprising result is that, in our worst case simulations, infectivity in isolation is not necessarily lower than infectivity outside of isolation. More and earlier isolation capacity may be problematic if it is ineffective. Again, the worst cases are either scenarios in which an initial underestimation of the size of the epidemic leads to an early increase in the reproduction number of the virus, or scenarios in which policies that are being implemented are counter-productive. In these worst cases, the EBOV outbreak is hard to curb. Figure 4(b) and 4(c) nevertheless show that the earlier a more proactive

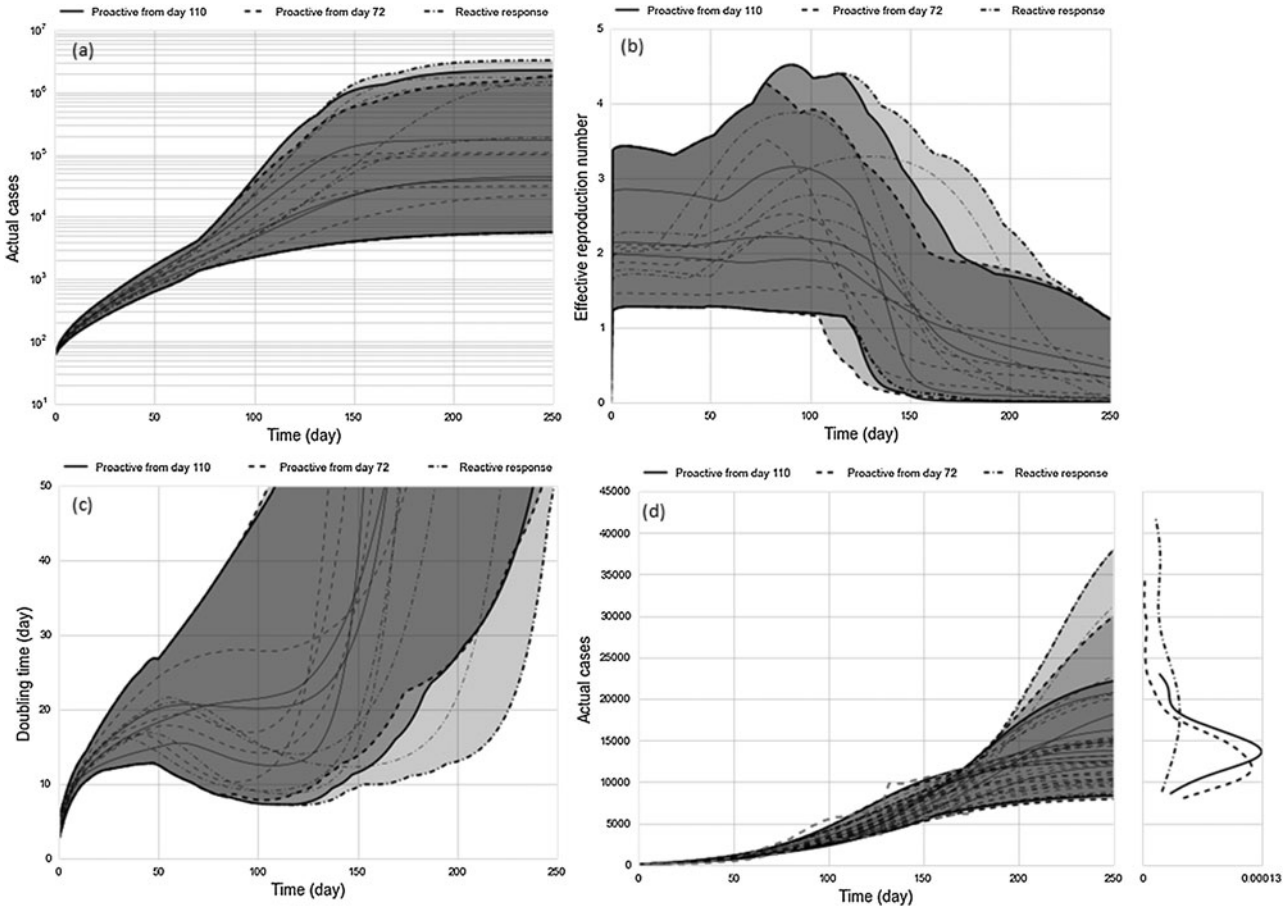

Figure 4. Dynamics of 30 randomly selected runs and the ensembles of a reactive response, a proactive response from day 110 on, and a proactive response from day 72 on for: (a) the cumulative number of actual cases, (b) the effective reproduction number, (c) the doubling time of the number of cases, and (d) the cumulative number of actual cases post-processed based on WHO data of 10 December 2014.

approach is adopted, the earlier the effective reproduction number drops and the doubling time rises. Therefore, adopting a more proactive approach is beneficial across the ensemble, even if measures are not as effective as they could or should be. Adopting an effective proactive approach is what is really needed.

The dominance of proactive approaches becomes clearer when post-processing later in time. Figure 4(d) shows the ensembles of the same policies post-processed between 80% and 150% of the number of reported cases on 10 December 2014. That is, all simulation runs that are not in line with the real-world estimates of 10 December 2014, plus/minus a slightly smaller uncertainty interval, are excluded from these ensembles. The upper bound applied in December 2014 is lower than the upper bound applied early September 2014 to account for more reliable data and a reduction in perceived uncertainty. Two observations could be derived from post-processing at this later point in time. First, 65.5% of all runs that are in line with the real-world data are generated with the adaptive policy from day 72 on, compared to 21.5% with the adaptive policy from day 110 on, and 13% with the reactive policy. That is, the adaptive policy from day 72 on corresponds better to what happened in the real-world than the adaptive policy from day 110 on, which, in turn, corresponds better to the real-world data than the reactive policy. This was to be expected given the massive international deployment of intervention capacities that took place in West Africa between September and December 2014. The real-world massive deployment could indeed be argued to have been proactive, because more was planned for than was needed at the moment of planning. Second, the long-term ensemble projections of the proactive approaches are much lower than the long-term ensemble projections of the reactive approach (see the Kernel density estimates of the terminal values at the right-hand side of Figure 4(d)).

The effectiveness of the intervention capacity development approach also largely depends on the phase of the epidemic. Proactive approaches are more effective when applied early in the growth phase of the epidemic. The potential gains are much smaller when the spread of

the virus is already decreasing and the doubling time is increasing.

4. Discussion

In this paper, we presented a simulation model with a detailed endogenous dynamic response to outbreaks. When developing simulation models to plan the response to an outbreak, it is important to explicitly account for the dynamic development of capabilities and the associated delays in the system. Models that do not include capabilities are likely to overestimate epidemics and may lead to unrealistic planning or calls not to use models for planning epidemic responses (Butler, 2014). However, models with static capabilities or capabilities development without delays are likely to underestimate epidemics and the epidemic responses needed.

We used the simulation model presented in this paper to generate ensembles of scenarios for the spread of the EBOV in Liberia and to project how the epidemic might evolve under deep uncertainty with reactive and proactive policies. Early real-world information was used to inform the model-building, and early real-world data (August and early September 2014) and late real-world data (10 December 2014) was used to post-process the policy ensembles (i.e. to remove simulation runs that were not compatible with real-world data from the policy ensembles) in order to test how well each of these policy ensembles corresponded to the real data.

Many of the individual scenarios generated by this model were worse than what happened in reality. There are several reasons why the actual disease spread could have been expected to be less dramatic than the worst-case scenarios presented in this theoretical study. First, geographic spread of the population leads to slower virus transmission. Due to geographic spread and spreading of the virus, the real susceptible population at any one time (i.e. the real population-at-risk) was smaller than assumed in our simulation model, and the susceptible and infectious populations outside isolation were assumed to be perfectly mixed. Second, a high upper uncertainty bound was used to select the scenarios for this study. Third, large uniform uncertainty ranges were used for each of the uncertain parameters. Fourth, worst-case planning assumptions about the effectiveness of ETCs were included in this study. Finally, this research was not exhaustive in terms of intervention measures considered. For example, essential medical supplies besides the medical staff and bed capacity in isolation were considered here.

A possible limitation of sampling from large uniform uncertainty ranges may be that simulation runs are generated with unrealistic combinations of inputs. Although post-processing introduces some correlation, the ensembles may still contain many implausible scenarios. Since these scenarios are not used as predictions, merely as sets of what-if analyses and as inputs for policy robustness testing, this is, according to us, not a major problem. After all, our focus is on testing the effectiveness of policies across large ensembles of scenarios (i.e. no matter what could happen), especially in case of worst-case scenarios. If policies happen to be effective across all cases, even for implausible scenarios, then implausible scenarios do not necessarily need to be identified and eliminated. For example, given the uniform distribution of the 'relative reduction in infectivity due to isolation' variable between 0.7 and 5 (see Table 1), many scenarios are simulated in which infectivity rises due to increased isolation of EVD cases. Proactive isolation-oriented policies could be expected to perform poorly for these counter-intuitive scenarios. However, proactive policies seem to perform reasonably well across all scenarios, even across these least surprising or implausible scenarios.

In our model, we have assumed that the intervention capacities developed would not be hindered by lack of resources like skilled medical personnel from foreign countries. Resources are nevertheless limited, both in the model and in reality, due to erroneous planning and due to normal planning and implementation delays.

The same principle nevertheless applies to all capability and resource under-capacities, whatever their cause: any under-capacity harms the effectiveness of the total intervention capability. That is, the entire intervention capability is as strong as the weakest non-redundant capacity in the chain.

Another limitation of our study relates to the consequences of the real-world geographic spread of virus transmission on real-world capacity planning. In this theoretical paper, we used a homogeneous mixing model, where any expected incidence and any capacity extension affects the whole population equally. In reality, heterogeneity and geographic spread mean that some parts of the population and territory are more heavily affected by the outbreak, which, given inherent uncertainty about the future geographic spreading of the virus, makes it more difficult to foresee where capacity expansions are needed. Although this limitation does not fundamentally alter the general insights of our study, it needs to be taken into account for real-world planning purposes. That is, either these suggested capacity additions are considered to be the absolute minimum capacity additions and estimates are revised upward based on local characteristics and spreading, or geospatial models should be used for real planning purposes. This is especially important in case of heterogeneous spreading in large heterogeneous regions.

5. Conclusions

In this paper, we have presented a simulation model with endogenous response related to the 2014 Ebola outbreak in Liberia. Our simulations show that both delayed responses and timely but ineffective measures can cause the effective reproduction number to increase. The consequence of such situations may be that the growth of the actual number of cases accelerates significantly. These findings were derived from an extended SEIR model with endogenously modelled intervention capacities parameterised for the EBOV outbreak in Liberia.

In early September 2014, our research suggested that the effective reproduction number of the 2014 Ebola epidemic could increase compared to the measured effective reproduction number (WHO Ebola Response Team, 2014) if the capacities of the different interventions were not brought to the minimally required level over time. During the first months of the 2014 outbreak in Liberia, which was characterised by a significant shortfall in bed capacity due to a lack of health care staff and a lack of operational bed capacity in Ebola treatment units (WHO, 2014a), intervention capacities were insufficient and ineffective.

This under-capacity may be the result of the reactive response to the initial exponential growth of the number of EVD cases. Early proactive approaches in building up the total spectrum of intervention capacities decrease, on an ensemble level, the final scale of the epidemic, especially if intervention capacities turn out to be effective. More proactive approaches in expanding the intervention capacities may, therefore, help in controlling epidemics like the 2014 West Africa EBOV. Such proactive approaches would at least have to take into account how the development time of these capacities relates to the doubling time of the disease, and the factor by which the measured cases may be under-reported (Farrar & Piot, 2014).

Note

1. According to Liberia's ambassador to the United States, Liberia has about 50 doctors – about one for every 90,000 citizens, not counting foreign physicians (see http://www.bbc.com/news/world-africa-29516663 and https://www.washingtonpost.com/world/africa/liberia-already-had-only-a-few-dozen-of-its-own-doctors-then-came-ebola/2014/10/11/dcf87c5c-50ac-11e4-aa5e-7153e466a02d_story.html). The CIA's World Fact Book reports that in 2008, there were 0.01 physicians per 1000 inhabitants (see https://www.cia.gov/library/publications/the-world-factbook/fields/2226.html - last consulted on 10 September 2015).

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Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on contributors

Willem Auping is a strategic analyst at HCSS and external PhD candidate at Delft University of Technology. He holds a Master's degree from Delft University of Technology's faculty of Technology, Policy, and Management, with a specialisation in modelling, simulation, and gaming.

Erik Pruyt is an assistant professor at Delft University of Technology. His research and teaching focuses on systems modelling, simulation and analysis for high-level decision-support related to dynamically complex and deeply uncertain issues. His main application domains are safety and security, public policy, and health policy.

Jan Kwakkel is an assistant professor at Delft University of Technology. His research focuses on model-based support for decision making under deep uncertainty. His main application domains are transport and climate adaptation in the water sector.

References

Althaus, C.L. (2014). Estimating the reproduction number of Ebola virus (EBOV) during the 2014 outbreak in West Africa. *PLOS Currents Outbreaks*. doi:10.1371/currents.outbreaks.91afb5e0f279e7f29e7056095255b288

Amblard, J., Obiang, P., Edzang, S., Prehaud, C., Bouloy, M., & Guenno, B.L.E. (1997). Identification of the Ebola virus in Gabon in 1994. *The Lancet, 349*(9046), 181–182. doi:10.1016/S0140-6736(05)60984-1

Bachinsky, A.G., & Nizolenko, L.P. (2013). A universal model for predicting dynamics of the epidemics caused by special pathogens. *BioMed Research International, 2013*, 467078. doi:10.1155/2013/467078

Borchert, M., Mutyaba, I., Van Kerkhove, M.D., Lutwama, J., Luwaga, H., Bisoborwa, G., … Van Der Stuyft, P. (2011). Ebola haemorrhagic fever outbreak in Masindi District, Uganda: Outbreak description and lessons learned. *BMC Infectious Diseases, 11*, 357. doi:10.1186/1471-2334-11-357

Bryant, B.P., & Lempert, R.J. (2010). Thinking inside the box: A participatory, computer-assisted approach to scenario discovery. *Technological Forecasting & Social Change, 77*, 34–49. doi:10.1016/j.techfore.2009.08.002

Butler, D. (2014). Models overestimate Ebola cases. *Nature, 515*, 18. doi:10.1038/515018a

Bwaka, M.A., Bonnet, M.J., Calain, P., Colebunders, R., De Roo, A., Guimard, Y., … Van den Enden, E. (1999). Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: Clinical observations in 103 patients. *Journal of Infectious Diseases, 179* (Supplement 1), S1–S7. doi:10.1086/514308

Camacho, A., Kucharski, A.J., Funk, S., Breman, J., Piot, P., & Edmunds, W.J. (2014). Potential for large outbreaks of Ebola virus disease. *Epidemics, 9*, 70–78. doi:10.1016/j.epidem.2014.09.003

CDC. (2014). 2014 Ebola outbreak in West Africa. Ebola Virus Disease. Retrieved from http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/index.html

Chowell, G., Hengartner, N.W., Castillo-Chavez, C., Fenimore, P.W., & Hyman, J.M. (2004). The basic reproductive number of Ebola and the effects of public health measures: The cases of Congo and Uganda. *Journal of Theoretical Biology, 229*(1), 119–126. doi:10.1016/j.jtbi.2004.03.006

Chowell, G., & Nishiura, H. (2014). Transmission dynamics and control of Ebola virus disease (EVD): A review. *BMC Medicine, 12* (1), 1–17. doi:10.1186/s12916-014-0196-0

EMA Group. (2011). Exploratory modelling & analysis (EMA) workbench. Retrieved from http://simulation.tbm.tudelft.nl/ema-workbench/contents.html

Farrar, J.J., & Piot, P. (2014). The Ebola emergency — Immediate action, ongoing strategy. *New England Journal of Medicine, 371*, 1545–1546. doi:10.1056/NEJMe1411471

Fisman, D., Khoo, E., & Tuite, A. (2014). Early epidemic dynamics of the West African 2014 Ebola outbreak: Estimates derived with a simple two-parameter model. *PLOS Currents Outbreaks*. doi:10.1371/currents.outbreaks.89c0d3783f36958d96ebbae97348d571

Forrester, J.W. (1961). *Industrial dynamics*. Cambridge, MA: MIT Press.

Fraser, C., Riley, S., Anderson, R.M., & Ferguson, N.M. (2004). Factors that make an infectious disease outbreak controllable. *Proceedings of the National Academy of Sciences of the United States of America, 101*(16), 6146–6151. doi:10.1073/pnas.0307506101

Gire, S.K., Goba, A., Andersen, K.G., Sealfon, R.S.G., Park, D.J., Kanneh, L., … Sabeti, P.C. (2014). Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. *Science, 345*(6202), 1369–1372. doi:10.1126/science.1259657

Hewlett, B.L., & Hewlett, B.S. (2005). Providing care and facing death: Nursing during Ebola outbreaks in Central Africa. *Journal of Transcultural Nursing, 16*(4), 289–297. doi:10.1177/1043659605278935

Kenah, E., Chao, D., Matrajt, L., Halloran, M.E., & Longini, I. (2011). The global transmission and control of influenza. *PLOS One, 6*(5), e19515. doi:10.1371/journal.pone.0019515.g001

Klepac, P., Bjørnstad, O.N., Metcalf, J.E., & Grenfell, B.T. (2012). Optimizing reactive responses to outbreaks of immunizing infections: Balancing case management and vaccination. *PLOS One, 7*(8), e41428. doi:10.1371/journal.pone.0041428

Kucharski, A.J., & Edmunds, W.J. (2014). Case fatality rate for Ebola virus disease in west Africa. *The Lancet, 384*(9950), 1260. doi:10.1016/S0140-6736(14)61706-2

Lane, D.C. (2000). Diagramming conventions in system dynamics. *Journal of the Operational Research Society, 51*(2), 241–245.

Lekone, P.E., & Finkenstädt, B.F. (2006). Statistical inference in a stochastic epidemic SEIR model with control intervention: Ebola as a case study. *Biometrics, 62*(4), 1170–1177. doi:10.1111/j.1541-0420.2006.00609.x

Luz, P.M., Vanni, T., Medlock, J., & Galvani, A. (2011). Dengue vector control strategies in an urban setting: An economic modelling assessment. *The Lancet, 377*, 1673–1680. doi:10.1016/S01406736(11)60246-8

McCaw, J.M., & McVernon, J. (2007). Prophylaxis or treatment? Optimal use of an antiviral stockpile during an influenza pandemic. *Mathematical Biosciences, 209*(2), 336–360. doi:10.1016/j.mbs.2007.02.003

Meltzer, M.I., Atkins, C.Y., Santibanez, S., Knust, B., Petersen, B.W., Ervin, E.D., … Washington, M.L. (2014). Estimating the future number of cases in the ebola epidemic – Liberia and Sierra Leone, 2014–2015. Morbidity and Mortality Weekly Report, *63*(3), 1–14. Retrieved from http://www.cdc.gov/mmwr/pdf/other/su6303.pdf

Moss, R., McCaw, J.M., & McVernon, J. (2011). Diagnosis and antiviral intervention strategies for mitigating an influenza epidemic. *PLOS One, 6*(2), e14505. doi:10.1371/journal.pone.0014505

Okware, S.I., Omaswa, F.G., Zaramba, S., Opio, A., Lutwama, J.J., Kamugisha, J., … Lamunu, M. (2002). An outbreak of Ebola in Uganda. *Tropical Medicine and International Health, 7*(12), 1068–1075. doi:10.1046/j.1365-3156.2002.00944.x

Pattyn, S.R. (Ed.). (1977). *Ebola virus haemorrhagic fever*. Antwerp: Elsevier. Retrieved from http://www.itg.be/internet/ebola/pdf/EbolaVirusHaemorragicFever-SPattyn.pdf

Pruyt, E. (2013). *Small system dynamics models for big issues: Triple jump towards real-world complexity*. Delft: TU Delft Library. Retrieved from http://simulation.tbm.tudelft.nl/smallSDmodels/Intro.html

Pruyt, E., Auping, W.L., & Kwakkel, J.H. (2015). Ebola in West Africa: Model-based exploration of social psychological effects and interventions. *Systems Research and Behavioral Science, 32*, 2–14. doi:10.1002/sres.2329

Roddy, P., Howard, N., Van Kerkhove, M.D., Lutwama, J., Wamala, J., Yoti, Z., … Borchert, M. (2012). Clinical manifestations and case management of Ebola haemorrhagic fever caused by a newly identified virus Strain, Bundibugyo, Uganda, 2007–2008. *PLOS One, 7*(12), e53986. doi:10.1371/journal.pone.0052986

Shoemaker, T., MacNeil, A., Balinandi, S., Campbell, S., Wamala, J.F., McMullan, L.K., … Nichol, S.T. (2012). Reemerging Sudan Ebola virus disease in Uganda, 2011. *Emerging Infectious Diseases, 18*(9), 1480–1483. Retrieved from http://doi.org/10.3201/eid1809.111536

Sterman, J.D. (2000). *Business dynamics: Systems thinking and modeling for a complex world*. New York, NY: McGraw.

Thompson, K.M., & Duintjer Tebbens, R.J. (2009). Using system dynamics to develop policies that matter: Global management of poliomyelitis and beyond. *System Dynamics Review, 24*(4), 433–449. doi:10.1002/sdr.419

Ventana Systems. (2010). *Vensim reference manual*. Harvard, MA: Author.

WHO Ebola Response Team. (2014). Ebola virus disease in West Africa — The first 9 months of the epidemic and forward projections. *New England Journal of Medicine, 371*(16), 1481–1495. doi:10.1056/NEJMoa1411100

WHO (1978a). Ebola haemorraghic fever in Sudan. *Bulletin of the World Health Organization, 56*(2), 247–270.

WHO (1978b). Ebola haemorrhagic fever in Zaire, 1976. *Bulletin of the World Health Organization, 56*(2), 271–293.

WHO. (2014a). *Ebola response roadmap situation report – 15 October 2014* (Vol. 15). Geneva: Author.

WHO. (2014b). Ebola virus disease – disease outbreak news. *Global Alert and Response (GAR)*. Retrieved from http://www.who.int/csr/don/archive/disease/ebola/en/

WHO. (2014c). Experimental Ebola vaccines. Retrieved from http://www.who.int/mediacentre/news/ebola/01-october-2014/en/index4.html

Appendix

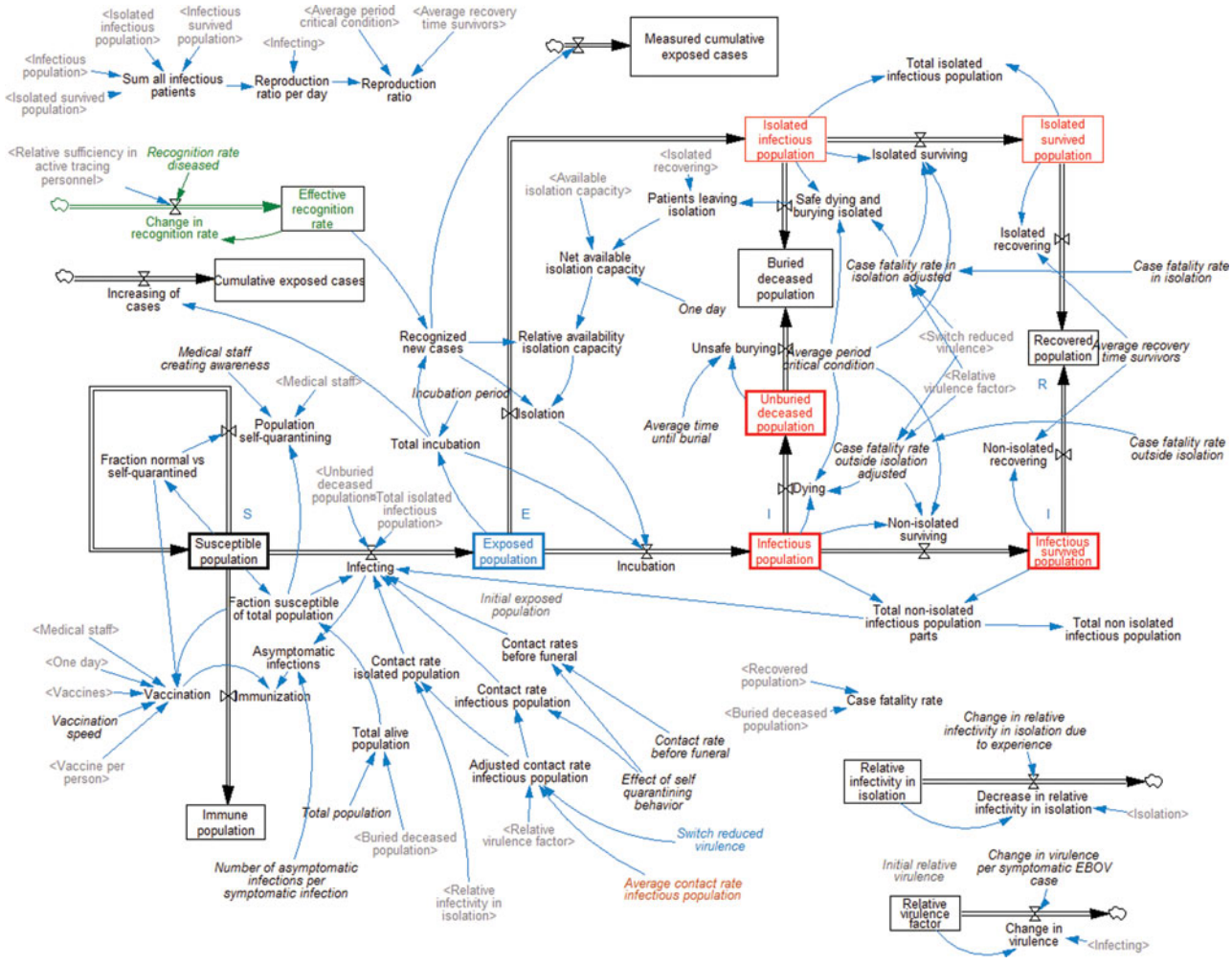

Figure A1. Detailed stock–flow diagram of the SEIR sub-model.

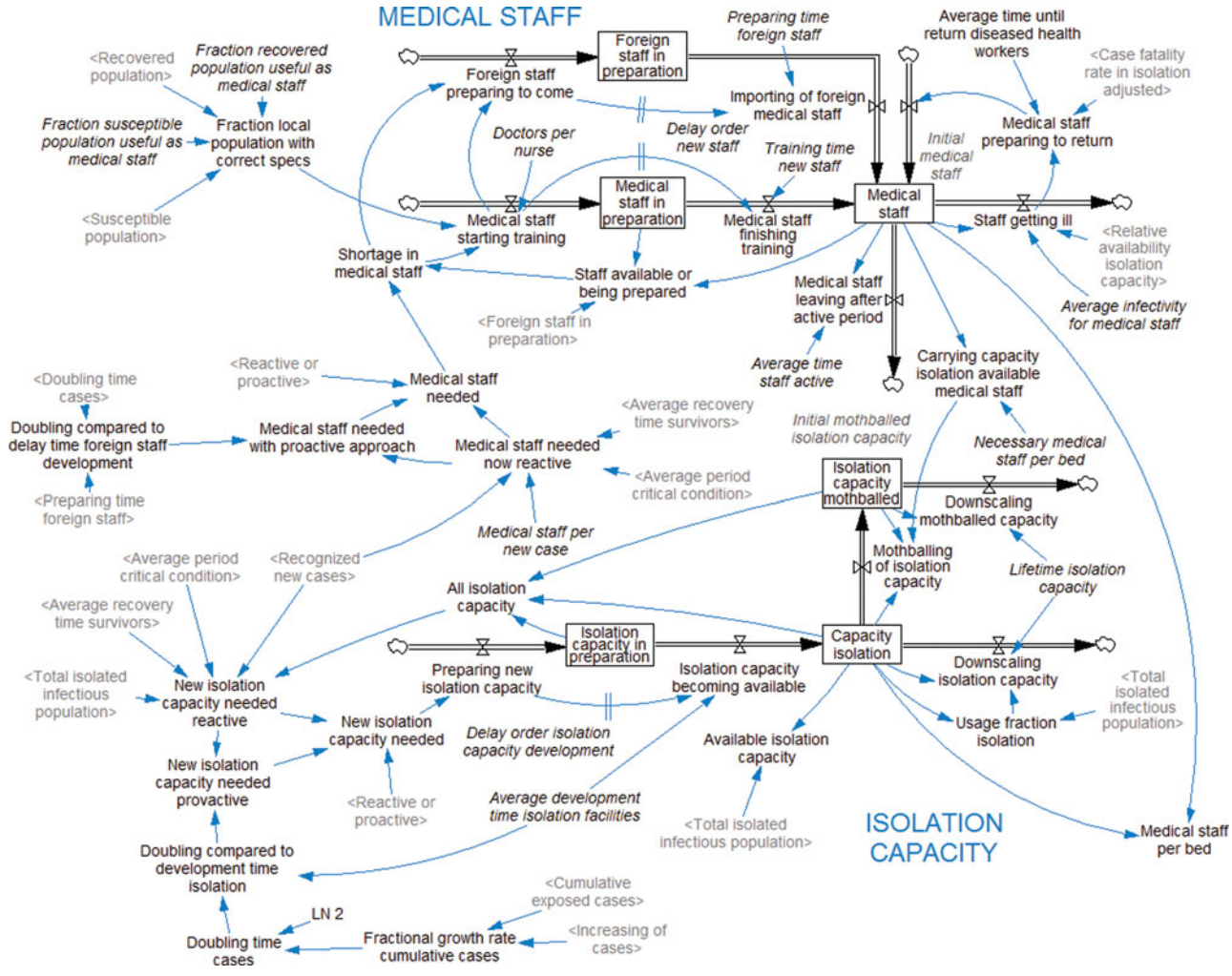

Figure A2. Detailed stock–flow diagram of the medical staff sub-model and the isolation capacity sub-model.

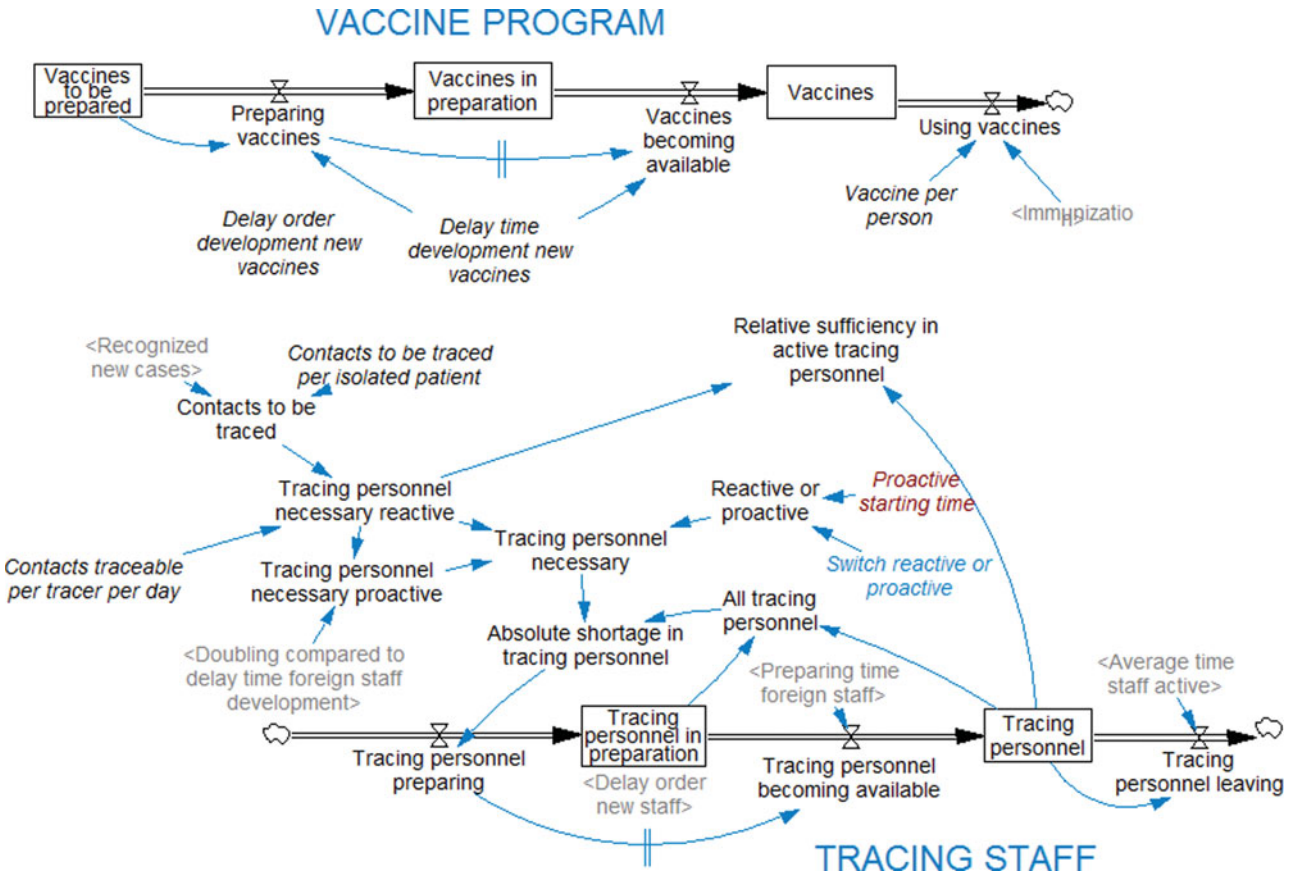

Figure A3. Detailed stock–flow diagram of the tracing staff sub-model and the vaccines program sub-model. In the vaccine program sub-model, it is assumed that one vaccine per person is being developed albeit with an uncertain delay, in line with WHO (2014c) estimates, such that vaccines would become available from the first half of 2015 on.