School closure is currently the main strategy to mitigate influenza A(H1N1)v: a modeling study

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Concerns about an imminent influenza pandemic have been intensified after the emergence of the new influenza A(H1N1) v strain. Mathematical modeling was employed on recent epidemiological data from Mexico in order to assess the impact of intervention strategies on the spread of influenza A(H1N1)v in the setting of the European region. When initiating the intervention of 100% school closure in a community of 2,000 people at a threshold of 1% cumulative attack rate, the total number of symptomatic cases is predicted to decrease by 89.3%, as compared to the non-intervention scenario. When this measure is coupled with treatment and home isolation of symptomatic cases as well as a 50% reduction of social contacts, a 94.8% decline in the cumulative attack rate is predicted along with a much shorter duration of influenza A(H1N1)v transmission. Active surveillance that will ensure timely treatment and home isolation of symptomatic cases in combination with school closure seem to form an efficient strategy to control the spread of influenza A(H1N1)v.

Introduction

The emergence of the new influenza A(H1N1)v strain in March-April 2009 prompted the World Health Organisation (WHO) to raise the pandemic alert level. Influenza A(H1N1)v has to date spread to 76 countries and has infected 35,928 individuals (confirmed cases as of 15 June 2009) [1]. Currently, there is uncertainty about key epidemiological parameters such as the age-specific attack rates, the case fatality rate and the basic reproductive number R_0 (i.e. the number of secondary cases attributed to one infected individual in a susceptible population) [2-4]. Since the epidemic in Mexico provides the most advanced insight into key epidemiological parameters [2], we used those parameters to simulate the potential spread of influenza A(H1N1)v in a model community situated in Greece and explored the effectiveness of various intervention strategies that could inform policies and decisions in the setting of the European region.

Table 1

Size of households and proportion of household members ≥65 or <15 years-old according to household size, Greece, 2001

Household size	Total % of households	% without ≥65	% with one ≥65	% with two ≥65	% with three ≥65	% with four ≥65	% with five ≥65
1	19.8	56.03	43.97	0.00	0.00	0.00	0.00
2	28.1	49.48	22.44	28.08	0.00	0.00	0.00
3	21.1	73.44	15.71	10.01	0.84	0.00	0.00
4	20.5	86.20	10.04	3.43	0.28	0.05	0.00
5	6.8	68.93	24.82	5.85	0.33	0.06	0.01
6	2.5	53.92	26.94	18.50	0.55	0.07	0.02
7	0.8	48.02	27.41	22.91	1.50	0.14	0.03
8+	0.5	49.69	25.88	21.47	2.40	0.44	0.12
Household size		**% without <15**	**% with one <15**	**% with two <15**	**% with three <15**	**% with four <15**	**% with five <15**
1	19.8	100.00	0.00	0.00	0.00	0.00	0.00
2	28.1	97.45	2.55	0.00	0.00	0.00	0.00
3	21.1	65.88	32.36	1.76	0.00	0.00	0.00
4	20.5	44.08	18.30	37.37	0.25	0.00	0.00
5	6.8	34.96	24.97	20.43	19.48	0.16	0.00
6	2.5	22.85	22.79	32.33	11.61	10.33	0.08
7	0.8	17.55	19.76	27.39	22.44	7.32	5.55
8+	0.5	13.15	15.63	26.46	20.60	15.29	8.88

Source: General Secretariat of National Statistical Service of Greece. Available from http://www.statistics.gr/Main_eng.asp

The simulation model

Simulation parameters

We used a discrete-time stochastic individual-based simulation model, employed in previous studies on influenza [5,6], to simulate the spread of influenza A(H1N1)v. A structured model community of approximately 2,000 people was generated to match the age-distribution, household size and number and size of schools of the Greek population (Tables 1-2).

The model community of 2,000 people was divided into four neighbourhoods of approximately equal size that share one kindergarden, one primary school and one high school. Influenza is introduced at day 0 by randomly assigning a number of initial infective individuals, and person-to-person transmission probabilities are used to simulate influenza spread over time. The transmission probabilities used elsewhere [5] were modified to yield the age-specific attack rates of the influenza A(H1N1)v outbreak in the community of La Gloria in Mexico [2]. As the population was assumed to be structured (households, schools, neighbourhoods and community), different transmission probabilities applied to different mixing groups. They were highest for contacts within households and lower for contacts within schools, followed by neighbourhoods and, finally, the entire community (Table 3). The transmission probabilities published elsewhere [5,7,8] were modified to yield the age-specific attack rates observed in the influenza A(H1N1)v outbreak in La Gloria [2].

Each day, all susceptible individuals in the community were exposed to a number of infective children (I_{hc}) and adults (I_{ha}) of their household, their school (if they are children) (I_s), their neighbourhood (I_n) and the entire community (I_{com}), with corresponding probabilities of transmission. The probability of an adult not becoming infected by children at home was:

$$(1 - p_{hca})^{I_{hc}}$$

Thus, in the simple case of an adult exposed on a specific day to I_{hc} infected children at home, I_n infected people in their neighbourhood and I_{com} infected people in the entire community, the probability of not becoming infected was:

$$\text{P(not being infected)} = (1 - p_{hca})^{I_c} (1 - p_n)^{I_n} (1 - p_{com})^{I_{com}}$$

Thus, each day, for each susceptible, the probability of becoming infected was calculated on the basis of who was infectious in their contact groups and of the group-specific transmission probabilities:

$$\text{P(infection)} = 1 - (1 - p_{hca})^{I_c} (1 - p_n)^{I_n} (1 - p_{com})^{I_{com}}$$

Once these daily probabilities are calculated for each susceptible individual, a uniform (0,1) random number was generated. If this number was lower than the probability of infection of the susceptible individual, then this person became infected. If susceptible people had been given antiviral prophylaxis, the transmission probabilities

Table 2

Proportion of Greek population by age compared to the EU-27, the two most affected European countries, Spain and the United Kingdom, as well as Mexico (data for 2006)

	0 to 14 years	15 to 64 years	≥65 years
Greece*	14.3	67.2	18.5
EU-27*	16.0	67.2	16.7
Spain*	14.5	68.9	16.7
United Kingdom*	17.8	66.2	16.0
Mexico**	30.6	63.6	5.8

* Eurostat yearbook 2008.http://epp.eurostat.ec.europa.eu/portal/page/portal/publications/eurostat_yearbook
** United States Census Bureau, International Data Base. http://www.census.gov/ipc/www/idb/tables.html

Table 3

Transmission probabilities among children and adults, by mixing group

Contact group	Infected	Susceptible	Transmission probabilities
Household	Child	Child 0-4 years-old	0.6
Household	Child	Child 5-17 years-old	0.08
Household	Adult	Child 0-4 years-old	0.2
Household	Adult	Child 5-17 years-old	0.03
Household	Child	Adult	0.03
Household	Adult	Adult	0.04
School	Child 4-5 years-old	Child 4-5 years-old	0.015
School	Child 6-11 years-old	Child 6-11 years-old	0.0145
School	Child 12-17 years-old	Child 12-17 years-old	0.0125
Neighbourhood	Anyone	Child 0-11 years-old	0.00004
Neighbourhood	Anyone	Child 12-17 years-old	0.00012
Neighbourhood	Anyone	Adult 18-65 years-old	0.00048
Neighbourhood	Anyone	Adult >65 years-old	0.00035
Community	Anyone	Child 0-11 years-old	0.00001
Community	Anyone	Child 12-17 years-old	0.00003
Community	Anyone	Adult 18-65 years-old	0.00012
Community	Anyone	Adult >65 years-old	0.00009

were multiplied by 0.70 (protective efficacy: 30%). If an infected person was taking an antiviral drug, the transmission probability from that person to a susceptible person was multiplied by 0.38 (antiviral efficacy for infectiousness: 62%) [9].

We assumed an infectious period of four days and a latent period of one day, as data on influenza A(H1N1)v as well as volunteer challenge studies suggest a short latent period [2,10]. The probability of developing symptoms if infected was assumed 67% and asymptomatic people were 50% as infectious per contact as symptomatic people [11].

Interventions

The interventions considered are summarised in Table 4.

Antiviral treatment and targeted antiviral prophylaxis (TAP) of household contacts are administered one day after onset of symptoms of the index case for a period of five and 10 days, respectively. Compliance with home isolation of symptomatic cases (90%) and of children during school closure (60%) was modeled by assuming that the compliant proportion stayed at home during the infectious period or during school closure, while non-compliant individuals continued circulation in the neighbourhood and the community as usual. Treatment and prophylaxis are assumed to reduce the probability of an infected person transmitting by 0.62 [9,12]. Prophylaxis is assumed to reduce the probability of being infected by 0.30 and, if infected, the probability of developing symptoms by 0.60 [9,12].

The threshold for initiating treatment and isolation of index cases and/or TAP in scenarios 1, 2, and 5-7 was set to 0.05% cumulative clinical attack rate (i.e. as soon as one symptomatic case occurs in the community of 2,000 people). The corresponding threshold for non-pharmaceutical interventions of scenarios 3-7

Table 4

Assumptions of the evaluated intervention strategies

	Treatment of symptomatic cases (Threshold: 0.05%)	Isolation of symptomatic cases (Threshold: 0.05%)	TAP (Threshold: 0.05%)	Social distancing (Threshold: 1%)	School closure (Threshold: 1%)
	% ascertainment of symptomatic cases / % compliance with receiving treatment	% compliance with staying home	% compliance with receiving prophylaxis	% reduction in community contacts	% of schools closing / % compliance of children with staying home
Scenario 0 (No intervention)	-	*	-	-	-
Scenario 1 (Treat and isolate)	80% / 100%	90%	-	-	-
Scenario 2 (Treat anc isolate, TAP)	80% / 100%	90%	100%	-	-
Scenario 3 (Social distancing)	-	-	-	50%	-
Scenario 4 (School closure)	-	-	-	-	100% / 60%
Scenario 5 (Treat and isolate, Social distancing)	80% / 100%	90%	-	50%	-
Scenario 6 (Treat and isolate, School closure)	80% / 100%	90%	-	-	100% / 60%
Scenario 7 (Treat and isolate, School closure, Social distancing)	80% / 100%	90%	-	50%	100% / 60%

Threshold indicates the illness attack rate for initiating the interventions.
TAP: Targeted antiviral prophylaxis of household contacts.
* 80%, 75% and 50% of symptomatic preschool children, school children and adults, respectively, withdraw voluntarily to the home.

Table 5

Simulated illness attack rates of influenza A(H1N1)v outbreaks and proportion of cases by age group in a community of 2,000 persons in Greece when one infected person initially seeded into the population and the corresponding data from the outbreak in La Gloria, Mexico

	Clinical attack rate (%)		% of cases by age	
Age group (years)	Community in Greece	La Gloria, Mexico	Community in Greece	La Gloria, Mexico
0-18	59.7%	61.1%	31.7%	50.2%
19-65	32.1%	29.6%	57.0%	45.3%
65+	23.8%	22.0%	11.3%	4.5%
Overall	36.0%	39.1%	100.0%	100%

was set to 1% (20 cases per 2,000 population). We investigated the effect of these interventions in 200 simulations assuming five infected individuals initially seeded into the population.

Results

Simulated spread of H1N1 under the non-intervention scenario

In the case of an outbreak of influenza A(H1N1)v in Greece according to our model, and in the absence of intervention, individuals under the age of 18 years would account for 31.7% of cases, as compared to 50.2% in Mexico, and individuals over the age of 65 years are expected to account for approximately 11 out of 100 cases (11.3% versus 4.5% in Mexico) (Table 5) [2].

The simulated epidemic curve of the H1N1 outbreak is depicted in Figure 1 and is very similar to that obtained from La Gloria in Mexico [2]. The basic reproductive number R_0 was estimated in 1,000 simulations as described in Longini *et al.* [5] and its average value was 1.51.

We examined in 200 simulations the effect of introducing simultaneously more than one infected person in the community of 2,000 people on day 0. Introducing one infected individual resulted in an outbreak in only 35.2% of the simulations. As the number of initially infected individuals increased to five and 10, the probability of an outbreak was 94.8% and 99.6%, respectively (Figure 2).

Impact of interventions

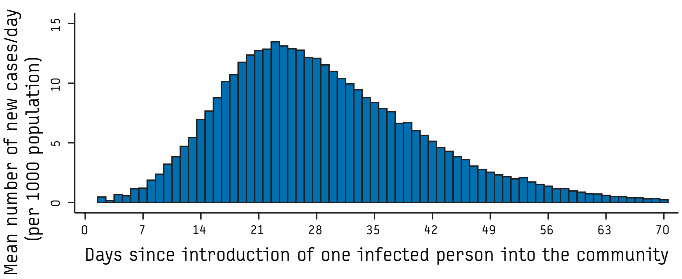
The effect of the intervention strategies is shown in Figure 3 and Table 6.

Compared to no intervention, the decrease in the illness attack rates when any of the intervention scenarios 1-4 were evaluated separately ranged from 40.9% to 89.3%. The combination of treatment, school closure and social distancing (scenario 7) resulted in an attack rate of 1.8% (decrease: 94.8%). Although school closure largely reduced the attack rate when used as a single intervention, transmission occurred over a prolonged period of time (day of occurrence of the last new infection: day 43). The addition of treatment and social distancing reduced the duration of virus transmission to 17 days. This scenario is predicted to limit the spread of influenza A(H1N1)v even in the case of 100 infected persons simultaneously introduced into the model community of 2,000 persons (Figure 4).

Figure 1

Simulated influenza A(H1N1)v outbreaks after the introduction of one infected person into the community (over 200 simulations)

A) Mean number of daily symptomatic infections per 1,000 population



B) Cumulative number of symptomatic cases per 1,000 population

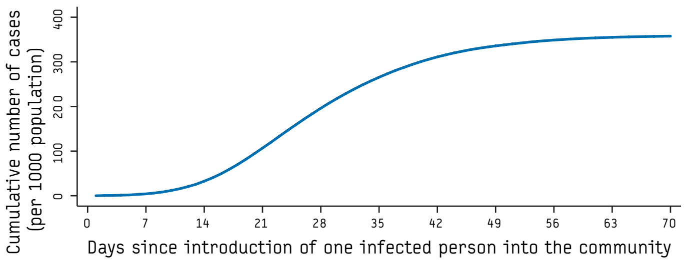


Figure 2

Distribution of the total number of secondary symptomatic cases in 200 simulations according to the initial number of infected persons seeded into the population

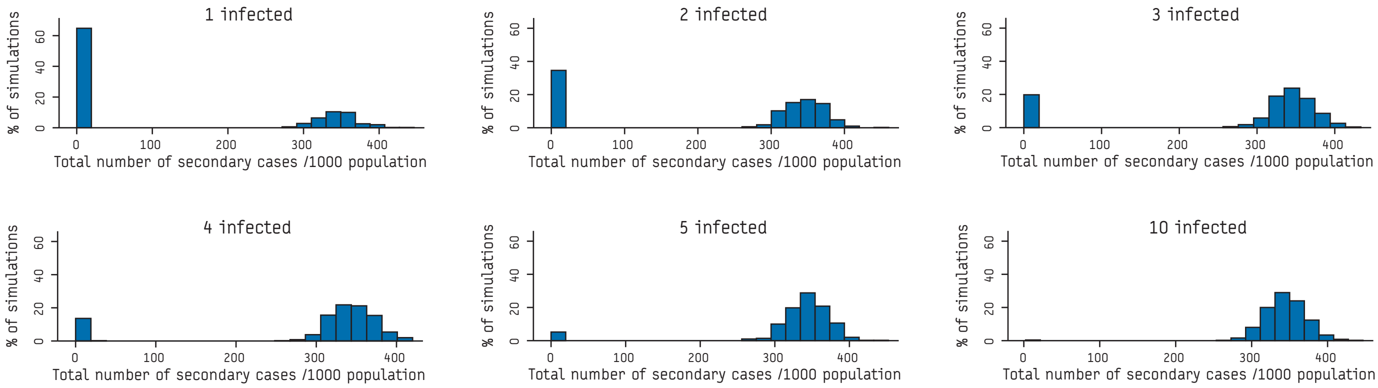
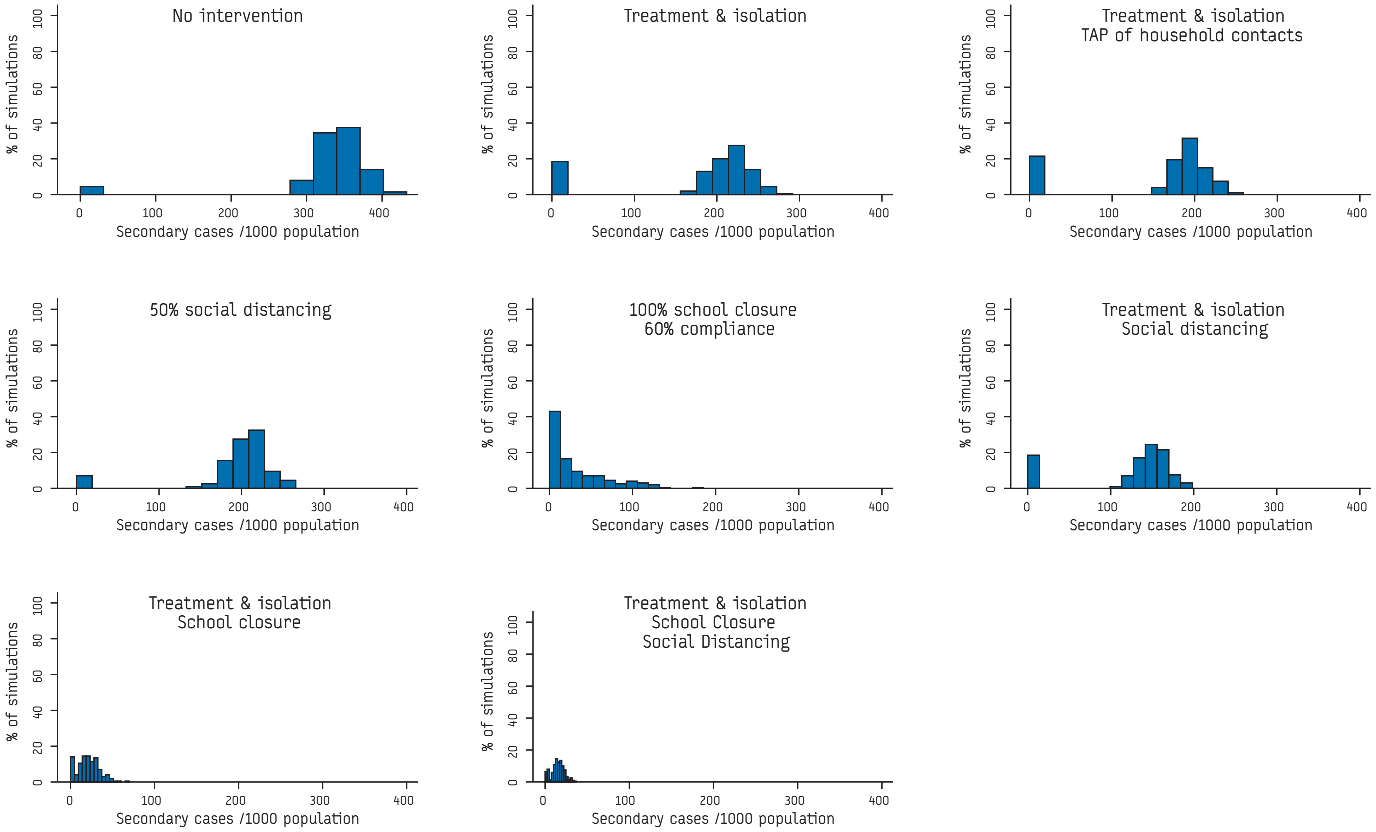


Figure 3

Distribution of the total number of secondary symptomatic cases in 200 simulations according to the intervention used (five infected individuals initially seeded into the population)



Threshold for initiating treatment and isolation of index cases, TAP of household contacts: 0.05%, for school closure and social distancing: 1% cumulative illness attack rate.
TAP: Targeted antiviral prophylaxis of household contacts.

Table 6

Simulated average illness attack rates and duration of influenza A(H1N1)v spread over 200 simulations according to different interventions used (five infected individuals initially seeded into the community)

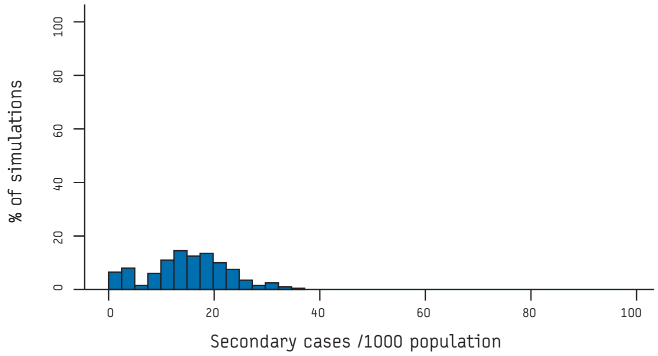
Intervention	Illness attack rates*		Day of the last infection*
	%	% decrease compared to no intervention	
0. No intervention	34.5%	-	54
Treatment-based interventions			
1. Ascertainment of 80% of cases, treatment and isolation of cases	18.8%	45.5%	41
2. Ascertainment of 80% of cases, treatment and isolation of cases, TAP of household contacts	16.3%	52.8%	40
Non-pharmaceutical interventions			
3. 50% social distancing	20.4%	40.9%	45
4. School closure (100% closure, 60% compliance)	3.7%	89.3%	43
Combination of treatment-based and non-pharmaceutical interventions			
5. Ascertainment of 80% of cases, treatment and isolation of cases and social distancing	13.1%	62.0%	35
6. Ascertainment of 80% of cases, treatment and isolation of cases and school closure	2.5%	92.8%	24
7. Ascertainment of 80% of cases, treatment and isolation of cases, school closure and social distancing	1.8%	94.8%	17

* The average estimates were computed over 200 simulations independently of whether an outbreak occurred or not.
TAP: Targeted antiviral prophylaxis of household contacts.

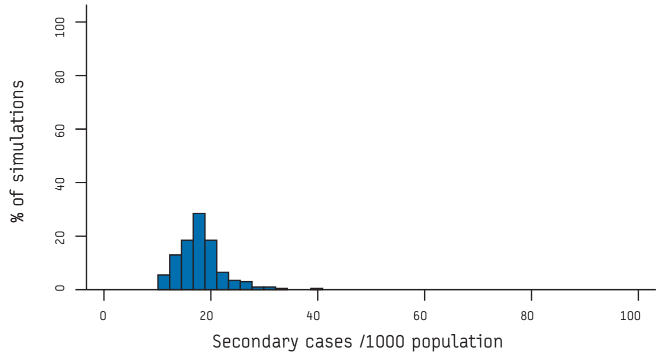
Figure 4

Distribution of the total number of secondary symptomatic cases (under intervention scenario 7 of Table 6) in 200 simulations according to the initial number of infected (secondary cases do not include the initial infected persons)

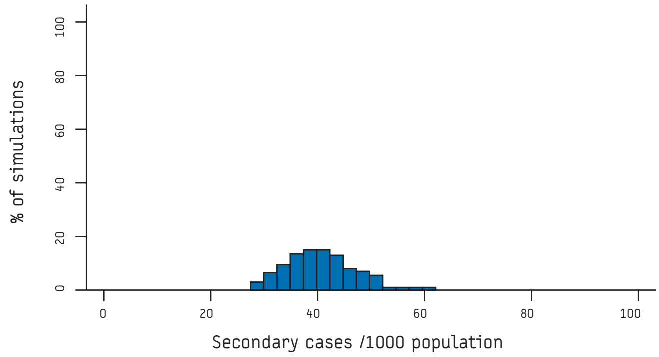
A) Five infected individuals initially seeded into the population



B) 40 infected individuals initially seeded into the population



C) 100 infected individuals initially seeded into the population



Discussion

A stochastic model was used to assess the impact of various intervention strategies on the spread of the new influenza A(H1N1)v in a Greek model community. Due to the similarity in the age structure of the Greek and the European population, it may be possible to apply the results to other communities in the European region. Uncertainty remains concerning key epidemiological parameters of influenza A(H1N1)v, such as the basic reproductive number R_0 that has been estimated to be in the range 1.4-1.6 [2] and less than 2.2-3.1 [4] for Mexico, and 2.3 for Japan [3]. In our analysis, we have modeled an R_0 of 1.5 based on the fist reported estimates [2]. Even with this low R_0, simultaneous introduction of five infected individuals in the model community of 2,000 people almost always lead to an outbreak in the absence of any intervention.

The combination of antiviral treatment with school closure and social distancing at the assumed thresholds was found to control the spread of influenza A(H1N1)v. Although school closure was found to be an effective strategy even when it used as the sole intervention, sporadic transmission occurred over a prolonged period. As a prophylactic vaccine is not available yet, the effect of this intervention was not evaluated.

The simulation model has been applied to a community of 2,000 people. Therefore, our results concerning the anticipated duration and peak of the outbreak do not apply for an epidemic in the whole country. However, an epidemic in a country occurs in subpopulations or regions at different times [5], and this is the process we attempted to model. Similar small community models have been used widely in exploring the effectiveness of different intervention strategies [5,6,13,14]. A further assumption of the small community model is that after the initially infected persons have been seeded into the community, that population remains isolated. Furthermore, our model did not consider workplaces as mixing groups but rather used higher transmission probabilities for contacts between adults than for children within the community and neighbourhoods.

The findings on the impact of school closure in mitigating pandemic influenza are variable [12-17]. This is most probably due to different assumptions regarding the implementation of school closure (such as the delay in closing schools, the duration of school closure etc.) and regarding contact behaviour of pupils during school closure as well as to widely varied epidemiological parameters. Closing schools is more effective when R_0 is low and attack rates in children are high in comparison to adults [17]. In the current influenza A(H1N1)v epidemic, attack rates are particularly high in children [2] and the median age of non-imported cases in Europe is 13 years [18]. Our results agree with a recent paper suggesting that active surveillance and school closures in Japan most likely have contributed to controlling influenza A(H1N1)v transmission [3]. However, implementation of school closure is expected to lead to work absenteeism of working parents and considerable costs [19]. The potential benefits and costs of school closure need to be further considered.

The current epidemiological data obtained from the outbreak in Mexico are valuable in planning our response to the spread of influenza A(H1N1)v, provided that the epidemiological and clinical characteristics will not change substantially. Until the production and use of a prophylactic vaccine, active surveillance that will ensure timely treatment and home isolation of symptomatic cases in combination with school closure seem to form an efficient strategy to control influenza A(H1N1)v spread.

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