A Sensitivity Analysis of Model Structure in Stochastic Differential Equation and Agent-Based Epidemiological Models

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Honours Dissertation

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Abstract

The dynamics of infectious diseases have been modelled by several universally recognised procedures. The most common two modelling methods are differential equation models (DEM) and agent based models (ABM). These models have both been used through the late 20th and early 21st century to gain an understanding of prevalence levels and behaviour of infectious diseases; and subsequently to forecast potential impacts of a treatment. In the case of a life-threatening disease such as Malaria, it is problematic to be working with incorrect predictions and an epidemic may result from a misinformed judgement on the required treatment program.

DEM and ABM have been documented to provide juxtapositioned results (and conclusions) in several cases, even whilst fitting identical data sets [Figueredo, *et al.* 2014]. Under the correct model, one would expect a fair representation of an infectious disease and hence an insightful conclusion. It is hence detrimental for the choice of treatment tactics to be dependent on the choice of model structure. This honours thesis has identified the necessity for caution on the model methodology and performs a sensitivity analysis on the incidence and prevalence of an infectious disease under varying levels of treatment.

This thesis hones in on modelling methodology under various structures: the procedure is applicable to any infectious disease, and this thesis provides a case study on Malaria modelling with a later extension into Ebola. Beginning with a simple Susceptible-Infected-Recovered-Susceptible (SIRS) model: immediately obvious differences are examined to give an indication of the point at which the models lose integrity in direct comparability. The SIRS models are built up to include varying levels of exposure, treatment and movement dynamics and examining the nature of the differences in conclusions drawn from separate models.

Contents

Introduction

The introductory section conveys the use of mathematical modelling: Agent-based and differential equation based models within epidemiology. The basic characteristics of the diseases to be simulated by the models are described, and the purpose of modelling them is explained.

Mathematical Modelling

Mathematical modelling is the representation of a system whilst under a set of pre-specified conditions. A practical application of this is an epidemiological model which allows for stochastic behaviour where one can portray a set of possible time-dependant events through a vector of associated probabilities. Specifically, a model of an infectious disease must be able to represent the possibility of both an epidemic and the dormancy or extinction of a disease based on parameter choice. Thus, any event known to be able to occur in the system should be represented in the model with a non-zero probability. This dissertation will specifically look at a comparison of two mathematical modelling techniques in epidemiology: i.e. agent-based (AB) and differential equation (DE) models; with a case study on the infectious disease Malaria, and extension into Ebola.

Malaria

Malaria is commonly found in more humid environments, in the presence of *Anopheles* mosquitos the carriers of *Plasmodium* (malaria parasites) [Stassen. 2008]. If a carrying *Anopheles female* bites a human, *plasmodium* may be transferred which then mature in the liver for 1-2 weeks before entering the bloodstream, upon which they multiply via infection and rupture of red blood cells. Early signs of malaria similar to those of a common cold (general discomfort, irregular temperatures and sweats etc.) will be seen in the initial phase of the parasite acquisition. During this period the multiplication rates of the *plasmodium* are low, indicating that the basic Malaria model should be of an SEIR or SEIRS form (Susceptible-Exposed-Infected-Recovered-Susceptible) [Koella and Antia. 2003]. Once past the initial exposed stage, if an infected person remains untreated with the parasite in the bloodstream, *plasmodium* effectively prevents blood flow to vital organs, the failure of any of which is fatal.

Malaria is not a communicable diseases; it cannot be transmittable directly between two people but is instead transmitted through vectors- the *Anopheles* mosquitos [Stassen. 2008]. Relying on a mosquito to acquire the disease from an infected human, and then transmit to an uninfected human. A simplified model will make assumptions about infection through surveyed mosquito densities and a more advanced model will attempt to model the mosquito population.

Ebola

Unlike instances of Malaria which are treatable, Ebola has no confirmed cure, yet advances in the treatment have been exponentially increasing over end of 2014 [Davis, 2014]. There is an associated death rate of 25-90 percent of cases. The outbreak of 2014 has tallied a higher infection count and death count since the first recorded epidemic in 1976 [WHO {2}, 2014].

The *World Health Organisation (WHO) High Level Meeting of 23 October 2014* has established the necessity of mass intervention [WHO {3}. 2014]. Due to research into the vaccination possibilities, there is production possibility at 24,000 units, with the intention to be increased to 230,000 by April 2015. There is currently no availability of an FDA- approved vaccination [Davis, 2014], yet protocol

for testing has been reduced to randomised clinical control trials. Rather than verifying safety of the vaccination, the WHO intends an implementation in advance of knowledge of the side-effects [WHO {3}. 2014].

Proposition: The Necessity of this Analysis

Infectious diseases are problematic within many populations due to the nature of a possible epidemic. The modelling of such diseases allows for estimations into rates of disease transfer and of the risk of an epidemic; as well as inference into the dynamics of a target population. Similarly, the models can allow predictions effectiveness of quarantine or vaccination policies. Often, implementation of policies is country-wide. This incorporates large costs, hence it necessary to implement the correct procedure the first time and not endure unnecessary costs. Additionally, a sub-optimal policy being implemented could directly result in more deaths.

This thesis incorporates a background discussion on model structure; and focusses on a sensitivity analysis agent based and differential equation models in modelling abilities under the same structure. Lastly, equivalent adjustments to the critical parameters in the models are made to observe how they affect a difference in performance between an ABM and DEM. This dissertation takes an in-depth look at the barriers faced in the sensitivity of results and recommendations to model methodology. Koella and Antia [2003] concluded the necessity of *"more detailed knowledge of the critical parameters"*, the lack of knowledge of these parameters (and which distibutional properties to implement) is a potential cause for differences between the agent-based and the differential equation model results. Measurements of interest are incidence, prevalence, treatment levels, and progression of the disease. Models of progressive steps of complexity are measured: incorporating treatment and death states in later models in addition to S (susceptible); E (exposed); I (infected); R (recovered).

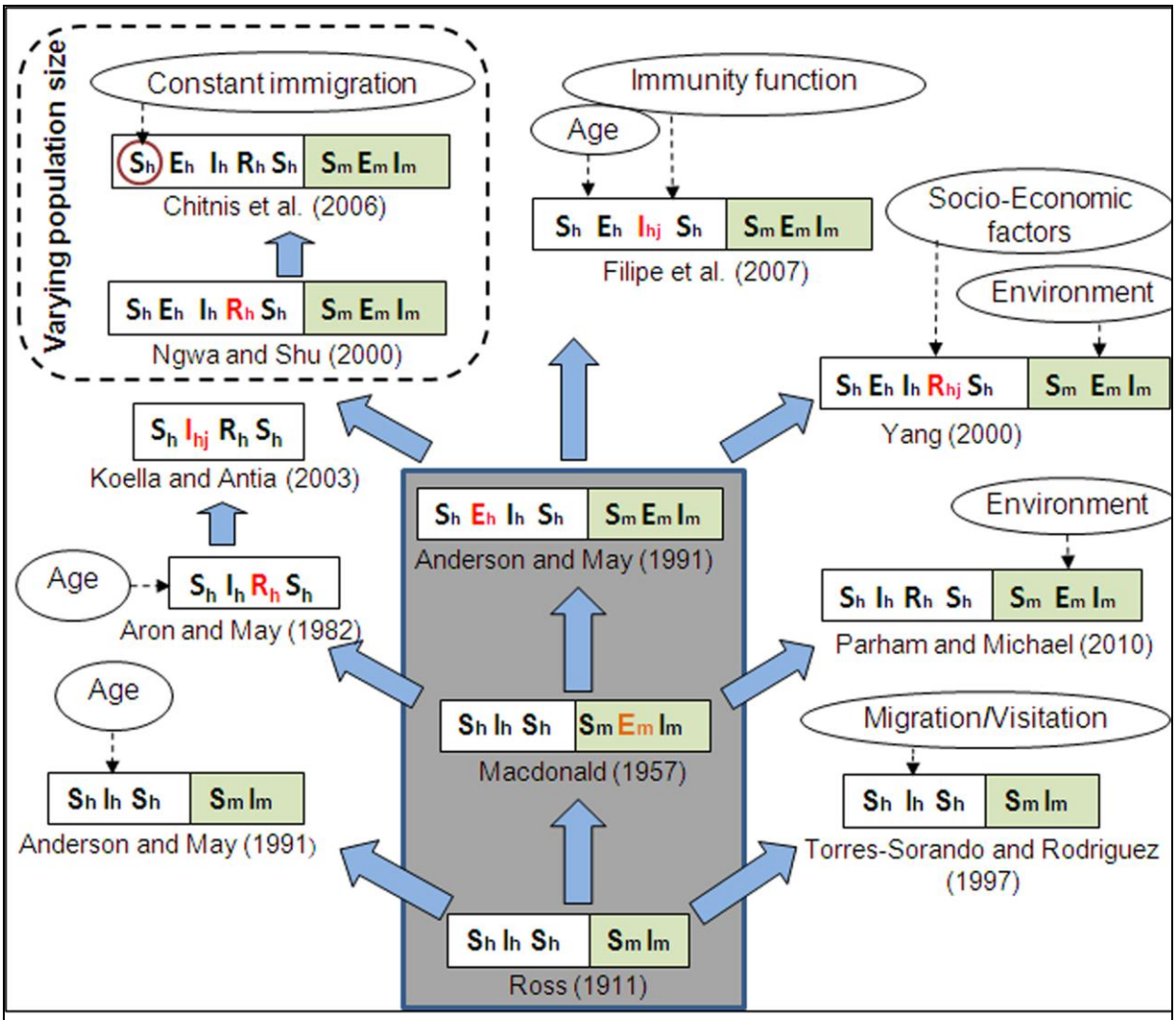
Literature review

The use of mathematical models in the field of epidemiology was first recorded in a proposed inoculation plan against smallpox by Daniel Bernoulli in 1760. This allowed for a depiction of the system through differential equations, including the first noted use of R_0 the "basic reproduction number" as a function of the force of infection: $R_0 = f(I, S, n)$ [Scherner and McLean. 2014]. The model was further extended to account for the force of infection with dependency of population demography by P.D. En'ko in 1873 [Dietz, *et al.* 1998].

Epidemiology modelling evolved into the Reed-Frost models of 1920 [Diekman. 1996]. The initial models are a simple extension of a Markov-chain into a chain-binomial model in ABM methodology. This allowed for time-dependant rates of movement between three states {susceptible, infected, recovered}. In a DEM this structure is seen in average rates or "flows" of transition from one state to another. Significant contributions to the flow between classes were brought in the early 1900s in the Kermack-McKendrick model [Kermack and McKendrick. 1927]. Subsequently, H. Soper introduced

into the Kermack-McKendrick SIR (Susceptible, Infected, and Recovered) model the possibility of death from the disease [Brauer. 1984] and the state-based models were designed to incorporate complexities of agent-based and stochastic transition between states.

A significant modelling procedure was established by Ross in 1911 [Smith, D. *et al.* 2012] who incorporated into a basic malaria model the dynamics of a mosquito infection Markov-Chain. This model is dependent on the densities of both the human and the mosquito populations in the various states. Ross's model was extended by the inclusion of a vector-incubation period (latency) period before infectiousness arose by Macdonald [1957]. Macdonald as also established the importance of the number of secondary infections *(R_0: see glossary p43)* produced by an infected human, termed the "basic reproduction number". An R_0 greater than one predicts an epidemic to occur. Spatial heterogeneity was introduced by Dye and Hasibeder [1986]. The Delayed-Ross-Macdonald model takes into consideration the latent period in more complicated forms [Ruan, *et al.* 2008]. This is easy to model in ABM methodology, but more complex in DEM, requiring segregation of the population into homogenous groups.



Evolution and grouping of different types of SEIR malaria models. Subscripts 'h' and 'm' represent respectively the human and mosquito states of infection. **Mandal *et al.* 2011**

Significant work in the epidemiological model is depicted in a flow diagram above. The focus of this dissertation is attributed to the body of work from Ross [Mandal *et al.* 2011] and Macdonald [1957]. Anderson and May introduced age dependant rates of susceptibility, which was closely followed by a model from Torres-Sorando and Rodriguez incorporating human movement in 1991. This idea was extended to mosquito-population genetic models in work from Yang (in 2000), and Parham and Michael (in 2010) who explicitly model environmental and climate-dependant demography and movement of mosquitos. Detailed flows between states from Koella and Antia [2003] were added to an extended cohort model from Aron and May (designed in 1982) who had allowed the flow of "partially immune" individuals into the susceptible state. Filipe is regarded as the most recent insight (2007) into the human-side of the malaria virus, scrutinising the acquisition of immunity via mathematical modelling. He provides coverage of immunity as a function of historical infection, allowing a non-memoryless rate of transfer between states. Allowing for an account of death caused by a virus has typically been given minimum prioritisation, setting total death equal to total births and hence working with a constant population size. Ngwa and Shu incorporated the effect of an increased force of mortality due to the disease, further extended by Chisnis in 2006 to allow for population immigration in and out of the model [Mandal, *et al.* 2011].

Specific works in the field of this paper are the establishments of differences between the agent-based models (ABM) and differential equation models (DEM). Both models have advantages, most significantly an ABM can readily capture heterogeneity amoungst a population, and DEM has a much faster computation time. It is potentially risky to use AB modelling if the dynamics of a population are in any way not well understood [Koella and Antia. 2003]. Rahmandad and Sterman [2008] expose discrepancy between the two models and begin a discussion of four parameters which are subject to heterogeneity: exposed contact rate; infectivity; emergence time and disease duration. This work was complimented by Bobashev *et al.* [2007] who discussed the danger of model structure causing a misrepresentation of a disease, and began discussion on a hybrid model. The theoretical discrepancies are proven by Sheetal *et al.* [2014] and in particular it is demonstrated that under treatment, a population's treatment probability is not necessarily representative of the treatment coverage. Figueredo *et al.* [2014) established the preference of stochastic techniques in ABM over DEM, specifically in the field of cancer. This dissertation aims to establish the underlying causes of the variation of results based on model structure, looking at treatment, incidence, prevalence, steady-state probabilities and parameter sensitivity.

The analysis in a comparison of ABM and DEM methodology in Model 3 of Malaria (later in paper) is readily applicable to a more fatal disease to which a mass-treatment policy can be applied. The Ebola virus disease (EVD) is also known as the Ebola Haemorrhagic Fever due to the haemorrhagic properties [Chan. 2014]. Analysis of the general properties of haemorrhagic virus properties has been performed by Lashley and Durham. The 2014 strain of Ebola is known as the *Zaire ebolavirus* strain [Blaize. 2014], the 5th recorded strain, first seen in 2013. Ebola is a rapid-acting virus, with an inoculation period of 2-21 days [Lashley and Durham. 2007] where it remains docile and non-transmissible. With the initial symptoms of a typical fever, cold or virus, EVD is transmittable from this point to those in contact with the either infected living individuals, or infected corpses, or infected wildlife. Transmission is possible through contact with bodily fluids, sinew or secretions. A total of 13,567 cases of EVD have been reported, with 4,951 fatalities and rising as at 31 October

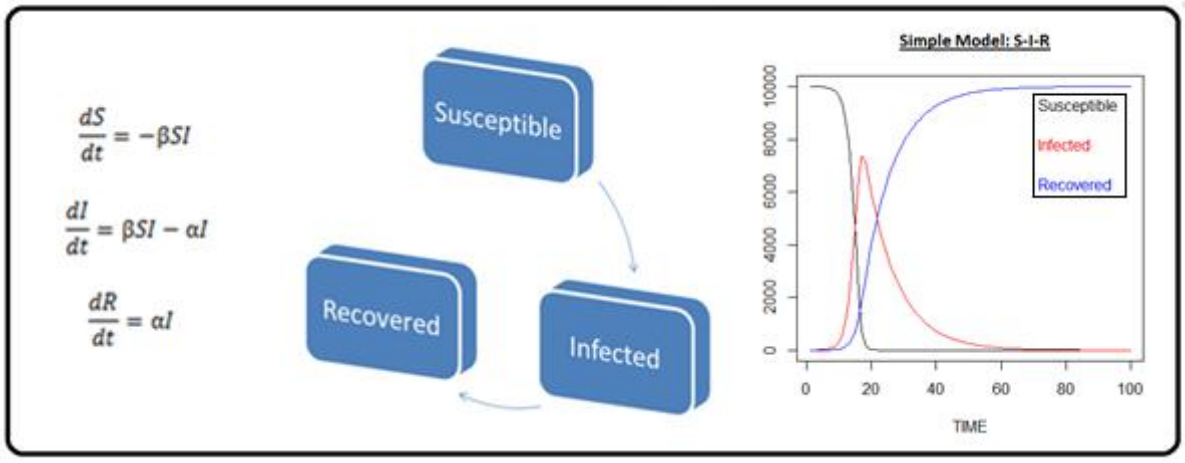
2014. With so many casualties, the *Zaire ebolavirus* is recorded as the most infectious and deadly epidemic of EVD [WHO {1}. 2014].

Epidemiological Methodology

An introduction into epidemiological modelling: the modelling of health and sickness patterns over a population; and the two selected methods of modelling the dynamics: ABM and DEM.

The mathematical methods of modelling epidemiological models form a description of the movement of the population through relevant phases of a disease. The modelling structure is the decision of which states to include in the model, which states communicates or allows one-directional flows, and what the rate of these flows is set to.

Simple Differential Equation Model of a system in States S; I; R



The basic model of disease transition proceeds through the states S-I-R (Susceptible-Infected-Recovered), depicted above. A simple model will assume a constant infections rate and recovery rate, often setting the population number as a controlled constant and allowing birth-rate to equal death rate [Rahmandad and Sterman. 2008]. For a lethal parasite, it is necessary to include a state-dependant possibility of transition into death which will thus allow accounting for deaths caused by the disease by denoting a higher force of mortality in the infected state [Brauer. 1984].

An Agent-based model operates in a very similar manner, allowing the same transitions to occur, but as opposed to a differential model which uses a rate of flow, multiplied by the proportion of individuals in state k as the flow from k: an ABM makes a binary decision per each individual in the population as to whether they move, or remain in the state k.

DEM movement in state K at time t:

$$\frac{dK}{dt} = -\beta K f(I) + \tau \bar{K} g(I)$$

Where $\bar{K}$ is the state with a flow into K

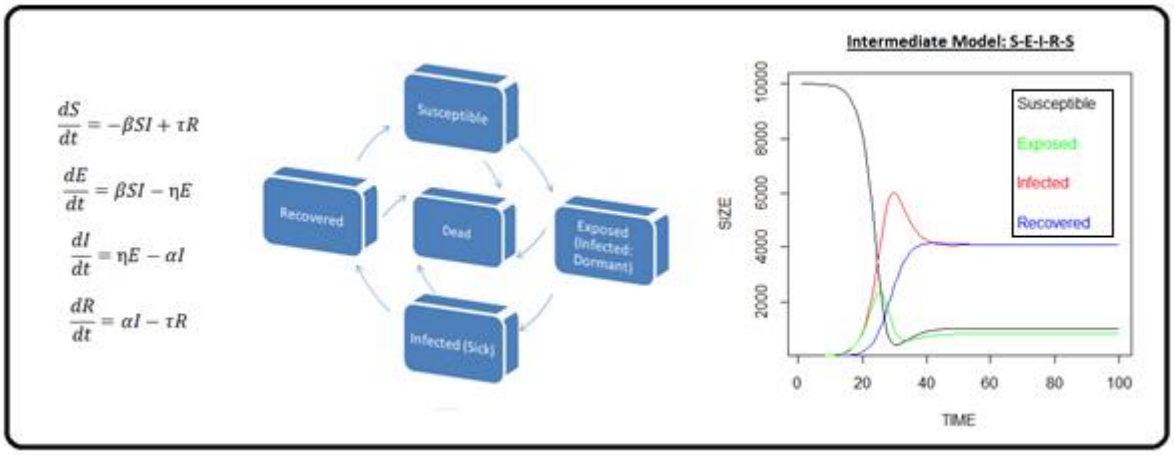
Above: K would be the infected state, with flow from S into infected as τSI and flow out of infected to recovered as βI)

ABM movement in state K at time t:

$$- \sum_{in\ state\ k\ at\ time\ t-1} \{\Omega \backslash \{k\} at\ time\ t\}$$
$$+ \sum_{in\ state\ \Omega \backslash \{k\} at\ time\ t-1} \{in\ state\ k\ at\ time\ t\}$$

Above: K would also represent the infected state, and the change between the numbers of individuals in K between times [t-1 : t]; is the numbers of individuals who arrived in state K less those who left state K.

Intermediate Differential Equation Model of a system in States S; E; I; R; D



Another commonly used modelling procedure is to allow for stochastic movement. The advantage of this is to allow for more realistic behaviour and for the occurrence of extreme events. When setting individualized parameters to a population (i.e. in an agent-based model), the dynamics of the population will need to be looked at under a probability field. The nature of an agent-based model will require transition between states to be a function of the entire population, hence there is often an extensive computational time required. This is not typically an issue with differential equation models, as the average population dynamics are used throughout. A mixed model [Bobashev, *et al.* 2007] will allow for the duel use of both modelling procedures; agent-based modelling for a start-up disease, until it has at least surpassed the threshold to be infectious to at least one other entity, where it can be swapped over to a DE to reduce computational time after infection has reached a second threshold.

In a brief summary model structure that are examined in this paper as both ABM and DEM:

Model Stage	States incorporated	Additional assumptions
Simple S-I-R-S	S-I-R-S Susceptible, Infected, Recovered, and revision to susceptible again once recovery has "worn off".	Assume deaths occur at same rate as births, and constant susceptibility to infections (dependant only on number of infective individuals in the system).
Treatment Model **Vaccination**- Allow treatment of susceptible and of exposed and infected individuals at varying rates of success. Performed under several policies to observe impacts and look for differences between models.	S-E-I-R-S, with a mirror class or each S^T; E^T; I^T; R^T for treated/ vaccinated individuals in the respective states.	Analyses impact of treatment level on the population which contains disease.
Treatment Model **Mass Screen and Treat**- mass drug administration	S-E-I-R/D Allowing death state within the model. Also allowing transfer from S, E or I successfully treatment/ non-susceptible.	Accounting for infectiousness of individuals at varying rates according to which infection state they are in, and incorporating a death state (disease-structure dependant)

Data and Measurements

A discussion of the intention of the underlying models in general cases as well as how this paper has selected the model structure, and what the measurements are taken with the purpose of.

Any Epidemiological model is designed to replicate the expected patterns of a disease. The "expected patterns" are not closed to be the average, but rather to represent the range of possibilities such that protocols can be designed to optimize the ability to deal with the disease; the exact dynamics of which are not known in advance. The best proxy for future dynamics are historical data and measurements; hence once a model has been designed for a disease, it can be verified and validated by seeing how the model can replicate incidences/ epidemics of the disease historically.

Where data is fitted to the above S-I-R-S and extended models in other papers, the Least-Squares algorithm is applied to estimate parameter values. The application of this dissertation is aimed towards Southern African populations where Malaria is prolific; hence parameters in this thesis have been selected from reports of disease from such areas. ABM and DEM models are then constructed to mimic the disease history, and are compared against one another. The emphasis of this paper is

to extract differences between the modelling procedures, not necessarily specific to one population but how they would appear in a type of population and how to optimize the modelling procedure.

All coding for this project has been completed using R version 3.1.0, a matrix oriented statistical language. The modelling of differential equations has been performed in discrete-time, and hence is represented Difference Equations, which are coded entirely by the author of this paper. Agent-based models have been constructed via imposition of statistical distributions onto the population parameters to represent a random sampling of the possible dynamics of the individuals within the population. Due to the high computational demand of the advanced model simulation, it was required to use the UCT high powered cluster for model simulation, allowing several thousand hours of computer-time to be completed in a matter of days.

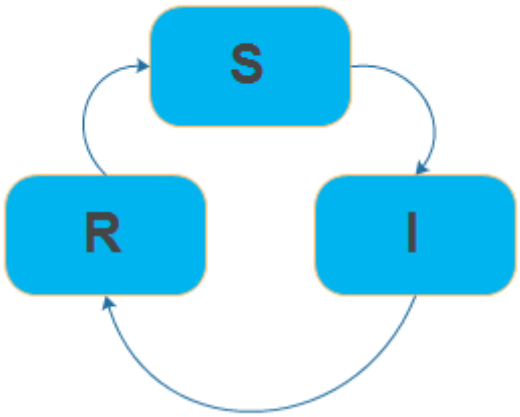
To perform a sensitivity analysis of the two models, the same population structure and dynamics are represented in both models and Monte-Carlo methods are used to extract the theoretical statistics of the Malaria (and later the Ebola) virus. This paper focusses on the points of discrepancy between the two models, attempting to establish where sensitivity lies in both models and what parameters are indicated to be responsible. Statistically significant discrepancies between the population dynamics whilst infected by Malaria are included in the report this is including, but not limited to analysis on the proportion of disease incidence, treatment coverage and spread of resistance.

Model 1: Simple Model

The initial comparison will be of an S-I-R-S model. There is transition from Susceptible to Infected, from Infected to Recovered, from Recovered to Susceptible, and under a discrete time probability chain, in the stationary distribution this is seen by Bobashev *et al.* [2007] as a stochastic Markov-chain there is transition from each state into itself. *See appendix C for parameters used within SIRS model.*

Structure and Methodology of Basic Model

Simple Model State Space and Flows



Differential Equation flows between States S; I; R

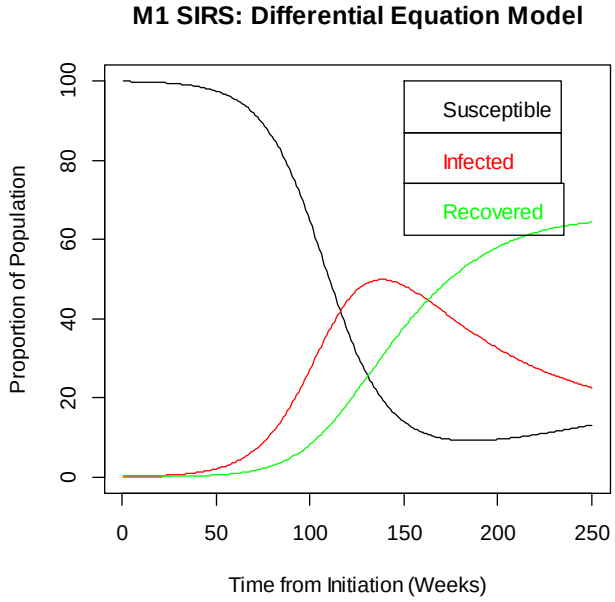
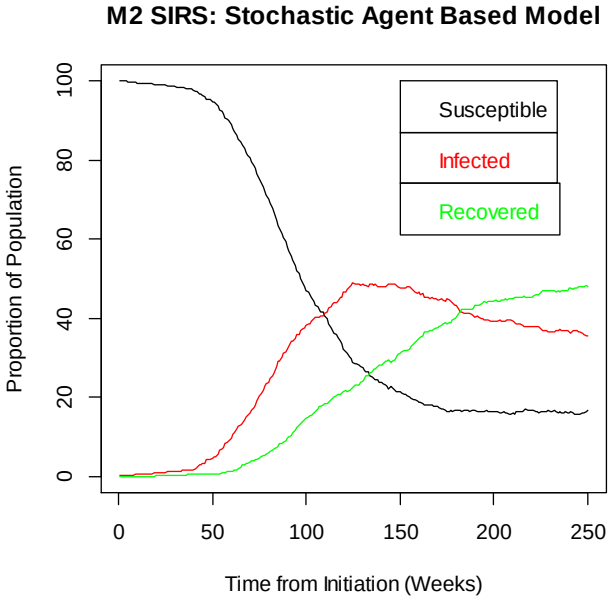
$$\frac{dS}{dt} = -\beta SI + \tau R \quad (1)$$

$$\frac{dI}{dt} = \beta SI - \alpha I \quad (2)$$

$$\frac{dR}{dt} = \alpha I - \tau R \quad (3)$$

β and α are constants with respect to the process, β is the proportionality constant for successful transitions of disease, leading to βI being an individual who state S's force of infection and α is the rate of recovery of an individual in state I. τ is the rate at which individuals become re-susceptible to the virus. Often a temporary immunity is built up, during which period an individual cannot be re-infected this is represented by the "Recovered" state.

This model ignores the population dynamics of mosquitos, the parameters used are indicated in *appendix A.* The parameter values are run through the above SIRS system under both a DE, and under an agent based model. The results are then compared against one another under a sensitivity analysis.

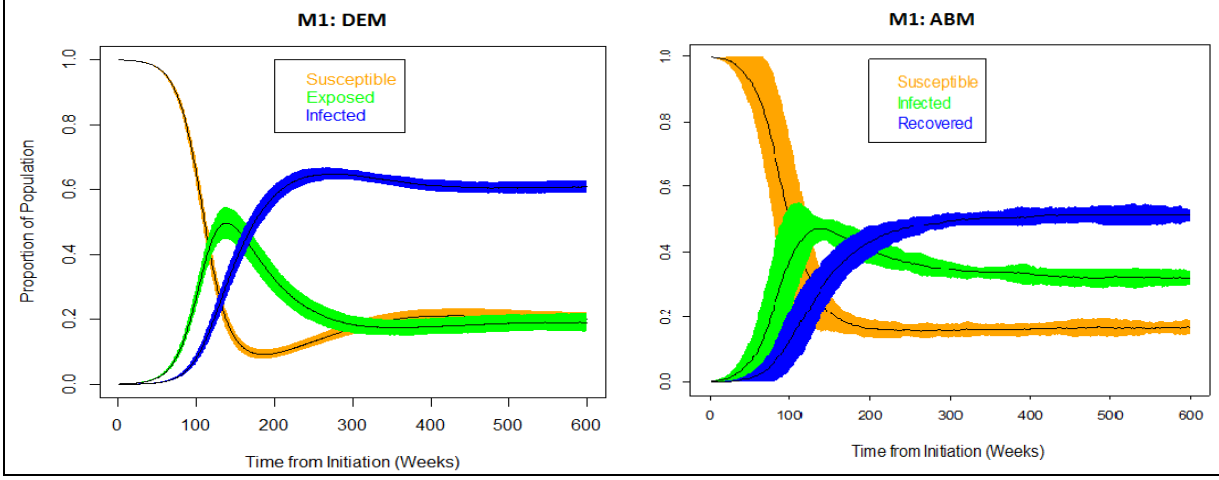
M1: DEM simulation *appendix A*	**M2: Single ABM simulation** *appendix A*
	

two models were simulated per ABM and DEM methodology, the first was simulated by applying the steady-state conditions blindly, model 1.1; and the second model 1.2 was applied in order to meet specific state conditions of infection levels after several years.

Results of the Basic Model

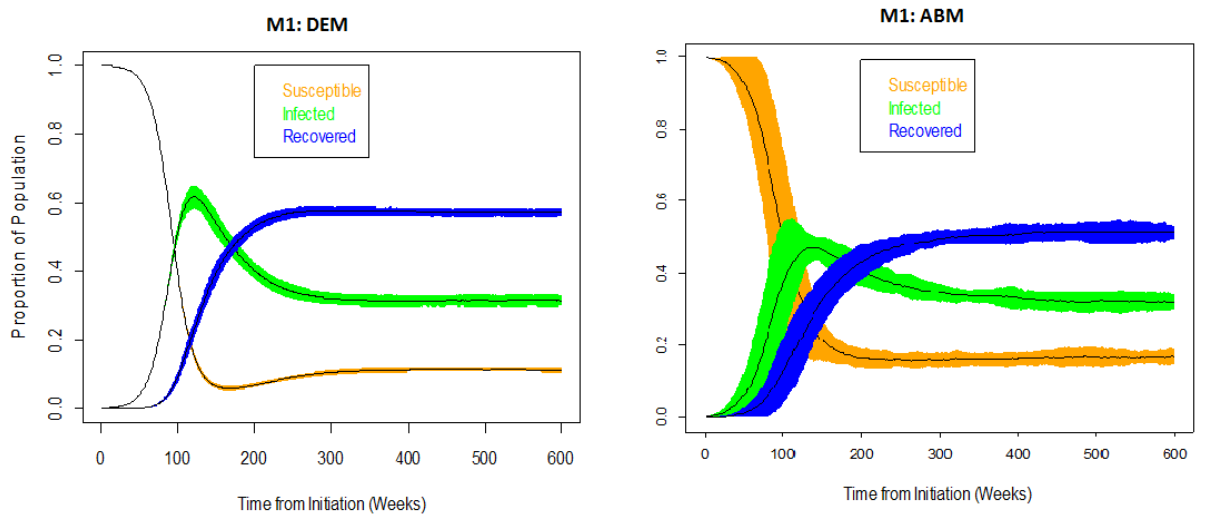
Refer to appendix D for output values.

Model 1.1: Simple SIRS model; applying identical model parameters under different methodology



There are clearly very different steady states met within the two different methodologies. The following model corrects for this explicitly, and is explained in the analysis section.

Model 1.2: Simple SIRS model; looking to replicate patterns of a fixed steady-state infection level



Analysis: Sensitivity of the basic Model

The agent based methodology is highly sensitive to bias in a disease dying out. There are dormancy periods of a disease in reality, but no extinction. There were, of 1,000 simulations 191 simulations in which the disease reportedly died out. This needed to be explicitly modelled within the ABM to prevent it from happening, after which the model acted in a more representative manner.

In model 1.1: Low movement was seen over aggregation of 1000 simulations, reaching the proportions by time 600 of

Agent Based Model

S	I	R
16.838	31.475	51.687

Differential Equation Model

S	I	R
20.028	19.108	60.864

After accounting for the flaw in an ABM of the probability of disease dying out, there is still a large discrepancy between the steady state conditions; particularly between the infected and the recovered states. The 95% confidence band of proportion in states by the end of the time period:

Agent Based Model Confidence Intervals

S	I	R
(22.281;14.556)	(22.281; 29.193)	(22.281; 49.405)

Differential Equation Model 95% Confidence Intervals

S	I	R
(18.076; 22.251)	(16.185; 21.885)	(59.045; 62.555)

This can be attributed to the choice in distribution of the parameters onto the individuals in an ABM. In particular, the truncated normal distribution allows for a large variation in transition rates from recovered to susceptible representing Rahmandad and Sterman's [2008] research where Malaria immunity can follow 5-year half-life or in some cases loss of immunity occurs rapidly. The truncated normal has caused several individual rates of movement from I to R to assume the value 0, hence allowing many individuals to remain indefinitely "recovered", skewing the proportions of time spent in each state.

Incidence rates can be compared at: $\frac{number\ of\ cases\ new\ cases\ over\ a\ time\ period}{number\ of\ susceptible\ individuals\ over\ \ the\ period}$

In the Differential Equation Model we see incidence rates to be 0.00160 after six months of population exposure to disease, in contrast to a very close 0.00151 in the Agent Based Model. Discrepancy is very evident whilst approaching steady state, after ten years the incidence rate in the DEM of 0.00623 in contrast to the incidence rate of 0.008824 in the ABM.

Statistic	Numbers in DEM	Numbers in ABM
Loss of immunity	After 4 years	Randomised, and causing several rates to assume a loss of immunity value of 0, and several to be very rapid.
Cases over a week in the first exposure of the disease (6 months after first exposure):	0.157 per 1,000 individuals in population	0.147 per 1,000 individuals in population, with a confidence interval of 0.147 ± 0.01253716 on average
Cases over a week towards steady state of the disease (10 years after initial exposure):	3.111 per 1,000 individuals in population	2.691 per 1,000 individuals in population, with a confidence interval of 2.691 ± 0.9290408 on average

In model 1.2: A similar analysis is performed to identify differences; however there is constant overlap of the 95% confidence intervals, implying no significant differences between the ABM and DEM methodology predictions into population proportions found in the different states.

Agent Based Model 95% Confidence Intervals

S	**I**	**R**
(22.281;14.556)	(22.281; 29.193)	(22.281; 49.405)

Differential Equation Model 95% Confidence Intervals

S	**I**	**R**
(18.076; 22.251)	(16.185; 21.885)	(59.045; 62.555)

Discussion of Basic Model Methodologies

From the simple model above, it is not possible to make any drastic conclusions as to discrepancies in the model. In particular, it is demonstrated by model 1.2 that it is simple to allow one model to replicate the other should the need arise. Model 1.2 was coded with the intention of using the model method at hand to deliberately end up with specific proportions of population in specific states. It is clearly acceptable for both of these methodologies to be used in epidemiology. It is however clear that the models cannot be used arbitrarily; and rather than focussing on steady state conditions and blindly plugging in parameter values; it is essential to rather find a parameter value such that the “expected” result is obtained (based on historical patterns).

Model 2: Vaccination Model

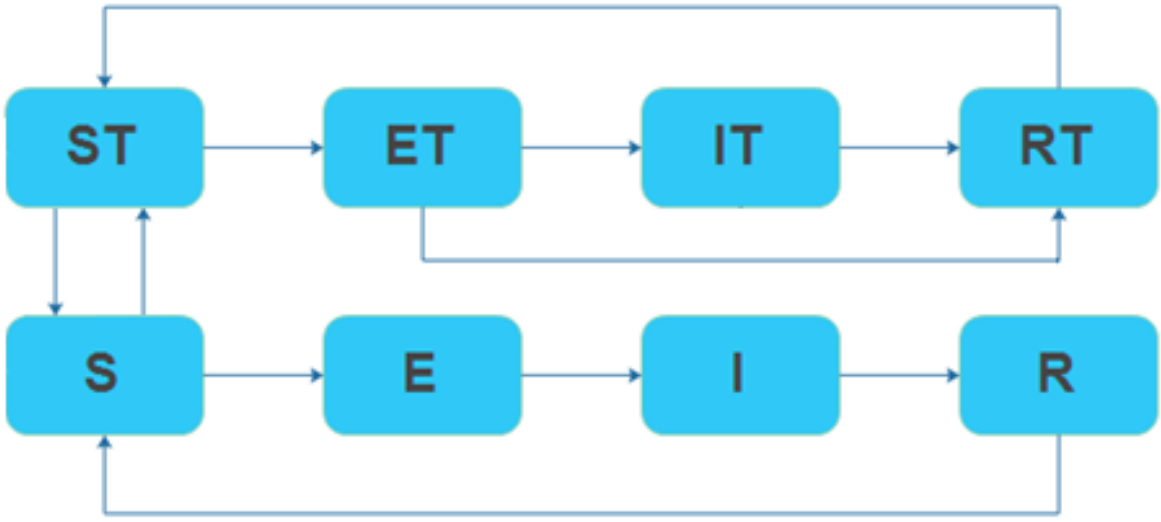
This is the second model of the paper. A direct extension of the first model; allowing for a latency period of "exposure" to the disease as opposed to immediate infection; as well as a set of states, discriminating by the infection status of the disease, and by treatment presence or absence.

It is possible to apply a nation-wide vaccine, and thus reduce the number of susceptibles, and/ or it is also possible to apply a treatment to known infecteds. With a treatment for an infected; stochasticity arises from the probability of success from the treatment. A vaccination model allows for treatment during any of the "susceptible", "exposed" or "recovered" states. Considering the knowledge of an epidemic occurring, it seems futile to wait for infection prior to seeking treatment when a vaccination is readily available. Hence the more complex vaccination-model version is chosen to model under a Differential Equation and an Agent Based approach.

Vaccination Model Structure

Under this model, movement into and out of vaccination protection is allowed. Individuals within a vaccinated state are indicated by the "T" suffix on the regular states. Additionally normal movement in the progression of Susceptible to Exposed to Infected to Recovered to Susceptible is allowed both within and outside of having the vaccination. An obvious adjustment for the rates is to reduce infection within the treatment group, as well as reduce duration of the disease in infected.

Vaccination Model: State Space and Flows



S	Susceptible	ST	Susceptible and vaccinated
E	Exposed	ET	Exposed and vaccinated
I	Infected	IT	Infected and vaccinated
R	Recovered	RT	Recovered and vaccinated

Model assumptions:

- Vaccination applied to individuals prior-infection with a non-zero probability

A vaccinated individual will have:

- a lower rate of infection
- a higher rate of recovery
- a lower force of mortality whilst in the infected state than would a non-vaccinated individual (ignored in this simulation due to equivalent birth and death rate assumptions, hence a non-necessity to model death in the model Koella [2003])

Allowance for any individual

- Zero or one state-changes maximum per time period
- Recovery can only occur from the "infected" state without treatment
- Recovery can occur from the "exposed" state and "infected" with treatment
- A temporary immunity is developed against the virus after recovery; hence while in the "recovered" state one cannot become re-infected immediately.
- All transitions are done so at a stochastic rate, hence there is no fixed duration over which an individual remains in a state
- States are explored according to an exponential distribution with rate as a function of the proportion of the population which is infected, a non-memoryless process

Additionally

- This model allows for transfer in and out of a treatment state.
- The model design imposes a lifespan of the vaccination of 4 years in steady state
- Additionally, the model assumes a *lower* risk for the vaccinated class against Malaria, proportional to the unvaccinated class.

As in the simple model; each simulation allows a time-based flow of the population density through the states of the model.

Model structures under this section:

Model 2A	A SEIRS with treatment policy, as presented above. Implementation of the vaccination as follows: 1. Vaccination effect: Applied to S, E and I Drastically reduces rate of infection, and spreads up recovery of those whom are exposed/infected. 2. When infection reaches above 10% of the population, assumed Government realizes the crisis, as imposes nation-wide vaccination policies immediately.

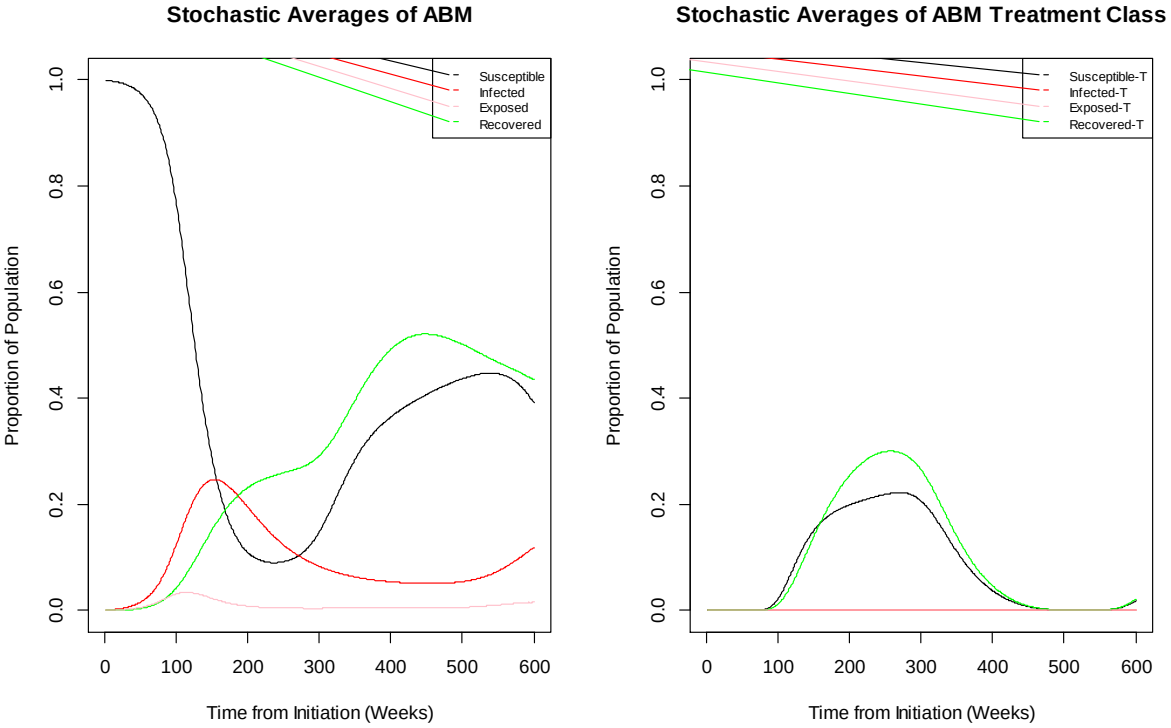
	3. When infection reduces below 2%, assumed policy was “successful”, and due to financial constraints, the vaccination policy is removed. This may be a realistic assumption is Western African countries, where internal medical structure is very limited. [Chan. 2014] 4. The vaccination is assumed to be temporary, and with an average of four years active.
Model 2B with policy intervention	In addition to the above: 5. Effective vaccination is used. This is representative of effective medical care, and seen in the model by those who have access to a vaccination to never have the vaccination wear off. This is practical under the circumstances of a perfect vaccination, or a population following a good health care system: and taking a new vaccination as soon as the previous one expires.
Model 2C with more effective vaccination policy	In addition to above: 6. Model explicitly controls levels of vaccination (to mimic historically suggested levels)

Refer to Appendix B for parameter calculations.

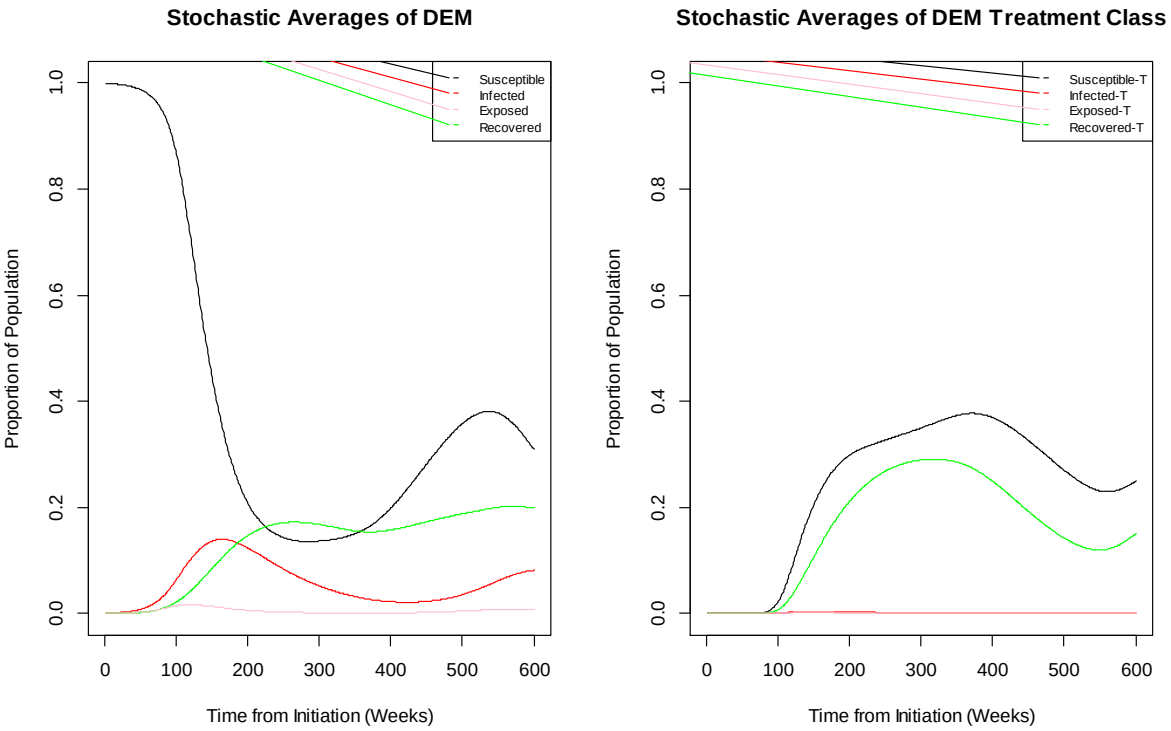
Analysis of Model 2: ABM vs DEM in vaccination

Model 2A: Average proportions of 1000 simulations (SEIRS with treatment)

Agent Based Model: Non-treated states on left; Treated States on Right



Differential Equation Model Non-treated states on left; Treated States on Right



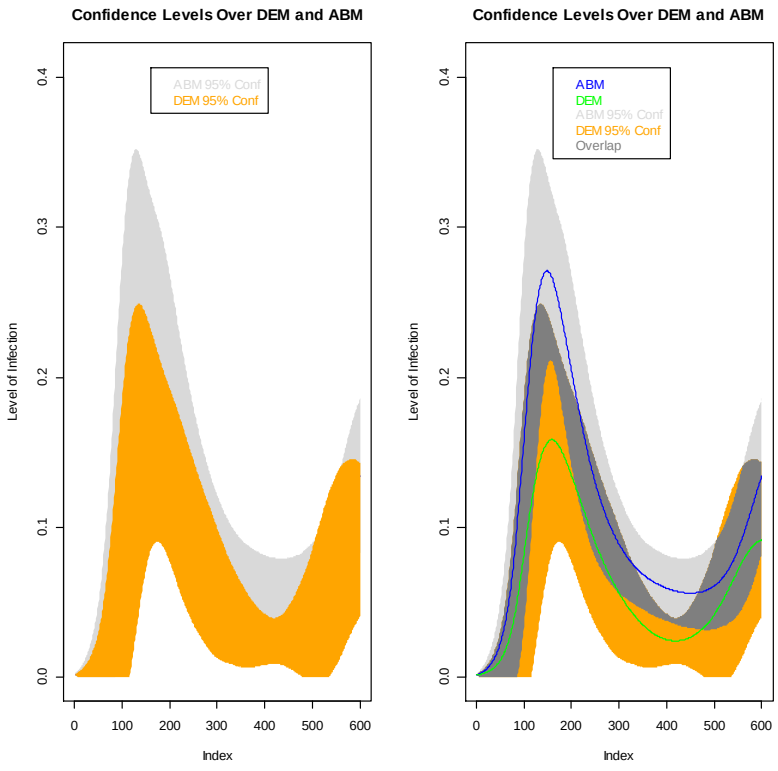
Discussion of rates in Model 2A Results

The above graphs are an aggregation of 1000 simulations of the models. Discrepancies are observed in the overall behaviour of the models, prolifically in the rate of loss of vaccination. The increased rate of decrease in vaccination over the ABM causes the level of vaccination to drop to 0, whereas the proportional decrease of the DEM imitates a half-life process (for the process between the removal of the vaccination and the re-application) and does not reach 0 on its trajectory.

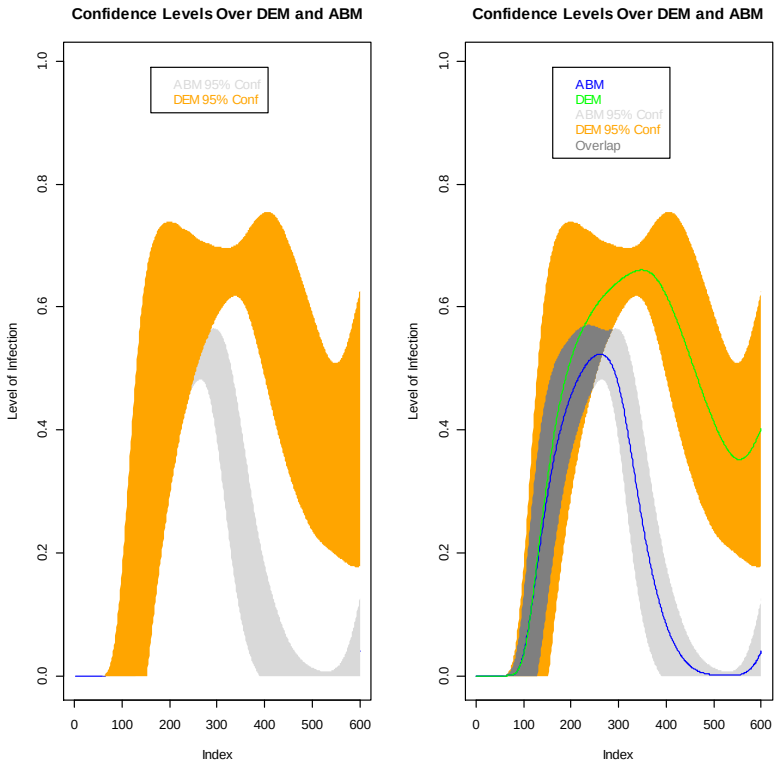
See appendix J for an output of several statistics of output from the model. **Statistics of interest are (foremost) the prevalence levels under the two methodologies and subsequently this paper discusses the vaccination levels, which were not controlled but allowed to vary.**

The Prevalence levels of the disease and the vaccination levels of the population are compared for both processes, and to compute a significant difference the confidence intervals are super-imposed onto the mean on the same plots. An overlapping confidence region is evidence that at the 5% significance level we cannot reject the possibility of there being equivalence between the two procedures over a single iteration.

Model 2A: Prevalence of infection over 1000 DEM and ABM simulations. Note the dark grey area as the overlapping confidence region.



Model 2A: Average Vaccination levels over population in 1000 DEM and ABM simulations. Note the dark grey area as the overlapping confidence region.



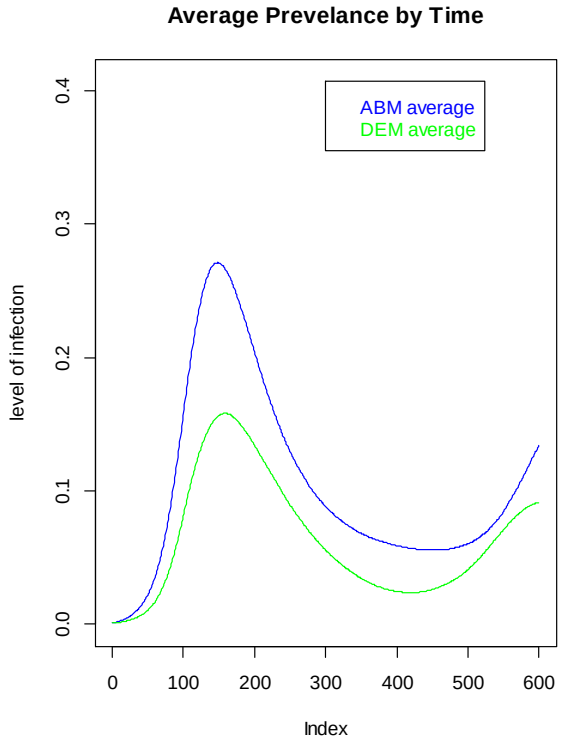
The magnitude of average prevalence of disease within the population in the ABM model dominates the DEM model in magnitude; however it is non-statistically significant. There is a statistically significant difference in the vaccination levels after time 250. After investigation into the cause of this discrepancy; it was established to be that within the ABM (but not the DEM) the number of infected individuals dropped below 2% in the majority of simulations (*See appendix J)*; allowing the vaccination policy to be removed from the system.

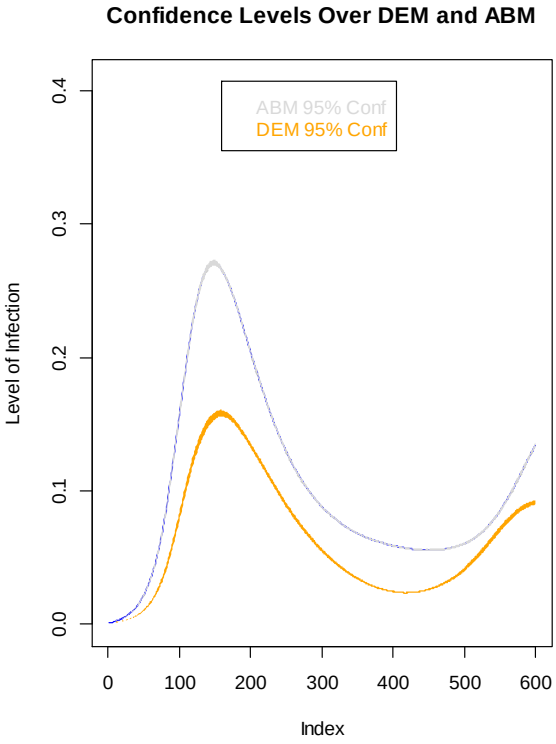
Incidences over the first year are higher in an ABM than in the DEM on average, with more exposed and infected individuals after a year in an ABM *see appendix J* (this pattern continues into further years, shown graphically above). The results are not statistically significant, with both models having confidence intervals which include 0 at 1 year. The volatility in the model was originally over predicted in the ABM, biased but the "extinction" allowed in the ABM which in naturally controlled in the DEM. This unnecessary volatility was removed for the graphs above by repeating the analysis under explicitly controlled conditions for extinction. The ABM allows variation in the individual movement in different simulations due to a better modelling ability of heterogeneity in the population.

Further looking at the difference in average levels between DEM and ABM in model 2A:

It is also possible to make a comparison of the **average** between both models. This has a much less intuitive interpretation; as it is not what would be expected in a single simulation. It is however a very good indicator as to whether, on average, the DEM and ABM modelled proportions are different from one another. 1000 simulations of each model have been taken, and the aggregated

results have been taken. In a comparison of averages, volatility has been decreased by a factor of$\sqrt{1000}$; a proof of the distributional benefits in variance reduction is derived in Appendix H.

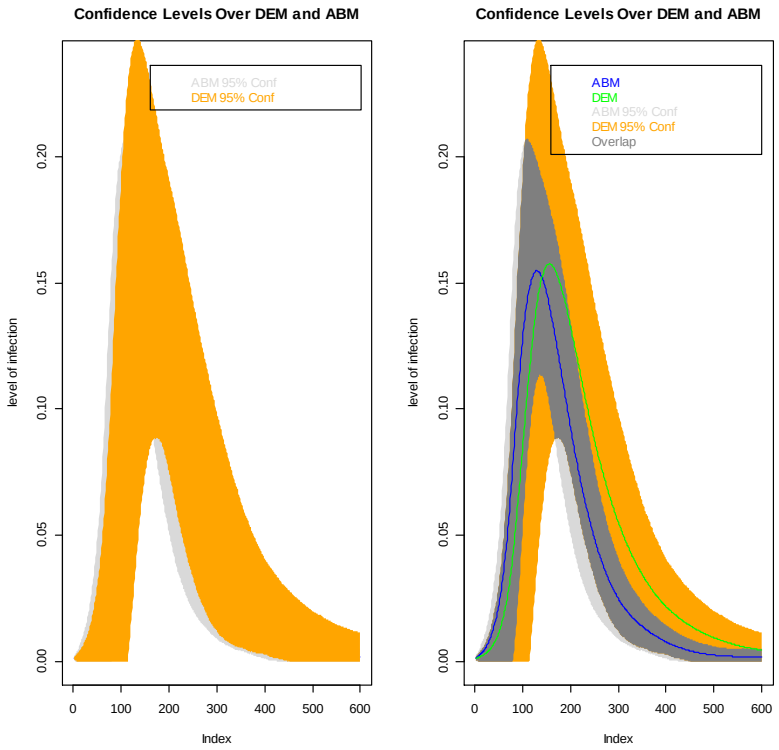




Additional model: Model 2B with policy intervention

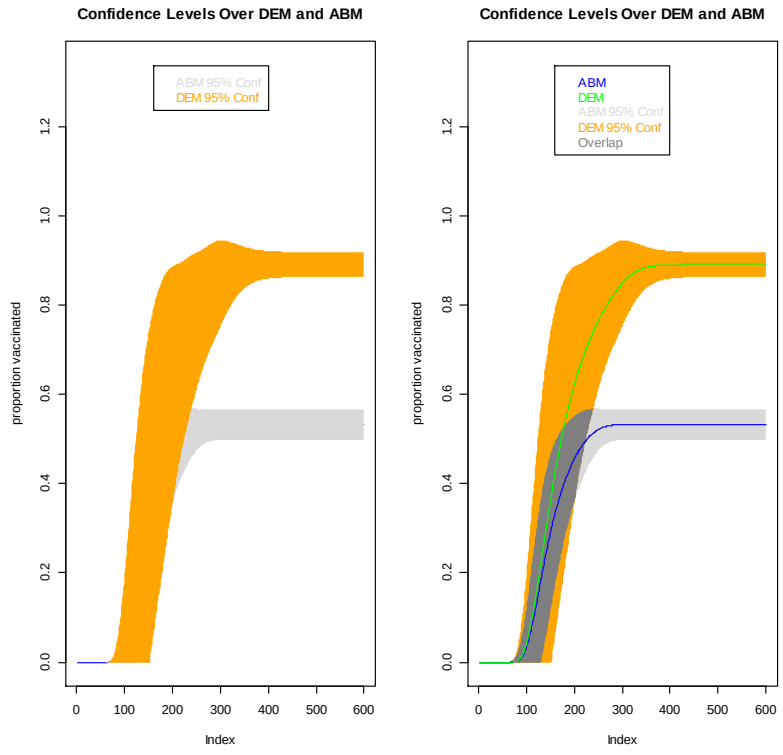
See *appendix K* for graphs of average state proportions by time. We find, in the diagram below, virtually no difference in the levels of prevalence of the disease. We do however observe a higher volatility in the DEM as opposed to the ABM.

Model 2B: Prevalence of infection over 1000 DEM and ABM simulations. Note the dark grey area as the overlapping confidence region.



No significant conclusions can be drawn from the initial 200-250 weeks, but after this (once infection is exceptionally low) the models reach significantly different equilibriums in level of population left vaccinated. There is a strong similarity in that there is a steady-state met in both models, but note the different levels, with the DEM having more than 150% of the vaccinated number of the ABM.

Model 2B: Average Vaccination levels over population in 1000 DEM and ABM simulations. Note the dark grey area as the overlapping confidence region.

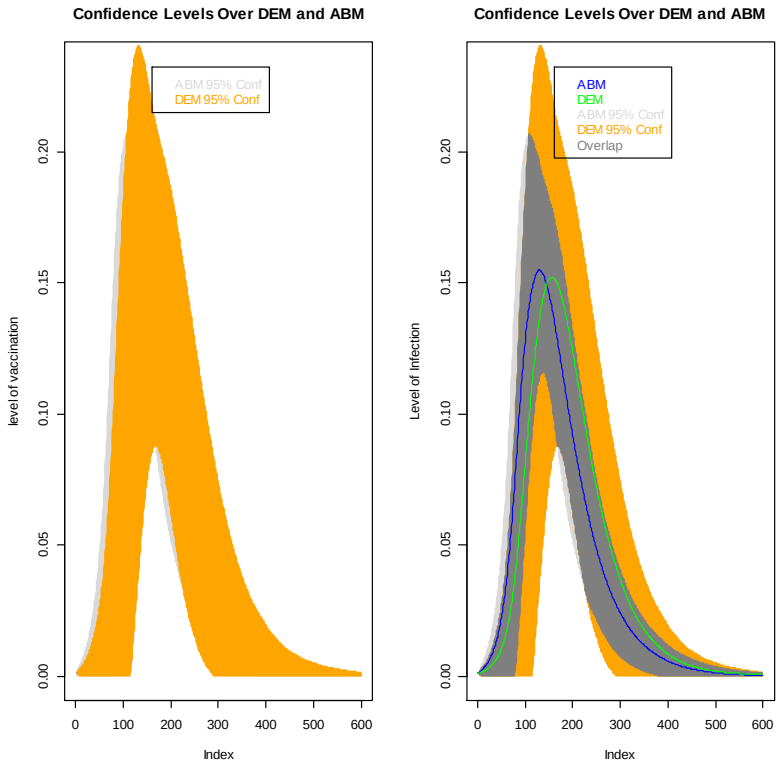


Similar differences between the models are exhibited as per model 2A. Within this structure: the differences in methodology are significant but the underlying nature creating these differences occurs from the same sources:

- ABM more reactionary, having more extreme distribution of rates due to natural heterogeneity in the data
- ABM more volatile
- DEM is more stable and rates of flows are more controlled. It is difficult to impose a volatile distribution onto a DEM as this affects variation of the entire population. This would require an addition of several (probably unrealistic) assumptions
- ABM reduces infections towards a “steady state”
- DEM tends towards “steady state”, but does not necessarily reach the steady state
- Without the second policy change, (of retracting the vaccination at 2% infection) the ABM model would fully reduce the level of infection, whereas DEM would reduce infection proportionately
- When vaccination policy taken away from ABM, under the DEM the process is occurring much slower, and more infected have been left in the model at this stage.
- This causes a second epidemic to occur faster in DEM than in ABM

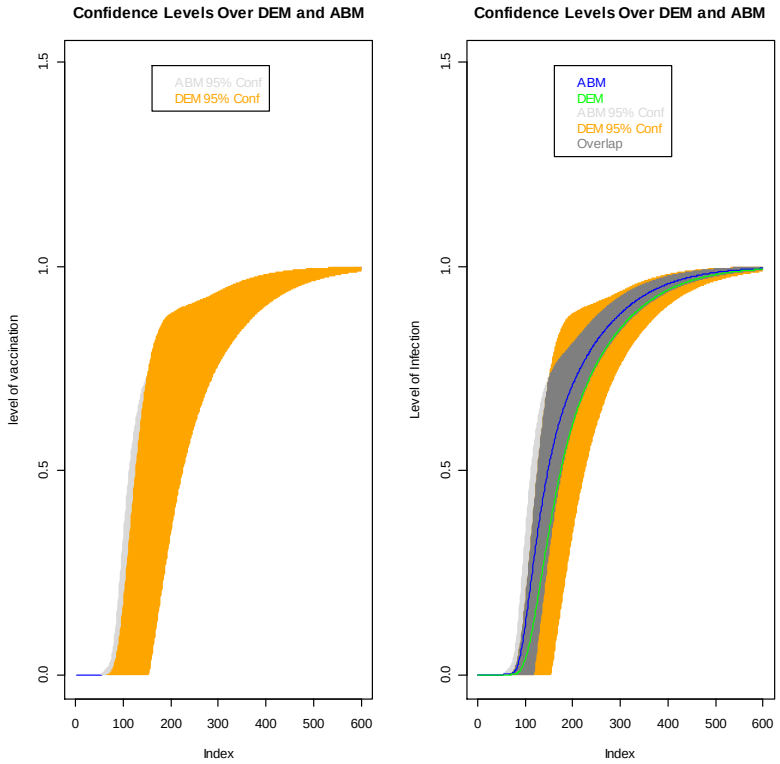
Additional model: Model 2C with more effective vaccination policy

Model 2C: Prevalence of infection over 1000 DEM and ABM simulations. Note the dark grey area as the overlapping confidence region.



No significant conclusions can be drawn from the initial 200-250 weeks, but after this (once infection is exceptionally low) the models reach significantly different equilibriums in level of population left vaccinated. There is a strong similarity in that there is a steady-state met in both models, but note the different levels, with the DEM having more than 150% of the vaccinated number of the ABM.

Model 2C: Average Vaccination levels over population in 1000 DEM and ABM simulations. Note the dark grey area as the overlapping confidence region.



As expected when explicitly controlling for specific attributes (here; controlling for the level of vaccination) we find both the models to be statistically identical in mean. There is constant overlapping of the confidence intervals. In the majority of the timeline in fact, we have that the 95% confidence interval of the ABM is contained within the 95% confidence interval of the DEM. So again it demonstrates that under realistic assumptions, an ABM exhibits more volatility. This can be interpreted as the ABM having the ability to model more possible dynamics that the population could exhibit, whereas the DEM is more accurate as replicating data/conditions exactly as they appear.

Discussion

It is evident that the DEM and ABM model structures are causing different results and predictions, as was hypothesised during the introduction. It is evident that the volatility can be caused by multiple sources and these can be determined empirically through application of mutual changes in both the models and analysis of the results. The nature of a Differential Equation model causes the steady-state equations to be approached asymptotically. In contrast, the steady state equations are reached by an Agent Based model more easily. This causes large discrepancy when an exogenous shock is forced onto the model, such an imposition or retraction of a policy. It has been concluded that the volatility can be exaggerated through focus on the steady-state equations. It should be noted that larger increments in uncertainty cause a larger variance and difference between the 2 models.

Additionally, it is possible to control for discrepancies by understanding the nature of the steady-stead in advance and applying the more suitable model.

Model 3: Mass Screen-and-Treat

Due to the recent epidemics of the Ebola haemorrhagic fever, this paper was extended to examine a mass-screen-and-treat policy for this disease.

Ebola Structure

It is necessary to differentiate the EVD model from all prior models under the following 2 conditions:

1) EVD, unlike Malaria, is transmitted through direct human-human contact; hence the interaction with vectors is not applicable, but special components are necessary.
2) There is a high infection rate, and a high death rate of the infected. Models must be equipped to deal with deaths and hence, an endogenously decreasing population.

Simulations are designed to reflect a West African Country, such as Guinea, Liberia and Sierra Leone where $R_0>1$ and there exist epidemics. The conditions of these three countries' health care systems are "lacking human and infrastructure resources"- WHO {2} [2014]. The access to medical facilities is highly limited, with an estimated 2 doctors per 100'000 individuals; and unsafe traditional burial procedures [Chan. 2014]. The primary purpose of containment is to hinder the infected individuals from posing as a further threat (via quarantine).

Ebola treatment:

This paragraph introduces the policies and practices intended to be introduced by the WHO, specifically designed to reduce the recent Ebola epidemic:

1. Reduce risk of hospitalized transmission
2. Reduce risk of public transmission
3. Reduce risk of wildlife to human transmission
4. Containment
5. Reduction in fatality

Sources: Chan, 2014. Lashley and Durham, 2007. WHO {2}, 2014. WHO {3}, 2014.

The WHO has established the optimal procedure to be a vaccination process, however under literature on treatment policy; medical author of this P. Davis PhD [2014] confirms that there is a treatment for Ebola, however not yet FDA-approved. The WHO [WHO {3}. 2014] has decided to implement a "vaccination" policy, of which there will be an estimated five million doses of treatment available by April 2015. This is not enough to meet the population levels of infected countries, and hence a screen-and-treat policy is more applicable. Additionally, the cost of misdiagnosis of healthy patients has not been tested yet, and as such it is preferential to minimize dosing healthy individuals.

See appendix L for further disclosure of the policy decisions in Ebola procedure: The outcomes of the WHO high-level meeting of October 2014.

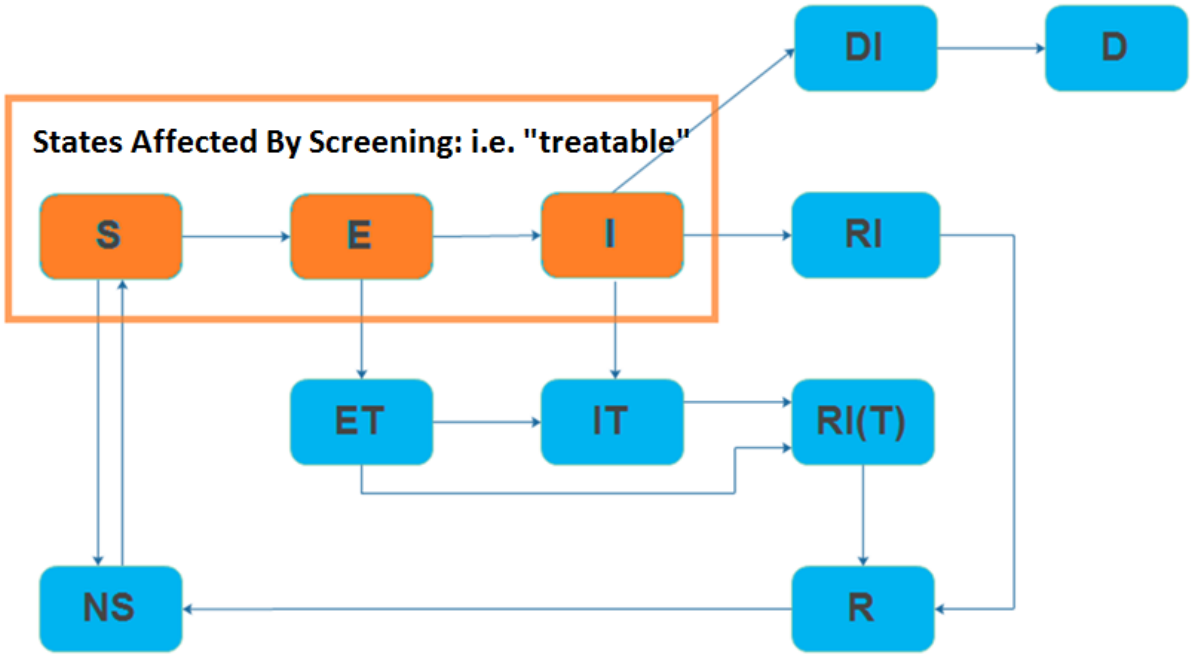
The controls of Ebola are to be modelled following two manners:

- allowing a lower rate of transfer for “known” infected due to a quarantine procedure
- lower death rate for treated infected, due to **Intravenous therapy** (injection of fluids) and **Oral hydration.**

Model Characteristics

This paragraph covers the details of the structure required in an epidemiological model of the Ebola haemorrhagic fever. The state space and the flows between states are presented.

Movement between states is coded in R by a random individualized movement according to exponential processes. *Refer to Appendix F for discussion of the randomness modelling distribution, and Appendix G for movement parameters*. Effectively, the states affected by the screen-and-treat process are those which are not known to be infected, treated, recovered or dead. Additionally, a treatment imposed on a recovered or non-susceptible individual will have no effect in movement. This leaves only 3 states, S, E and I, from which being vaccinated/treated will allow them to move into non-susceptible; exposed-treated and infected-treated respectively.



The large dispersion of the population allows for specific areas to be infected more than others. Hence due to an inadequate health care system not everyone can be reached so focus will logically be placed only on areas known to be infected. This is simulated via setting a very low rate of vaccination for non-exposed individuals. This is a closed population and the assumption of natural death being offset by natural birth accounts for exits and entrance to the population and a fixed population size (aside from virus-induced death, which is accounted for separately).

Spatial Dynamics

The models are required to account for dynamics of spatial patterns. Ebola is transmitted through contacts; hence the number of infectious contacts needs to be modelled relative to proximity of infected individuals.

Condition to be replicated: within a 3rd world population, there is segregation in living environments. There are large distances between villages in the outskirts of the urban environments. It has been documented that up to 60% of Ebola transfer is from unsafe burial rituals [Chan. 2014]. This affects only the individuals close to the infected dead; and is not carried into neighbouring villages with the same high rate. Movement between villages will allow transfer of the virus, but as a much lower rate than those in close proximity; i.e. the same village.

In an Agent-Based Model

Similarly to an implicit stratification technique: Individuals are divided into subgroups. This is done by ordering the list of individuals and maintaining the order; then allowing a specific number of interactions within a range forward and backwards from the position this individual is in. A binomial distribution is fitted to each individual within a range k of the infected individual. Additionally, separate parameters are necessary for individuals whom are known to be infected, and those who are unknown, or improperly dealt with [Chan, 2014]. *Refer to Appendix G for full model*. For the models, it was chosen to select 10 and 4 as the distances, and 0.1 and 0.02 as daily infection probabilities for individuals within these distances in respectively unknown and known infected individuals.

π	Measured, for each individual in the respective state by: Binomial(10,0.1)	Rate of transfer of infection from those who are unknowingly mingling in population
π^*	Measured, for each individual in the respective state by: Binomial(4, 0.02)	Rate of transfer of those who are "Quarantined/ hospitalized" and treated correctly given the abilities of the country: I.e. the successful outcomes of a screen and treat protocol

In a Differential Model

Since it is not possible for a DEM to incorporate a form of individualistic proximity measures; a different measure must be constructed to account for the spatial discrepancy. This can be done in one do two manners: either by subgrouping the population and assuming homogeneity within the groups, or by a function $f(\frac{S}{\text{population size}}, \mathrm{E}, \mathrm{I}, \mathrm{EV}, \mathrm{IV}, \mathrm{RI}, \mathrm{DI})$ to correct for the inability to reach further than k individuals away in distance. The first approach is a simpler method, and effectively uses ABM methodology in allowing separate characteristics for separate groups. It is more valid when performing a sensitivity analysis to use the direct DEM approach, applying $f(\frac{S}{\text{population size}}, \mathrm{E}, \mathrm{I}, \mathrm{EV}, \mathrm{IV}, \mathrm{RI}, \mathrm{DI})$ a decreasing function with the proportion of the population remaining uninfected, and as such allowing for harder "reach" of individuals in distant uninfected villages, or those hiding away from their own village for fear.

Rate of change of state E (See appendix G for full model): $\frac{dE}{dt} = \lambda SI^* - \varphi E - \gamma E$

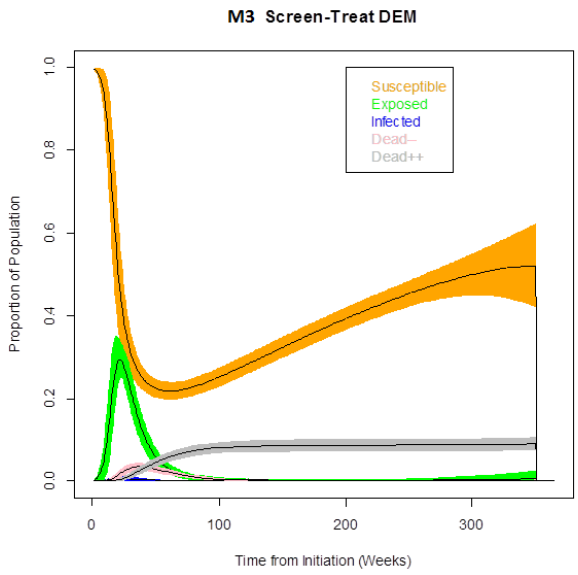
λI^*	$f(\frac{S}{\text{population size}}, \text{E, I, EV, IV, RI, DI})$ linear or non-linear model, with coefficients π, π^* as with ABM	Rate of gaining infection, a function of the number of infecteds

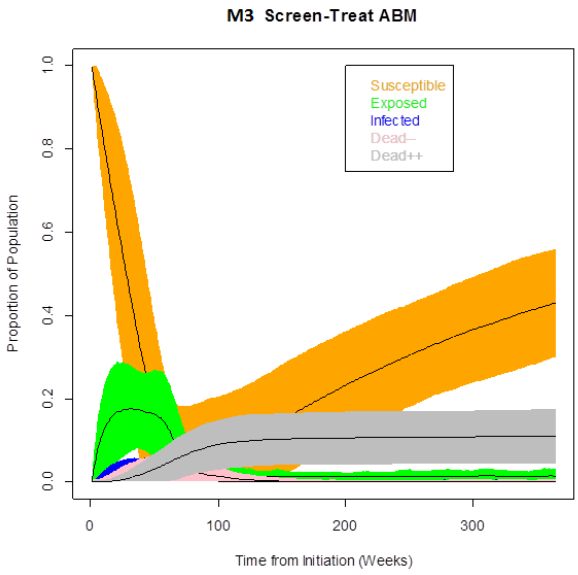
Results

See appendix H for parameters and rates used.

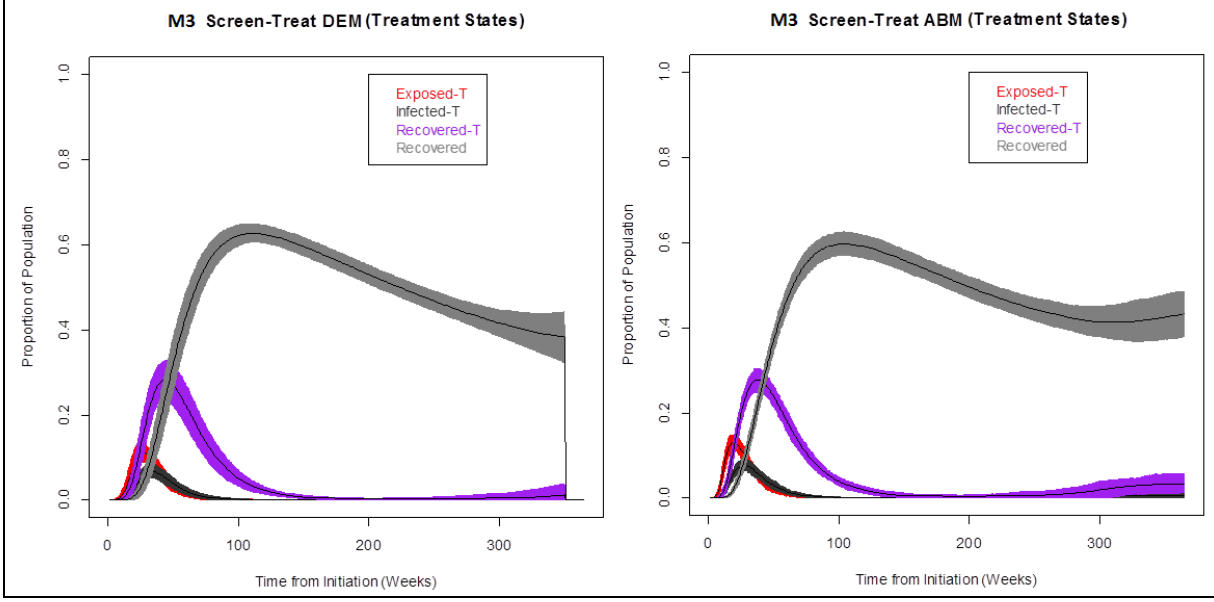
Model 3: Comparison

Comparison of Susceptible; Exposed; Infected; Dead-- (infectious); Dead++ (non-infectious)	
In a Differential Equation Model	***In an Agent Based Model***





Comparison of Exposed $^{\text{with treatment}}$; Infected $^{\text{with treatment}}$; Recovered $^{\text{with treatment}}$; Recovered	
In a Differential Equation Model	***In an Agent Based Model***



Between the ABM and the DEM screen-and-treat models, there are no significant differences in the initial phases of implementation. There is consistency in description of most of the dynamics of the population, with a few model specific details: *See appendix M for enhances images.*

I) DEM: ***With explicit compensation for spatial dynamics***

In this procedure, a function of the states is used to alter the rate at which individuals are selected. The objective is to mimic an ABM, and there is no statistical difference in this model and the ABM counterpart. The function was selected via trial-and-error, and is also affected by the number of individuals in the population. Under the observed model; the initial spike in exposure is slightly higher (statistically insignificant) than an implicitly stratified ABM and marginally, (but statistically significant) lower than a compensated ABM.

Refer to Appendix I for further details of selection of optimal $f\left(\frac{S}{\text{population size}}, \text{E}, \text{I}, \text{EV}, \text{IV}, \text{RI}, \text{DI}\right)$.

$$Model\ above\ sets\ f = [\pi(E + I + DI) + \pi^{*}(EV + IV + D)] \times \frac{e^{\frac{S}{\text{population size}}} - 1}{4}$$

II) ABM: ***With direct modelling procedure for spatial dynamics***

There is a large increase in variance using spatial dynamics, as there is no knowledge in advance of the exact dynamics of interactions either within or between the strata. This aggregation incorporates models which allow for several segregations and interactions

within the population, hence due to a large stochasticity as opposed to the other models, there is a higher variance in the model. This procedure is able to account for all realistic variations between outcomes.

The variability difference in the implicitly stratified ABM is due to the nature of agent-based interactions, which can be controlled and fully modelled within the ABM but cannot be moderated under differential movements. A DEM provides a much more regulated procedure as opposed to the variability of the ABM: this is seen to be due to the DEM inability to model extreme-events as can be done under a spatially-distinguished ABM. Agents-based exposure has been designed to incorporate stratified interactions based on a heterogeneous population, and hence transmitting exposure in different manners in different simulations, whereas the DEM cannot be programmed in a manner that logically captures both dynamics of stochastic exposure to individuals based on relative position to infected individuals. The DEM can only account for a stochastic average exposure of susceptibles, and hence provides a much less volatile, and in so a less realistic spread in representation of possible system outcomes.

Further exploration of the Methodology

Two additional models are viewed: the first is a DEM, simulated for the purpose of finding a natural differential approach to the problem, without any assumptions or adjusting equation. The second model is an ABM simulated with the purpose of estimating the DEM results, i.e. allowing the same adjustment to be applied to "compensate" for special discrepancies, not explicitly applying special differences as the above Model 3 ABM does. *See appendix M for the graphical plots.*

III) DEM: ***Without explicit compensation for spatial distinction in population***
This model naturally falls short of the ability to compare to an explicitly spatially-distinguished ABM. There are significant differences in the initial phases of the model. The uptake of the screen-and-treat procedure is not equivalent to that of an ABM. In the initial 50 days of the uptake of the policy, there is a large spike in exposed individuals to the virus, slightly higher (statistically significant) than an implicitly stratified ABM and marginally, (but statistically insignificant) lower than a compensated ABM.

IV) ABM: ***With explicit compensation for spatial distinction in population***
There is a relatively small confidence band for all states within the initial period. The model is less volatile than any of the predecessors, yet becomes as volatile during the intermediate time period. The general dynamics of the system are equivalently presented in this model as with the two agent based models.

Discussion

There are positive attributes through the ABM approach should there be a segregation of the population within the model. This segregation must necessarily be known in advance and have the model fitted around it. *Appendix E[I]* displays the dilemma caused by an ABM modelling of the

behaviour of a process with stochastically programmed segregation: the probability distribution of each state is too wide to allow meaningful interpretation. However, with the segregation known in advance, research power, time and money would be required to find model representative of the population. Similarly, unless programmed against it, an ABM has the possibility of a disease dying out. Often this is unrealistic as vector-strains of the population cannot be controlled, however this needs to be explicitly stated and then modelled. *Appendix E[II]* contains a diagram portraying a large confidence bound, when including the possibility of a disease dying out there would be a constant proportion of "susceptibles" at 100% and all other states at 0%, resulting in very biased estimates of the averages and variances, and non-interpretable results.

Model 3 (IV) an ABM: ***With explicit compensation for spatial distinction in population*** provides the conclusions that even in complexity; it appears possible for an ABM to produce results which are not statistically different to those produced by a DEM. However, model 3 (III) a DEM: ***Without explicit compensation for spatial distinction in population*** suggests that the natural forms of the ABM for modelling spatially-distinguished spaces appears superior to what a DEM is able to achieve.

Implications and Model-Shortfalls

As with any disease modelling, regardless of the complexity of the model it is a simplified representation of the epidemiological process. A model accurately representing a system relies on the inclusion of all relevant contributing factors, some of which are difficult to impossible to model.

The models I have constructed have been under the intention of targeting differences between an ABM and a DEM model. The data has been directly designed from report summaries of medical records, yet still it has been self-constructed. My project has covered the umbrella forms of the ABM and DEM models, but they have failed to account for niche factors within specific populations. Hence to make an accurate statement of the discrepancies between the models per population, it is necessary to formulate the parameters accordingly to the specific dynamics of the targeted population.

Modelling populations without extensive medical records (as is the case in a West Africa [Chan. 2014]) comes with many difficulties due to the nature of right-censored individuals: those whom are vaccinated and then fail to be recorded again due to poor tracking and data management in third-world countries, as well as left-truncated individuals: non-vaccinated individuals who will only enter the observational design if they contract the disease. Ebola is prevalent in third world countries; hence the accessibility of medical care is not an immediately-available amenity to the majority of the populations; especially considering the initial symptoms resemble a common flu, and may remain unreported. Observations are hence disproportionately missing, likely in a non-random manner. The presence of non-randomness requires imputation, and the best imputation will be based on other countries observational data. Thus, the model will be biased towards countries with more complete data sets.

Additionally even if individuals are treated, due to the third world health practices, there is no guarantee of an accurate record of Malaria/Ebola data, adding to the missing observation problem. And lastly, it is impossible to perform experimental studies for ethical reasons on infected human

individuals. Thus the trials will be case-control studies, based on exposure status to the vaccination, suffering from the right-censored and left-truncated data problems. In summary, these model comparison techniques cannot be used to exactly establish the model discrepancies, but they give a good indication.

Extensions

Further Analysis of Differences owing to model structure

This paper has covered several aspects of difference analysis between an Agent Based Model and a Differential Equation Model, but none of the analysis has been performed to a full conclusive extent. Evidence of differences has been shown to exist, and general trends in location of differences have been described (predominantly steady-state conditions, and ability to account for population dynamics in inter and intra-stratum). Further areas for research to be considered are the optimal form on the function $f\left(\frac{S}{\text{population size}}, \text{E}, \text{I}, \text{EV}, \text{IV}, \text{RI}, \text{DI}\right)$, which allows for a DEM to be comparable to a stratified ABM, and if a generic case $f\left(\frac{S}{\text{population size}}, \text{E}, \text{I}, \text{EV}, \text{IV}, \text{RI}, \text{DI}, \text{n}, \text{S}\right)$ could be developed to apply to all cases rather than attempting to minimize the difference between the ABM and DEM by first principles. Similarly, work can be done into the optimal procedure to model the disease extinction, as opposed to the model restrictions used in this paper which entirely prevent less than one person to be infected in an ABM and hence coerce the disease to remain an active threat as opposed to a dormant state which is seen in reality but not in the models presented.

Improved Disease Modelling

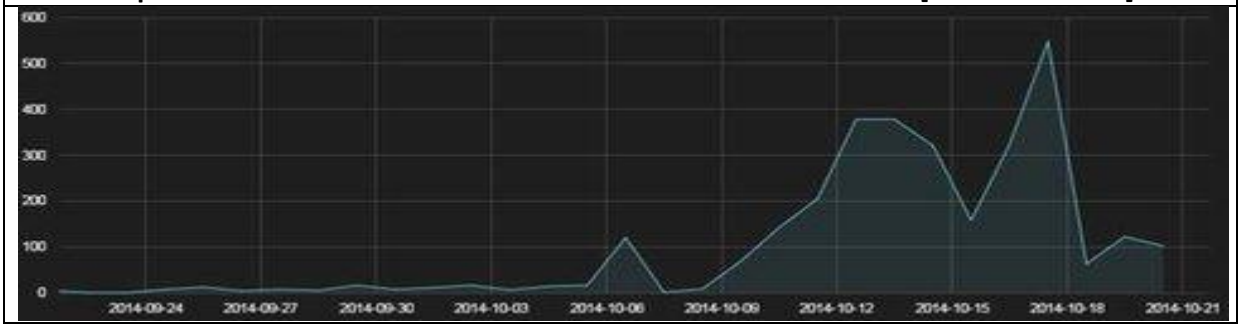
The model comparison technique used in the paper can be used to recommend a superior model procedure for the diseases under examination. Recommendations to establish model accuracy: find more reliable data; hence a population-specific recommendation can be made on model preference. The discrepancies I have established are theoretical based on generalized disease properties, and hence have highlighted areas to be cautious of. To allow these models to provide recommendations, a more thorough and complete survey is required.

Other extensions include Cyber-Terrorism (not-recommended), Bio-Terrorism (not recommended) and Counter-Bio-Terrorism.

Cyber-Terrorism

The onset of fear in society is a drive to reach out for protective measures. Johnston and Warkentin have demonstrated the empirical impacts of fear within the IT world [2010]; specifically how under the influence of fear, computer users are on average more susceptible to fraud under a clouded judgment. Several hackers have used this as an opportunity to install malware on computers, sending seemingly informative emails on Ebola policies, claiming to contain procedural protocols from the World Health Organisation [Perlroth. 2014]. Although not a direct implication, statistical models can be used to predict the impact of a disease outbreak on the level of cyber-terrorism related to the disease. More directly, there are applications of infectious disease modelling in both pro- and counter-bio-terrorism.

Reported Incidences of Ebola-related emails with Harmful Intent – [Perlwroth. 2014]



Bio-Terrorism and Counter Bio-Terrorism

Without further evidence, conspiracy theories will not be discussed in this report; the discussion will look solely at the possibilities of bio-warfare from an epidemiological perspective. Lashley F. Durham D. [2007] mention the possibility of haemorrhagic fevers in Bio-Terrorism, and several more impactful HFs are mentioned as being "preferential" to Ebola. Opinions of the role of haemorrhagic fevers (HFs) in Bio-terrorism from experts in disease control possibilities range from dismissive to it being an active concern which is exhibited in research performed by Lashley and Durham.

The primary reasons provided against the plausibility of haemorrhagic fever viruses (HVs) include but are not limited to

1. the lack of aerosol ability of an HV
2. instability of the HV
3. high profile of infected
4. lack of access to the virus

Jagminas and Antosia [2006] have looked at the potential of viral haemorrhagic fevers which currently have been classified as a Biological Warfare Agent (BWA) of category A, implying a high toxicity, but a low range. Category C relates to the most problematic BWA, which are unpredicted, and require policies to readily be in operation in order to avoid a crisis [Balili-Mood, *et al.* 2013].

With the new strain of *Zaire ebolavirus,* there is an increased accessibility to the virus, a higher level of stability and clearly a high ability to cause death. Balili-Mood*, et al*. [2013] discloses that meeting even one such condition is enough for the virus to pose the potential to be weaponized. The Majority of (Lashley and Durham's understanding of) expert reasoning against the potential use of haemorrhagic viruses as BWA is not valid with the outbreak of the Zaire ebolavirus, and it hence stands as a potential choice for bio-terrorism activity in Category C. Clearly, the same models used by statisticians to model the effectiveness of treatment policies can be used with minor changes by bio-terrorists to model the optimal manner of execution of a biological warfare agent. Historically, it is plausible that the ineffectiveness of an HV would have been indicated to bio-terrorist criminals through a process of model simulation.

All aforementioned authors on the topic of bio-terrorism have mentioned the necessity of preparation as the first step to hinder a Category C BWA. Governmental protocols must already be

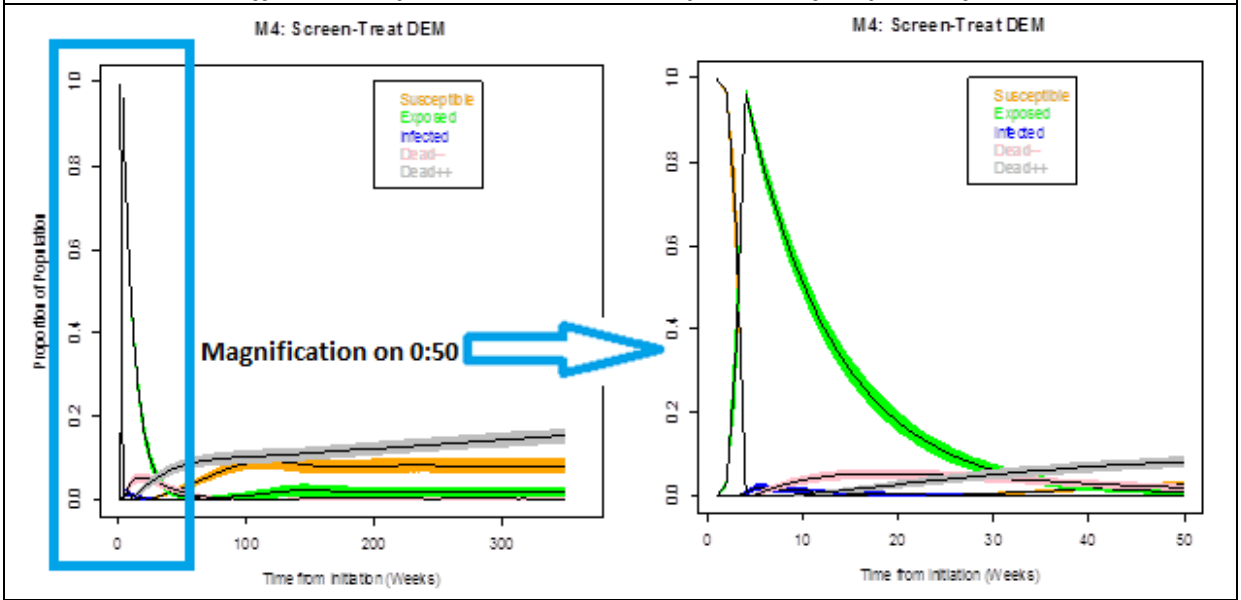
in place, such that the reaction to a bio-warfare onset is instantaneous. An epidemic requires an R_0 value above 1, and a Category C BWA is designed with this intention. Due to the exponentially increasing rate at which a population becomes infected, it is the first few cases of an infectious disease which are most crucial to stop. Similarly, it is necessary to prioritize the correct dynamics of the disease, whether they are treating infected individuals, containment, etc. The most effective methods to quell an epidemic, be it quarantine, contact-tracing, mass screen-and-treat, can only be determined under the correct model assumptions. Hence, it is crucial in counter-bio-terrorism to be fully engaged in accurate model building, primarily, accurate model structure.

A brief analysis of a bio-terrorist implementation of an infectious disease is given in Model 4:

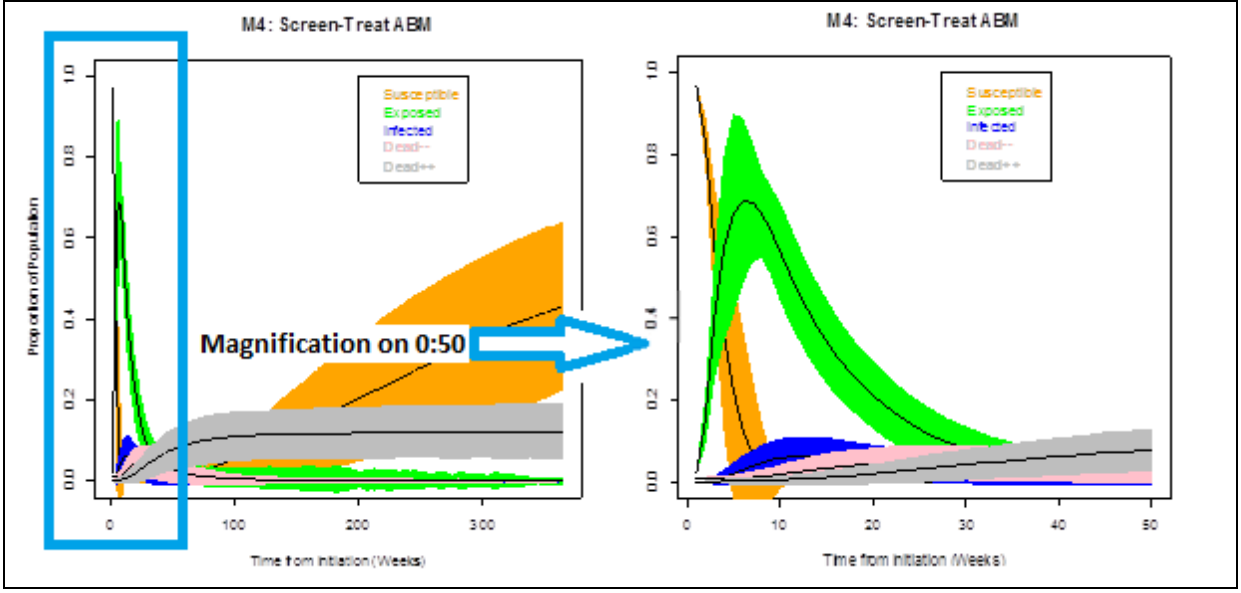
Model 4: Introductory Model to Bio-Terrorism

Comparison of Susceptible; Exposed; Infected; Dead-- (infectious); Dead++ (non-infectious)

In a Differential Equation Model with compensation for spatial dynamics

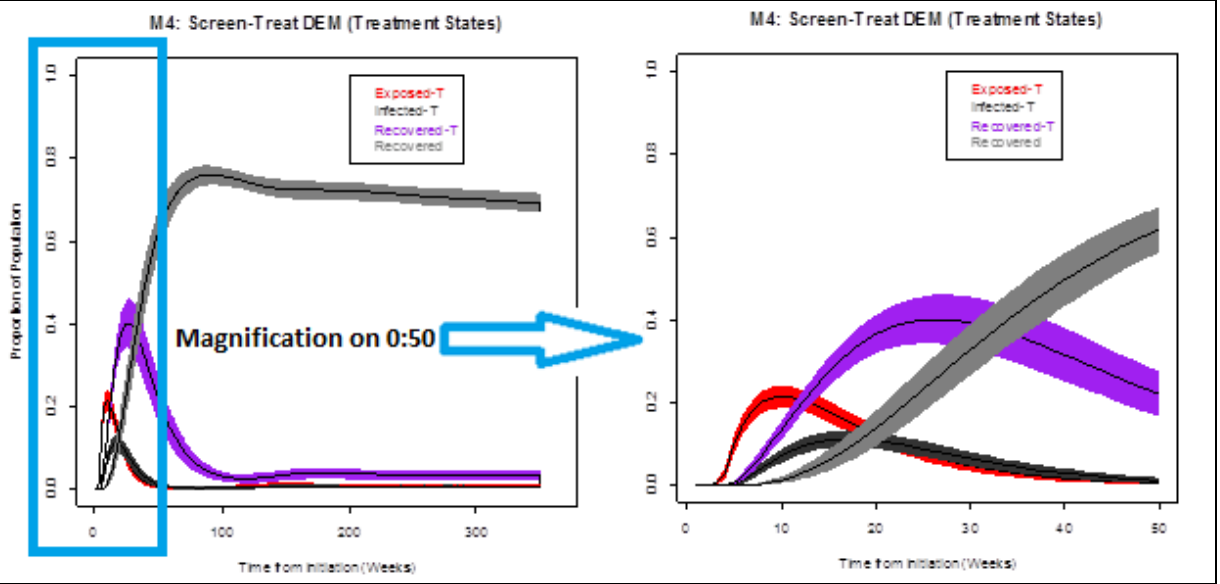


In an Agent Based Model with direct spatial dynamics

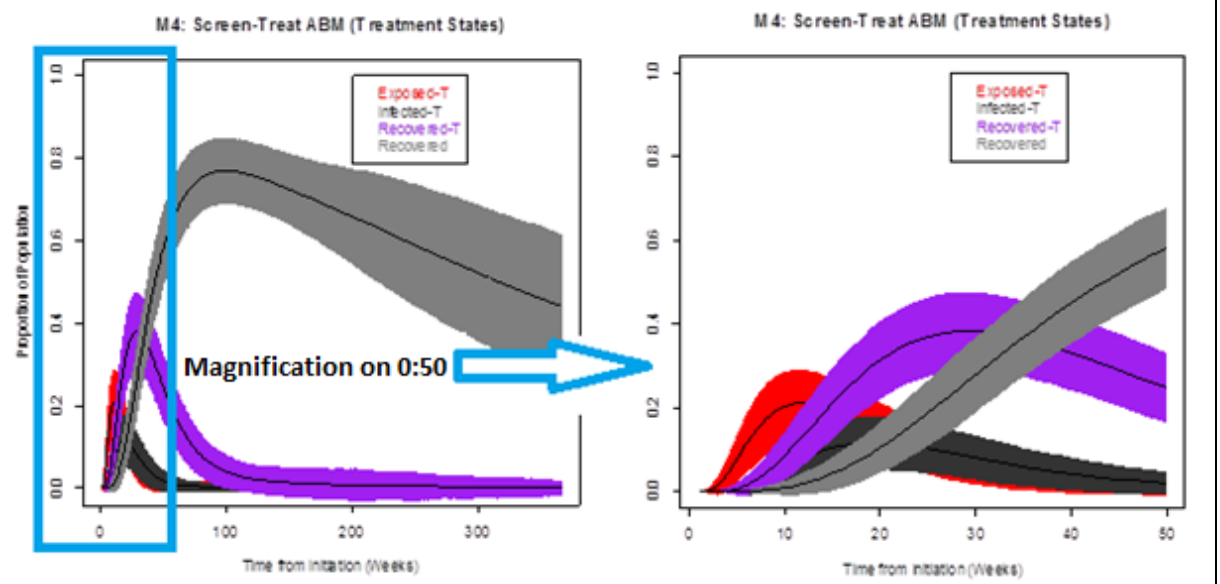


Comparison of Exposed $^{\text{with treatment}}$; Infected $^{\text{with treatment}}$; Recovered $^{\text{with treatment}}$; Recovered

In a Differential Equation Model with compensation for spatial dynamics



In an Agent Based Model with direct spatial dynamics



Model 4: Analysis of results

Very similar patterns to model 3 are exhibited in model 4, with the obvious exception of the initial (days 1-5) high rate of infection. There is a fast-acting infection period, specifically parameterised to allow for a 90% infection of the population within the first week. This is exhibited with statistical indifference in the mean between both above modelling procedures. There is a much higher variance in a spatially incorporated ABM. This is due to the possible coverage of all population movement dynamics that a spatial ABM allows, which is very difficult to replicate with other models as discussed previously. The sharp drop in DEM susceptible levels does not have a right tail comparable to the ABM: it is seen that the DEM does not account for spatial distance well and more detailed analysis must be done before finding an appropriate DEM model. Additionally; allowing a higher compensation for the initial rate of infection in the DEM would result in a smaller decline in

recovered individuals (dark grey), which is already lower in magnitude than the ABM. Restructuring of the models to follow one another would be necessary, but it is worthwhile to note that without the restructuring, both models offer different predictions as they have not yet reached their steady states, and thus the stead-state conditions mentioned in the discussion of model 2 do not hold, and until steady-state is reached, the dynamics of the population under the two models are different.

Conclusions

There are certainly discrepancies between different modelling methodologies. The most pronounced differences become evident with more complex models. Specifically, if dynamics of a population's infection status are dependant explicitly on individuals within the population (such as individual spatial statistics) an ABM can account for this easily, where as a DEM requires an additional set of assumptions. Additionally, a DEM has been seen to introduce additional uncertainty in the model where it is not necessary. When making decisions in terms of the optimal methodology to select, it is important to bear in mind the computational time required by an ABM in comparison to a DEM (this paper's relatively simplistic ABM models required up to 600 hours in computing time per model reported). A DEM can in most instances approximate ABM results relatively well and this alone may be justification enough to not use agent-based methodology in some situations.

There is a downside to both models in the start-up period; in a DEM there is the assumption of fractional movement, which is unrealistic in a situation of very few infections and less than one new individual becoming infected in one time unit. Similarly, an ABM requires distributional assumptions which are highly influential on the initial phases, and could make large differences in rate of progression of a disease. The ABM allows for a realistic volatility measure, under the assumption that the model has been validified and verified and is representing the true population movements. There is a necessity in agent-based methodology not to allow for extinction of the disease, and hence a minimum number of infected individuals are held within the population, which may cause bias in the ABM results.

A DEM is inferior to an ABM in modelling heterogeneous individuals within a population. Restructuring a DEM to account for spatial (or another) dynamic requires verification, and finding the optimal form of $f\left(\frac{S}{\text{population size}}, \mathrm{E}, \mathrm{I}, \mathrm{EV}, \mathrm{IV}, \mathrm{RI}, \mathrm{DI}\right)$ which is difficult to impute due to a lack of historical data. A DEM has generally is able to mimic an ABM if required, however this requires first designing the ABM and then the DEM to mimic it. This introduces unnecessary variation and consumes additional time. In this instance, it appears that an ABM is a superior choice.

Agent based methodology appears naturally more reactionary with regards to shocks since the model has the ability to adjust at heterogeneous rates, however similar patterns are seen in both models. An important conclusion between both models is that discrepancy does arise from the steady-state nature. And as such, if modelling both models according to average flows, the ABM will approach a steady state faster than the DEM. A steady state does exist for both methods, and once in steady-state they are equally well maintained regardless of methodology.

The most important conclusion to be drawn from this paper: as a result of the steady-state nature, one should not take a measurement from a model which has not been explicitly validated within the model. In advance of deciding the methodology to use; one must analyse the data, (or the summary

statistics to be replicated) and decide on the appropriate structure (choice of states and flows) and the measurements to be used (such as incidence, prevalence, vaccination levels). The methodology must then ensure capturing of the relevant quantities to be measured, and these must be controlled within the model. To determine the efficiency of a model; it should be verified in its ability to not only replicate historical observations and historical data sets; but the model should also be able to show a reasonable amount of volatility and as such not only show the expected outcome, but the range of possible outcomes.

Bibliography

Antosia, R. 2006. *Handbook of Bioterrorism and Disaster Medicine.* Springer US. p95-99.

Anderson, R. May, R. 1991. *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, Oxford, UK

Balali-Mood M; Moshiri M; Etemad L. 2013. *Medical Aspects of Bio-Terrorism*. Toxicon: Official Journal of the International Society on Toxinology, ISSN: 1879-3150, 2013 Jul; Vol. 69, p131-142

Bobashev, G. Goedecke, D. Yu, F. Epstein, J. 2007. *A Hybrid Epidemic Model: Combining the Advantages of Agent-Based and Equation-Based Approaches*. Proceedings of the 2007 Winter Simulation Conference. U.S.A.

Brauer, F. (1984). *Mathematical Epidemiology*. Lecture Notes in Mathematics. Vancouver, Canada: Department of Mathematics, University of British Columbia.

Blaize S. 2014 October. *Emergence of Zaire Ebola Virus Disease in Guinea.*N Engl J Med 2014; 371:1418-1425. Available online at http://www.nejm.org/doi/full/10.1056/NEJMoa1404505. Accessed 5 November 2014.

Branswell. 2014 October. *Canadian Ebola vaccine license holder moving ahead with safety trials.* Online at http://o.canada.com/health/canadian-ebola-vaccine-license-holder-moving-ahead-with-safety-trials. Accessed 4 November 2014.

Chan M. September 2014. *Ebola Virus Disease in West Africa — No Early End to the Outbreak.* N Engl J Med 2014; 371:1183-1185. Available Online at: http://www.nejm.org/doi/full/10.1056/NEJMp1409859. Accessed 1 November 2014.

Davis C. 2014. *Ebola Vaccination: Is it Safe?* Available online at http://www.medicinenet.com/ebola_vaccine_is_it_safe/views.htm. Accessed 4 October 2014

Diekman, O. (1996). *Mathematical Epidemiology of Infectious Diseases.* Available online at http://oai.cwi.nl/oai/asset/13562/13562A.pdf Accessed 21 April 2014.

Dietz, K. Molineaux, L. Thomas. A. (1974). *A malaria model tested in the African savannah*. Bull World Health Organ. 50(3-4), 347-357.

Dye C, Hasibeder G. (1986). *Population dynamics of mosquito-borne disease: effects of flies which bite some people more frequently than others*. Trans R Soc Trop Med Hyg. 80(1), 69-77.

Dietz, K. (1998). *The First Epidemic Model: a Historical Note On P.D. En'ko*. Journal of Statistics, 56-65.

Figueredo G. Siebers, P. Owen, MR. Reps, J. Aickelin, U. (2014) *Comparing Stochastic Differential Equations and Agent-Based Modelling and Simulation for Early-Stage Cancer*. PLoS ONE journal 9(4): e95150. doi:10.1371/journal.pone.0095150Jagminas,

Johnston A, Warkentin M. 2010. *Fear Appeals and information Security Behaviors: An Empirical Study. MIS Quarterly.* Sep2010, Vol. 34 Issue 3, p549-566.

Lashley F. Durham D. (2007). *Emerging Infectious Diseases*. New York: Springer Publishing Company. 139-149.

Kermack, W. O. and McKendrick, A. (1927). *A Contribution to the Mathematical Theory of Epidemics*. Proceedings of the Royal Society, 700-721.

Koella, J. and Antia, R. (2003). *Epidemioliology models for the spread of anti-malerial resistance* . Malaria Journal 2:3.

Macdonnald, G. (1957). *The Epidemiology and Control of Malaria.* London: Oxford University Press.

Mandal, S. Sarkar, R. Sinha, S. (2011). *Mathematical models of malaria - a review*. Malaria Journal, 10:202.

Perlroth N. 2014 [October]. *Malicious Ebola-Themed Emails Are on the Rise.* Available online at: http://bits.blogs.nytimes.com/2014/10/24/malicious-ebola-themed-emails-are-on-the-rise/?action=click&contentCollection=US%20Open&region=Article&module=Promotron. Accessed 4 November 2014.

Rahmandad, H. Sterman, J. (2008). *Heterogeneity and Network Structure in the Dynamics of Diffusion: Comparing Agent-Based and Differential Equation Models*. Management Science, Vol 54, no5. 998-1014.

Ruan, S. Xiao, D. Beier, J. (2008). *On the Delayed Ross–Macdonald Model for Malaria Transmission*. Bull Math Biol. 70(4), 1098–1114.

Scherner, A. McLean, A. (2014). *Mathematical models of vaccination*. British Medical Bulletin. Accessed 07 14, 2014, from Mathematical models of vaccination: http://bmb.oxfordjournals.org/content/62/1/187.fullSilal, S.

Little, F. Barnes, K. White, L. (2014). *Sensitivity to Model Structure: A Comparison of Compartment models in Epidemiology*. Cape Town, South Africa: University of Cape Town.

Stassen, W. (2008). Maleria: *Things You Should Know*. Available online at http://www.health24.com/Medical/Malaria/All-about-prevention/Malaria-things-you-should-know-20120721 Accessed 21 April 2014.

Smith, D. Battle, K. Hay, S. Barker, C. Scott, T. 2012. *Ross, Macdonald, and a Theory for the Dynamics and Control of Mosquito-Transmitted Pathogens*. Online at: http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1002588. Accessed 26 July 2014.

WHO 2014 [1]. *Ebola Response Roadmap Situation Report Update*. World Health organization. Available online at *http://apps.who.int/iris/bitstream/10665/137424/1/roadmapsitrep_31Oct2014_eng.pdf?ua=1*. Accessed 1 November 2014.

WHO 2014 [2]. *Ebola Virus Disease Fact Sheet No.103*. *World Health Organization*. Available online at *http://www.who.int/mediacentre/factsheets/fs103/en/*. Accessed 1 November 2014.

WHO. 2014 [3]. *Summary report of a WHO High-level meeting on Ebola vaccines access and financing*. Available online at: w*ttp://www.who.int/mediacentre/news/ebola/23-october-2014/en/*. Accessed 4 November 2014

Glossary

R_0 is defined as the number of secondary infections. Statistically; it is equivalent to the expected number of infections which are caused per newly infected individual.

$R_0 > 1$ is generally enough to define an epidemic to occur

Appendix A: Parameters M1 (Dietz, *et al.* 1974)

$$\frac{dS}{dt} = -\beta SI + \tau R; \qquad \frac{dI}{dt} = \beta SI - \alpha I; \qquad \frac{dR}{dt} = \alpha I - \tau R$$

Parameters	S-I-R-S Estimate	Description: Daily Rates
β	2.1×10^7	$a \times b \times \frac{I}{N}$ Rate of infection
α	0.0023±0.0005 days	Rate of recovery
a	0.022/day	Number of secondary contacts from an infected human
b	0.097±0.017	Infection susceptibility
τ	0.005 (200 weeks)	Rate of loss of immunity
δ	0.0001 / day	Death rate= birth rate
N (population size)	1000	

$\tau = \frac{(h+\delta)e^{-(h+\delta)\times N\times\frac{I}{N}}}{1-e^{-(h+\delta)\times N\times\frac{I}{N}}}$ (Koella and Antia. 2003) (4)

τ Rate of loss of immunity against malaria, τ can reportedly be as short as 2 weeks. For a simplistic model, τ is assumed to be independent of the proportion of infected, instead set as a constant immunity level of 4 years, approximately thus a weekly recovery rate of 0.005.

I proportion of infected humans

S proportion of susceptible humans

R proportion of recovered humans

$R + S + I = 1$

m = proportion of mosquitos per human

Appendix B: Parameters M2 (Dietz, *et al.* 1974. And Mandal, *et al.* 2011)

Parameters	S-I-R-S Estimate	Description: Daily Rates
β	2.1×10^7	$a \times b \times \frac{I}{N}$ Rate of infection
α	0.0023±0.0005 days	Rate of recovery
a	0.022/day	Number of secondary contacts from an infected human
b	0.097±0.017	Infection susceptibility
τ	0.005 (200 weeks)	Rate of loss of immunity
δ	0.0001 / day	Death rate= birth rate
N (population size)	1000	
(1) ʉ	0.25 (4 weeks)	Rate of evidence of disease within exposed patients (transfer from E to I)
(2) ɾ	0.01	Rate of Administration of Vaccination

(1) ʉ : Rate of transfer from E to I. The inverse of time spend with Malaria, infected but without a high enough *plasmodium* count to pass on the infection to a susceptible mosquito is estimated (Mandal *et al*. 2011):

a. mosquitos: t_m=10 days
b. humans: t_h=21 days

This is aggregated as 4 weeks in a DEM-rate parameter of 0.25; and imposed over a probability distribution of 0.1+0.3 x U(0,1) under the ABM model.

In the differential equation Model, this is structured by assuming the steady state incidence rate 0.3111, we need to find a parameter that allows for an ʉ of 0.25.

$$\sum_{i=0} p^i = {}^1\!/_{1-p} = 4$$

$$Solving\ for\ p, obtain\ p = 0.75$$

Hence the Exposed state will allow emission of 0.750, adjusting the total time spent by an "individual" in state E to be 4 weeks.

(2) ɾ : Susceptible individuals are assumed to successively be vaccinated with a 50% probability over a year period. This translates to a weekly rate of movement from S to ST of approximately 0.01.

$$\sum_{i=1}^{52} p(1-p)^i = {}^{1-p^{52}}\!/_{1-p} = 0.5$$

$$solving\ for\ p = 0.014$$

Exposed individuals will receive vaccination with 20% success upon entry into E.

Appendix C: Coding Discrepancies

The table below highlights the differences accounted for in the coding behind the two models:

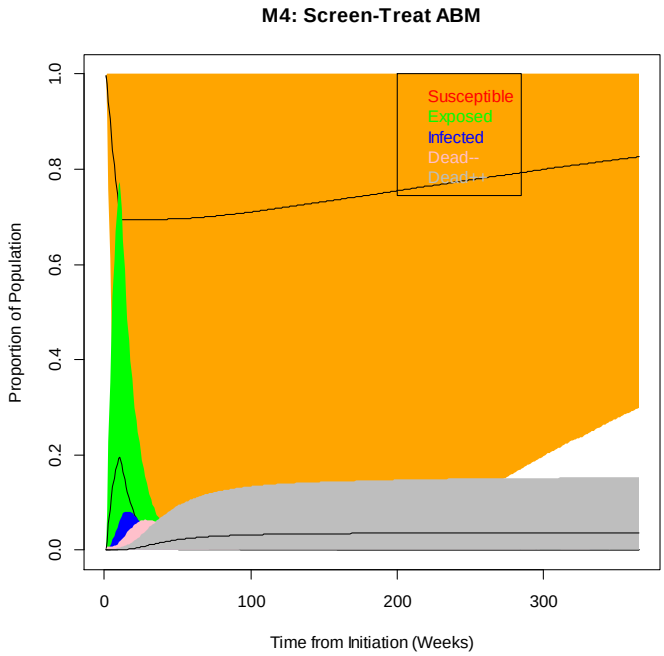
Model Qualities to be represented	**Agent-Based**	**Differential Equation**
S, I, E, R	Proportion of the total population in represented state ϵ [0,1]	
β	$a^2 mb \times U(0,2)$	$a^2 mb$
α	$\exp(\frac{1}{rate\ of\ recovery})$	$rate\ of\ recovery$
τ	$Truncated\ Normal(\mu, \sigma^2)$; A normal distribution defined over (0,+Inf) and rescaled to integrate to 1.	$\mu = rate\ of\ losing\ immunity$

Appendix D: M1 Output

	DEM			ABM		
Time to reach Steady State. Since there appears to be very little cyclical movement, we will allow a "low movement" to be approximated by a movement of under 0.1% in proportion of population in S, I and R for 1 month.	Low movement occurs after time 262:			Low movement occurs after time 220:		
	S	**I**	**R**	**S**	**I**	**R**
	14.124	21.196	64.679	32.691	33.083	34.226
	14.209	21.095	64.697	32.646	33.010	34.344
	14.292	20.995	64.713	32.613	32.940	34.448
	14.376	20.897	64.727	32.587	32.872	34.541
	By time 600 there has been further deviation to steady states:			By time 600 there has been further deviation to steady states:		
Proportion in SS	20.028	19.108	60.864	32.794	26.072	41.134
Proportion of time extinction of disease occurred:	0			0.191		
Loss of immunity	After 4 years			Randomised, and causing several rates to assume a loss of immunity value of 0, and several to be very rapid.		
Cases over a week in the first exposure of the disease (6 months after first exposure):	0.157 per 1000 individuals in population			0.147 per 1000 individuals in population, with a confidence interval of 0.147 ± 0.01253716 on average		
Cases over a week towards steady state of the disease (10 years after initial exposure):	3.111 per 1000 individuals in population			2.691 per 1000 individuals in population, with a confidence interval of 2.691 ± 0.9290408 on average		

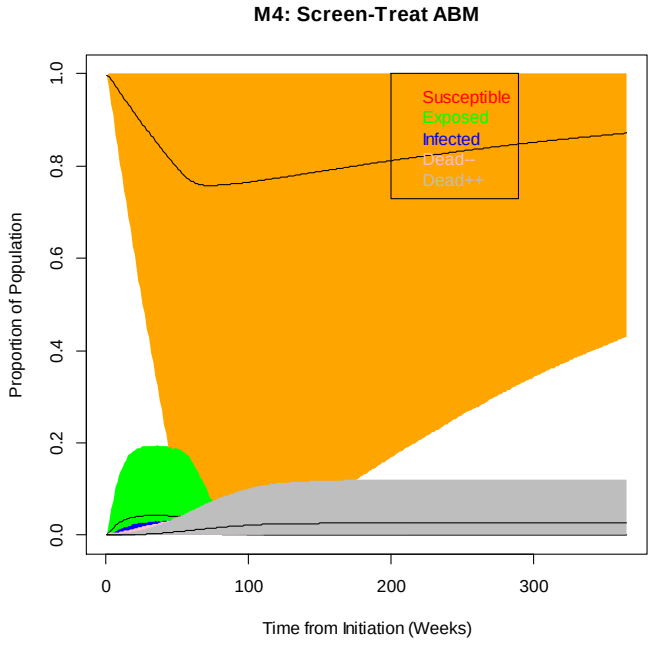
Appendix E[I]: M4 Complexity I

Stochastic behaviour of relationship structure; if one does not know the relationships in advance.



Appendix E[II]: M4 Complexity II

System cures itself. Hence there is a chance of 0 infections immediately… then entire system breaks down, massive volatility between those which are not cures within. [Same issue as above, but time 1 & 2 are the deciders]



Appendix F: Distribution Equivalence

Given 2 processes, $X \sim \exp(\alpha)$, and $Y \sim \text{pois}(\alpha)$

$$P(X < 1)$$

$$= 1 - e^{-\alpha}$$

$$= 1 - \frac{\alpha^0 e^{-\alpha}}{0!}$$

$$= 1 - P(Y = 0)$$

$$= P(Y \geq 1)$$

Hence, it is equivalent to model the binary event $\{X < 1\}$, with $X \sim \exp(\alpha)$ as the probability of at least one occurrence of a Poisson process with the same parameter.

Appendix G: Parameters M3

$\frac{dS}{dt} = -\lambda SI^* + \tau R - S\eta;$ $\frac{dE}{dt} = \lambda SI^* - \varphi E - \gamma E;$ $\frac{dI}{dt} = \gamma E - \varphi\tau I - \delta I - \alpha I\ ;$

$\frac{dRI}{dt} = \alpha I + \alpha^*(IT + ET) - \beta(\text{RI})$ The remainder of the flows follow accordingly.

Parameters	Model Estimate	Description: Daily Rates
φ	0.8	screening process
τ	0.1	constant, reduction of screening effectiveness
γ	~exp(0.1)	Transfer E to I, rate of infectivity
α	~exp(1/7)	rate of recovery from infected
α^*	~exp(1/7) Note, not competing with death movement.	adjusted rate of recovery for treated individuals
δ	~exp(1/7)	rate of death, allowing for 50% death over a 14 day period
β	~runif(1,21)	rate of losing infectiousness post-recovery
η	0	Rate of false discovery
λI^*	f(E,I,EV,IV,RI,DI) linear model, with coefficients π, π^*	Rate of gaining infection, a function of the number of infecteds
π	Measured, for each individual in the respective state by: Binomial(10,0.1)	Rate of transfer of infection from those who are unknowingly mingling in population
π^*	Measured, for each individual in the	Rate of transfer of those who are "Quarantined/ hospitalized" and treated correctly given the

	respective state by: Binomial(8, 0.1)	abilities of the country: I.e. the successful outcomes of a screen and treat protocol

Appendix H: Sample Statistics

An averaged confidence interval of the form below provides the expected 95% confidence interval of time in the system.

$$\bar{\bar{x}} \pm 1.96 \times \bar{s}$$

Where $\bar{s}$ is the aggregated sampling variation of the 1000 samples. Note $(n-1)\frac{s^2}{\sigma^2} \sim \boldsymbol{\chi^2_{n-1}}$

$$s_i{}^2 = \frac{\sum_{j=1}^{n_i}(x_{ij} - \bar{x_i})^2}{n_i - 1}$$

s_i is an asymptotically unbiased estimate of σ, however with a small sample of only the set of observations within the bias can be reduced by aggregating the estimates of the sample standard error and reduce the likelihood of overestimating or underestimating the confidence interval for the completion times.

Asymptotically $Var(s^2) = Var\left(\frac{\sigma^2}{n-1}\boldsymbol{\chi^2_{n-1}}\right) = \left(\frac{\sigma^2}{n-1}\right)^2 \times 2(n-1) = \frac{\sigma^4}{n-1}$.

$$s_i{}^2 \sim N(\sigma^2, \frac{\sigma^4}{n_i - 1})$$

Not if we look at the weighted average of 1000 $s_i{}^2$'s

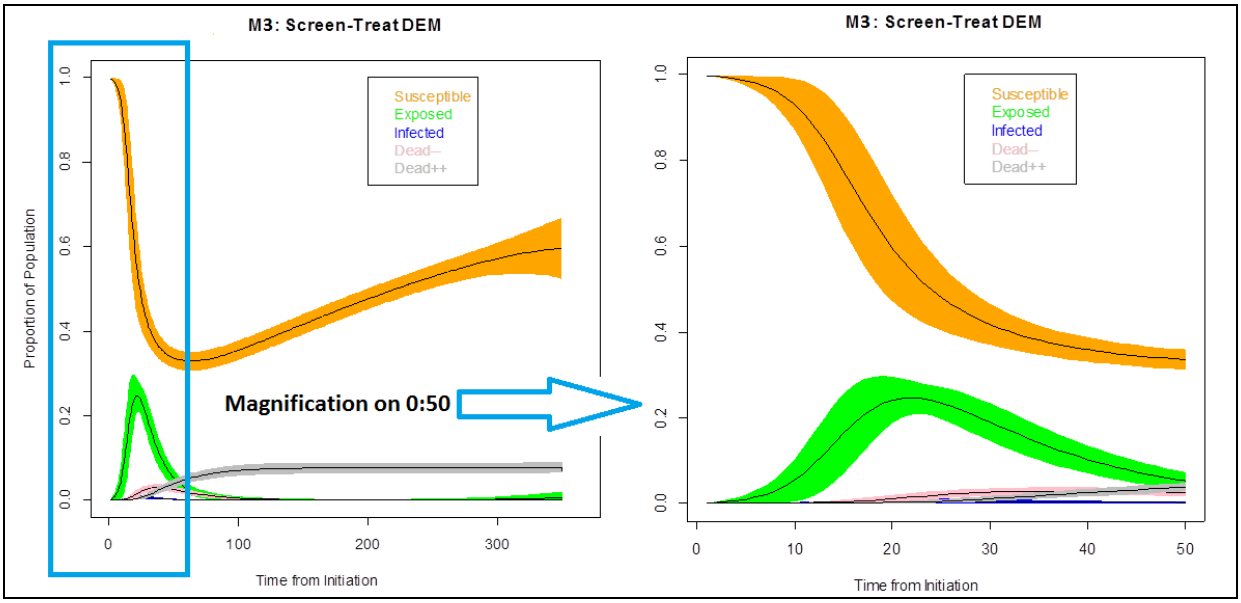
$$\bar{s}^2 = \sum_{i=1}^{1000} \frac{\sum_{j=1}^{n_i}(x_{ij} - \bar{x_i})^2}{1000(n_i - 1)}$$

$$\bar{s}^2 \sim N(\sigma^2, \frac{\sigma^4}{1000(n-1)})$$

Where $\frac{\sigma^4}{1000(n-1)}$ is an upper bound of the variance of $\bar{s}^2$ n=min(n_i, i=1,2,…,1000).

Appendix I: M3 Extended Plots

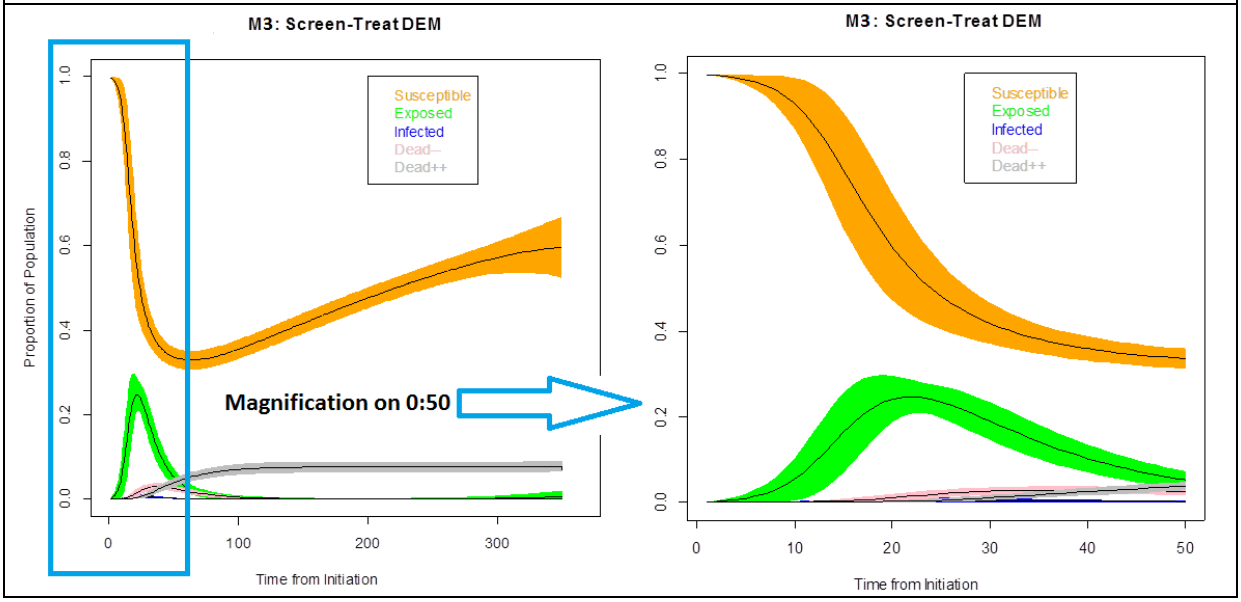
DEM model: explicitly accounting for stratification
$$f\left(\frac{S}{\text{population size}}, \text{E, I, EV, IV, RI, DI}\right)$$ $$= [\pi(E + I + DI) + \pi^*(EV + IV + D)] \times \frac{S}{\text{population size}}$$



DEM model: explicitly accounting for stratification

$$f\left(\frac{S}{\text{population size}}, \text{E, I, EV, IV, RI, DI}\right)$$

$$= [\pi(E + I + DI) + \pi^*(EV + IV + D)] \times \frac{e^{\frac{S}{\text{population size}} - 1}}{4}$$



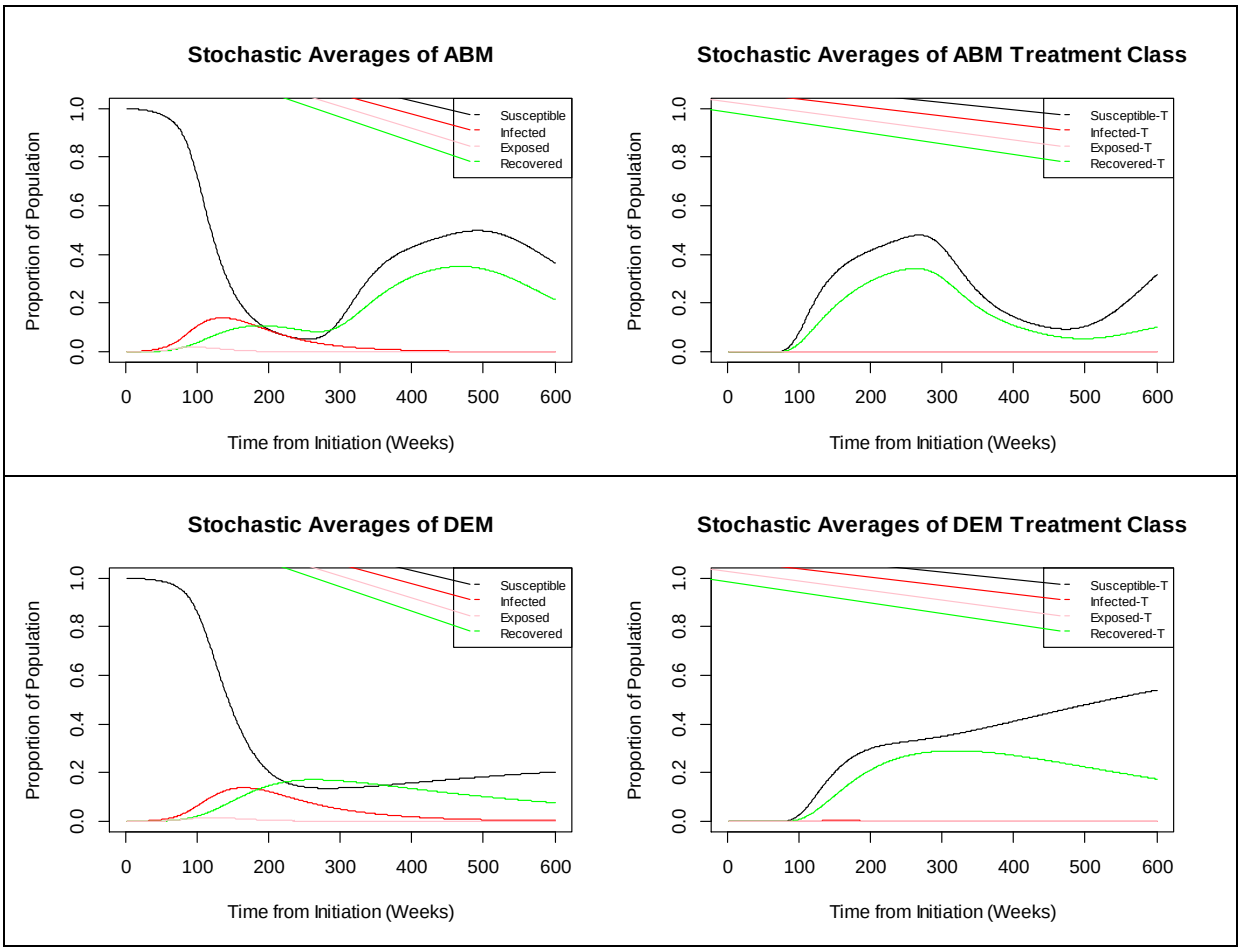
Appendix J: M2: Numerical Summary Outputs

	Mean ABM states at 1 year	SD ABM states at 1 year	Lower 95% Bound states at 1 year	Upper 95% Bound states at 1 year	Mean DEM states at 1 year	SD DEM states at 1 year	Lower 95% Bound states at 1 year	Upper 95% Bound states at 1 year
Susceptible	0.9709	0.01781	0	2.075	0.9845	0.0134	0.1537	1.815
Exposed	0.006373	0.004556	0	0.2887	0.0031	0.003263	0	0.2054
Infected	0.01812	0.0117	0	0.7436	0.009648	0.008862	0	0.5589
Recovered	0.004572	0.003041	0	0.1931	0.002752	0.002409	0	0.1521
S (with Vac)	0	0	0	0	0	0	0	0
E (with Vac)	0	0	0	0	0	0	0	0
I (with Vac)	0	0	0	0	0	0	0	0
R (with Vac)	0	0	0	0	0	0	0	0
Vaccination (Binary)	0.001	0.03162	0	1.961	0	0	0	0
	states at 2 years	states at 2 years	states at 2 years	states at 2 years	states at 2 years	states at 2 years	states at 2 years	states at 2 years
Susceptible	7.28E-01	1.41E-01	0.00E+00	9.47E+00	8.24E-01	1.60E-01	0.00E+00	1.07E+01
Exposed	3.24E-02	1.03E-02	0.00E+00	6.72E-01	1.59E-02	8.91E-03	0.00E+00	5.68E-01
Infected	1.38E-01	5.76E-02	0.00E+00	3.71E+00	7.59E-02	4.88E-02	0.00E+00	3.10E+00
Recovered	5.20E-02	2.78E-02	0.00E+00	1.78E+00	2.76E-02	2.05E-02	0.00E+00	1.30E+00
S (with Vac)	3.14E-02	3.35E-02	0.00E+00	2.11E+00	3.98E-02	6.64E-02	0.00E+00	4.15E+00
E (with Vac)	1.14E-04	3.62E-04	0.00E+00	2.26E-02	1.28E-03	2.17E-03	0.00E+00	1.36E-01
I (with Vac)	8.20E-05	3.22E-04	0.00E+00	2.00E-02	1.38E-03	2.33E-03	0.00E+00	1.46E-01
R (with Vac)	1.79E-02	2.13E-02	0.00E+00	1.34E+00	1.43E-02	2.64E-02	0.00E+00	1.65E+00
Vaccination (Binary)	8.32E-01	3.74E-01	0.00E+00	2.40E+01	3.79E-01	4.85E-01	0.00E+00	3.05E+01
	flows over duration	flows over duration	flows over duration	flows over duration	flows over duration	flows over duration	flows over duration	flows over duration
S->E	8.50E-04	3.57E-04	0.00E+00	2.30E-02	1.49E-03	2.08E-03	0.00E+00	1.31E-01
R->S	2.12E-03	2.57E-03	0.00E+00	1.62E-01	6.56E-04	8.85E-04	0.00E+00	5.55E-02
I->R	1.12E-03	1.20E-03	0.00E+00	7.57E-02	9.18E-04	1.22E-03	0.00E+00	7.67E-02
E->I	1.36E-03	1.55E-03	0.00E+00	9.75E-02	1.04E-03	1.59E-03	0.00E+00	9.97E-02

E->T	1.52E-03	2.04E-03	0.00E+00	1.28E-01	4.39E-04	1.01E-03	0.00E+00	6.33E-02
S->T	2.53E-04	7.79E-04	0.00E+00	4.85E-02	1.52E-03	2.45E-03	0.00E+00	1.53E-01
R->T	5.53E-04	1.31E-03	0.00E+00	8.15E-02	7.47E-04	7.97E-04	0.00E+00	5.01E-02
IT->I	2.95E-04	7.76E-04	0.00E+00	4.84E-02	6.36E-06	8.50E-06	0.00E+00	5.33E-04
RT->R	1.51E-04	4.03E-04	0.00E+00	2.51E-02	8.16E-04	5.42E-04	0.00E+00	3.44E-02
ST->S	5.13E-02	2.98E-02	0.00E+00	1.90E+00	1.21E-03	6.90E-04	0.00E+00	4.40E-02
ET->E	5.64E-02	3.25E-02	0.00E+00	2.07E+00	3.69E-06	6.37E-06	0.00E+00	3.98E-04
ST->ET	9.21E-05	3.10E-04	0.00E+00	1.93E-02	3.00E-04	6.10E-04	0.00E+00	3.81E-02
RT->ST	2.64E-04	5.46E-04	0.00E+00	3.41E-02	4.05E-04	6.91E-04	0.00E+00	4.33E-02
IT->RT	3.48E-04	6.18E-04	0.00E+00	3.86E-02	1.38E-04	4.13E-04	0.00E+00	2.57E-02
ET->IT	4.62E-05	2.17E-04	0.00E+00	1.35E-02	1.47E-04	2.67E-04	0.00E+00	1.67E-02
ET->RT	4.75E-05	2.21E-04	0.00E+00	1.37E-02	5.87E-04	1.02E-03	0.00E+00	6.37E-02
	prevelance	prevelance	prevelance	prevelance	prevelance	prevelance	prevelance	prevelance
At First Month	0.001453	0.000763	0	0.04875	0.000402	0.000901	0	0.05623
Over First Month	0.001244	0.001688	0	0.1059	0.000207	0.001854	0	0.1151
At First Year	0.02449	0.0157	0	0.9973	0.0062	0.006526	0	0.4107
Over First Year	0.008789	0.005328	0	0.339	0.002378	0.002122	0	0.1339
Over 12 Years	0.09484	0.005328	0	0.425	0.002378	0.002122	0	0.1339
	vaccination	vaccination	vaccination	vaccination	vaccination	vaccination	vaccination	vaccination
First Imposition	89.97	18.19	78.08	101.9	117.4	28.78	115.6	119.1
First Withdrawal	410.6	63.19	369.3	451.8	277.8	31.39	275.9	279.8
First Duration	77890	77890	0	230500	280	280	0	828.9
	incidence	incidence	incidence	incidence	incidence	incidence	incidence	incidence
Over First	0.0005458	0.000344	0.000524	0.000567	0.000283	0.000259	0.000267	0.000299

Year Over Month Prior to Vac	0.005244	0.000957	0.005184	0.005303	0.006412	0.00121	0.006336	0.006487
Year Over Month Post Vac	0.005742	0.001222	0.005666	0.005818	0.007033	0.001381	0.006947	0.007119

Appendix K: Model 2 Additional Graphical Outputs



Appendix L: WHO Control Policies for Ebola

1. **Reduce risk of hospitalized transmission**
   - **Health care workers to be given first priority on vaccination**
   - **Mass screen-and-treat**
   - **Protocol of protective equipment**
   - **Quarantine of Suspected, Probable, and Confirmed cases**
2. **Reduce risk of public transmission**
   - **Contact tracing- whereby all interactions of Suspected, Probable, and Confirmed cases (in order of increasing necessity) are investigated and quarantined in suspected cases**
3. **Reduce risk of wildlife to human transmission**
   - **All raw meat thoroughly cooked**
   - **Protective equipment (gloves) when dealing with suspected animal meat**
4. **Containment**
   - **Quarantine of all Suspected, Probably and Confirmed cases**
   - **Prompt and safe Burial**
   - **Monitoring those in contact with individual for 21 days**

5. Reduction in fatality

Intravenous therapy (injection of fluids)

Oral hydration

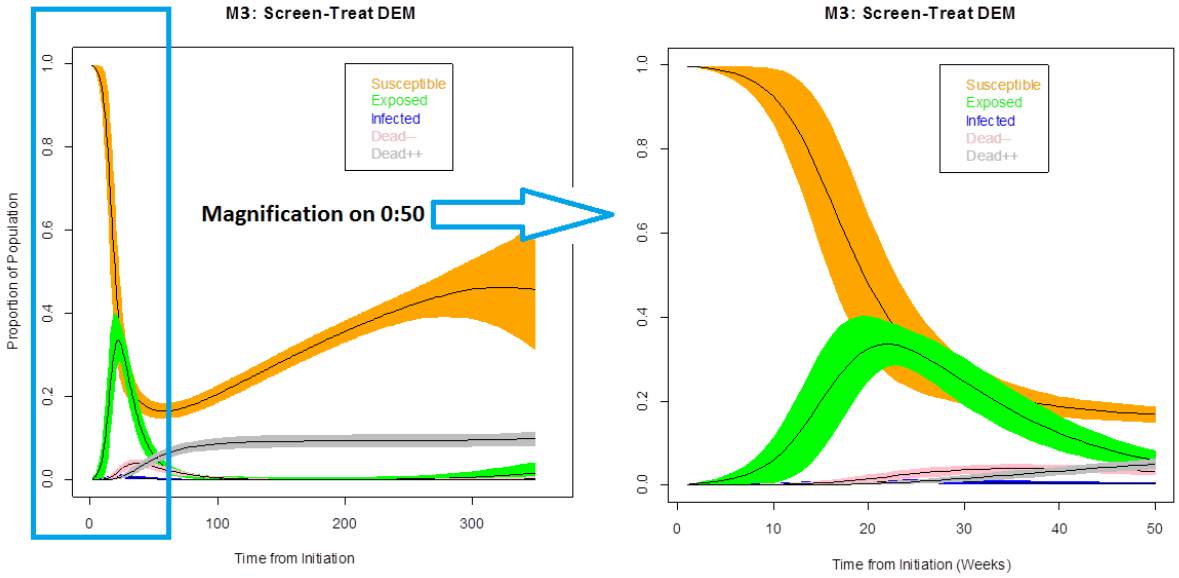
Sources: Chan, 2014. Lashley and Durham, 2007. WHO {2}, 2014. WHO {3}, 2014.

Appendix M: M3 Additional Models

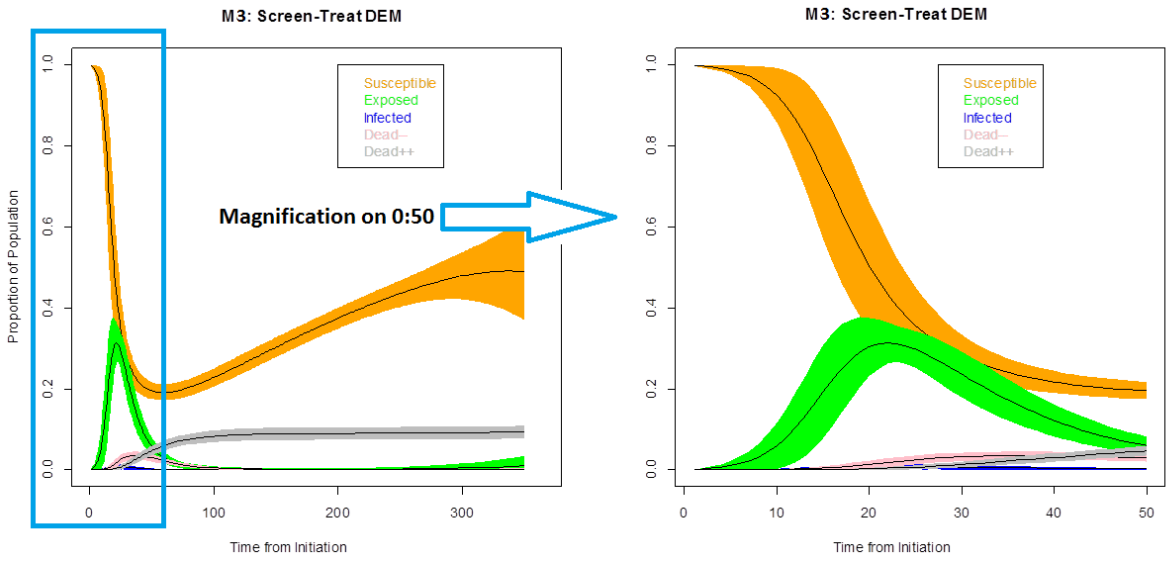
Comparison of Susceptible; Exposed; Infected; Dead-- (infectious); Dead++ (non-infectious)

In a Differential Equation Model

Without explicit compensation for spatial dynamics

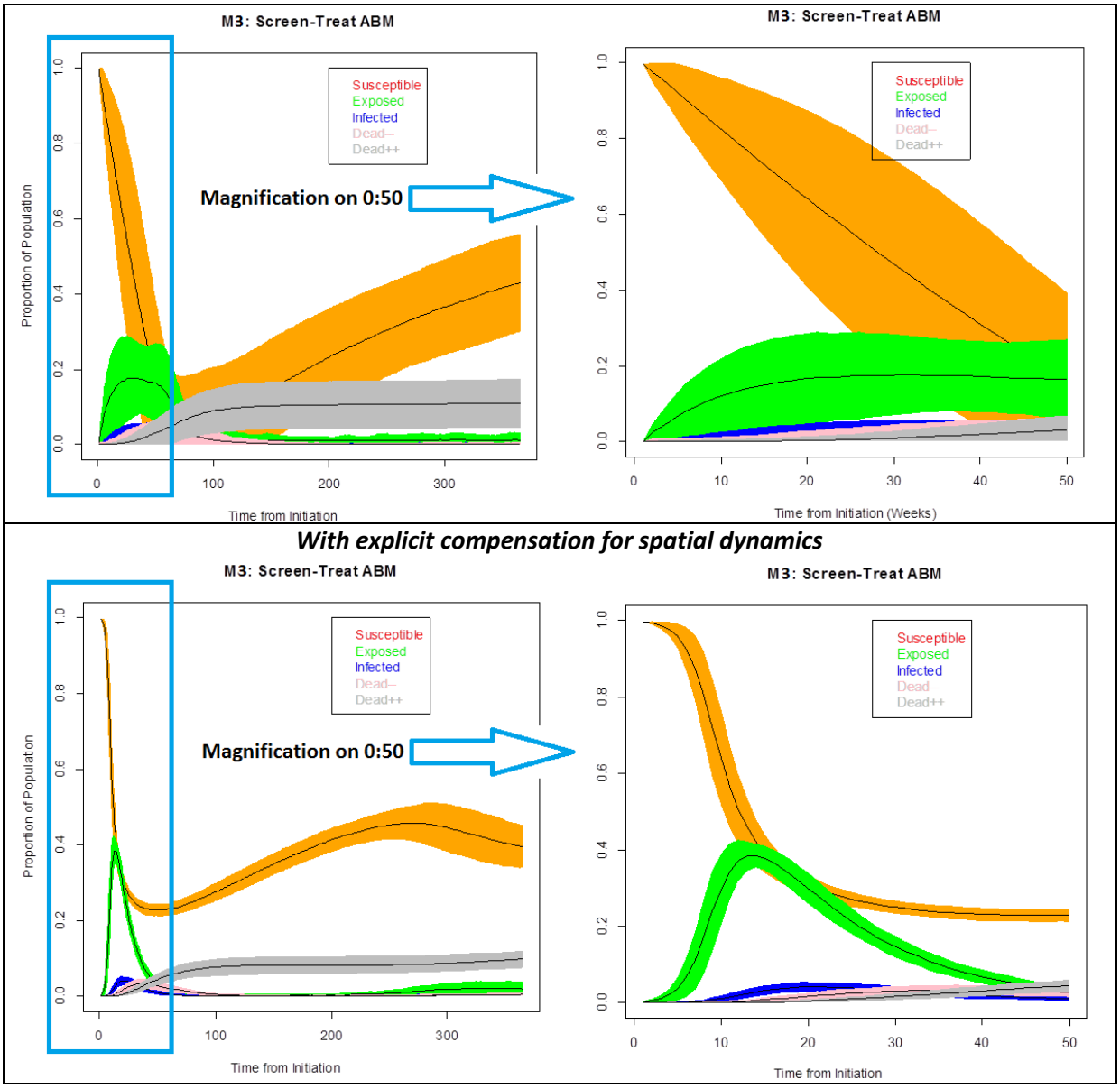


With explicit compensation for spatial dynamics

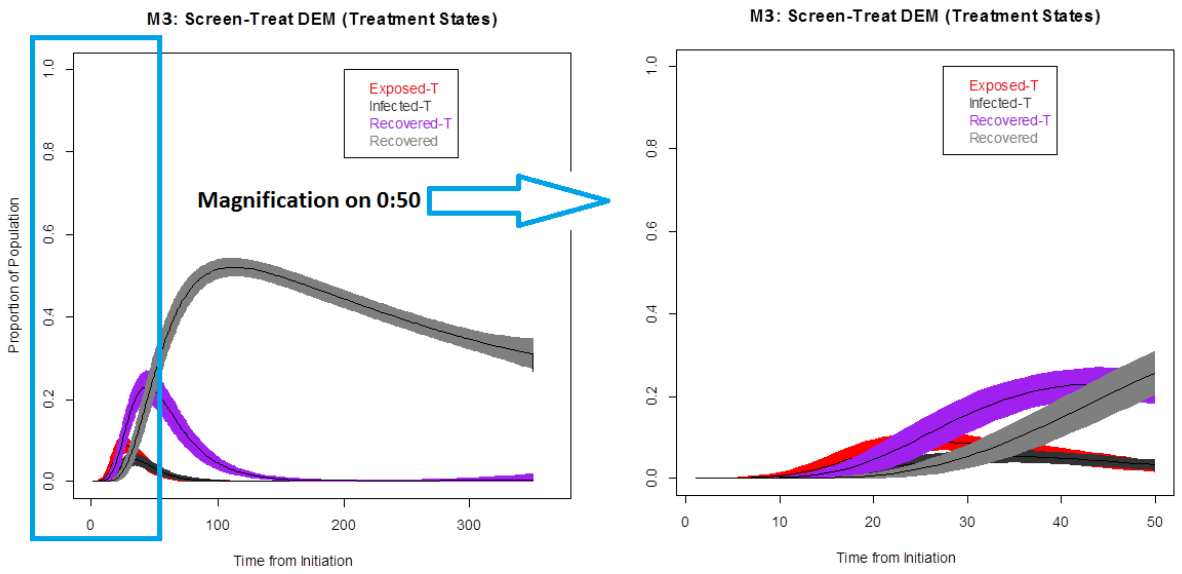


In an Agent Based Model

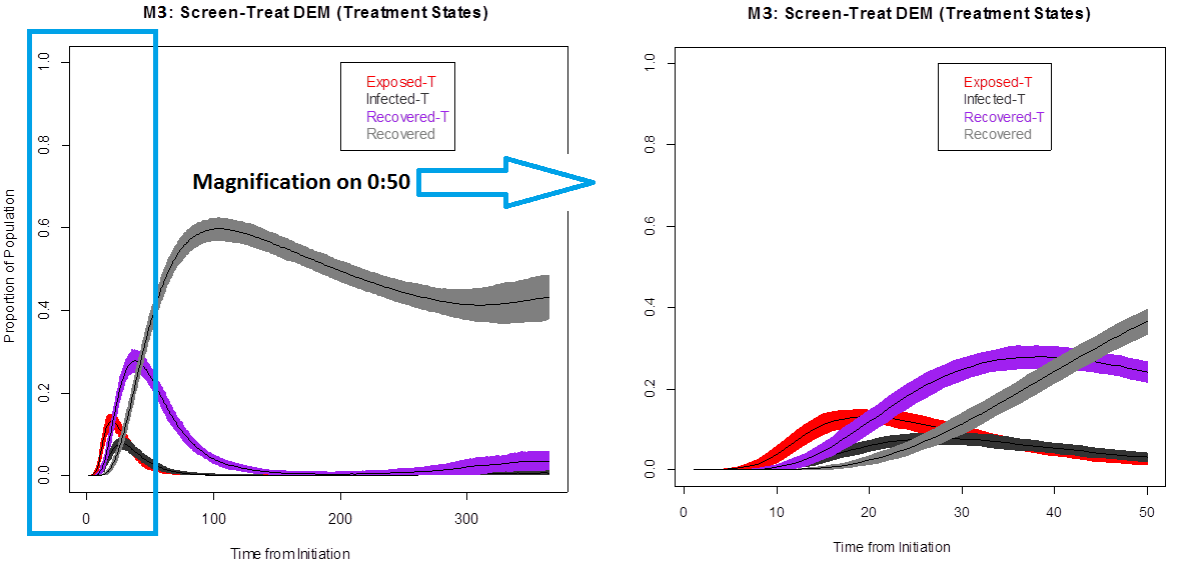
With explicit spatial dynamics



Comparison of Exposed $^{\text{with treatment}}$; Infected $^{\text{with treatment}}$; Recovered $^{\text{with treatment}}$; Recovered
In a Differential Equation Model
Without explicit compensation for spatial dynamics

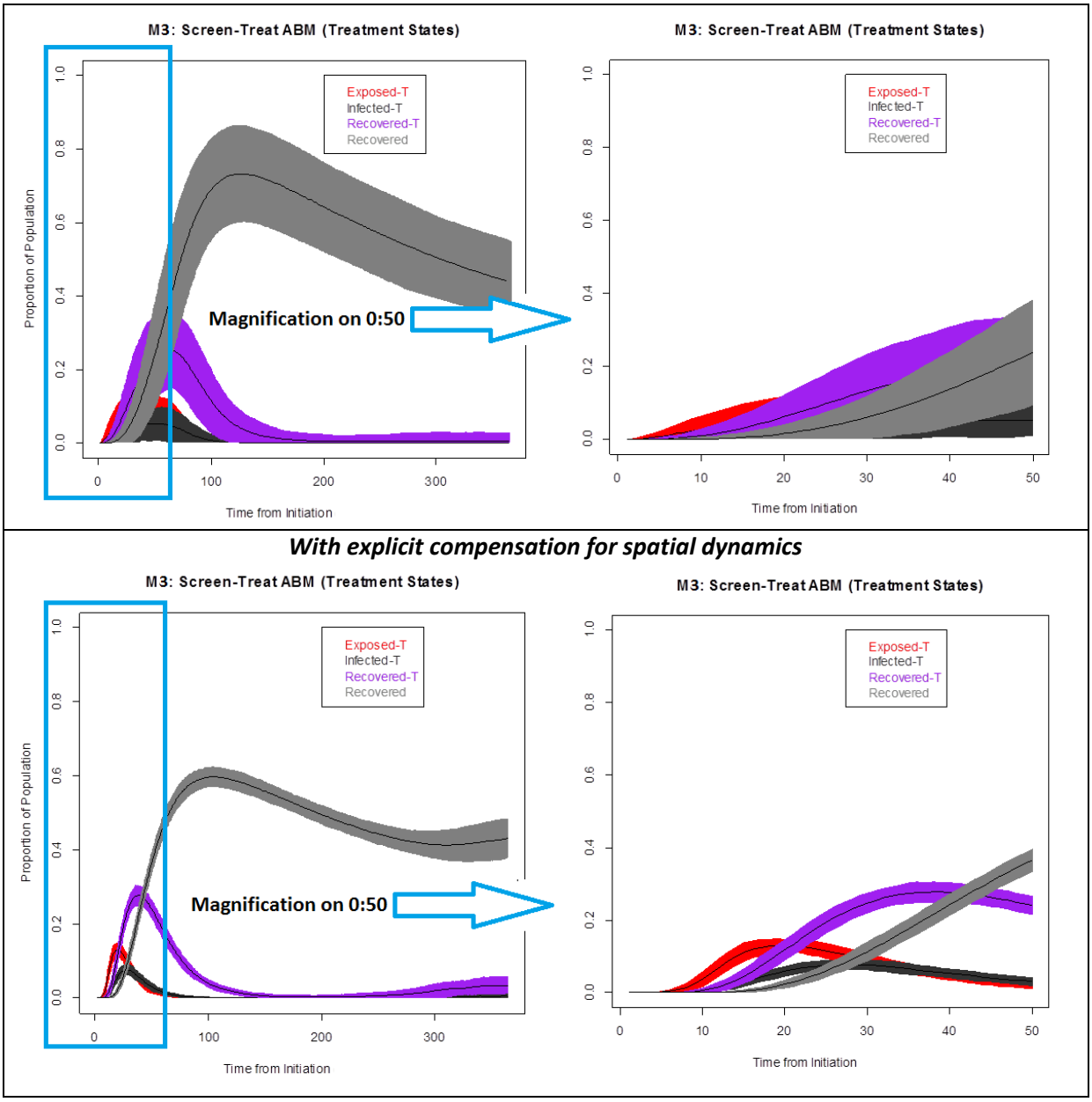


With explicit compensation for spatial dynamics



In an Agent Based Model

With explicit spatial dynamics


M3: Screen-Treat ABM (Treatment States)
Exposed-T
Infected-T
Recovered-T
Recovered
Proportion of Population
Time from Initiation
Magnification on 0:50
M3: Screen-Treat ABM (Treatment States)
Exposed-T
Infected-T
Recovered-T
Recovered
Time from Initiation
With explicit compensation for spatial dynamics
M3: Screen-Treat ABM (Treatment States)
Exposed-T
Infected-T
Recovered-T
Recovered
Proportion of Population
Time from Initiation
Magnification on 0:50
M3: Screen-Treat ABM (Treatment States)
Exposed-T
Infected-T
Recovered-T
Recovered
Time from Initiation