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A STOCHASTIC EQUATION-BASED MODEL OF THE VALUE OF INTERNATIONAL AIR-TRAVEL RESTRICTIONS FOR CONTROLLING PANDEMIC FLU

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ABSTRACT

International air travel can be an important contributing factor to the global spread of infectious diseases, as evidenced by the outbreak of Severe Acute Respiratory Syndrome in 2003. Restrictions on air travel may therefore be one response to attempt to control a widespread epidemic of a disease such as influenza. We present results from a stochastic, equation-based, global epidemic model which suggest that air travel restrictions often provide only a slight delay in the epidemic. This delay may give valuable time in which to implement other disease control strategies; however, if other strategies are not implemented, the use of travel restrictions alone may lead to a more severe epidemic than if they had not been imposed. Our results also indicate that the particular network of cities chosen for modeling can have a great influence on the model results.

1 INTRODUCTION

The outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 highlighted the role that international air travel can play in the rapid spread of contagious diseases throughout the world. No country is isolated from the threat of a pandemic or a large regional epidemic. A global model of the spread of a disease can therefore provide an important complementary view to those given by more focused country-, region-, or city-specific models. Such a global epidemic model could allow estimation of the time available to prepare for a local or regional outbreak of a disease given an outbreak in another part of the world, and of the likely effects of potential intervention and disease containment strategies.

Early global influenza epidemic models were based on deterministic systems of coupled, city-level compartmental models (Baroyan, Mironov, and Rvachev 1981; Rvachev and Longini 1985). More recent models have updated population and travel data, used larger networks of cities, added seasonality, interventions, or stochasticity, or focused on other diseases (Grais, Ellis, and Glass 2003; Grais et al. 2004; Cooper et al. 2006; Colizza et al. 2006a; Colizza et al. 2006b; Colizza et al. 2007; Hufnagel, Brockmann, and Geisel 2004; Epstein et al. 2007). Equation-based models often assume homogeneous mixing within the population and mass-action kinetics, and thus provide a mean-field view of the dynamics of the system. In contrast, agent-based models, which track individuals rather than groups, have been developed to capture finer levels of behavioral detail and their effects on the macro-level behavior of the model (Ferguson et al. 2005, Ferguson et al. 2006, Longini et al. 2005, Germann et al. 2006, Eubank et al. 2004). However, the increased complexity and level of detail of agent-based models means that they are often much slower and more computationally expensive than equation-based models. The choice of using an equation-based model or an agent-based model for a given system often depends on this trade-off between the desired level of detail and the computational resources available.

In this paper, we present a stochastic, equation-based model for the spread of pandemic influenza, and some results regarding the potential effectiveness of air travel restrictions as a disease control strategy. In Section 2, we give a brief overview of the details of the model. Results are presented in Section 3, and conclusions and possible future work are described in Section 4.

2 MODEL DETAILS

We created a stochastic, equation-based model utilizing a global network of cities connected by air travel. Travel and population data are from several publicly available sources (Brinkhoff 2005; ESRI 2005; Helders 2005; IBGE 2006; Mongabay.com 2004; Population Division of the Department of Economic and Social Affairs of the United

Nations Secretariat, World Population Prospects 2004; Population Division, U.S. Census Bureau 2004; Guimerà et al. 2005). Natural history parameters for the H5N1 influenza virus align with those published previously (Ferguson et al. 2005, Ferguson et al. 2006, Longini et al. 2005, Germann et al. 2006).

Within each city is a homogeneously mixed, SEIR-type epidemiological model, with the city's population divided among four possible disease states: Susceptible (S), Exposed (E), Infectious (I), and Recovered (R). Members of the Susceptible group are those who have not yet been infected, but who are susceptible to infection given contact with a member of the Infectious group. Those in the Exposed group have been infected but the disease is in a latent disease state, in which they show no symptoms and are not yet able to infect others. Those in the Infectious group are symptomatic and able to infect others. Recovered persons are no longer infectious, and have acquired immunity to further infection.

Members of the Susceptible, Exposed, and Recovered groups can travel between cities. Members of the Infectious group are assumed not to travel. Thus, the disease is spread within cities by contact between Susceptible and Infectious persons, while an outbreak in a previously uninfected city is caused by Exposed travelers who become Infectious while in that city.

Stochasticity in the model allows for characterization of variability of the possible outcomes for a given scenario, rather than describing only the mean behavior of the system. There are two sources of stochasticity in this model: the daily number of infectious contacts between Susceptible and Infectious persons, and the daily numbers of travelers between cities.

The number of newly Exposed persons within a city on a particular day is the expected daily number of infectious contacts between susceptible and infectious members of that city's population. In the deterministic case, within city i at the start of day $t+1$, this number is given by

$$E_i(0, t+1) = \lambda_i(t)\frac{S_i(t)}{T_i(t)} I_i(t), \qquad (1)$$

where λ_i is the infectious contact rate and T_i is the total population of city i.

We incorporate disease seasonality and geographic effects into the model by allowing the infectious contact rate to vary both with time and location. Thus $\lambda_i(t) = \lambda(t, latitude_i)$. Assuming that random contacts between pairs of individuals are independent events and that the total number of contacts that occurs in the time interval from t to $t+\Delta t$ does not depend on either the previous number of contacts or on t, we can make equation (1) stochastic by instead choosing the value of $E_i(0, t+1)$ from a Poisson distribution with its mean value equal to $\lambda_i(t)S_i(t)I_i(t)/T_i(t)$.

The deterministic number of Susceptible travelers from city i to city j on day t is given by $S_i(t)\cdot pT_{ij}$, where pT_{ij} is the probability of traveling from city i to city j. With n cities in the model, the net number of travelers into and out of city i is then given by

$$\Omega[S_i(t)] = \sum_{j=1}^{n}\left[S_j(t)\cdot pT_{ji}(t) - S_i(t)\cdot pT_{ij}(t)\right].$$

Because a traveler from one city could travel to any one of multiple destinations, the stochastic number of daily travelers to each destination is drawn from a multinomial distribution. The numbers of Exposed or Recovered travelers are calculated similarly.

To prevent small fractions of Exposed travelers from prematurely initiating outbreaks in previously uninfected cities, if the net number of Exposed travelers to a city is below a threshold value, it is set equal to zero.

Scenarios involving the imposition of travel restrictions are implemented by reducing the probability of all travel into or out of a given city by a pre-set percentage when the cumulative disease incidence in that city or in another city to which it is directly connected reaches a threshold value. Travel restrictions are thus implemented on a city-by-city basis as the epidemic approaches, rather than being implemented simultaneously worldwide. Once restrictions are implemented in a given city, they remain in effect for the duration of the model run. For the results presented this paper, the threshold value for imposing restrictions was set to 1000 cases, and the travel reduction level was set to 95%.

3 MODEL RESULTS

For this paper, we ran several model scenarios varying three factors: epidemic origination date (January 1 vs. July 1), imposition of travel restrictions (no restriction vs. 95% travel restriction), and city network (largest population vs. largest air travel). In each scenario, the origin of infection was Hong Kong, the number of cities in the network was 155, and the basic reproduction number of the virus, R_0, was 1.7. Each scenario was run 50 times. Results reported here are mean results unless stated otherwise.

The maps in Figures 1 and 2 clearly show the difference in the population-based and the travel-volume-based networks. The network based on largest population sizes is much more geographically diverse, providing significantly more coverage of Africa and South America. The network based on largest air travel volumes is significantly more concentrated in the United States and Western Europe.

Figure 1: Map of the network of 155 cities by largest city population that was used in the model.

Figure 2: Map of the network of 155 cities by largest air travel volume that was used in the model.

Figures 3 and 4 present the mean epidemic curves for Los Angeles, using the largest-population based network, to demonstrate that imposing travel restrictions can have a significant effect at the local level on the time course of an epidemic, and that those effects can be either positive or negative, based on the timing of the initial outbreak. For an outbreak starting in Hong Kong in January, if there are no interventions, the incidence peaks in Los Angeles in May, past the usual flu season. With travel restrictions imposed, the peak is pushed to mid-June and its size is greatly reduced.

For an outbreak originating in Hong Kong in July, however, the epidemic peaks in Los Angeles in late November, and is much more severe. In this case, travel restrictions delay the peak to late December, at the height of the flu season, and thus make the local epidemic worse than if the restrictions had not been imposed. From Figure 4, it can be seen that the final cumulative number of cases in Los Angeles is not significantly changed by the imposition of travel restrictions, in the case of an initial outbreak in either January or July.

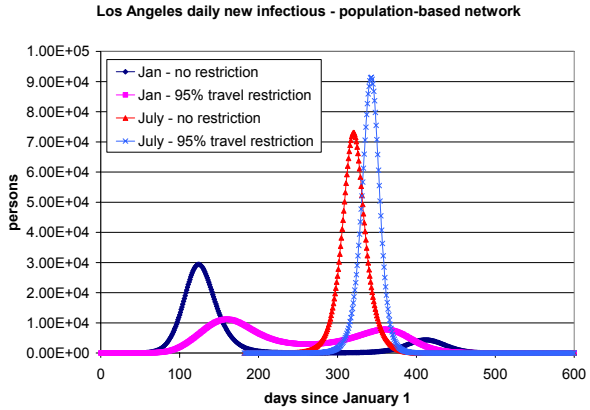

Figure 3: Epidemic curves for Los Angeles, using the largest-population based network. Daily number of newly Infectious persons. The dark blue and pink lines represent an epidemic originating in Hong Kong on January 1, with and without 95% travel restrictions, respectively. The red and light blue lines represent an epidemic originating in Hong Kong on July 1, with and without 95% travel restrictions, respectively.

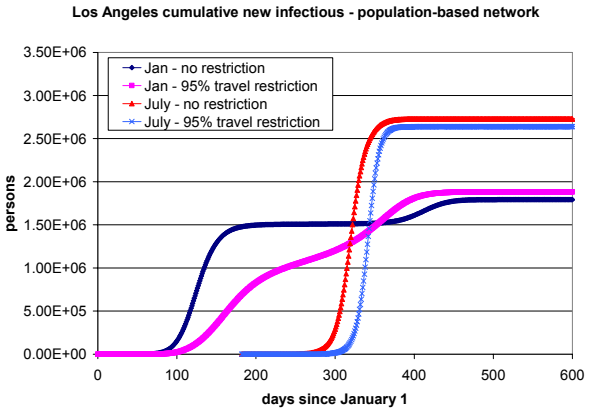

Figure 4: Epidemic curves for Los Angeles, using the largest-population based network. Cumulative number of newly Infectious persons. The dark blue and pink lines represent an epidemic originating in Hong Kong on January 1, with and without 95% travel restrictions, respectively. The red and light blue lines represent an epidemic originating in Hong Kong on July 1, with and without 95% travel restrictions, respectively.

Figures 5 and 6 show very different results for Los Angeles when the epidemic is modeled on the network based on largest air travel volumes. For both January and July outbreaks in Hong Kong, the peak incidence in Los Angeles is earlier than in the case of the population-based network, and the delays induced by the travel restrictions are much shorter – a few days, rather than approximately a month. However, the epidemic duration in Los Angeles is

also shortened in the case of travel restrictions, with the net effect that there is a significant reduction in the cumulative number of cases.

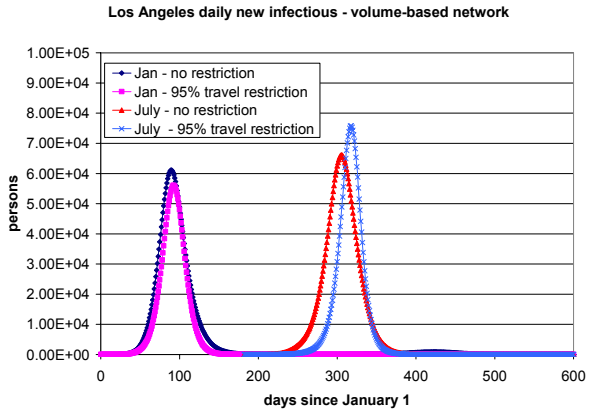

Figure 5: Epidemic curves for Los Angeles, using the largest-travel-volume based network. Daily number of newly Infectious persons. The dark blue and pink lines represent an epidemic originating in Hong Kong on January 1, with and without 95% travel restrictions, respectively. The red and light blue lines represent an epidemic originating in Hong Kong on July 1, with and without 95% travel restrictions, respectively.

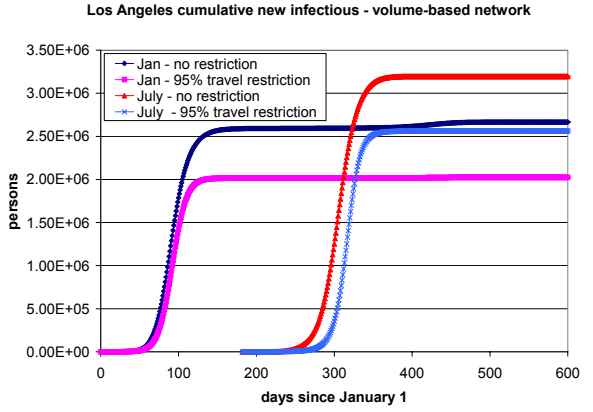

Figure 6: Epidemic curves for Los Angeles, using the largest-travel-volume based network. Cumulative number of newly Infectious persons. The dark blue and pink lines represent an epidemic originating in Hong Kong on January 1, with and without 95% travel restrictions, respectively. The red and light blue lines represent an epidemic originating in Hong Kong on July 1, with and without 95% travel restrictions, respectively.

4 CONCLUSIONS

We have presented a model of the potential effects of using international air travel restrictions as a method to control an epidemic of a contagious disease such as H5N1 influenza. Our results indicate that such restrictions can delay the spread of the disease, but that delays may be short. If no other control measures than travel restrictions are implemented, then local epidemics may be either more or less severe, as they are delayed either into or out of the local peak epidemic season. The choice of the underlying network of cities to be modeled is also extremely important. The time course and the cumulative severity of the epidemics were significantly different for our population-based and travel-based networks. Combining a number of such criteria as well as criteria based on network characteristics such as degree or betweenness, may be most appropriate.

This model does not currently include rural populations, ground transportation, or detailed heterogeneity within the cities. Each of these may have a large impact on model results, and are the subjects of continuing work.

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REFERENCES

Baroyan, O. V., G. A. Mironov, and L. A. Rvachev. 1981. An algorithm modeling global epidemics of mutant origin. *Programming and Computer Software* 6(5):272–277. English translation from *Programmirovanie* 5:73–79. 1980 (in Russian).

Brinkhoff, T. 2005. Mato Grosso City Population. Available via <http://www.citypopulation.de/Brazil-MatoGrosso.html>

Colizza, V., A. Barrat, M. Barthélemy, and A. Vespignani. 2006a. The role of the airline transportation network in the prediction and predictability of global epidemics. *Proceedings of the National Academy of Sciences of the U. S. A.* 103(7):2015–2020.

Colizza, V., A. Barrat, M. Barthélemy, and A. Vespignani. 2006b. The modeling of global epidemics: Stochastic dynamics and predictability. *Bulletin of Mathematical Biology* 68:1893–1921.

Colizza, V., A. Barrat, M. Barthelemy, A. J. Valleron, and A. Vespignani. 2007. Modeling the worldwide spread of pandemic influenza: Baseline case and containment interventions. *PLoS Medicine* 4(1):e13.

Cooper, B. S., R. J. Pitman, W. J. Edmunds, and N. J. Gay. 2006. Delaying the international spread of pandemic influenza. *PLoS Medicine* 3(6):e212.

Epstein, J. M., D. M. Goedecke, F. Yu, R. J. Morris, D. K. Wagener, and G. V. Bobashev. 2007. Controlling Pandemic Flu: The Value of International Air Travel Restrictions. *PLoS ONE* 2(5):e401.

ESRI. 2005. ArcGIS 9 World, Europe, Canada, and Mexico: 1996, 1998, Winter 1993/1994. [Computer software and data files 20000101, 2000, 20000225, 20010128, 20000612, 20020314, 20021115, 2000, 2003]. Redlands, CA: ESRI.

Eubank, S., H. Guclu, V. S. A. Kumar, M. V. Marathe, A. Srinivasan, Z. Toroczkai, and N. Wang. 2004. Modeling disease outbreaks in realistic urban social networks. *Nature* 429:180–184.

Ferguson, N. M., D. A. T. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn, and D. S. Burke. 2005. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 437:209–214.

Ferguson, N. M., D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley, and D. S. Burke. 2006. Strategies for mitigating an influenza pandemic. *Nature* 442:448–452.

Germann, T. C., K. Kadau, I. M. Longini Jr, C. A. Macken. 2006. Mitigation strategies for pandemic influenza in the United States. *Proceedings of the National Academy of Sciences of the U. S. A.* 103(15):5935–5940.

Grais, R. F., J. H. Ellis, and G. E. Glass. 2003. Assessing the impact of airline travel on the geographic spread of pandemic influenza. *European Journal of Epidemiology*. 18:1065–1072.

Grais, R. F., J. H. Ellis, A. Kress, and G. E. Glass. 2004. Modeling the spread of annual influenza epidemics in the U.S.: The potential role of air travel. *Health Care Management Science* 7:127–134.

Guimerà, R., S. Mossa, A. Turtschi, L. A. N. Amaral. 2005. The worldwide air transportation network: Anomalous centrality, community structure, and cities' global roles. *Proceedings of the National Academy of Sciences of the U. S. A.* 102(22):7794–7799.

Helders, S. 2005. World Gazetteer. Available via <http://www.world-gazetteer.com> [accessed April 20, 2006].

Hufnagel, L., D. Brockmann, and T. Geisel. 2004. Forecast and control of epidemics in a globalized world. *Proceedings of the National Academy of Sciences of the U. S. A.* 101(42):15124–15129.

Instituto Brasileiro de Geografia e Estatística (IBGE). 2006. Available via <http://www.ibge.gov.br> [accessed April 20, 2006].

Longini, Jr., I. M., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. T. Cummings, and M. E. Halloran. 2005. Containing pandemic influenza at the source. *Science* 309:1083–1087.

Mongabay.com. 2004. World Population Figures. Available via <http://population.mongabay.com> [accessed April 24, 2006].

Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, World Population Prospects. 2004. World Urbanization Prospects: The 2003 Revision Population Database. Available via <http://esa.un.org/unup> [accessed April, 2006].

Population Division, U.S. Census Bureau. 2004. Table 1. Annual Estimates of the Population of Metropolitan and Micropolitan Statistical Areas: April 1, 2000 to July 1, 2004 (CBSA-EST2004-01). Available via <http://www.census.gov/population/www/estimates/Estimates%20pages_final.html> [accessed April, 2006].

Rvachev, L. A., I. M. Longini, Jr. 1985. A mathematical model for the global spread of influenza. *Mathematical Biosciences* 75:3–22.

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