Scenarios of diffusion and control of an influenza pandemic in Italy

C. Rizzo[1,2], A. Lunelli[3], A. Pugliese[3], A. Bella[1], P. Manfredi[4], Gianpaolo Scalia Tomba[5], M. Iannelli[3], M.L. Ciofi degli Atti[1] on behalf of the EPICO working group

[1]National Centre for Epidemiology Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome, Italy; [2]Department of Pharmaco-Biology, University of Bari, Italy; [3]Department of Mathematics, University of Trento, Italy; [4]Department of Statistic and Economical applied Mathematics, University of Pisa, Italy; [5] Department of Mathematics, University of 'Tor Vergata', Roma, Italy.

Corresponding Author:

Caterina Rizzo

National Centre for Epidemiology, Surveillance and Health Promotion

Istituto Superiore di Sanità

Viale Regina Elena, 299

Rome, Italy

Tel: +39 06 4990 4277, Fax: +39 06 44232444,

e-mail: caterina.rizzo@iss.it

Running head: Influenza pandemic diffusion and control

Author's contributions

CR, and MLCdA designed the study and contributed equally to interpreting the results, drafting and editing the manuscript.
AL and AP designed and implemented the model and ran the simulations.
AB, PM, GST and MI contributed to interpreting the results, and to editing the manuscript.

Abstract

To predict the spread of a pandemic strain of influenza virus in Italy and the impact of control measures, we developed a SEIR deterministic model with a stochastic simulation component. We modelled the impact of control measures such as vaccination, antiviral prophylaxis and social distancing measures. In the absence of control measures, the epidemic peak would be reached approximately 4 months after the importation of the first cases in Italy, and the epidemic would last approximately 7 months. When combined, the control measures would reduce the cumulative attack rate to approximately 4.2%, at best, though this would require an extremely high number of treated individuals. In accordance with international findings, our results highlight the need to respond to a pandemic with a combination of control measures.

INTRODUCTION

Following the emergence in 1997 of a new strain of avian influenza, A(H5N1), which is capable of infecting humans (1), and the spread of this strain to Europe in 2005 (2), concerns were raised over the occurrence of a pandemic caused by A(H5N1) or a closely related strain (3;4). Consequently, countries have been urged to strengthen their preparedness for an influenza pandemic (5), an important aspect of which is predicting the spread of infection.

According to the predictive models used to date (6-12), influenza would spread worldwide over a period of 2 to 6 months, depending on the basic reproductive number (R_0), and reducing transmission would entail combining control measures, specifically, reducing contacts and performing both antiviral prophylaxis (AVP) and vaccination (7-9;11;13).

We developed an SEIR (susceptible – exposed, but not yet infectious - infectious – recovered, and no longer susceptible) deterministic model with a stochastic simulation component to predict the spread of pandemic influenza in Italy and to evaluate the impact of vaccination, AVP and social distancing measures.

METHODS

The SEIR model

We developed an SEIR model in which the population is structured according to age and region of residence. We defined six age classes: infants 0-2 years of age, children 3-14 years of age, teenagers 15-18 years of age, young adults 19-39 years of age, adults 40-64 years of age and elderly aged 65 and older. In the model, the national population (56,995,744 inhabitants) was also distributed in Italy's 20 regions, according to national demographic data obtained from the 2001 Census (14). The contact matrix was defined by considering, separately, household, school/work-place and random contacts, and by using data on household composition, school attendance, and employment status. The transportation matrix was defined using data on national airline traffic (15). The model consists of a system of differential equations, reported in the Appendix.

We also introduced a stochastic component that takes into account all of the random effects that are important during a pandemic's initial and final stages, when the number of infected individuals would be low. Precisely, whenever the deterministic prediction of the number of infected individuals in an age class/region was below the threshold value of 10, it was replaced by a Poisson variable with the same mean. In each simulation, the pandemic began with the introduction of 5 infected adults in the Lazio Region, where Rome's intercontinental airport is located.

Based on published studies (16) and using the method described by Diekmann et al. (17), we computed the R_0=1.8, which, when applying the contact matrix, corresponds to a cumulative infected attack rate (AR) of 35%.

Based on the literature (6;8;17), in the model we assumed an incubation period of 1 day and an infectious period of 3.9 days. The results were obtained by averaging over 200 simulations for each scenario. For all of the results, the 5-95% percentile values of the AR estimates were within 11%.

Control measures

We considered both single and combined control measures, most of which are included in the Italian National Plan for preparedness and response to an influenza pandemic (19). We assumed that two doses of vaccine would be administered, one month apart. The target population was divided into 4 categories: i) personnel providing essential services (15% of the 25-60-year-old working population) (14); ii) elderly persons (≥65 years); iii) children and adolescents aged 2-18 years; and iv) adults aged 40-64 years. We assumed vaccination coverage of 60% of the target population, based on the 2005-2006 national influenza coverage (20). We assumed that a period of two weeks would be necessary for administering the vaccine to each target category. For vaccine effectiveness (VE) we made two different assumptions: i) VE of 70% for all categories; and ii) VE of 50% for all categories; for both assumptions, we assumed that the VE would be reached beginning 15 days after the second dose.

We considered different scenarios of vaccine availability; in one scenario, adequate VE would be reached 4 months after the first national case; in the second scenario, it would be reached after 5

months. An adequate VE at 4 months would be feasible only if the first dose contained an avian virus precursor of the pandemic strain (3), followed by a dose of pandemic vaccine; the actual VE of this regimen was assumed to be equal to that of two doses of the pandemic vaccine.

The AVP for uninfected individuals was assumed to reduce susceptibility by 30% and infectiousness by 70% (8). We considered the administration of one course of antiviral drugs. We assumed that AVP would be provided to all household contacts of 80% of the clinical cases (66% of all infected individuals). We considered administering AVP for the entire epidemic period; however, since the feasibility of actually doing this would be limited, we also considered other scenarios, that is, administering AVP only for 2, 4, 8, or 16 weeks after the occurrence of the first Italian case. AVP was assumed to reduce the transmission rate among household contacts, based on the consideration that those household contacts already infected at the time of beginning AVP would have a reduced infectiousness, so that it would be as if only a fraction of them were actually infected; those not yet infected when beginning AVP would benefit from both lower susceptibility and lower infectiousness.

We considered the nationwide closing of all schools, public offices, and public gathering places (e.g., restaurants, cinemas, and churches). We simulated school closure for 3 weeks, public-office closure for 4 weeks, and public–gathering-place closure for 8 weeks. We assumed that these measures would be introduced simultaneously at different times (i.e., 2, 4 or 8 weeks after the start of the pandemic). In the model, school closure would reduce the contacts among children and teenagers (the school component of the transmission rate) by 75%; workplace closure would reduce the job component of the transmission rate by 16%; closure of public gathering places would reduce the random component of the transmission rate by 50%.

Sensitivity analysis

We evaluated how the results would change depending on different levels of pathogen transmissibility, with a resulting R_0 of 1.6, 1.8 or 2.0. We also considered the resulting AR for the

three R_0 values for the baseline scenario and for scenarios that differed in terms of the specific control measures adopted.

RESULTS

Baseline dynamics

In the absence of control measures, the epidemic peak would be reached approximately 4 months after the identification of the first case, with a total of 3 million cases during the peak week. The epidemic would be over in 7 months, with a cumulative infected AR of 35% (approximately 20 million cases). The dynamics of the epidemic were similar in all age-groups, whereas the cumulative infected AR varied markedly by age-group. The incidence would be particularly high among 15-18 year-olds, with a cumulative infected AR of 54% (Figure 1).

Because of the model's stochastic component, the introduction of few infectious individuals in the population did not always result in an outbreak; in fact, in around 40% of the simulations, the number of infected individuals in the early stages of the pandemic was insufficient for sustaining transmission, and the epidemic expired spontaneously.

Single control measures

The impact of single control measures is shown in Table 1. The introduction of control measures frequently increased the probability of stochastic extinction of the pandemic. Vaccination seems to be the most effective measure, especially when VE is reached at 4 months. Vaccinating three of the four target categories (i.e., personnel providing essential services; elderly persons; and 2-18 year-olds) would reduce the cumulative infected AR from 35% to 25%, with almost 5 million cases avoided by treating approximately 17 million individuals. Vaccinating also the fourth target category (i.e., 40-64-year-olds) would not result in an important additional reduction in the cumulative infected AR. If protective VE were reached at 5 months (2 doses of pandemic vaccine), vaccinating all four categories, the cumulative infected AR would be 32.5%. Assuming a VE of 50% for all categories would not greatly affect the cumulative infected AR; in fact, the cumulative

infected AR would be only 2 or 3 percentage points higher than the AR when assuming a 70% VE for all categories (Table 1).

Social distancing measures and AVP were not effective in reducing the cumulative infected AR. However, providing AVP for 16 weeks after the identification of the first Italian cases and implementing social distancing measures starting at week 4 or 8 would delay the epidemic peak by one or three weeks, respectively.

Combined control measures

The combination of control measures would be more effective than single measures (Table 2 and Table 3). The highest reduction (from 35% to 4.2%) would be obtained by starting social distancing measures at week 4, providing AVP for the entire epidemic, and performing vaccination with a VE of 70% at 4 months (when combining measures, we assumed that vaccination would be provided to all categories). This would allow for 17 million cases to be avoided by vaccinating around 26 million individuals and by providing AVP to approximately 3 million individuals. The cumulative infected AR would be higher (11%) if VE were reached at 5 months, avoiding 13 million cases by treating 25 million individuals and 7 million individuals with vaccine and AVP respectively (Table 2). Providing AVP for 16 weeks, instead of for the entire epidemic period, would increase the cumulative infected AR to 8.4% or 16.6% if VE were reached at 4 or 5 months, respectively. However, this would determine an important reduction in the number of treated individuals (approximately 150,000). Combining control measures would also increase the probability of stochastic extinction during the initial phases of the epidemic, due to a low number of infectious individuals. A VE of 50% for all categories considered would affect the cumulative infected AR estimates, but only when considering adequate VE at 4 months. In fact, the cumulative infected AR would be 6 to 8 percentage points higher than the AR assuming a VE of 70%, with a remarkable difference in terms of the number of avoided cases (Table 3). The impact of combined control measures (pre-pandemic vaccine in all categories and AVP and/or social distancing measures), compared to the baseline dynamics of the influenza pandemic, is shown in Figure 2.

Sensitivity analysis

The results of the sensitivity analysis are shown in Figure 3. For R_0=1.6, the epidemic could be mitigated with moderate efforts; all strategies would be successful independently of the timing of vaccination, of the duration of providing AVP, and of the timing of social distancing measures. For R_0=1.8, vaccinating the target categories with a pre-pandemic vaccine, providing AVP for 16 weeks, and implementing social distancing measures for 4 weeks would reduce the cumulative infected AR from 35% to10%. For R_0=2, this combination of control measures would result in a less marked decrease in the cumulative infected AR, from 42% to approximately 20%.

CONCLUSIONS

Our results, considering an R_0 value of 1.8, confirmed the need to combine different control measures (7-9). In fact, none of the single measures was shown to be effective in containing the pandemic, with the cumulative infected AR decreasing at most from 35% to 24%. Combining measures would be more effective, especially if using the pre-pandemic vaccine (reaching VE at 4 months). In this case, the cumulative infected AR would be 4.2%, but this would require an extremely high number of AVP doses. Providing AVP for 16 weeks only would increase cumulative infected AR to 8.4%, which is similar to what observed during severe seasonal epidemics (21), with a considerable reduction in the number of doses provided. Moreover, if the time to reach adequate VE were 5 months, assuming a different VE (i.e., 70% or 50% in all categories) would not substantially affect the cumulative infected AR. However, if the time to reach adequate VE were 4 months, a VE of 70% would result in an AR of 4.2%, compared to 11.0% if assuming a VE of 50% (i.e., a 50% difference in the AR). In any case, using a less effective vaccine (i.e., with a VE of 50%) would nonetheless allow the pandemic to be contained, with an AR below 18% (range 11.0-18.1%).

Combining different measures markedly increased the probability of stochastic extinction during the early phases of the pandemic. To the best of our knowledge, most of the SEIR models used to

simulate a pandemic do not consider the stochastic factors, which can strongly influence the dynamics of the pandemic in its early phases. However, we assumed that no other infectious individuals would enter the country after the few initial cases. If we were to assume that infectious individuals continued to enter the country, then stochastic extinction would be less important.

Another important finding is that the decrease in the cumulative infected AR would depend on which target groups were vaccinated. If a pandemic were to occur, vaccine supplies would be limited and the target groups would have to be prioritized (i.e., personnel of essential services, elderly persons and persons with chronic disease, children and young adults, and healthy adults) (19), requiring the vaccination of 26 million persons with two doses, that would be very difficult to put in practice if a pandemic will occur. However, as reported in other studies (9), our results showed that, independently of the VE, the vaccination of children and young adults would considerably reduce the incidence also in other age groups (i.e., resulting in "herd immunity"), probably because of the important role of children and adolescents in the spread of influenza, as also observed in inter-pandemic periods (22).

In interpreting our results, some limitations need to be considered. Firstly, we assumed that AVP provided to household contacts would decrease transmission within households but not in other contexts, which could have resulted in an underestimate of the effect of this measure. Secondly, the parameters used in our model obviously influenced the time estimated for the pandemic to evolve, though our estimate is similar to those obtained in other studies based on deterministic SEIR models on a global (13) or local (23) scale or individual-based models (6-9). We examined this issue by performing a sensitivity analysis; clearly, the success of control strategies would be strongly influenced by the R_0: for R_0=1.6, all strategies would be quite successful, whereas for R_0=2 only the combined strategy with a pre-pandemic vaccine would satisfactorily mitigate the pandemic. Although the absolute effect of control strategies is strongly influenced by the different values of R_0, the relative worth of strategies are independent from the different R_0 values.

Another important limitation is that mathematical models cannot take into account the fact that the past influenza pandemics in Europe and Italy occurred over two consecutive winters, with the highest AR in the second winter (24-26). This two-wave pattern is probably an effect of the closing of schools during the summer. Thus our model probably depicts a "worst case scenario", which could be useful in evaluating control measures (9).

Our simulations show that appropriate and prompt measures, when combined, could be effective in containing an influenza pandemic. Timing is also essential, and measures that at first glance appear to be less important, such as increasing social distancing, could be extremely useful in delaying the epidemic peak and thus providing more time for vaccines to be produced. Implementing such measures, however, would entail organizing a variety of both medical and non-medical resources, and some measures, such as the closing of schools, would also have a social impact.

Table 1. Effectiveness of single control measures on the dynamics of an influenza pandemic with an R_0 of 1.8 and an attack rate of 35%, for different values of vaccine effectiveness (VE)

Control Measures	Attack rate*	Avoided cases	Treated individuals
Adequate vaccine effectiveness at 5 months (VE=70%)			
Category I and II	33.0% (29.1-34.1)	974,151	12,076,619
Category I, II, III	32.6% (26.4-34.0)	1,203,363	17,006,817
Category I, II, III, IV	32.5% (25.9-34.0)	1,260,666	25,542,092
Adequate vaccine effectiveness at 4 months (VE=70%)			
Category I and II	28.9% (27.1-30.5)	3,323,574	12,076,619
Category I, II, III	25.3% (17.8-29.2)	5,386,482	17,279,633
Category I, II, III, IV	24.4% (13.1-29.0)	5,902,209	25,814,908
Adequate vaccine effectiveness at 5 months (VE=50%)			
Category I and II	33.4% (30.5-34.2)	744,939	12,076,619
Category I, II, III	33.0% (28.3-34.2)	974,151	17,008,452
Category I, II, III, IV	33.0% (27.8-34.1)	974,151	25,543,727
Adequate vaccine effectiveness at 4 months (VE=50%)			
Category I and II	30.4% (29.1-31.6)	2,464,030	12,076,619
Category I, II, III	27.5% (22.5-30.4)	4,125,818	17,278,523
Category I, II, III, IV	26.6% (18.5-30.2)	4,641,545	25,814,799
Antiviral			
2 weeks	34.7% (34.7-34.7)	0	50
4 weeks	34.7% (34.7-34.7)	0	355
8 weeks	34.7% (34.7-34.7)	0	12,389
16 weeks	33.9% (33.3-34.6)	458,424	2,993,052
Entire epidemic	29.6% (29.6-29.6)	2,922,454	18,758,578
Social distancing measures			
From week 2	34.7% (34.7-34.7)	0	not applicable
From week 4	34.7% (34.6-34.7)	0	not applicable
From week 8	34.1% (33.3-34.7)	343,818	not applicable

*Value in brackets represent the 5-95 percentile values of the Attack Rate estimates

Table 2. Effectiveness of combined control measures on the dynamics of an influenza pandemic with an R_0 of 1.8 and an attack rate of 35%, with 70% vaccine effectiveness (VE)

Interventions		Attack rate*	Avoided cases	Treated individuals	
				With vaccine	With antiviral
Adequate vaccine effectiveness at 5 months (VE=70%)					
Social distancing measures from week 2	Antiviral for 2 weeks.	24.6% (17.5-29.2)	5,787,603	25,821,426	55
	Antiviral for 4 weeks.	23.6% (15.4-26.9)	6,360,633	25,825,375	182
	Antiviral for 8 weeks.	22.1% (15.5-26.0)	7,220,178	25,831,314	717
	Antiviral for 16 weeks.	18.3% (11.3-22.0)	9,397,697	25,837,928	258,992
	Antiviral for the entire epidemic.	13.0% (6.2-16.7)	12,434,757	25,837,928	8,224,930
Social distancing measures from week 4	Antiviral for 2 weeks.	23.7% (15,1-28.5)	6,303,330	25,824,246	51
	Antiviral for 4 weeks.	22.7% (12.7-27.6)	6,876,360	25,828,371	373
	Antiviral for 8 weeks.	20.5% (12.3-25.1)	8,137,026	25,835,232	1690
	Antiviral for 16 weeks.	16.6% (10.5-21.2)	10,371,848	25,837,926	159,521
	Antiviral for the entire epidemic.	11.3% (5.5-15.8)	13,408,909	25,837,928	7,177,152
Adequate vaccine effectiveness at 4 months (VE=70%)					
Social distancing measures from week 2	Antiviral for 2 weeks.	12.6% (8.7-16.9)	12,663,963	25,837,928	55
	Antiviral for 4 weeks.	11.9% (8.0-14.3)	13,065,084	25,837,928	182
	Antiviral for 8 weeks.	10.9% (7.9-13.3)	13,638,114	25,837,928	717
	Antiviral for 16 weeks.	9.0% (5.8-10.7)	14,726,878	25,837,928	247,028
	Antiviral for the entire epidemic.	5.0% (1.8-7.0)	17,018,999	25,837,928	3,193,698
Social distancing measures from week 4	Antiviral for 2 weeks.	12.0% (7,9-15,9)	13,007,781	25,837,928	51
	Antiviral for 4 weeks.	11.5% (6.8-14.9)	13,294,296	25,837,928	373
	Antiviral for 8 weeks.	10.1% (6.6-12.6)	14,096,538	25,837,928	1,690
	Antiviral for 16 weeks.	8.4% (5.3-10.2)	15,070,696	25,837,928	152,056
	Antiviral for the entire epidemic.	4.2% (1.4-6.4)	17,477,424	25,837,928	2,673,736

*Value in brackets represent the 5-95 percentile values of the Attack Rate estimates

Table 3. Effectiveness of combined control measures on the dynamics of an influenza pandemic with an R_0 of 1.8 and an attack rate of 35%, with 50% vaccine effectiveness (VE)

Interventions		Attack rate*	Avoided cases	Treated individuals	
				With vaccine	With antiviral
Adequate vaccine effectiveness at 5 months (VE=50%)					
Social distancing measures from week 2	Antiviral for 2 weeks.	26.4% (18.8-30.0)	4,756,151	25,821,812	55
	Antiviral for 4 weeks.	26.0% (19.9-28.8)	4,985,363	25,826,670	183
	Antiviral for 8 weeks.	25.0% (17.8-27.8)	5,558,394	25,830,892	745
	Antiviral for 16 weeks.	22.1% (17.5-24.8)	7,220,182	25,837,928	258,992
	Antiviral for the entire epidemic.	16.5% (11.9-19.4)	10,429,151	25,837,928	10,494,921
Social distancing measures from week 4	Antiviral for 2 weeks.	26.0% (20.7-29.8)	4,985,363	25,824,256	51
	Antiviral for 4 weeks.	25.4% (19.5-29.0)	5,329,182	25,828,178	367
	Antiviral for 8 weeks.	23.8% (19.2-27.2)	6,246,030	25,835,286	1665
	Antiviral for 16 weeks.	20.9% (16.9-24.1)	7,907,818	25,837,926	159,520
	Antiviral for the entire epidemic.	15.4% (11.5-18.7)	11,059,485	25,837,928	9,763,649
Adequate vaccine effectiveness at 4 months (VE=50%)					
Social distancing measures from week 2	Antiviral for 2 weeks.	18.1% (15.7-20.7)	9,512,302	25,837,928	55
	Antiviral for 4 weeks.	17.7% (15.8-19.5)	9,741,515	25,837,928	183
	Antiviral for 8 weeks.	17.3% (15.4-18.7)	9,970,727	25,837,928	745
	Antiviral for 16 weeks.	16.2% (15.1-17.0)	10,601,060	25,837,928	250,341
	Antiviral for the entire epidemic.	11.4% (8.7-12.6)	13,351,606	25,837,928	7,232,024
Social distancing measures from week 4	Antiviral for 2 weeks.	17.9% (15,9-20.3)	9,626,909	25,837,928	51
	Antiviral for 4 weeks.	17.6% (15.8-19.8)	9,798,818	25,837,928	367
	Antiviral for 8 weeks.	16.9% (15.7-18.3)	10,199,939	25,837,928	1,664
	Antiviral for 16 weeks.	16.0% (15.1-16.7)	10,715,666	25,837,928	154,130
	Antiviral for the entire epidemic.	11.0% (8.6-12.2)	13,580,818	25,837,928	6,983,830

*Value in brackets represent the 5-95 percentile values of the Attack Rate estimates

Figure 1. Weekly attack rate, by age group, with no control measures

Figure 2. Impact of different combinations of control measures considering the use of a pre-pandemic vaccine provided to all categories (I to IV)

Figure 3. Total attack rates for different values of R_0, with no control measures or selected control measures

Acknowledgment

We are grateful to Mark Kanieff for revising the manuscript.

Founding

This work has been partially funded by the EPICO Project, of the Provincia Autonoma di Trento, Italy.

Competing interests: No competing interests to declare

References

(1) Li KS, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. Nature 2004 July 8;430:209-213.

(2) Outbreak news. Avian influenza, Turkey--update. Wkly Epidemiol Rec 2006;81:42-43.

(3) Monto AS. Vaccines and antiviral drugs in pandemic preparedness. Emerg Infect Dis 2006 January;12:55-60.

(4) Stephenson I, et al. Development and evaluation of influenza pandemic vaccines. Lancet Infect Dis 2006;6:71-72.

(5) Influenza Team ECDPaC. Pandemic preparedness in the European Union – multi-sectoral planning needed. Euro Surveill 2007;12:E070222.1.

(6) Ferguson NM, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature 2005;437:209-214.

(7) Ferguson NM, et al. Strategies for mitigating an influenza pandemic. Nature 2006;442:448-452.

(8) Longini IM, et al. Containing pandemic influenza at the source. Science 2005;309:1083-1087.

(9) Germann TC, et al. Mitigation strategies for pandemic influenza in the United States. Proc Natl Acad Sci U S A 2006;103:5935-5940.

(10) Carrat F, et al. A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics. BMC Med 2006;4:26.

(11) Colizza V, et al. Modeling the Worldwide Spread of Pandemic Influenza: Baseline Case and Containment Interventions. PLoS Med 2007;4:e13.

(12) Cooper BS, et al. Delaying the international spread of pandemic influenza. PLoS Med 2006;3:e212.

(13) Flahault A, et al. Strategies for containing a global influenza pandemic. Vaccine 2006 24(44-46):6751-6755.

(14) Istituto Nazionale di statistica. 14° Censimento Generale della Popolazione e delle Abitazioni. ISTAT 2001(Available from: http://dawinci.istat.it/daWinci/jsp/MD/dawinciMD.jsp). Accessed 1 May 2007.

(15) Istituto Nazionale di statistica. Statistiche del trasporto aereo - Anno 2003. ISTAT 2006 (Available from: http://www.istat.it/dati/catalogo/20060509_01/inf0606statistiche_trasporto_aereo03.pdf). Accessed 1 May 2007.

(16) Glezen WP. Emerging infections: pandemic influenza. Epidemiol Rev 1996;18:64-76.

(17) Diekmann O, Heesterbeek JAP Mathematical Epidemiology of Infectious Diseases, Wiley, 2000

(18) Flahault A, et al. Modelling the 1985 influenza epidemic in France. Stat Med 1988;7:1147-1155.

(19) Ministero della Salute. Piano Nazionale di preparazione e risposta ad una pandemia influenzale 2006 (Available from: http://www.ministerosalute.it/imgs/C_17_pubblicazioni_511_allegato.pdf). Accessed 1 May 2007.

(20) Ministero della Salute. Influenza Vaccination Coverage. 2005. (Available from: http://www ministerosalute it/promozione/malattie/malattie jsp)

(21) Bella A., et al. FLU-ISS: Sistema di sorveglianza sentinella dell'influenza basata su medici di medicina generale e pediatri di libera scelta. Rapporto sulla stagione influenzale 2004-2005. ISS; 2005. Report No.: 22.

(22) Brownstein JS, Kleinman KP, Mandl KD. Identifying pediatric age groups for influenza vaccination using a real-time regional surveillance system. Am J Epidemiol 2005;162:686-693.

(23) Roberts MG, et al. A model for the spread and control of pandemic influenza in an isolated geographical region. J. Royal Society Interface 2007;4:325-330.

(24) Viboud C, et al. Influenza epidemics in the United States, France, and Australia, 1972-1997. Emerg Infect Dis 2004;10:32-39.

(25) Viboud C, et al. Multinational impact of the 1968 Hong Kong influenza pandemic: evidence for a smoldering pandemic. J Infect Dis 2005;192:233-248.

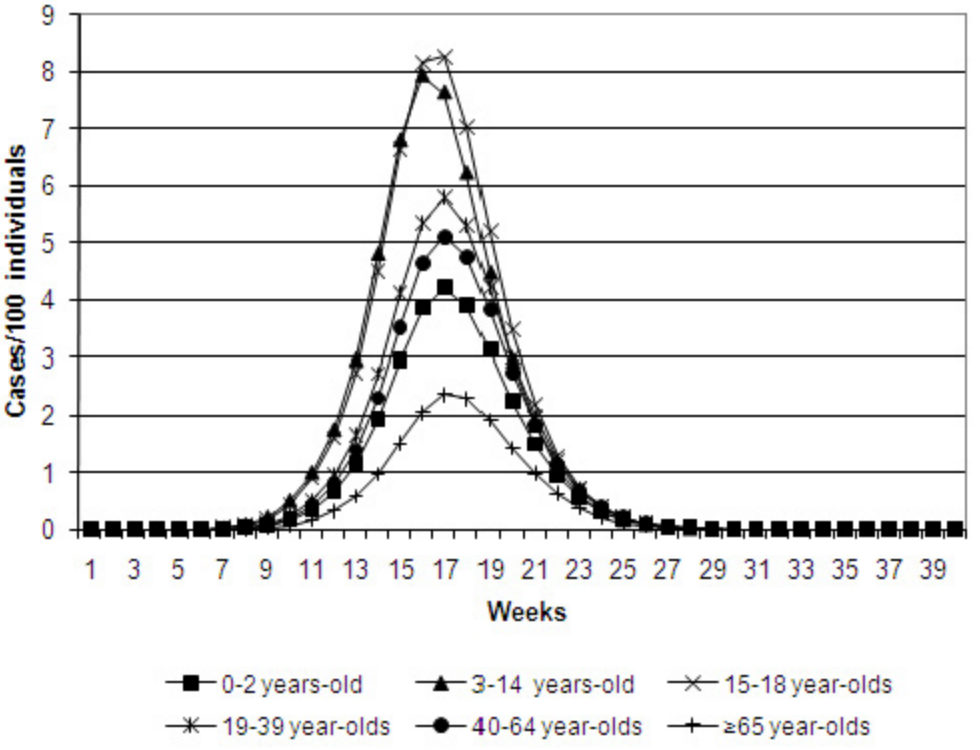
(26) Rizzo C, et al. Trends for Influenza-related Deaths during Pandemic and Epidemic Seasons, Italy, 1969-2001. Emerg Infect Dis 2007;13:694-699.

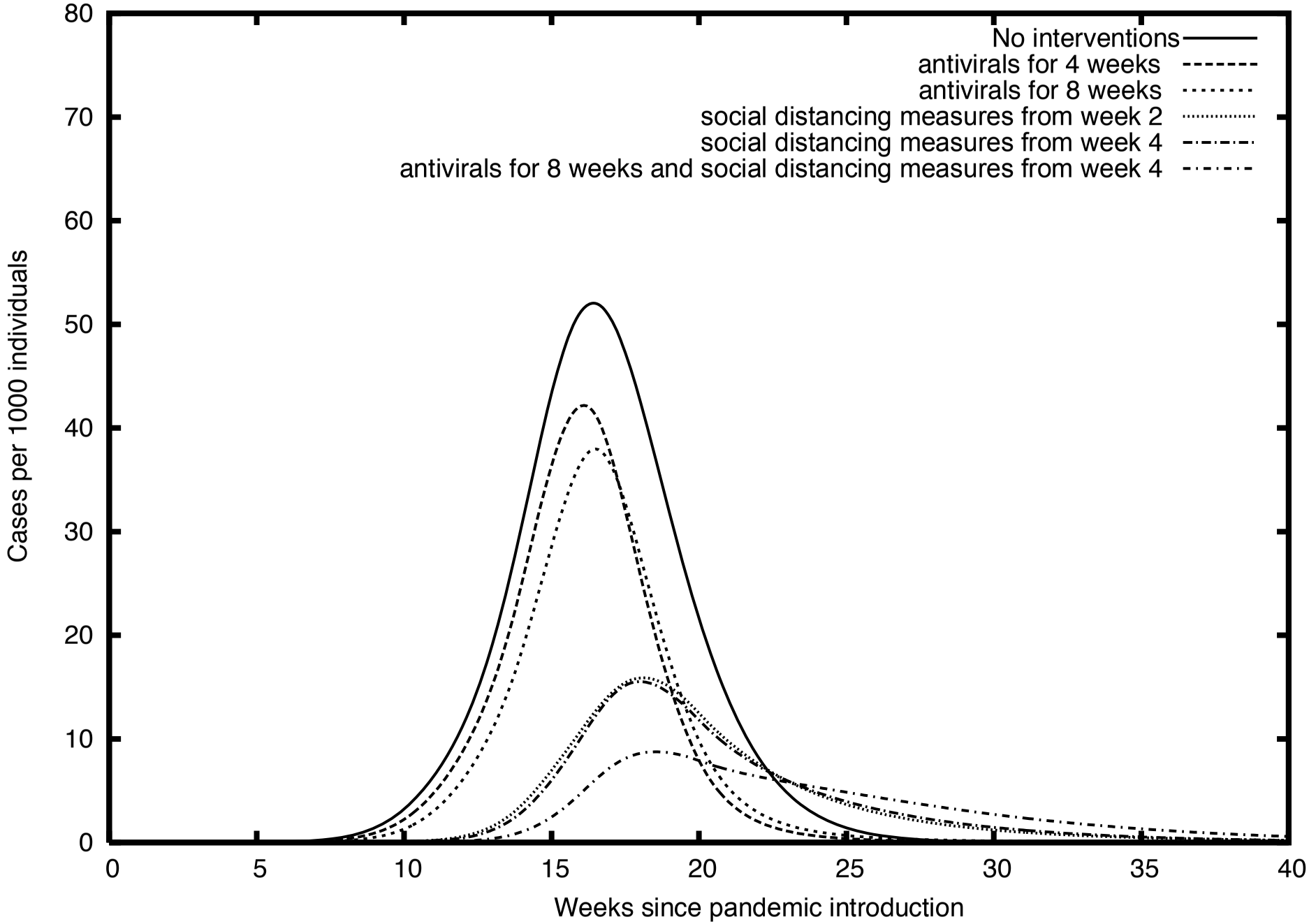
Appendix

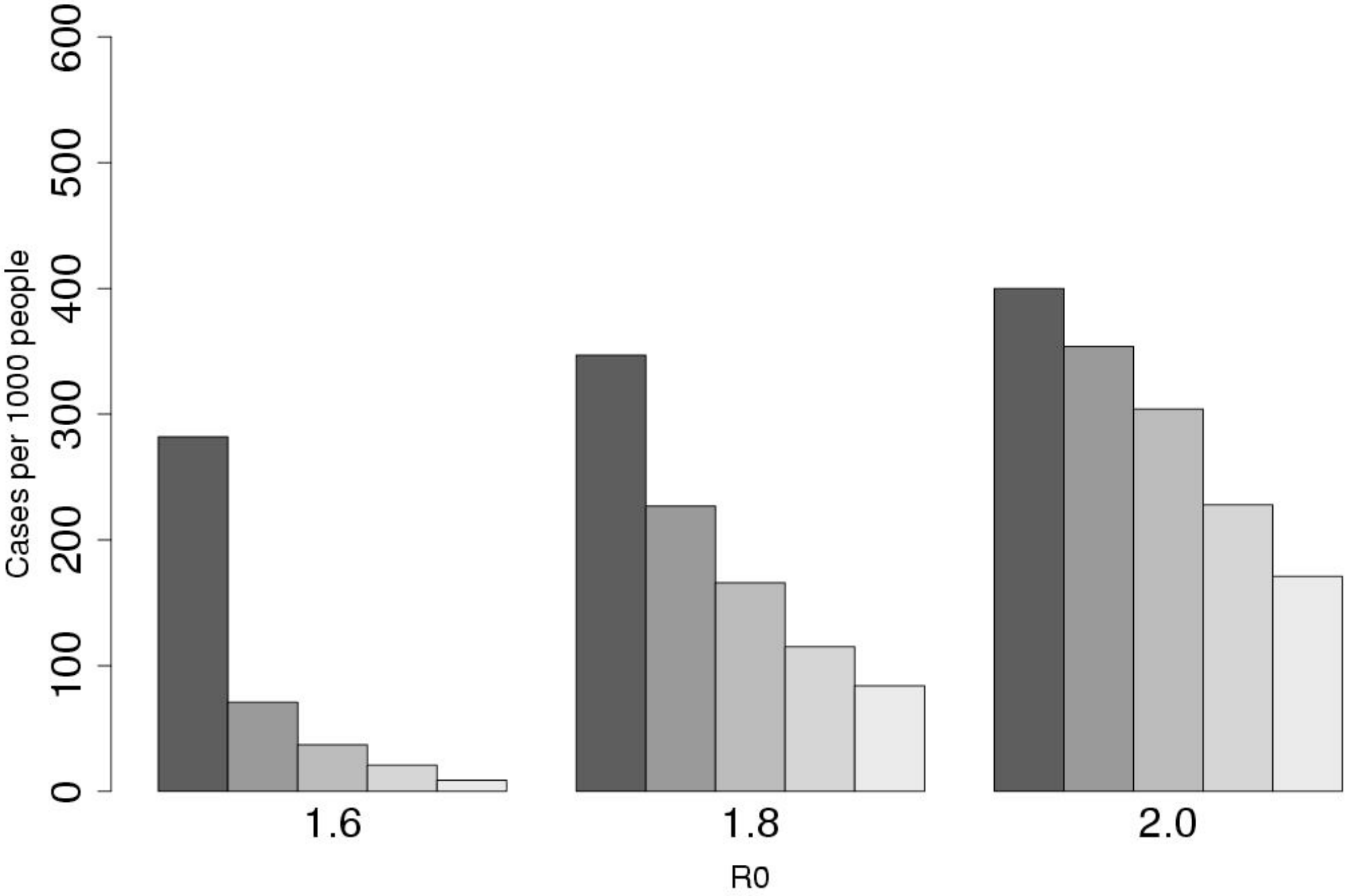
The equations of the model are

$$\begin{cases} \dot{S}_i^p = -\dot{S}_i^p \sum_{j,q} \beta_{i,j}^{p,q} \frac{I_j^q}{N_j^q} \\ \dot{E}_i^p = \dot{S}_i^p \sum_{j,q} \beta_{i,j}^{p,q} \frac{I_j^q}{N_j^q} - \eta E_i^p \\ \dot{I}_i^p = \eta E_i^p - \gamma I_i^p \\ \dot{R}_i^p = \gamma I_i^p \end{cases}$$

where 1/η and 1/γ represent, respectively, the mean length of the latent and the infectious periods and $\beta_{i,j}^{p,q}$ is the transmission rate between an individual of class *i* in region *p* and an individual of class *j* in region *q*.


Cases/100 individuals
0
1
2
3
4
5
6
7
8
9
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39
Weeks
0-2 years-old
3-14 years-old
15-18 year-olds
19-39 year-olds
40-64 year-olds
≥65 year-olds


No interventions
antivirals for 4 weeks
antivirals for 8 weeks
social distancing measures from week 2
social distancing measures from week 4
antivirals for 8 weeks and social distancing measures from week 4
Cases per 1000 individuals
Weeks since pandemic introduction
0
10
20
30
40
50
60
70
80
0
5
10
15
20
25
30
35
40


Cases per 1000 people
0
100
200
300
400
500
600
1.6
1.8
2.0
R0