A Multi-Agent Model for Adaptive Vaccination during Infectious Disease Outbreaks

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Abstract—**Infectious disease outbreaks are a huge burden on healthcare, causing hospitalizations, deaths and rigorously impairing the economy. In this work, an age-structured multi-agent model has been developed to simulate an epidemic spread among the US population and strategize adaptive vaccination planning to control the spread. The population was split into six distinct groups of agents depending upo on their age. In addition, the calibration of the multi-agent model parameters for H1N1 2009 pandemic, validation of the model using H1N1 2009 pandemic data from Centers for Disease Control and Prevention (CDC, US) was carried out. Using these data, the model was calibrated such that the H1N1 deaths predicted by the model was comparable to that of the deaths reported by CDC, while the H1N1 hospitalizations predicted were within the 95% confidence interval. A series of hypothetical simulations of a H1N1 like pandemic outbreak among the US population to illustrate the effectiveness of various adaptive strategies proposed in the literature will be presented. Each set of simulation was replicated 100 times so as to average the stochastic effects of parameter(s) uncertainty. The multi-agent model developed in this work can be used as a decision support system to systematically gauge the effectiveness of various interventions so as to aid healthcare policy makers to design dynamic, optimal health interventions to counter disease outbreaks.**

Keywords —Multi-agent modeling; H1N1 Pandemic; Adaptive interventions; Vaccine allocation; Age-structured models; Decision support system.

I. INTRODUCTION

Infectious disease outbreaks have occurred frequently throughout history, as in 2009, with the outbreak of influenza A H1N1/09. Infectious disease outbreaks are a huge burden on health and social sectors, causing deaths, and severely impairing society and the economy. Hence, it is imperative to carefully manage outbreaks of infectious diseases even at an early stage so as to contain their spread and to minimize fatalities. Infectious disease modeling can aid healthcare policy makers to design dynamic, optimal health interventions to counter disease outbreaks. The 2009 flu pandemic is of special interest to this research. It was caused by a novel strain of H1N1 influenza virus, escalating to being declared a pandemic by the World Health Organization in June 2009 [1]. H1N1 pandemic was declared to be non-threatening in August 2010, by which time there were laboratory confirmed cases in more than 214 countries, and over 18,000 deaths. The severity of the pandemic, coupled with the modern measures available to handle it, led to a coordinated worldwide response. Hence, this pandemic has been carefully studied and extremely well-documented, particularly in the United States, where healthcare resources are adequate. In addition, vaccination efforts were carried out, and these were also studied extensively. Therefore, there is a wealth of information available regarding the 2009 flu pandemic, making it a prime candidate as a case study for our epidemiological research. It is for these reasons that the 2009 flu pandemic in the United States has been chosen as a case study to investigate the effects of optimizing interventions for the effective control of epidemic. Quarantine, public awareness campaigns, antiviral prophylaxis, school closures and vaccine allocations are the most commonly used interventions. One powerful containment measure is the implementation of mass vaccination programs. Vaccines have the effect of enhancing an individual's immunity to specific diseases. Hence, mass vaccination programs are able to protect significant numbers of a population from an infectious disease outbreak by preventing them from being infected [2]. Unfortunately, vaccines are often in short supply during epidemics as was the case in the recent 2009 H1N1 pandemic. Also, outbreaks are often due to new viral strains for which lengthy vaccine research and development timelines hinder mass production of vaccines. Hence, health authorities implementing mass vaccination programs have only very limited quantities of vaccines to work with, and have an urgent need to optimize how the vaccines are to be allocated. Vaccine allocation can immensely affect the eventual outcome of the outbreak depending on how the various risk groups in a population are vaccinated. Established vaccine allocation practices are not well optimized and are often static, focusing on specific risk groups such as the young and the elderly throughout the entire duration of outbreaks, when it may be more prudent to switch tactics at certain time points for higher disease management efficacy.

Modeling and simulation can help to systematically gauge the effectiveness of various pharmaceutical and non-pharmaceutical interventions. Currently, the spread of an infectious disease outbreak is modeled [3] using two

approaches: the equation based approach and the micro-simulation approach. The most commonly preferred equation based approach uses average parameter values for the entire population and does not address the interactions occurring at the micro level. The assumption is that the entire population moves and interacts in the same manner – this is not realistic. Agent based modeling [4] can handle the emergence property and our research exploits this advantage to develop realistic models and design optimal interventions to manage epidemic outbreaks.

II. Agent-based Epidemiological Model

An age-structured agent-based epidemiological model was developed to simulate an epidemic spread among the US population. The population was split into six distinct groups of individuals, based on their age. Age-specific risk factors relevant to the spread (such as contact patterns), morbidity and mortality of pandemic influenza, age-specific probabilities of hospitalizations and subsequent deaths and efficacies of vaccination were based on studies of the 2009 H1N1 pandemic outbreak and other relevant influenza outbreaks. Such age-wise stratification improved the characterization of differing levels of risk to pandemic influenza and hence better represented the impacts of an age-wise selective vaccine allocation strategy. The age-structured agent-based epidemiological model used in this study is adapted from literature [5]. It comprises of a set of differential equations describing the time-dependent movement of individuals in a population through a series of infection and vaccination states. Each age group of the population is classified into nine compartments to represent the different disease states: S_i (susceptible), V_i (effectively vaccinated but not yet protected), U_i (ineffectively vaccinated), P_i (protected by vaccination), E_i (exposed), I_i (infectious), H_i (hospitalized), R_i (recovered from infection) and D_i (dead due to infection). An overview of the model is depicted in Figure.1. The epidemic is initiated by one infected agent and the rest of the population start out as susceptible individuals S_i. Susceptible individuals in age group i come into contact with infectious and hospitalized individuals in age group j and are thereby exposed to the pandemic influenza at the rate of the age-specific force of infection λ_i The transmission rate β_{ij} is a product of q, the probability of transmission per contact with infectious or hospitalized individuals, and c_{ij}, the age-specific rate that an individual in age group i contacts an individual in age group j. Individuals exposed to the influenza move to the exposed compartment E_i at the rate of the age-specific force of infection λ_i, these individuals stay latently infected for some time before becoming infectious, moving them to the infectious compartment I_i at the rate k. An infectious individual may then get well to recover and move to the recovered compartment R_i at the rate γ_1. Alternatively, the infectious individual has an age-specific probability of p_{Hi} of needing to be further hospitalized, for which, he/she moves to the hospitalized compartment H_i at the age-specific rate of $\alpha_i = \frac{p_{H_i}}{1-p_{H_i}}\gamma_1$. Individuals who are hospitalized may manage to recover and move to the recovered compartment R_i at the rate γ_2, or, alternatively, have an age-specific probability CFP_i of not recovering and succumbing to the disease, moving to the death compartment D_i at the age-specific rate of $\delta_i = \frac{CFP_i}{1-CFP_i}\gamma_2$.

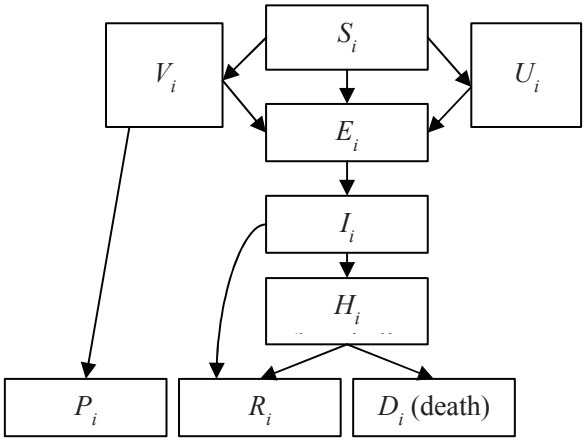

Fig. 1: Flow chart of movements among the compartments in the epidemiological model

The compartments of V_i (effectively vaccinated but not yet protected), U_i (ineffectively vaccinated) and P_i (protected by vaccination) particularly apply to individuals who have been vaccinated against the particular strain of influenza. These three compartments will significantly affect the success of the mass vaccination program. Vaccination will be applied to individuals in the susceptible compartment and will have varying effects. Vaccinated individuals have an age-specific probability ε_i of being effectively vaccinated (U_i) at the vaccination rate $v(t)$. However, they are not yet protected from infection until the effects of the vaccine are triggered within their bodies, and they therefore remain susceptible to infection until they move to the protected compartment P_i at the rate η. Once protected, like those in the recovered compartment, it is assumed that there is no further risk of infection to them. There is also an age-specific probability $(1-\varepsilon_i)$ for susceptible individuals to get ineffectively vaccinated at the vaccination rate $v(t)$ whereby the vaccination will not protect them from getting infected. The age-structured agent-based epidemiological model as described above can be incorporated into the following system of differential equations:

$$\frac{dS_i}{dt} = -v(t)S_i - \lambda_i S_i \quad (1)$$

$$\frac{dV_i}{dt} = \varepsilon_i v(t)S_i - \eta V_i - \lambda_i V_i \quad (2)$$

$$\frac{dU_i}{dt} = (1-\varepsilon_i)v(t)S_i - \lambda_i U_i \quad (3)$$

$$\frac{dP_i}{dt} = \eta V_i \quad (4)$$

$$\frac{dE_i}{dt} = \lambda_i(S_i + V_i + U_i) - kE_i \quad (5)$$

$$\frac{dI_i}{dt} = kE_i - (\alpha_i + \gamma_1)I_i \quad (6)$$

$$\frac{dH_i}{dt} = \alpha_i I_i - (\gamma_2 + \delta_i)H_i \quad (7)$$

$$\frac{dR_i}{dt} = \gamma_1 I_i + \gamma_2 H_i \quad (8)$$

$$\frac{dD_i}{dt} = \delta_i H_i \quad (9)$$

$$for\ i = 1, \ldots 6.$$

III. Model Calibration

Population and epidemiological parameters used in model calibration are listed in Table 1. Population details for the model were sourced from the U.S. 2010 census. Age-specific contact rates among individuals in the virtual population were sourced from a study of contact patterns in eight European countries. Age-specific hospitalization and case fatality rates for hospitalized cases were based on a Bayesian analysis study of Pandemic H1N1 Influenza in the United States [6]. Vaccinated individuals are assumed to develop protection after 10 days of vaccination. Vaccine efficacy is assumed to be 77.5% for individuals under 65 years old and 35% for individuals over 65 years old, based on various influenza vaccine immunogenicity studies. Rate of progression from exposed to infectious compartments are taken to be 1/1.9, based on influenza antiviral studies. Recovery rates for infectious and hospitalized individuals were parameterized based on studies conducted on pandemic influenza [7-10].

A. Basic Reproduction Number Calibration

The probability of transmission given contact was tuned to result in a basic reproduction number (R_0) calculated using standard methods based on various epidemiological analyses of the pandemic spread of influenza A (H1N1) in literature [11]. R_0 can be obtained with the next-generation operator method, i.e.$R_0 = r(FW^{-1})$ for R_0 to be expressed as the spectral radius of the next generation matrix FW^{-1}.

B. Calibration of q (Probability of Transmission per Contact)

Statistics of the 2009 H1N1 pandemic outbreak released by the CDC were used for the calibration of q, the probability of transmission of influenza through every contact with infectious individuals. This data includes the estimated hospitalizations and deaths due to H1N1 infection. These corresponded to epidemiological data for the period up to October 17, 2009, and so were taken to be representative of the impact of other interventions on H1N1, before the vaccination programs were initiated. Using these reported data, the value for q was calibrated such that for the period before vaccination was initiated (the first 182 days between the first identified case on April 13, 2009, and the first account of vaccine distribution on October 14, 2009), the H1N1 deaths predicted by the model was comparable to that of the deaths reported by CDC, while the H1N1 hospitalizations predicted were within the bounds of the confidence interval. The resultant R_0 value evaluated from this calibration was 1.4.

C. Vaccine Availability

Vaccination programs only start some weeks into the outbreaks due to constraints such as time needed to develop, produce and/or import vaccines, and also, time needed to observe the progress of the outbreak for a decision to be made on whether a vaccination program is necessary. In this work, it is assumed that the vaccines were available in 60 days. The supply of vaccines was assumed to match records of H1N1 vaccine shipment in the U.S. released by the U.S. Centers for Disease Control and Prevention's (CDC) for the entire period of October 14, 2009 to January 27, 2010. Thereafter, the CDC ceased releasing vaccine supply records, due to sufficiently ample supplies of H1N1 vaccine. Hence, following this period, a constant vaccine supply was assumed

TABLE I. Population and epidemiological parameters used in model calibration

Parameter	Value
Basic reproduction number, R_0	1.4 (calibrated based on the details given in next section)/1.6/1.8
Fraction of clinical cases that are hospitalized	$[0.0245; 0.0061; 0.03; 0.03; 0.0184; 0.0184]$
Probability of death following hospitalization (Case Fatality Proportion)	$\left[\frac{0.00026}{0.0245}; \frac{0.00010}{0.0061}; \frac{0.00159}{0.03}; \frac{0.00159}{0.03}; \frac{0.00090}{0.0184}; \frac{0.00090}{0.0184}\right]$
Rate at which individuals attain protection after vaccination (1/day)	1/10
Vaccine efficacy	[77.5%; 77.5%; 77.5%; 77.5%; 35%; 35%]
Rate of progression from exposed state to infectious state, or 1/length of latent period (1/day)	1/1.9
Recovery rate for infectious state (1/day)	1/3.5
Recovery rate for hospitalized state (1/day)	$[1/5; 1/5; 1/8; 1/8; 1/10; 1/10]$

IV. Results

A series of hypothetical simulations of a H1N1 pandemic outbreak among the US population were carried out, to evaluate the performance of adaptive vaccination schemes proposed in the literature. A baseline scenario, in which no vaccination was applied over the entire course of the pandemic, was additionally run as a control. A series of hypothetical simulations were carried out, to evaluate the performance of adaptive vaccination schemes proposed in the literature. The details of the adaptive vaccination schemes used for comparison purposes are as follows:

- The first, labelled 'AdaptHi', updated the age-specific vaccination ratios to match the last-reported age-specific ratios of individuals currently hospitalized due to H1N1 flu infection.
- The second, labelled 'AdaptHc', updated the age-specific vaccination ratios to match the last-reported cumulative age-specific ratios of individuals that have been hospitalized due to H1N1 flu infection over the course of the pandemic thus far.
- The last, labelled 'AdaptDc', updated the age-specific vaccination ratios to match the last-reported cumulative age-specific ratios of death cases for individuals who have succumbed to H1N1 flu infection over the course of the pandemic thus far.

Each set was replicated 100 times so as to average out the stochastic effects of uncertainty in parameter estimates. Stochasticity was included for the two key parameters, in the form of a triangular random distribution, for the fraction of clinical cases that are hospitalized (pH) and probability of death following hospitalization (CFP, Case Fatality Proportion). The 10 different set of values were sampled from the confidence interval of the parameters reported in the literature. The performance of these three strategies when used to deal with an outbreak with R_0 value of 1.6 and with vaccination applied from the 60^{th} day of the outbreak onwards, averaged over 100 stochastic runs each, are outlined in Figure 2. Error bars indicate ranges of values. The horizontal dotted line indicates the baseline scenario when no vaccination is applied at all. From Figure 2, it is clear that the three strategies result in numbers of deaths and hospitalizations that are statistically similar (within margins of error). However, if we look at mean values alone then it can be slightly discernible that the Adapt_Hc strategy performs the best, producing the least numbers of both deaths and hospitalizations, followed by Adapt_Dc, and lastly, Adapt_Hi. Adapt_Hi can easily be expected to perform the worst as it is memory-less and does not base its recommendations on useful information accumulated over the outbreak, instead relying on instantaneous information. Nevertheless, it still manages to perform at a level comparable with the other two strategies.

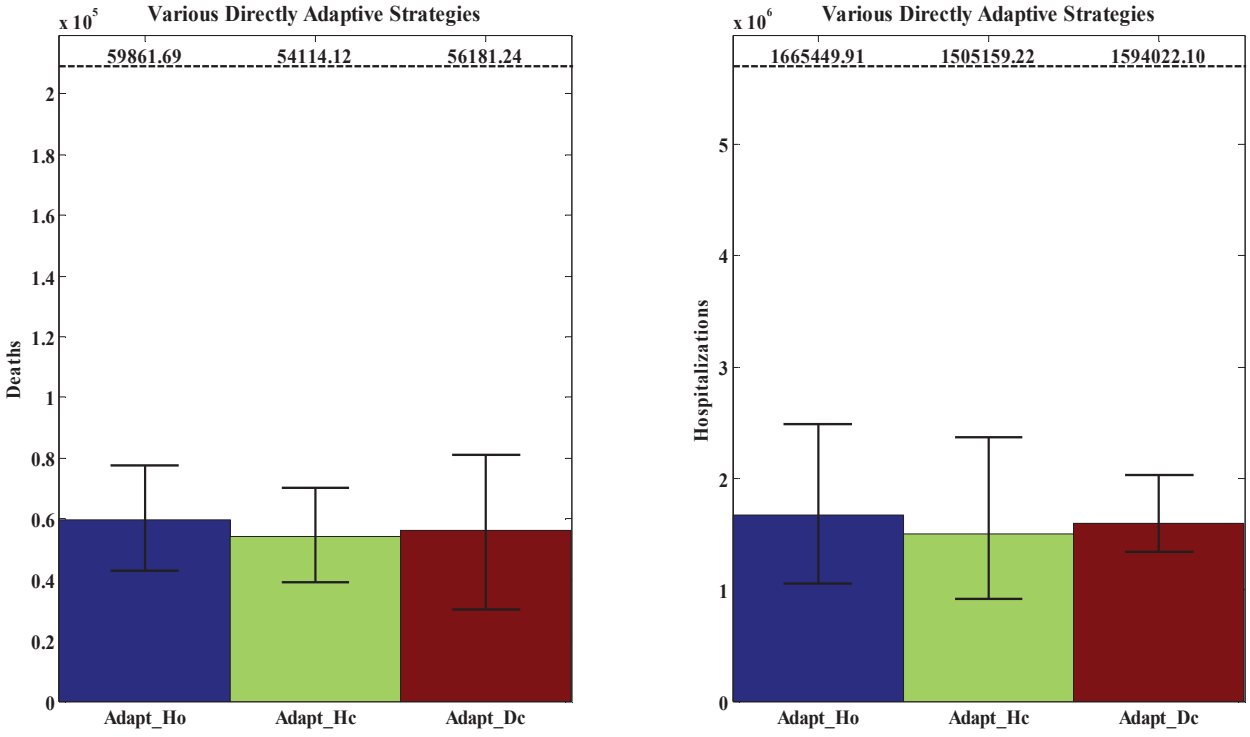

Fig 2: Comparison study among the three hypothetical adaptive strategies

V. Conclusion

This work presented an age-structured agent-based epidemiological model calibrated for H1N1 2009 pandemic. The effectiveness of various adaptive strategies proposed in the literature was studied using the developed model. Between Adapt_Hc and Adapt_Dc, Adapt_Hc seems to be slightly superior in performance. This may be because from the state chart, the trend for deaths can be consistently forecasted in advance by tracking hospitalization trends. An optimization strategy that accounts for hospitalizations will hence be more effective in preventing individuals from entering the hospitalization states, thereby lowering the number of individuals entering the strongly correlated death state as well. Overall, the three strategies produced comparable performances – all of them managed to avert at least two-thirds of the deaths and hospitalizations that would have occurred were no vaccinations applied, and hence can be considered as reasonably successful. However, these schemes utilize feedback control, wherein the adaptive strategies try to match vaccine allocation to hospitalization or death trends that have already occurred. However, the vaccine allocation can be substantially improved by using predictive control, forecasting the future epidemiological trends and optimizing vaccine allocation in preparation for future vaccine requirements accordingly.

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