Pandemic Influenza Mitigation in Cambodia: Costs, Consequences and Uncertainty

CamFlu Project
Research Briefing Note

February 2013

OVERVIEW

The 'CamFlu' project aims to improve priority setting for pandemic mitigation[1] investment in Cambodia by assessing whether various pandemic mitigation options could be considered a good use of scare resources. Using generalised cost effectiveness analysis (CEA), we compared the costs and effects of pandemic mitigation options and calculated an incremental cost effectiveness ratio (ICER). Policy makers can use evidence on the cost effectiveness of different investment options to prioritise investments which are likely to maximise health benefits.

The CamFlu project is supported by Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH

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On behalf of the German Federal Ministry for Economic Cooperation and Development (BMZ)

BMZ Bundesministerium für wirtschaftliche Zusammenarbeit und Entwicklung

The project was implemented by:
London School of Hygiene and Tropical Medicine (LSHTM)
Communicable Disease Control Department (CDCD),
Ministry of Health Cambodia
Centre for Livestock and Agriculture Development (CelAgrid)

Principle Investigator:
Prof Richard Coker (LSHTM)

Co-Investigators:
Dr Sok Touch (CDCD)
Dr Khieu Borin (CelAgrid)

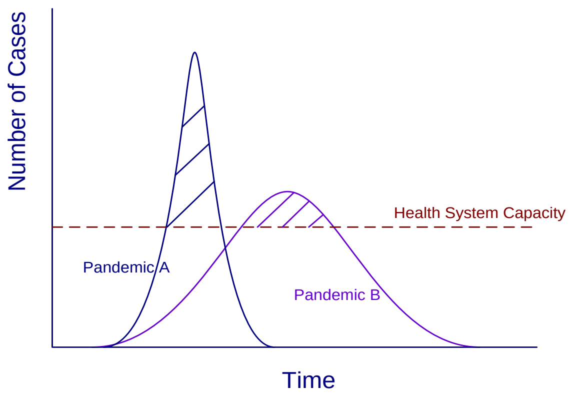
Lead Researcher:
Tom Drake (LSHTM)

Contact Information:
Faculty of Public Health, Mahidol University,
Bangkok 10400, Thailand
Tel/Fax: +66 2 354 6044
Email: thomas.drake@lshtm.ac.uk
www.searn.org

[1] Activities which reduce mortality or morbidity in the event of a pandemic.

CEA for pandemic mitigation is highly complex and there is only a very small research base of less than 50 published studies to date (Perez-Velasco *et al.*, 2012). Unlike CEA for endemic diseases, empirical research for epidemic or pandemic events is challenging and of limited use since a future scenario is likely to be different from any current event. Therefore, the core of this project was to use, and improve on, state-of-the-art modelling techniques to explore the costs and effects of interventions in a large number of possible pandemic scenarios. The model we developed integrates influenza transmission, clinical care and economic components of a pandemic. Unlike prior pandemic CEA models, we incorporated data on health system resources to model health system capacity.

Figure 1. The interaction between health system capacity and epidemic curve



In addition to model development, we undertook a number of sub-studies, both to collect information for the model and as informative studies in their own right. We held interviews with key stakeholders to assess current opinion in priority setting for pandemic mitigation in Cambodia. We conducted a household survey of over 2000 people in three provinces to collect i) data on human-to-human contact patterns and ii) information on treatment seeking behaviour for influenza-like illnesses (ILI). We conducted a detailed analysis on human cases of H5N1 avian influenza in Cambodia to assess both outcomes and, importantly, the economic cost of illness. During model development and following the literature critique, we realised the importance of uncertainty in pandemic models and established that time-to-pandemic uncertainty is a critical factor in pandemic cost effectiveness models. Finally, we conducted an analysis of the distribution of pandemic related health resources in Cambodia and compared this with both population density and level of poverty.

Cost effectiveness analysis findings from this project are likely to have a limited impact on policy because data for intervention characterisation could not be obtained or had been called into question. Obtaining financial information on investment in pandemic related hospital resources was challenging, as neither private nor public hospitals were willing to disclose financial information. Also, the effectiveness of oseltamivir (Tamiflu) has been brought into question by a 2012 Cochrane report (Jefferson et al., 2012) and associated transparency campaign by the British Medical Journal (www.bmj.com/tamiflu).

Initial results from the analysis of cost effectiveness of antiviral stockpiling in Cambodia are outlined below. However, in the absence of strong data to characterise investment scenarios for cost effectiveness analysis, we planned an uncertainty analysis to identify where new information could best reduce uncertainty in CEA results and therefore improve evidence for decision making. This work is ongoing.

1. LITERATURE CRITIQUE

Ideally, pandemic influenza policy making would draw on a solid evidence base including findings from cost-effectiveness analyses. This evidence base is currently small but has grown rapidly since 2009. However, research scope is narrow and there is considerable methodological variation between studies. To improve quality and consistency within this emerging study area we identify four opportunities for improving scope and methods: i) increased focus on low resources settings, ii) greater inclusion of non-pharmaceutical interventions, iii) incorporation of health system surge capacity, and iv) more robust analysis and presentation of pandemic event uncertainty.

Project Paper:
Drake T, *et al.* (2012) **Cost-effectiveness analysis of pandemic influenza preparedness: what's missing?** Bulletin of the World Health Organization, 90, 940-941.

2. STAKEHOLDER PERSPECTIVES

We conducted semi-structured interviews with 14 key informants in Cambodia. Interviewees were asked to score ten policy areas in terms of perceived importance and comment on how they reached their decisions. WHO-recommended interventions all scored above four out of five. However, there was a lack of consensus on which pandemic preparedness policy areas might be the most important in Cambodia. Some informants raised specific concerns about particular policy areas, but collectively these were not consistent and informants were unable to prioritise between intervention options.

Policy makers in Cambodia and other low income countries face real challenges in prioritising pandemic preparedness investment options. This is in part due to a shortage of informative evidence. This could be improved by generating better information on the cost and effectiveness of pandemic influenza interventions and communicating these findings appropriately.

Project Paper:
Huszar A, *et al.* (2013) **Prioritising in pandemic influenza preparedness: a study of key informants in Cambodia,** South East Asian Journal of Public Health **(in press).**

3. MATHEMATICAL MODEL

We developed a mathematical model to simulate pandemic scenarios and estimate the impact of pandemic mitigation strategies.

The model (Appendix 1) comprises two main components:

1. A transmission model, which simulates the spread of influenza.
2. A "severe case" model, which tracks the availability of healthcare resources.

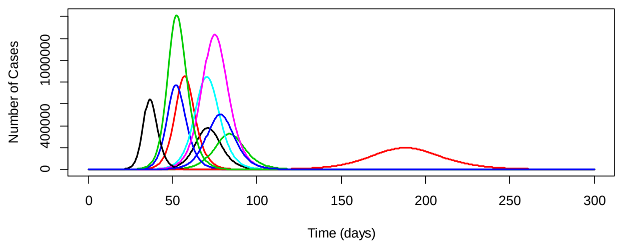
The model is designed to allow exploration of a diverse range of interventions including: (i) antiviral (oseltamivir) stockpiling and allocation strategies, (ii) increasing hospital capacity, and (iii) contact reduction (e.g. school closure).

Model inputs (parameters) are derived from:

- Surveys on human contact patterns and treatment seeking behaviour in Cambodia (see sections below);
- Healthcare resource data for Cambodia; and
- A review of secondary data from previous pandemics and severe influenza cases.

Due to considerable uncertainty surrounding future pandemics, most model inputs are randomly selected from a range of possible values. Thus, the model can generate a wide range of plausible pandemic scenarios (Figure 2)

Figure 2. Diversity of possible pandemic scenarios, illustrated by ten examples of model simulations



The model can be used to address questions such as: "For a given, finite stockpile of oseltamivir, what is likely to be the best allocation strategy?" (Figure 3).

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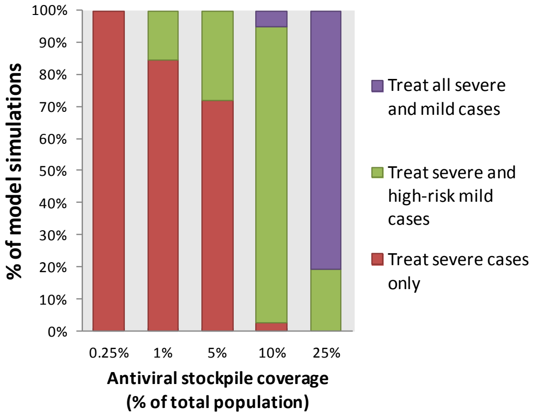
Figure 3. Optimum oseltamivir allocation strategies (in terms of reduction in pandemic deaths) for different stockpile sizes



Project Paper:

Rudge JW, *et al.,* **A mathematical model to evaluate pandemic mitigation strategies, with application in Cambodia (in preparation).**

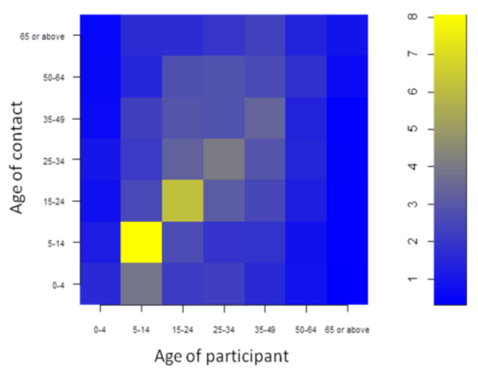
4. POPULATION SURVEY

4.1 Human contact networks

We conducted a survey of 2,041 people in urban and rural sites across three provinces: Phnom Penh and Kandal[2]; Kampot; and Kratie. The survey included a human contact diary, in which the participants were asked to record all 'contacts' with another person in a 24 hour period. A contact was defined as a one to one conversation in the physical presence of the other person or skin-to-skin contact.

The average number of contacts per person in Phnom Penh and Kandal was 11.5, compared with 19.5 in Kampot, and 12.8 in Kratie. Approximately 60% of contacts were made at home and 75% of contacts were made on a daily basis and lasted in excess of an hour. Mixing patterns were highly age-structured, with the highest rates of contact among school age children and young adults (Figure 4).

Figure 4. Social contact matrix for Cambodia showing the mean number of contacts per day by age



[2] Treated as urban and rural counterparts of the same area in this survey.

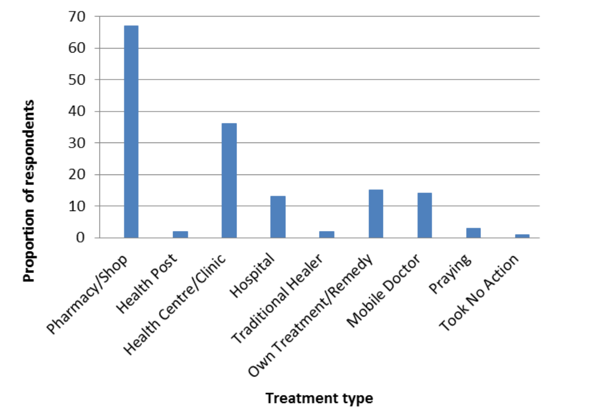
4.2 Treatment seeking behaviour and costs

Data on treatment seeking behaviour and costs for patients with influenza like illness (ILI) were collected from a survey of 2,014 Cambodians.

The most common place to seek treatment for ILI was at a pharmacy (67% of respondents), followed by health centres (36%). Of the three main types of public health facility, use of hospitals (13%) and health posts (2%) was lower than health centres. More patients saw mobile doctors (14%) than health posts or hospitals. Only a small number of respondents reported using prayer (3%) or a traditional healer (2%) and all of these also sought at least one other form of treatment (Figure 5).

Financial cost or distance did not seem to be the main factors for those choosing to visit medical facilities, as the combined average cost of treatment and travel to health posts (20,082 Riel) is less than at health centres (35,437 Riel) or hospitals (54,957 Riel).

Figure 5. Treatment seeking behaviours for influenza-like illness in Cambodia



5. AVIAN INFLUENZA CASE COSTS AND OUTCOMES

Human cases of highly pathogenic avian influenza H5N1 have been occurring sporadically in Cambodia since 2005. We carried out a study to assess the treatment costs and outcomes of all 18 H5N1 avian influenza cases identified in Cambodia as of August 2011. We reviewed the patient case notes, undertook interviews with health workers at district and provincial hospitals, and obtained information from officials at the Ministry of Health.

Of the 18 patients studied, 11 (61%) were under the age of 18 years. The majority of patients (16, 89%) died, eight (44%) within 24 hours of hospital admission. There was an average delay of seven days between symptom onset and hospitalisation with patients, travelling an average of 148 kilometres (8-476km) to the admitting hospital. Five patients were treated with oseltamivir, of whom two received the recommended dose. The average per patient cost of H5N1 influenza illness was US$300; of this, 85% represented direct medical provider costs, including diagnostic testing (41%), pharmaceuticals (28%), hospitalisation (10%), oxygen (4%) and outpatient consultations (1%).

Cases of avian influenza in Cambodia have been characterised by delays in hospitalisation, deficiencies in some aspects of treatment and a high fatality rate. The costs associated with medical care, particularly diagnostic testing and pharmaceutical therapy, were major contributors to the relatively high cost-of-illness.

Project Paper:
Humphries-Waa K, *et al.*, **Human H5N1 influenza infections in Cambodia 2005-2011: case series and cost-of-illness (under review).**

6. TIME-TO-PANDEMIC AND MODEL UNCERTAINTY

Pandemic preparedness requires upfront investment and the benefits of this investment are only realized during the course of the next pandemic, an unknown number of years after the investment.

We used a decision tree model and Monte Carlo parameter sampling to consider the cost effectiveness of antiviral stockpiling in Cambodia under parameter uncertainty. Measures of mean elasticity and mutual information were used to assess parameter importance and the importance of time-to-pandemic compared with other parameters.

Table 1. Historical pandemic events and sensitivity analysis of change in cost effectiveness of an antiviral stockpile investment with time-to-pandemic

Pandemic	Pandemic Year	Pandemic Interval (years)	Cost per Death Averted [1] (US$)
Swine Flu	2009	41	29342
Hong Kong Flu	1968	11	3345
Asian Flu	1957	39	25387
Spanish Flu	1918	29	12309
Russian Flu	1889	59	107984
	1830	49	52358
	1781	52	65058
	1729	-	-
Mean		**30**	**42255**

[1]Based on stockpile of one million treatment courses purchased in 2009, pandemic impact is adjusted for time-to-pandemic using historical intervals.

We found that in the economic evaluation of pandemic preparedness investments the uncertainty in time-to-pandemic is a dominant factor in model uncertainty. Table 1 illustrates the importance of time-to-pandemic using historical pandemic intervals. For full results please refer to the paper (currently under review).

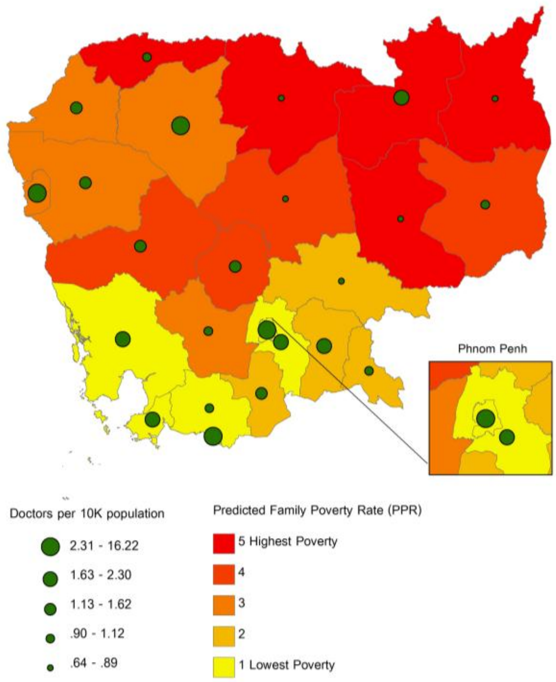
Mathematical models to assess the cost-effectiveness of pandemic preparedness options requiring upfront investment should include probabilistic sensitivity or uncertainty analysis of time-to-pandemic. In addition, further research should establish true population time preferences for pandemic consequences.

Project Paper:
Drake T, *et al.* **Does uncertainty in pandemic timing affect cost effectiveness results? (under review).**

7. RESOURCE DISTRIBUTION ANALYSIS

Information on the availability of over 50 health system resource items important for pandemic influenza control was collected throughout Cambodia at the hospital and district levels in 2009. Of these, five key resource types – inpatient beds, doctors, nurses, oseltamivir, and mechanical ventilators – were used for the final analysis. Distribution of these five key health resources, weighted by population, was analysed at both the Province and Operational District levels. In general, numbers of inpatient beds, doctors and nurses tended to be highest in the more populated areas of the country, especially in Phnom Penh Province and the Siem Reap Operational District. Supplies of the two other key resources, oseltamivir and mechanical ventilators, were low or absent across the country, with small pockets of supplies scattered across Provinces and Operational Districts. Figure 6 shows distribution of doctors compared with poverty levels, mapped at the Province level.

Figures 6. Per capita density of all doctors (hospital- and district-based) compared with poverty rates, at the Province level



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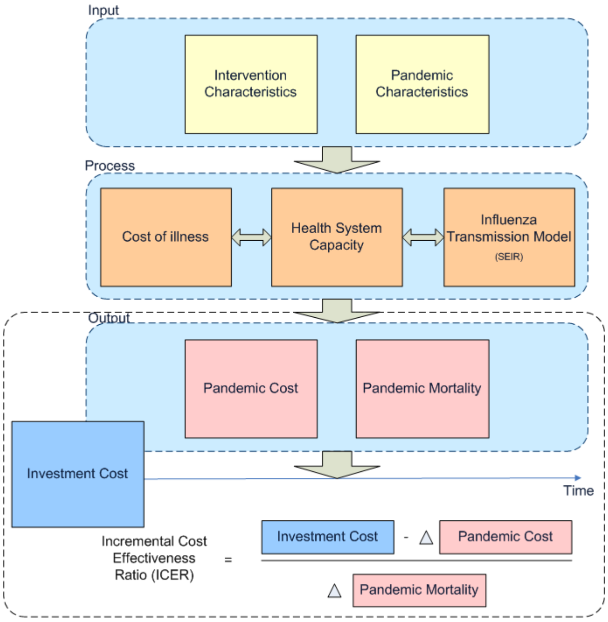
A possible relationship between poverty and resource distribution was explored in a number of different ways. Results of these analyses showed that there is wide variation in the distribution of resources by type, healthcare facility (hospital vs. district-based health facility), and administrative level (Operational District vs. Province). Most notably, hospital-based inpatient beds were most heavily concentrated in the wealthiest areas, but district-based inpatient beds showed a clear trend toward better availability at higher poverty levels. Similarly, hospital-based doctors and nurses were very heavily concentrated in the wealthiest Provinces and Operational Districts, largely due to the high numbers of healthcare workers based in Phnom Penh Province; at the district-based facilities, however, concentrations of nurses increased in areas with higher poverty rates.

Project Paper:
Schwanke-Khilji S, *et al.,* **Distribution of pandemic related resources in Cambodia (in preparation)**

8. COST EFFECTIVENESS OF ANTIVIRAL STOCKPILING IN CAMBODIA: PRELIMINARY RESULTS

In order to calculate the cost effectiveness of a pandemic mitigation option, we needed to provide information on intervention characteristics along with pandemic characteristics. This information was processed by the model to create outputs of pandemic cost and pandemic mortality. The same pandemic scenario was run with and without the intervention to calculate the net pandemic cost and net pandemic mortality. These outputs were discounted to adjust for differential timing between the investment and the pandemic and an incremental cost effectiveness ratio (ICER) was calculated (Figure 8).

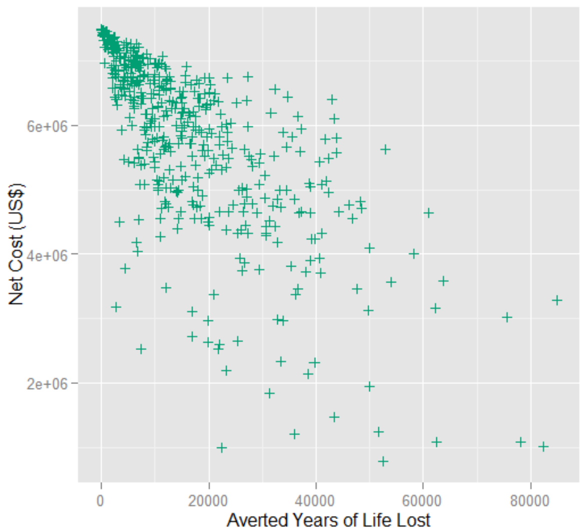
Figure 8. Schematic overview of the cost effectiveness model



We repeated this process 1000 times, drawing different values for pandemic characteristics and other model parameters, to calculate 1000 ICERs reflecting cost effectiveness estimates for a wide range of possible scenarios.

We considered an investment scenario for substantially increasing the current stockpile of antivirals from approximately 75,000 to 500,000 treatment courses (<5% of the population), costing US$ 7.5 million. Preliminary results found that 69% of simulations were cost effective at the standard threshold of US$ 900 (that is, gross domestic product per capita in Cambodia) per averted year of life lost.

Figure 9. Scatter plot of economic cost (US$) against averted years life lost (YLL) for an antiviral stockpiling investment scenario



In Figure 9, we can see that the majority of scenarios cost money overall and a small number are cost saving due to reduced cost of illness. Similarly, in the majority of simulations, the investment had a modest health impact but in a small number of severe pandemic scenarios there was a substantial impact on health.

Contributors

London School of Hygiene and Tropical Medicine
Tom Drake
James Rudge
Aronrag Meeyai
Sara Schwanke Khilji
Marco Liverani
Leah Holzwoth
Karen Humphries-Waa
Anthony Huszar
Richard Coker

Communicable Disease Control Department, MOH
Dr Sok Touch
Dr Teng Srey
Mr Sok Samnang

Centre for Livestock and Agriculture Development
Khieu Borin
Pok Samkol
Chhay Ty
Chiv Phiny
Seng Sokerya

Many thanks to:
Arnaud Tarantola (Pasteur Institute, Cambodia)
Tapley Jordanwood (University Research Company, Cambodia)
Irwin Chavez (Mahidol University, Thailand)
David Fedson

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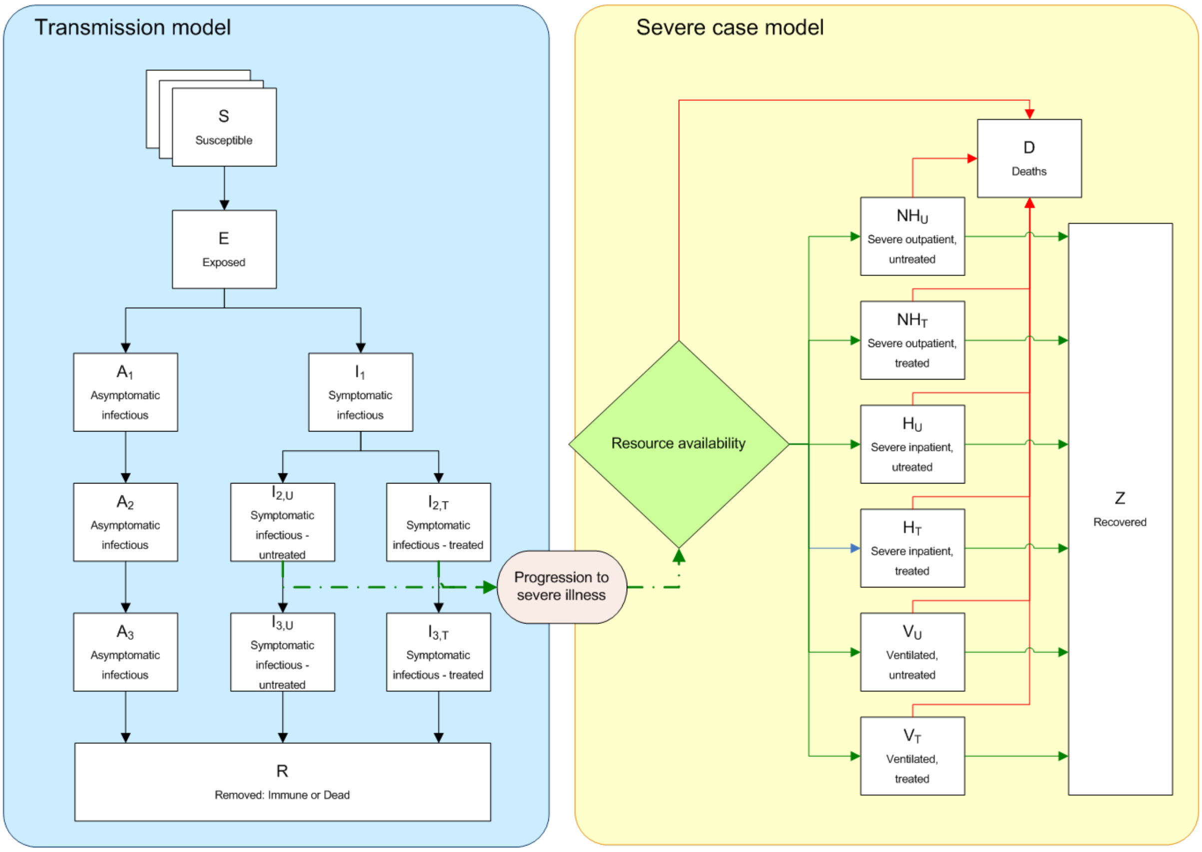
Appendix 1: Schematic of the pandemic model



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