Modeling Preventive Measures During an Influenza Pandemic in Italy: A Real Time Simulation Strategy

Stefano Merler[1], Caterina Rizzo[2,3], Marco Ajelli[1,4], Marco Massari[2], Gianpaolo Scalia Tomba[5], Cesare Furlanello[1], Marta Luisa Ciofi degli Atti[2]

[1]Bruno Kessler Foundation (IRST), Trento, Italy; [2]National Center for Epidemiology Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome, Italy; [3]Department of Pharmaco-Biology, University of Bari, Italy; [4]Department of Information Technology, University of Trento, Italy; [5]Department of Mathematics, University of 'Tor Vergata', Rome, Italy

We developed a stochastic individual-based discrete-time model to assess the impact of pandemic influenza containing strategies. The spread of influenza was then modeled with specific levels for households, schools/workplaces, and random contacts. We considered different R_0 values (1.4, 1.7, 2), evaluating the impact of combined preventive measures (vaccination, antiviral prophylaxis (AVP), border restrictions and increased social distancing). For each measure, various scenarios were considered, assuming different target populations, timing and duration of interventions. The model took about 10 minutes to run on a standard computer (Pentium D 3.20GHz, 4 GB RAM). With R_0 values 1.4-1.7, the use of combined measures would reduce attack rates (AR) from 34-56% using XX to 4-10% using YY. Assuming R_0= 2, AR can be reduced from 69% to 20% only if vaccination starts 4 months after isolation of the pandemic strain, in combination with a 99% reduction in airport traffic, closure of schools/workplaces for 4 weeks and AVP of close contacts of clinical cases. The results show that this individual-based model is a convenient tool allowing simulation of influenza spread, and estimation of the impact of various control measures.

Introduction

Different mathematical models have been recently implemented to examine the feasibility of pandemic containment using different strategies [1-7]. In particular, individual-based models can provide reliable estimates about the worldwide spread of influenza [1, 2]. These models have shown that the worldwide spread of influenza would occur over a period of 2 to 6 months, depending on the basic reproductive number (R_0), and that, to reduce transmission, it would be necessary to implement multiple control measures [2-4,6,8]. In this study, we evaluate the diffusion of pandemic influenza in Italy and the impact of various control measures (antiviral prophylaxis, social distancing measures, including travel restrictions, and vaccination, both pandemic and pre-pandemic vaccine), assuming different R_0 values. In order to reduce the computational time, we modeled the random spread of infection, using national commuting data. Since it has been shown that seasonal influenza vaccine effectiveness is higher in adults than in elderly and children [9-11], we also assumed that both pandemic and pre-pandemic vaccine effectiveness varies by age.

Methods

The worldwide spread of pandemic influenza and the consequent importation of cases in Italy were modelled using a global deterministic SEIR model [7]. We assume that infectious individuals are all symptomatic and no longer travelling and that exposed individuals are asymptomatic and possibly travelling before the infectious phase. To estimate the number of imported cases we couple the results of the global SEIR model with 2003 data on arrivals and departures in Italy's 38 international airports [13]. The national impact of pandemic influenza and of various control measures were predicted using a stochastic individual-based model (IBM) [1]. All parameters implemented in the model were based on published studies [1, 2, 6, 8]. We considered different transmission rates to obtain R_0 values of 1.4, 1.7, and 2, which in the IBM corresponded to cumulative infected attack rates (AR) of 34.0, 55.6, and 68.7%, respectively, indicating a mild, moderate and severe scenario [12]. Data for the Italian population was obtained from the 2001 Census, which includes information on age structure, household size, household composition (e.g., singles or couples with or without children), school attendance, employment categories, municipality of residence, and data on the population that commutes daily within national borders [14]. Based on previous studies showing that work commutes are a good predictor of the spread of influenza [1, 2,15], we used data on commuting, available from 2001 Census data [14]. Schools and workplaces were generated using previously reported methods [1]. Infection can be transmitted within households, schools/workplaces, and among random contacts. While we assumed homogeneous mixing in households, schools and workplaces, random contacts depend on each individual's specific social network. We modeled random contacts on the basis of commuting data [14]. The R_0 of the simulated epidemics were estimated according to a previously published model [16]. *Control measures: Social distancing.* We considered the nationwide closing of all schools and some public offices not providing essential services. We assumed that school and office closings begin after the onset of the first 20 symptomatic cases in Italy and that this measure be maintained for 4 weeks. We considered travel restrictions that would reduce incoming international flights by 90% or 99% for two months after the first national case. *Antiviral prophylaxis.* AVP for uninfected individuals (household contacts and contacts in school or workplace) was assumed to reduce susceptibility to infection by 30% and infectiousness by 70% [3]. We assumed that AVP be provided to 90% of close contacts of clinical cases (50% of all infected individuals). We did not consider the therapeutic use of antiviral, since it has been demonstrated that it does not affect virus transmission [18]. *Vaccination.* Vaccine effectiveness (VE) was assumed to be 70%. It was also assumed that VE varies by age: i) 59% in 2-18 year-old individuals [10]; ii) 70% 40-64 year-old individuals [9]; and iii) 40% in ≥65 year-old individuals [11]. We assumed that an adequate supply of vaccine could be reached at 4, 5 and 6 months after the first world case. We assumed that we would administer two vaccine doses, one month apart. Vaccination coverage was fixed at 60% of the target population, basing on 2005-2006 National influenza coverage [17]. The target population was divided into 4 categories: i) personnel providing essential services (15% of the 25-60-year-old workers) [25]; ii) ≥65 year-old individuals; iii) 2-18 year-old individuals; and iv) 40-64 year-old individuals.

Results

Our model took about 10 minutes for a single run, allocating about 3GB of RAM memory on a Pentium D 3.2GHz workstation, allowing for real-time simulations using a standard computer. For different R_0 scenarios, the results of the global SEIR model showed that the number of imported cases would be 160,000, 226,000 and 315,000, with the first Italian case appearing, respectively, after 133, 85 and 50 days from the first world case. The epidemic peak would be reach after 259, 162 and 104 days, respectively, for the three different scenarios. The cumulative infected AR would be 34%, 55.6% and 68.7%, for the three scenarios. Border restriction, antiviral prophylaxis and social distancing measures are effective in delaying the epidemic's arrival and dampening the peak, allowing us to gain time for developing vaccines and implementing preparedness measures. However, none of these measures singly implemented is sufficient to contain a moderate to severe epidemic. Our results show that applying all containment measures to a mild to moderate epidemic, AR decreased from 34% to 4.4% and from 56% to 10%, respectively (Figure 1). In the severe scenario, only the immediate vaccine availability (4 months from the first world case), along with severe border restrictions (90% of airport traffic reduction for two months), social distancing measures (closure of schools and workplaces for 4 weeks), and antiviral prophylaxis of close contacts of the clinical cases can reduce the impact of the epidemics (with attack rates decreasing from 69% to 20%) (Figure 1). The assumed VE (i.e., 70% for all target categories or different VE for different target categories) would not substantially affect the cumulative infected AR. If vaccinating personnel providing essential services (15% of the 25-60-year-olds Italian workers), elderly persons, and 2-18 year-olds, the AR would also decrease among individuals 19-64 years of age. In particular, it would reduce by approximately two times the AR in unvaccinated 30-50-year-old adults. Excluding the elderly from vaccination would not affect the infected AR in the other age groups.

Discussion

The containment of an emergent pandemic strain of influenza is feasible, but it requires a combination of different interventions such as pre-pandemic vaccination, prophylactic use of antiviral drugs and social distancing measures. As other recent analysis show [1, 3], the outbreak could be mitigated through a combination of antiviral prophylaxis and reduction of social contacts. Vaccinating 2-18 year-olds would reduce by approximately two times the AR in unvaccinated adults, showing a clear herd immunity effect. These findings suggest that vaccinating children should be a higher priority than vaccinating elderly [20]. The role of restricting international travel remains controversial [2, 6, 7, 15, 23-24]. Our results show that assuming a R_0 <2, the role of such restrictions is limited, but has a role if the R_0 were 2. The results of this study show that this individual based model is a convenient tool allowing the simulation of influenza spread and estimation of the impact of control measures with little computational effort.

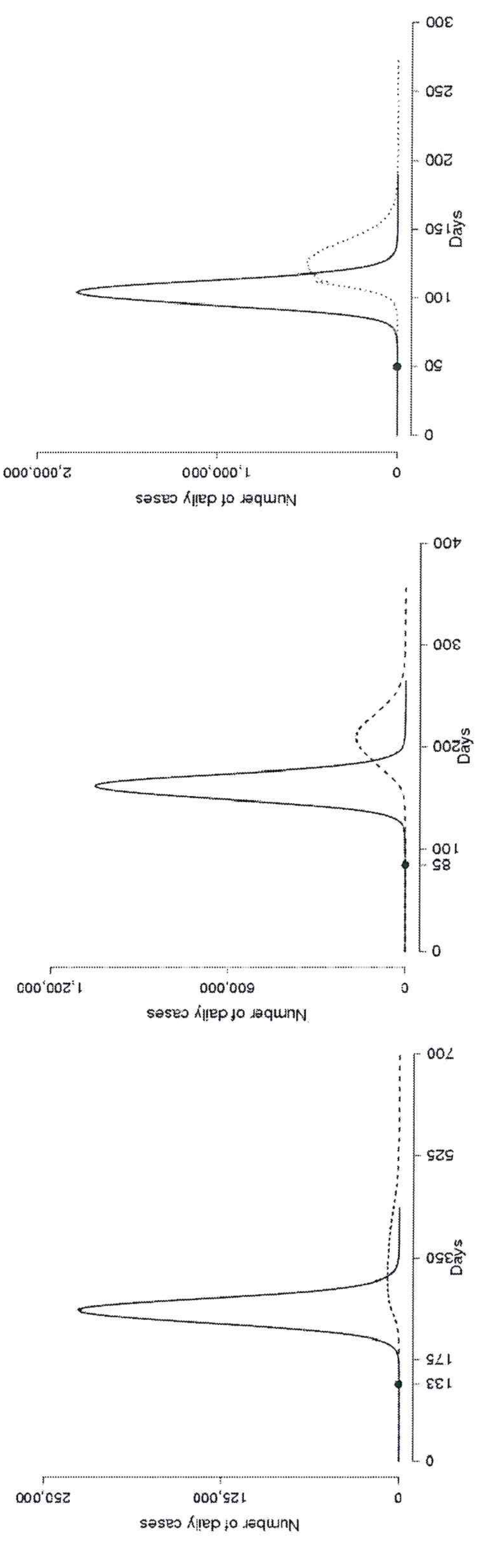

Figure 1. Number of daily cases in the absence of interventions (solid lines) and by applying all the control measures (dashed lines) for R_0=1.4 (left), R_0=1.7 (middle) and R_0=2 (right). Circles represent the day of the first Italian case.

References

1. Ferguson NM, Cummings DA, Cauchemez S, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature*. 2005 Sep 8;437(7056):209-214.
2. Ferguson NM, Cummings DA, Fraser C, et al. Strategies for mitigating an influenza pandemic. *Nature*. 2006 Jul 27;442(7101):448-452.
3. Longini IM, Jr., Nizam A, Xu S, et al. Containing pandemic influenza at the source. *Science*. 2005 Aug 12;309(5737):1083-1087.
4. Germann TC, Kadau K, Longini IM, et al. Mitigation strategies for pandemic influenza in the United States. *Proc Natl Acad Sci USA*. 2006 Apr 11;103(15):5935-5940.
5. Carrat F, Luong J, Lao H, et al. A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics. *BMC Med*. 2006;4:26.
6. Colizza V, Barrat A, Barthelemy M, et al. Modeling the Worldwide Spread of Pandemic Influenza: Baseline Case and Containment Interventions. *PLoS Med*. 2007 Jan 23;4(1):e13.
7. Cooper BS, Pitman RJ, Edmunds WJ, et al. Delaying the international spread of pandemic influenza. *PLoS Med*. 2006 June;3(6):e212.
8. Flahault A, Vergu E, Coudeville L, et al. Strategies for containing a global influenza pandemic. *Vaccine*. 2006 June 12.
9. Demicheli V, Rivetti D, Deeks JJ, et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev*. 2004;(3):CD001269.
10. Jefferson T, Smith S, Demicheli V, et al. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. *Lancet*. 2005 Feb 26;365(9461):773-780.
11. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*. 2006 Feb 20;24(8):1159-1169.
12. Glezen WP. Emerging infections: pandemic influenza. *Epidemiol Rev*. 1996;18(1):64-76.
13. Istituto Nazionale di statistica. Statistiche del trasporto aereo - Anno 2003. ISTAT 2006. Available at: http://www.istat.it/dati/catalogo/20060509_01/inf0606statistiche_trasporto_aereo03.pdf
14. Istituto Nazionale di statistica. 14° Censimento Generale della Popolazione e delle Abitazioni. ISTAT 2001. Available at: http://dawinci.istat.it/daWinci/jsp/MD/dawinciMD.jsp
15. Viboud C, Bjornstad ON, Smith DL, et al. Synchrony, waves, and spatial hierarchies in the spread of influenza. *Science*. 2006 Apr 21;312(5772):447-451.
16. Chowell G, Hengartner NW, Castillo-Chavez C, et al. The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda. *J Theor Biol*. 2004 Jul 7;229(1):119-126.
17. Ministero della Salute. Influenza Vaccination Coverage. http://www ministerosalute it/promozione/malattie/malattie jsp 2005.
18. Monto AS. Vaccines and antiviral drugs in pandemic preparedness. *Emerg Infect Dis*. 2006 Jan;12(1):55-60.
19. Eurostat. Total fertility rate. Eurostat 2007. Available at: http://epp.eurostat.ec.europa.eu/portal/page?_pageid=1996,39140985&_dad=portal&_schema=PORTAL&screen=detailref&language=en&product=Yearlies_new_population&root=Yearlies_new_population/C/C1/C12/cab12048
20. Glezen WP, Simonsen L. Commentary: Benefits of influenza vaccine in US elderly--new studies raise questions. *Int J Epidemiol*. 2006 Apr;35(2):352-353.
21. Unicef: international demographic. 2007. http://www unicef org/infobycountry/industrialized html.
22. Lee J, Wang F. Malthusian models and Chinese realities: the Chinese demographic system 1700-2000. *Population and Development Review*. 1999;25(1):33-65.
23. Brownstein JS, Wolfe CJ, Mandl KD. Empirical evidence for the effect of airline travel on inter-regional influenza spread in the United States. *PLoS Med*. 2006 Sept 12;3(10).
24. Epstein JM, Goedecke DM, Yu F, et al. Controlling pandemic flu: the value of international air travel restrictions. *PLoS ONE*. 2007;2:e401.