

Modeling influenza pandemic in Italy: an individual based approach¹

Modellazione della pandemia influenzale in Italia: un approccio micro

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Riassunto: Il rischio di una pandemia influenzale è diventato più sostanziale e persistente alla fine del 2003, quando si è osservata una rapida crescita della diffusione del virus A(H5N1). In questo lavoro proponiamo un modello stocastico ad agenti individuali per verificare l'efficacia di alcune strategie di contenimento, quali vaccinazione, profilassi antivirale, misure per l'aumento della distanza sociale e limitazione dei voli aerei internazionali. Il modello è formato da a) un modello sociodemografico dell'intera popolazione italiana, b) un modello epidemiologico a base individuale per la descrizione dell'evoluzione spazio-temporale dell'epidemia e c) un modello SEIR alle derivate ordinarie per la descrizione dell'evoluzione a livello globale dell'epidemia che permette in particolare di stimare il numero di casi importati tramite voli aerei internazionali.

Keywords: pandemic, influenza, microsimulation, vaccination, antiviral prophylaxis, social distancing

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1. Introduction

During the last century there were 3 influenza pandemics. Their mortality impact ranged from devastating (the 1918 'Spanish' A(H1N1) influenza, which killed 20 to 50 million people worldwide) to moderate (the 1957 Asian A(H2N2) pandemic) to rather mild (the 1968 'Hong Kong' A(H3N2) virus) (Glezen, 1996).

Actually dating back to the end of 2003, when the outbreaks of Asian influenza of the A/H5N1 (Li *et al.*, 2004) virus became endemic in birds in the Far East, with the virus causing serious infections also in humans (World Health Organization, 2006), the risk of an influenza pandemic has become more substantial and persistent. Furthermore, since 2005, outbreaks of avian influenza have been documented also in Europe, and in 2006 there have been cases of transmission to humans in Turkey. By April 11 2007, some 291 human infections with A/H5N1 had been reported to WHO, of which 172 died. The greater mobility of the population at a global level and the greater speed of means of transport would make the control of the spread of infection particularly problematic.

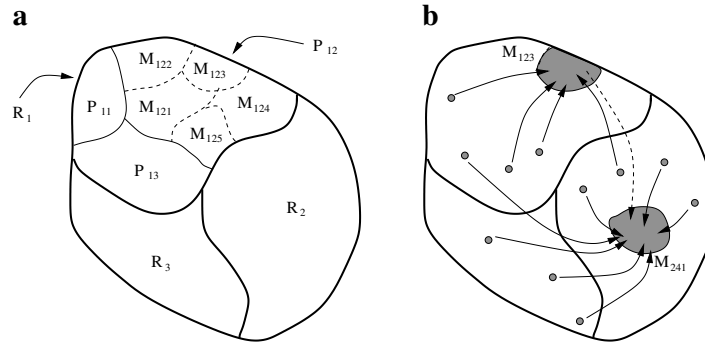
For this reason the WHO has recommended that all countries prepare a Pandemic Plan to be updated constantly and following established guidelines (World Health Organization, 2005). In this scenario, a number of European countries have developed or updated a national influenza preparedness plan. In Italy, the 'National Plan for Preparedness and Response to an Influenza Pandemic' (Ministero della Salute, 2006), as in other European countries, has been developed in accordance with the WHO recommendations of 2005 (Ciofi degli Atti *et al.*, 2006), and it updates and substitutes the previous Italian Multi-phase Plan for Pandemic Influenza, published in 2002.

The plan includes measures to be adopted in case of a pandemic phase as prophylaxis with antiviral drugs for close contacts of cases, use of pandemic vaccine identifying the priority categories to be given the pandemic vaccinations (listed according to priority: health care personnel, personnel connected with services essential for security and emergency needs, personnel in public utility services, persons with a high risk of severe or fatal complications due to influenza, healthy children and adolescents aged between 2-18 years, healthy adults). In addition, social distancing measures are to be considered in the early phase of new virus transmission.

A number of countries have already attempted to estimate the burden of an influenza pandemic (Hak *et al.*, 2006; Chun, 2005; Meltzer *et al.*, 1999; Fock *et al.*, 2002) and some have investigated the impact of interventions (Doyle *et al.*, 2006; Gensheimer *et al.*, 2003; van Genugten *et al.*, 2003; Jennings, 2005; Ferguson *et al.*, 2006, 2005; Germann *et al.*, 2006; Longini *et al.*, 2005). These studies use scenario analysis or more sophisticated mathematical modeling to investigate the epidemiological impact of influenza vaccination and antiviral prophylaxis and social distancing measures.

Here we employ a large scale individual based model, adapted from that proposed by Ferguson *et al.* (Ferguson *et al.*, 2005), specific to the Italian population structure, in order to evaluate the impact of various control measures. Regarding vaccination, we chose to evaluate the use of a single dose of pre-pandemic vaccination, followed by one dose only of pandemic vaccine (Daems *et al.*, 2005). Hence, this model permits a detailed exploration of the options for the use of influenza pre-pandemic vaccination, prophylactic use of antiviral drugs and social distancing measures separated or combined.

Figure 1: **a** Hierarchical structure of municipalities (dashed lines, M), provinces (solid thin lines, P) and regions (solid thick lines, R). **b** Social network of contacts of an individual living in municipality M_{123} and traveling to municipality M_{241} consists of all the individuals living in the two municipalities and the individuals traveling to one of the two municipalities (small filled circles).



2. Modeling influenza pandemic

The model, adapted from that proposed by Ferguson *et al.* (2005), is a stochastic, spatially structured, individual based discrete time simulation. Infection can be spread in three ways: within households, within schools and workplaces, by random contacts in the population (see Glezen (1996)). The model consists of (A) a sociodemographic model, in which individuals are co-located in households, schools, workplaces on the basis of census and commuting data, (B) an epidemiological model describing the temporal evolution of the epidemic and (C) a global SEIR model describing the worldwide temporal evolution of the epidemic and allowing for the estimate of the number of imported cases by international flights.

2.1 Sociodemographic model

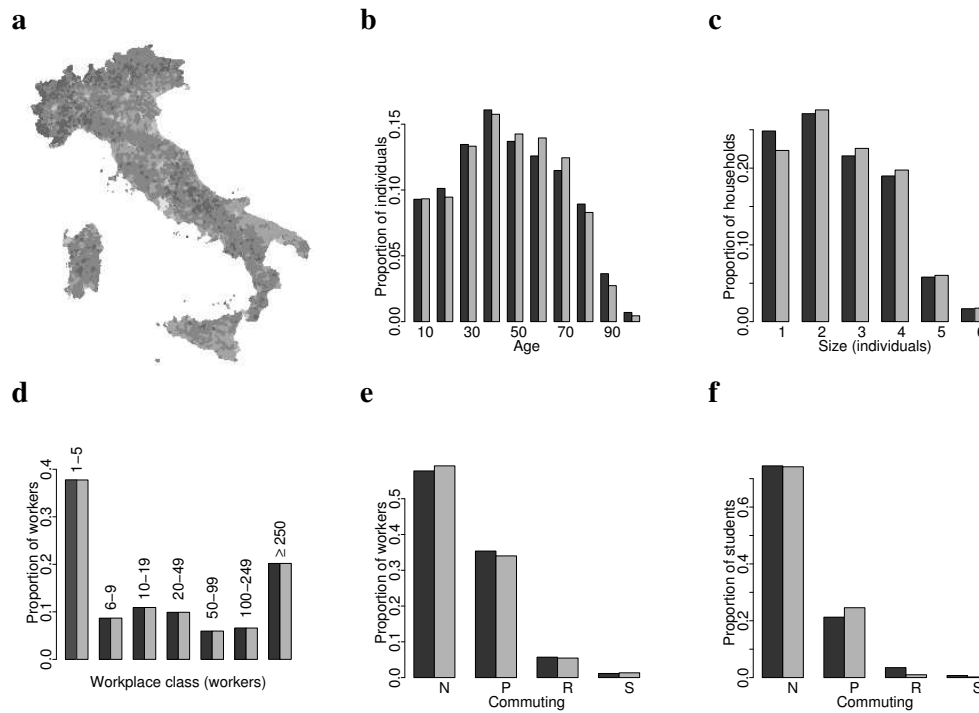
Population data of Italy (57,004,425 individuals) are obtained from census data⁶ and are hierarchically grouped by municipalities (8,101), provinces (103) and regions (20), according to the political borders of the study area (see Fig. 1a). Number of individuals by municipality ranges from 33 to 2,546,804 (Rome municipality) with an average of 7,035 and a standard deviation of 39,326 (see Fig. 2a). Census data on age structure and household size and type⁷ (9 types, depending on the composition: singles or couples with or without children, etc.) are used to randomly assign age and co-locate individuals in households (see Fig 2b-c), considering the following additional constraints:

- any household must contain at least 1 adult (age ≥ 18);
- the age of any child is between 43 and 18 years less than that of the youngest parent;
- spouses age differs by no more than 15 years.

⁶Data available on-line at <http://dawinci.istat.it/MD/>

⁷Documents available on-line at http://www.istat.it/dati/catalogo/20060621_03

Figure 2: **a** Population data by municipality: colors ranging from dark gray (municipalities with less than 1,000 inhabitants) to light gray (more than 1,000,000 inhabitants, Rome and Milan) represent number of individuals on a $\log_{10}$ scale. **b** Age distribution from census data (dark gray) and simulated (light gray). **c** As in **b** but showing household size. **d** Proportion of workers for class of workplace from industry census (dark gray) and simulated (light gray). **e** Commuting destinations of workers from census data (dark gray) and simulated (light gray). Symbols are defined in the main text. **f** As in **e** but showing commuting destinations of students. Census data are available only for individuals of age ≥ 15 while simulated data refer to all students.



Demographic, school⁸ and industry⁹ census data are used for randomly assigning an employment category to each individual on the basis of age. Population is structured as follows: 20,559,595 workers, 11,360,556 students and 25,084,274 unemployed or retired. Students are deterministically assigned to a specific school type (6 types, from nursery school to university) on the basis of age. Workers are assigned to a random workplace type (7 types, depending on the workplace size, i.e., the number of employees, see Fig. 2d). Students are grouped in classes, whose average size depends on the type. Specifically, the average size is 20 in nursery schools, 40 in kindergartens, 19 in primary school, 21 in middle and high schools, 34 in universities; we also consider close colleagues of workers: in small workplaces (less than 10 employees) all workers are close colleagues. In bigger workplaces employees are clustered in groups of size 5. Commuting destinations are assigned to fit available commuting data⁶ (see Fig. 2e-f). In particular, the proportion of individuals with age ≥ 15 working or attending school in the

⁸Documents available on-line at <http://www.miur.it/ustat/documenti/pub2005>

⁹Data available on-line at <http://dwcis.istat.it/cis>

same municipality of residence (N) is available for each municipality, together with the number of individuals traveling either to a municipality of the same province they live in (P), or outside the province but within the same region (R), or outside the region (S). Once the commuting type is defined, the destination municipality is assigned by employing a gravity model, i.e. by randomly sampling among the M admissible municipalities with probability p_m increasing with the population size i_m , in order to increase the probability of traveling towards large population municipalities, and decreasing with the distance d_m :

$$p_m = \frac{i_m(1 - a \tan^{-1}(b) + a \tan^{-1}(-cd_m + b))}{Z},$$

where Z is a normalization factor and a , b and c are fixed positive constants. Commuting data, for both workers and students, are available only for individuals of age ≥ 15 . We allow younger students to travel only within the province which they live in. Schools and workplaces are finally generated to fit data on number and size and commuting data.

2.2 Epidemiological model

For each individual i we define:

- h_i as the set of the n_i individuals belonging to the same household of the individual i ;
- l_i^j as the set of the m_i^j individuals attending the same school (index $j = 1, \dots, 6$ identifies school type) or sharing the same workplace (index $j = 7, \dots, 13$ identifies workplace type) of the individual i ;
- S_i as the set of the s_i individuals belonging to social network of contacts of the individual i .

Any susceptible individual i , at any time t of the simulation has a probability $p_i = 1 - e^{-\lambda_i \Delta t}$ of becoming infected, where $\Delta t = 0.25$ days is the time-step of the simulation and λ_i is the instantaneous risk of infection. It is the sum of three sources of infection:

1. contacts with infectious members of the household (first term in Eq. 1),
2. contacts with infectious individuals working in the same workplace or attending the same school (second term in Eq. 1),
3. contacts with all the infectious individuals belonging to his social network of contacts (third term in Eq. 1).

$$\begin{aligned} \lambda_i = & \sum_{k|h_k=h_i} \frac{I_k \beta_h \kappa(t - \tau_k) [1 + C_k(\omega - 1)]}{n_i^\alpha} \\ & + \sum_{j,k|l_k^j=l_i^j} \frac{I_k \beta_p^j \kappa(t - \tau_k) [1 + C_k(\omega \psi_p^j(t - \tau_k) - 1)]}{m_i^j} \\ & + \sum_{k \in S_i} \frac{I_k \beta_r \kappa(t - \tau_k) [1 + C_k(\omega - 1)]}{s_i} \end{aligned} \quad (1)$$

The terms in Eq. (1) are defined as follows:

- $I_i = 1$ if individual i is infected, 0 otherwise;
- $\beta_h = 0.65/\text{day}$ is the within-household transmission coefficient, β_p^j are the within-school/workplace transmission coefficients: in particular, $\beta_p^j = 1.29/\text{day}$ for $j = 1, \dots, 6$ and $\beta_p^j = 0.65/\text{day}$ for $j = 7, \dots, 13$. β_r is the transmission coefficient for random contacts and is set to $0.36/\text{day}$: this choice implies that the three sources of infections contribute equally to the instantaneous risk of infection and allows us to model the worst case. This choice of the transmission coefficients leads to a reproductive number $R_0 = 1.7$. Different transmission coefficients were employed to simulate epidemics with different R_0 values;
- τ_i is the time individual i became infectious and $\kappa(T)$ is a lognormal function describing infectiousness over time. Estimates of incubation period (1.48 ± 0.47 days) and infectiousness period ($\int_0^\infty T \kappa(T) dT$) lead to a generation time $T_g = 2.6$ days;
- $C_k = 1$ for severe cases (we suppose the 50% of cases to be severe), 0 otherwise. Since $\omega = 2$, the infectiousness of severe cases doubles the one of mild cases;
- $\alpha = 0.8$ scales the household transmission rates with household size;
- $\psi_p^j(T)$ is a function accounting for induced absenteeism and it is defined as follows: if $T > 0.25$ (the minimum time for recognizing the infection) $\psi_p^j(T)$ is set to 0.1 for $j = 1, 2$, 0.2 for $j = 3, 4$, 0.25 for $j = 5$ and 0.5 for $j = 6, \dots, 13$, 1 otherwise.

The third term of Eq. (1) accounts for the risk of infection coming from random contacts in the population. In particular, it depends on a specific social network S_i of contacts. We use commuting data to model S_i : for non-traveling individuals we define S_i as the set of individuals living or traveling to the same municipality which they live in. For traveling individuals we additionally consider the individuals living or traveling to the same municipality to which they travel (see Fig. 1b).

Differently from (Ferguson *et al.*, 2005), where all the individuals are potential contacts of an infectious individual and the risk of being infected decreases with the distance, we assume that the risk of infection depends on the behavior of the individuals rather than on relative distance among them. In fact, contacts of a infectious individual i with individuals living or traveling to the municipality where i travels are much more likely than random contacts with individuals living in very close municipalities but non-traveling to school or workplace. Namely, places where people meet as trains, airplanes, restaurants, etc., are among the most important routes of infection transmission (Glezen, 1996). Consequently, we expect that no clear spatial pattern of infection diffusion will be observable and that the infection jumps rapidly among large population municipalities, as discussed in (Longini *et al.*, 2005).

Of course, touristic flows data, air and train travel data and, finally, data regarding various sources of people aggregations such as theaters, cinemas and churches could be used to improve the modeling of the social networks of contacts.

Results reported in Section 3. are obtained by averaging over 20 simulations for each scenario: the implemented containing strategies are described in Section 2.4.

2.3 Infection seeding

The worldwide spread of pandemic influenza and the consequent importation of cases in Italy is described using a global ODE SEIR-model (susceptible - exposed, but not yet infectious - infectious - recovered, and no longer susceptible). In this model, 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. We couple

the results of the global SEIR model with 2003 data on arrivals and departures in Italy's 38 international airports¹⁰. Specifically, the number of imported exposed individuals is expressed as $\frac{E(t)}{N}a$, where $E(t)$ is the number of exposed individuals obtained with the global SEIR model at time t , N is the world population, and a is the total number of persons arriving daily (an average of 70,000). The probability of importing infections to municipalities with international airports is given by $p_i = \frac{a_i}{a}$, where a_i is the number of international travellers arriving daily in the i -th airport (ranging from 0.1 to 22,000).

2.4 Modeling of interventions

We consider the combination of the following control measures: a) vaccination; b) antiviral prophylaxis (AVP), and c) social distancing, including travel restrictions.

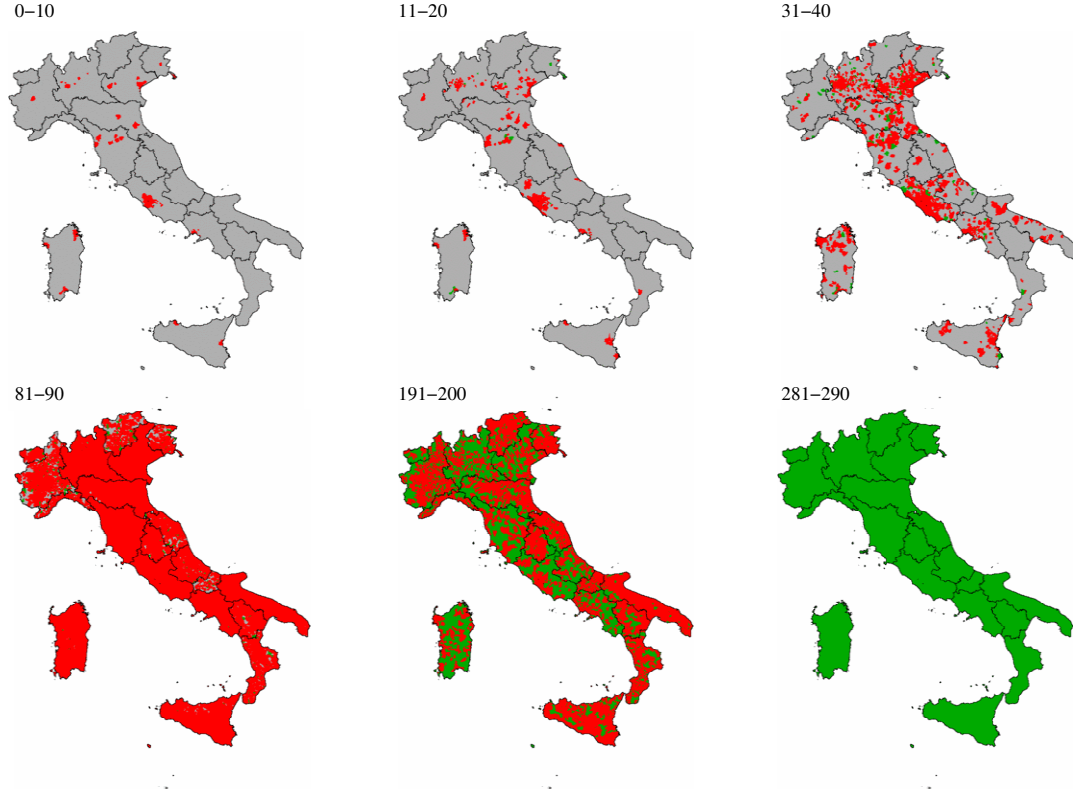
Vaccination The target population is divided into 4 categories: i) personnel providing essential services (15% of the 25-60-year-old Italian population⁹); ii) elderly persons (≥ 65 years of age); iii) children and adolescents from 2 to 18 years of age; and iv) adults from 40 to 64 years of age. Vaccination is modelled by reducing the proportion of susceptible individuals in the target population. This proportion depends on vaccination coverage (VC) and vaccine efficacy (VE). We assume that vaccination consists of two vaccine doses administered one month apart and that VC is 60% of the target population. VE is assumed to be 70%, beginning 15 days after administration of the second dose. We also make different assumptions regarding VE, assuming that it varies by target category: i) 59% in individuals aged 2-18 years (Jefferson *et al.*, 2005); ii) 70% in individuals aged 40-64 years (Demicheli *et al.*, 2004); and iii) 40% in individuals ≥ 65 years (Goodwin *et al.*, 2006). We consider different scenarios of vaccine availability, assuming that adequate VE is reached at 4, 5 and 6 months after the first world case. An adequate VE at 4 months would be feasible only if the first dose were to contain an avian virus precursor of the pandemic strain (Monto, 2006), followed by a dose of pandemic vaccine. The actual VE of this regimen is assumed to be equal to that of two doses of the pandemic vaccine.

Antiviral prophylaxis AVP for uninfected individuals is assumed to reduce susceptibility to infection by 30% and infectiousness by 70% (Longini *et al.*, 2005). We assume that AVP is provided to 90% of close contacts of clinical cases (50% of all infected individuals) throughout the entire epidemic in Italy or during the first 8 weeks of the epidemic. Two different definitions of contacts are used: i) household contacts only and ii) household contacts plus close contacts in school (classmates) or workplace (close colleagues).

Social distancing We consider travel restrictions that would reduce incoming international flights by 90% or 99% for two months after the first Italian case, or the entire duration of the epidemic. We consider the nationwide closing of all schools and some public offices not providing essential services, corresponding to 20% of all employees in these types of offices⁹. We assume that school and office closings begin 4 weeks after the onset of the first 20 symptomatic cases in Italy and that this measure is maintained for 4 weeks. We also assume that symptomatic individuals spontaneously limit their school/work attendance. The proportion of symptomatic individuals staying at home from

¹⁰Documents available on-line at http://www.istat.it/dati/catalogo/20060509_01/

Figure 3: Pattern of spatial spread of an epidemic with $R_0 = 1.7$. Red indicates presence of new cases while green indicates absence of new cases. Time (in days) is reported on the top of each image (time = 0 corresponds to the first italian case)



school/workplace would vary by age, from 90% among children < 6 years of age to 50% among the working population.

3. Results

We suppose that the infection is imported by international travellers and we consider three main scenarios: 'mild' ($R_0=1.4$), 'moderate' ($R_0=1.7$) and 'severe' ($R_0=2$). Fig. 3 shows a typical pattern of spatial spread with $R_0 = 1.7$. New cases are confined in the seeding region for the first 20 days. At 30-40 days new cases arise far from the seeding region in large population municipalities. From 60 to 100 days, during the exponential growth phase, infection spreads almost everywhere. For $R_0 = 1.7$, the epidemic peak is observed at about 90 days and the epidemic attack rate is about 55.6%. Simulations carried on with $R_0 = 1.4$ and $R_0=2$ lead to attack rates of 34.0% and 68.7% respectively.

As in the baseline situation, a large outbreak arises in all the simulations regardless the adopted containing strategies. The probability of eliminating a large outbreak is estimated as $1 - (1 - p_c)/(1 - p_n)$, where p_c and p_n are the proportions of simulations in which epidemic extinguishes quickly with and without containing strategies respectively. For all containing strategies, the probability of eliminating a large outbreak is negligible, due to

the fact of continuous importation of new cases by international arrivals. Border restriction, antiviral prophylaxis and social distancing measures are effective in delaying epidemic's arrival and peak allowing us to gain time for developing vaccines and implementing preparedness measures. However, we show that none of these measures is sufficient to contain a moderate to severe epidemic. Consequently, only the combination of all these strategies can result effective in containing a pandemic. More in detail, our results show that it is feasible to contain a mild to moderate epidemic, with attack rates decreased from 34% to 4.4% and from 56% to 10% respectively. 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), social distancing measures (closure of schools and workplaces for 4 weeks), and antiviral prophylaxis of close contacts of the clinical cases can result effective in reducing the impact of the epidemics (with attack rates decreasing from 69% to 20%).

4. Conclusions

Our results indicate that 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 (Ferguson *et al.*, 2005; Longini *et al.*, 2005), the outbreak could be mitigated through a combination of antiviral prophylaxis and reduction of social contacts. Many diffusion scenarios are possible, depending notably on seasonality, virus transmissibility, and geographic origin of the pandemic. A detailed prediction of pandemic dynamics is consequently hard to achieve, as extensively shown by the problems faced by public health response planning.

The use of this type of models will increasingly become a standard for preparedness planning and modeling of new disease outbreaks for each country in which a pandemic preparedness plan is available. In fact, this class of models is particularly suitable for analyzing the effectiveness of containing strategies based on social distancing measures or prophylactic use of antiviral drugs on a social basis. Moreover, on a Pentium D 3.2GHz workstation a single run requires about 10 minutes and allocates about 3GB RAM memory, allowing for real-time simulations using a standard computer.

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