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An ongoing measles outbreak in Bulgaria, 2009

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After seven years without indigenous transmission of measles in Bulgaria, an increasing number of cases have been reported since 15 April 2009. By 19 June, the total number of notifications reached 84. To date, 64 were confirmed as measles cases and 15 cases, for whom laboratory results are pending, have been classified as probable. The present measles outbreak affects mostly the Roma population living in the north-eastern part of the country. The most affected age groups are young children below 1 year of age and children 1 to 9 years of age. An immunisation campaign was started in the affected administrative regions, targeting all persons from 13 months to 30 years of age who had not received the complete two-dose MMR vaccination.

Introduction

Measles has been a notifiable disease in Bulgaria since 1921. National case-based notification was initiated in 2004 and the European Union (EU) case definition and case classification have been adopted since 2005 [1,2]. The Bulgarian National program for elimination of measles and congenital rubella infection (2005-2010) was approved by the Council of Ministries of Republic of Bulgaria in 2005 [3].

Measles immunisation was introduced in Bulgaria in 1969 [4] and in 1972 it became universal. Until 1982 the routine vaccination included one dose measles vaccine administered at ≥10 months of age. During the period 1983-1992 a two-dose schedule using monovalent measles vaccine was applied, firstly at 12 months and 4 years of age, and later at 12 and 24 months of age. In 1993, the measles, mumps, rubella (MMR) vaccine was introduced into the national vaccination schedule. Until 2000, the routine measles immunisation consisted of the first dose with MMR vaccine given at 13 months of age and the second dose with monovalent measles vaccine at 12 years of age. Since 2001 a routine two-dose immunisation with MMR vaccine has been implemented, administered at 13 months and 12 years of age. According to the official data, collected by the National Center of Health Information, the vaccine coverage in Bulgaria with MMR is high (Table).

The last indigenous cases of measles in Bulgaria were reported in 2001 [5]. From 2002 to 2008 only six measles cases have been registered, all of them imported: three from China (2005); one from Ukraine (2006); one from Germany (2007) and one from United Kingdom (2008) [6,7].

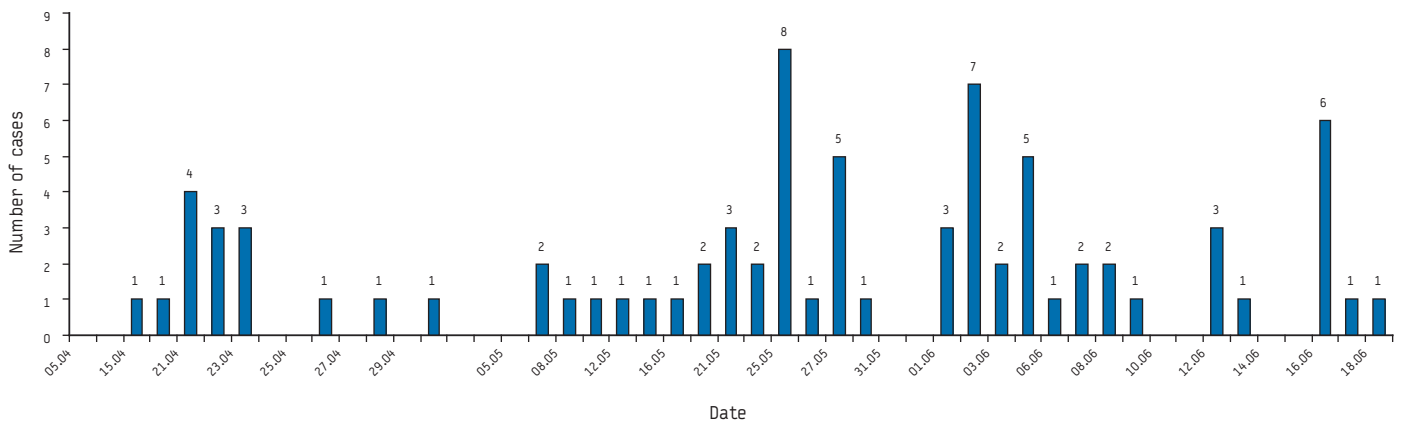
Table

National immunisation coverage with measles, mumps, rubella (MMR) vaccine, Bulgaria, 2005-2008

MMR dose	2005	2006	2007	2008
First dose (13 months)	96.2%	95.7%	96.0%	95.9%
Second dose (12 years)	92.4%	93.3%	94.0%	94.3%

Figure 1

Number of probable and confirmed measles cases reported in Bulgaria between 15 April and 19 June 2009, by date of notification (n=79)



Outbreak description

After seven years without indigenous transmission of measles in Bulgaria, an increasing number of cases have been reported since 15 April 2009 (Figure 1).

By 19 June, the total number of notifications reached 84. Of these, five were discarded (one patient who presented with a rash 10 days after MMR vaccination was considered as a case of adverse events following immunisation (AEFI), and four suspected cases tested IgM-negative). Of the remaining 79, to date, 64 were confirmed as measles cases (61 laboratory-confirmed by the National Reference Laboratory for Measles, Mumps and Rubella in Sofia, and three having clinical symptoms and an epidemiological link with laboratory-confirmed cases); the remaining 15 cases for whom laboratory results are pending, have been classified as probable.

The epidemiological investigation demonstrated that the index case was imported in March from Germany. The patient, a 24-year-old man, became ill on 12 March, four days after arrival from Hamburg, where he works. The initial symptoms included high fever, cough, runny nose, malaise and rash, developed three days later. The clinical presentation was compatible with measles and fulfilled the clinical criteria of measles. The patient was not hospitalised but consulted an infectious diseases specialist. A serum sample was tested and the case was classified as confirmed by the National Reference Laboratory and notified as an imported case (included in Figure 1).

The subsequent three measles cases occurred among his close contacts (family members). They were laboratory-confirmed by the National Reference Laboratory in Sofia. The samples were then sent to the WHO Regional Reference Laboratory (RRL) for Measles and Rubella in Berlin for reconfirmation and measles virus (MV) genotyping. The nucleotide sequences of the variable part of measles virus N gene (450 nt) derived from these three cases were identical and classified as genotype D4. Their sequence is represented by the official WHO name MVs/Shumen.BGR/15.09/1(D4). Later on samples collected from four further cases in epi-week 21 were sent to the RRL Berlin. The sequences derived from these cases (represented by MVs/Silistra.BGR/21.09/1[D4]) were identical to MVs/Shumen.BGR/15.09/1[D4] demonstrating that the seven analysed cases belonged to a single chain of MV transmission. The same genetic variant of MV was previously detected during an outbreak observed between January and June 2009 in northern Germany. This confirms the assumption that the Bulgarian index case was imported from Hamburg. Outbreaks due to the introduction of imported MV (D6, D4 and B3) into the hard-to-reach populations were recently reported also from other European countries [8]. The strain name MVs/Shumen.BUL/15.09(D4) was included in the WHO/EURO CISID database. [Information in this paragraph was kindly provided by Dr Annette Mankertz and Dr Sabine Santibanez from the Robert Koch-Institut, Berlin, Germany].*

All 78 cases following the index case occurred as a result of local transmission and were shown to be epidemiologically linked.

The present measles outbreak affects mostly the Roma population living in the north-eastern part of the country – in Razgrad, Shumen, Silistra and Dobrich regions (Figure 2). This population is characterised by large families living together and frequently moving from one place to another, looking for seasonal work in Bulgaria as well as abroad. Until now, several family clusters have been registered among this group.

The outbreak affects both genders almost equally, with male to female ratio 30/49. The most affected age groups are young children below 1 year of age (non-immunised because of the young age) and children 1 to 9 years of age, who are eligible to immunisation.

Because of the crowded households and poor living conditions of affected Roma families a large proportion of cases (51 of 79, 64.5%) were hospitalised. Complications were observed in 46.8% of cases (37/79): 33 cases developed pneumonia and four cases had abdominal disorders with diarrhea and acute abdominal pain.

The immunisation status of all reported 79 measles cases is shown in Figure 3.

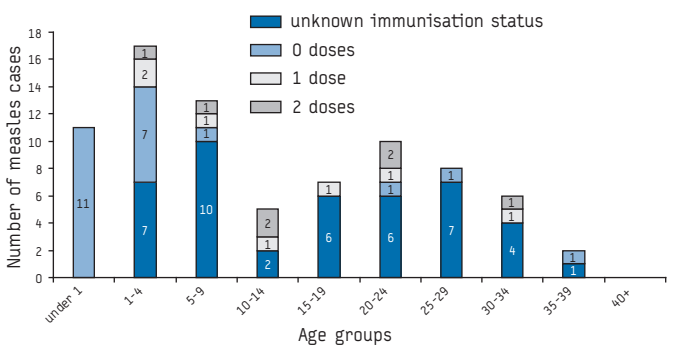
Considering the age of cases, 68 of the total of 79 measles cases should have been immunised with at least one dose of measles vaccine. However, in the majority of cases (n=43, 54.4%) the vaccination status was unknown because of the lack of documentation. Twenty-two cases were known not to have been vaccinated (including 11 below the age of one year). Only seven cases (10.3%) have received one dose and another seven (10.3%)

Figure 2

Measles cases spread by regions, Bulgaria, April-June 2009 (n=79)

Figure 3

Distribution of reported measles cases by immunisation status and age group, Bulgaria, April-June 2009 (n=79)



both doses of the measles vaccine. Of note is that among those immunised with two doses, three cases received the second dose during the catch-up campaign organised in response to the outbreak in May 2009, and it is most likely that they were harbouring a measles infection in the incubation period during that time, because soon after the immunisation, they fell ill with measles.

Control measures

The outbreak and the investigations are still ongoing, and therefore the data presented are preliminary. The public health authorities expect more cases to occur, especially among the Roma population.

The control measures are in progress: the Bulgarian Ministry of Health issued a press release regarding the situation and future immunisation and surveillance activities. General practitioners and other medical staff were requested to pay special attention to rash/fever symptoms and to strengthen routine immunisation of children aged 13 months (first dose) and 12 years (second dose) by directly reaching the parents and explaining the benefits of vaccination.

An immunisation campaign was started on 27 April in the affected administrative regions, targeting all persons from 13 months to 30 years of age who had not received the complete two-dose MMR vaccination. The MMR vaccine is supplied by the Ministry of Health and is offered free of charge through the routine immunisation services (family doctors) and special outreach teams. These supplementary immunisation activities are still ongoing.

Discussion and conclusions

Despite the high national immunisation coverage with MMR vaccine, the current measles outbreak clearly demonstrates the existence of pockets of non-immunised population, here specifically the Roma population. A quick risk assessment made by the epidemiologists investigating the outbreak concluded that the minority groups and living in closed communities as described above are at higher risk of measles infection and should be offered a supplementary measles immunisation.

In recent years, similar outbreaks, affecting unvaccinated groups, have been reported in a number of European countries, however, it seemed that the epidemic did not spread to the eastern part of Europe. During 2008, a total of 7,821 measles cases were reported to the EUVAC.NET, and most of them (90%) were from six countries: Switzerland, Italy, the United Kingdom, Germany, France and Austria [9-12].

Acknowledgements

We thank Dr Annette Mankertz and Dr Sabine Santibanez (Robert Koch-Institut, Berlin, Germany) for the prompt investigation and identification of the origin of Bulgarian measles strains. We thank all colleagues from the Bulgarian regional inspectorates for public health prevention and control in Razgrad, Shumen, Silistra and Dobrich for providing essential epidemiological data.

*Authors' correction:
On request of the authors, the paragraph on genotyping results was modified and a figure was deleted from the article after the publication. This change was made on 9 July 2009.

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Plague outbreak in the Libyan Arab Jamahiriya

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Plague is circulating regularly in localised areas worldwide, causing sporadic cases outside Africa and remains endemic or causes limited outbreaks in some African countries. Furthermore, some notable outbreaks have been reported in Asia in the last 20 years. A limited outbreak with five cases has recently been notified by the health authorities of the Libyan Arab Jamahiriya.

Introduction

Plague is a zoonosis caused by the bacillus *Yersinia pestis*. This disease may have caused over 200 million deaths in the history of humanity [1]. The disease is principally transmitted from animal to animal by fleas. Humans usually become infected through the bite of an infected flea (mainly *Xenopsylla cheopis*). The occurrence of bubonic plague cases is therefore the result of the presence of fleas, rodents and humans in a given place at a given time.

Since the first description of what may have been a plague outbreak in 430 BC in Ancient Greece [2], the plague has spread worldwide during the course of several pandemic waves. Between 1998 and 2008, more than 23,278 cases were reported including 2,116 fatalities (case fatality ratio, CFR, of approximately 9%) in 11 countries [3]. Over 95% of the 23,278 cases, however, were reported in Africa with well-identified endemic plague foci (mainly in three countries: Madagascar, the Democratic Republic of Congo [DRC] and Tanzania).

The bubonic plague is the most common form of the disease (93% of plague cases in Madagascar [4] and 81% of plague cases in the United States (US) [5]. Without adequate treatment, the case-fatality rate of bubonic plague ranges from 50 to 90%. Bubonic plague does not give rise to direct human-to-human transmission.

Pulmonary plague is not the most frequent form of the disease (3% of the plague cases in the US, 8% in DRC, sometimes more frequent in outbreaks with sustained human-to-human transmission), but is deadly in almost all cases in absence of adequate and timely treatment. This clinical presentation may give rise to human-to-human transmission through droplet transmission.

Table

Reported human plague cases/outbreaks since January 1945

Country	Year	Location	Confirmed or probable cases	Deaths
Morocco No cases reported since 1945	1945	Countrywide, mainly around Marrakech	811	ND
Algeria No cases reported from 1950 to 2003	1945-1946	Oran	12	1
	1945	Algiers	5	ND
	1946-1950	Countrywide	8	ND
	2003	Kahelia (Tafraoui, Oran)	18	1
	2008	Laghouat	4	3
Tunisia No cases reported since 1945	1944-1945	Bizerte/Ferryville	34	27
Libya No cases reported from 1984 to 2009	1972	Nofilia	18	3
	1976-1977	Tobruk	30	12
	1984	Tobruk	9	ND
	2009	Betnane (Tobruk)	12	1
Egypt No cases reported since 1947	1945	Port-Said, Suez, Ismailia	218	ND
	1946	Port-Saïd, Suez, Ismailia, Damietta	66	ND
	1946-1947	Alexandria	145	39

Source: Department of international and tropical diseases, Institut de Veille Sanitaire (DIT-InVS) based on numerous reports and the literature

Available evidence points to effective prevention of human-to-human transmission of pneumonic plague through isolation and treatment of cases and the observance of standard precautions completed by droplet and contact precautions during healthcare [6,7]. There is no available vaccine for large-scale use.

Outbreak report

On 14 June 2009, the health authorities of the Libyan Arab Jamahiriya reported suspected cases of bubonic plague (including one death) to the World Health Organization in compliance with the Revised International Health Regulations (IHR). The case definition proposed by the World Health Organization was used [8]. The outbreak occurred in a semi-nomadic setting. Subsequent epidemiological investigations by an international team ascertained a total of five cases. Three of these occurred in a family cluster in the Tobruk rural area (near the border with Egypt). The first identified case was a child who presented with pneumonic plague and died. Two siblings were subsequently identified as having bubonic plague. Two other epidemiologically unlinked cases occurred in young women living in the same district. Confirmatory testing is ongoing. Rodent control measures have been implemented locally.

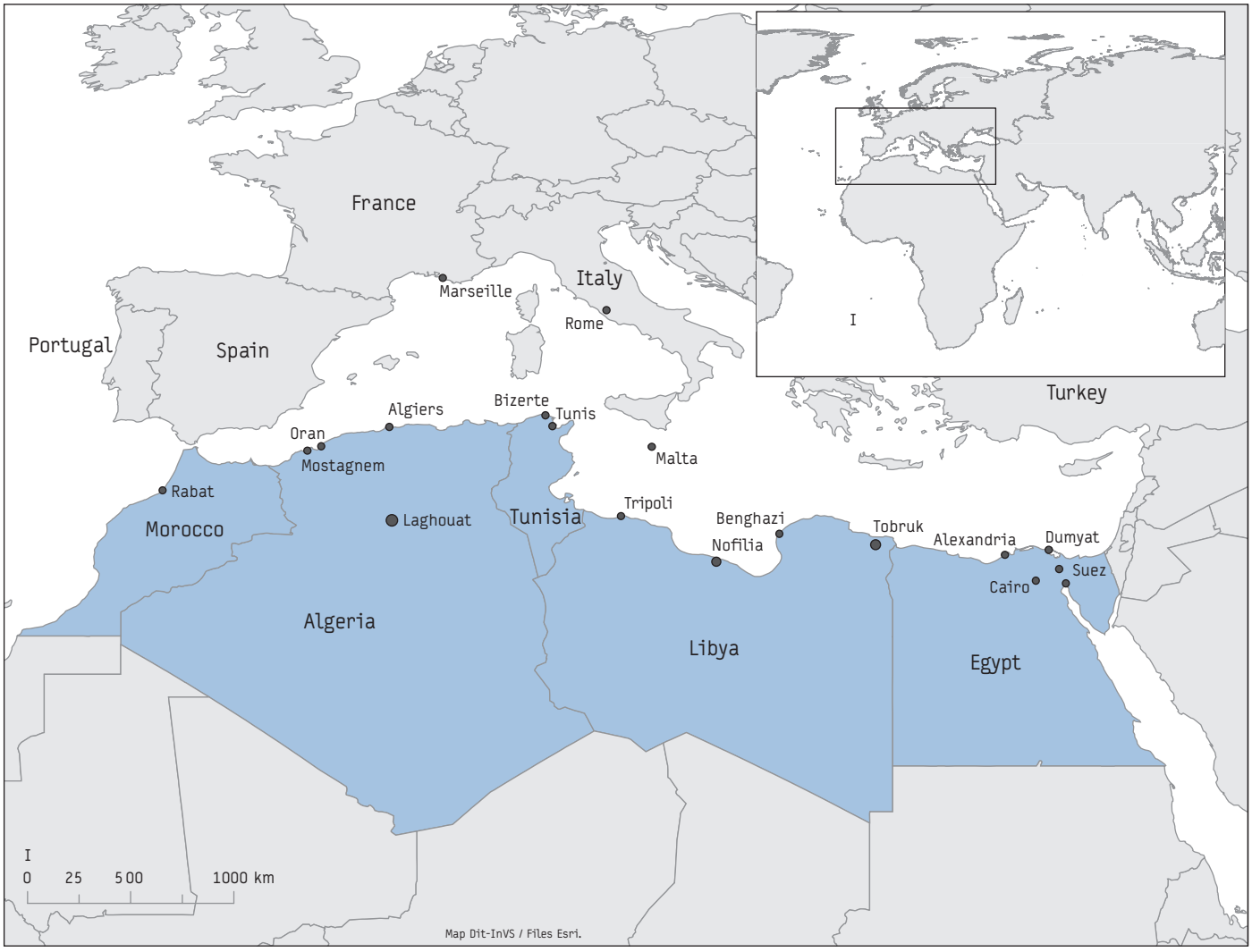
The last outbreak reported in the Maghreb to date occurred in Algeria in July 2008. At that time, the Algerian health authorities reported four cases including three fatalities in Laghouat [WHO, unpublished data]. All identified cases presented with bubonic plague. The last outbreak reported by the Libyan Ministry of Health occurred in 1984 with eight cases of bubonic plague (no deaths) [1]. The last deaths due to plague reported in that country occurred during a 1977 outbreak that affected 11 people (six deaths).

Discussion and conclusion

The implementation in 2007 of the revised IHR and improved surveillance in many countries has strengthened communication

Figure

Map of the Mediterranean region, including locations where plague cases have been reported since 1945.



Source: Department of international and tropical diseases, Institut de Veille Sanitaire (DIT-InVS)

between countries and the World Health Organization. Regional networks have also emerged which facilitate cross-border and regional exchange of public health alerts. The Libyan health authorities have been prompt in describing and reporting the outbreak described here, thereby enabling speedy confirmation and the implementation of control measures.

The Maghreb is no longer considered an endemic area for plague [9]. The recent human plague clusters, however, raise the issue of the persistence of a large focus or of several limited natural foci which have been quiescent for decades and remain capable of "re-emergence" at various dates and locations (Table, Figure). These clusters of human cases are generally sporadic and limited, but they may continue to occur despite the necessary extensive rodent control measures which will probably be insufficient to eradicate the plague reservoir in wild animals. Healthcare workers require training to better recognise signs of a disease which is no longer endemic. Informing and increasing awareness of populations living in and around plague foci, strengthening of local health systems and targeted public health measures around the cases remain the key control strategies in plague-prone areas. Improved knowledge of the natural foci is also a pre-requisite for any rational vector and rodent control

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Modelling of the influenza A(H1N1)v outbreak in Mexico City, April-May 2009, with control sanitary measures

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We use a time dependent modification of the Kermack and McKendrick model to study the evolution of the influenza A(H1N1) v epidemic reported in the Mexico City area under the control measures used during April and May 2009. The model illustrates how the sanitary measures postponed the peak of the epidemic and decreased its intensity. It provides quantitative predictions on the effect of relaxing the sanitary measures after a period of control. We show how the sanitary measures reduced the maximal prevalence of the infected population from 10% to less than 6% of the total population. We also show how the model predicts the time of maximal prevalence and explains the effect of the control measures.

Introduction

In this work we present an analysis based on theoretical considerations, with the aim of understanding quantitatively the effects of the sanitary controls and their relaxation on the evolution of the influenza A(H1N1)v outbreak in Mexico City in the period from April to May 2009. Since the only controllable parameter during an outbreak of this infectious disease is the contact rate, the World Health Organization (WHO) recommends reducing it by avoiding gatherings, closing schools, restaurants, cinemas, etc. These actions result in decreasing the maximum number of infected individuals, and the delay of the epidemic peak. We show that these sanitary measures, followed by a period with measures such as frequent hand washing and other prophylactic measures, can control the outbreak. Using this regime, our model is consistent with the currently available data. Finally, we present a less positive scenario which shows a second peak of the incidence curve after the return to school on 11 May, which might be seen in the real data, once the complete information on incident cases becomes available.

Methods

We used a simple model in terms of the number of parameters, the Kermack and McKendrick model [1,2]. The purpose of using such a simple model was to have a small number of parameters, first to give a rough estimate of the time of maximal prevalence, and second, to analyse the behaviour of the contact rate under the sanitary measures recommended by the WHO. It is generally accepted that the influenza A(H1N1) virus is transmitted by direct contact. There is no evidence that vaccination for seasonal influenza creates cross-immunity to influenza A(H1N1)v virus. Moreover, once the outbreak started there was some evidence of spatial homogeneity in the Mexico City area with cases being reported in different parts of the city. For these reasons, it was possible to use the Kermack and McKendrick model, without considering vaccination, in terms of the proportions

$s(t)=S(t)/N$, $i(t)=I(t)/N$, and $r(t)=R(t)/N$

of the total number of susceptible S(t), infected I(t), and removed R(t) individuals, where the total population N was assumed constant.

The equations for the time evolution of the epidemic outbreak take the form:

$$ds/dt = -\beta N\, s\, i,$$
$$di/dt = \beta N\, s\, i - a\, i,$$
$$dr/dt = a\, i.$$

Here, 1/a was the expected infectious period with an estimated value of 3 days, and βN was the contact rate which in this case controlled the reproduction number Ro. The initial conditions and the initial time for the applicability of the model were determined from the data on the onset of the epidemic (between 10 and 20 April) available from the Mexican Secretariat of Health (Secretaría de Salud de México) [3]. The control measures established on 23 April, changed the contact rate and their effects were modelled using a time-dependent contact rate. We calculated the prevalence and incidence curves integrating numerically these equations. The results were then used to assess the effect of the sanitary measures on the evolution of the epidemic. Finally, we comment that the delay due to the incubation period was not included because according to the Mexican Secretariat of Health, infected individuals become contagious soon after their infection, even before presenting symptoms.

Results

The basic reproductive number Ro=βN/a was estimated at the beginning of the outbreak using the force of infection and an exponential fitting of the data from the Mexican Secretariat of Health. We assume i(t)=exp(λt) at the onset of the epidemic, and substitute this expression in the equation for the infected proportion to obtain the relation Ro=1+λ/a, where λ is estimated fitting the data by least squares method. We used this approach to obtain Ro=1.72 for the outbreak in Mexico City. For the La Gloria community in the state of Veracruz, this same approach yielded an Ro of 1.716, which to two decimal places is the same as the Ro for Mexico City. This estimate is in good agreement with the results of Fraser et al. [4]. From this expression for Ro and from a=0.333, we obtained βN=0.57. This fit in addition gave the interval from 10 to 20 April as the possible time of onset. Moreover, assuming a population of 8x106 individuals, we obtained from the fitting the estimate of 730 actually infected individuals for each reported case. Finally, using the estimated parameters, we calculated the numerical solution of the model and compared it with the observational data reported at the National System of Epidemic Surveillance of the Mexican Secretariat of Health [3].

In curve a) of Figure 1, we show the solution of the model starting at t=P0, which coincided well with the data from before the controls were started. When the control measures were implemented on 24 April, the Mexican Secretariat of Health reported that Ro was approximately equal to 1.3 [3]. With this value we estimated a contact rate βN of 0.44. Assuming this decay of the contact rate, curve b) shows the evolution of the epidemic as calculated from the model. We observed a substantial reduction of the maximal prevalence, at the expense of a delay of the maximum.

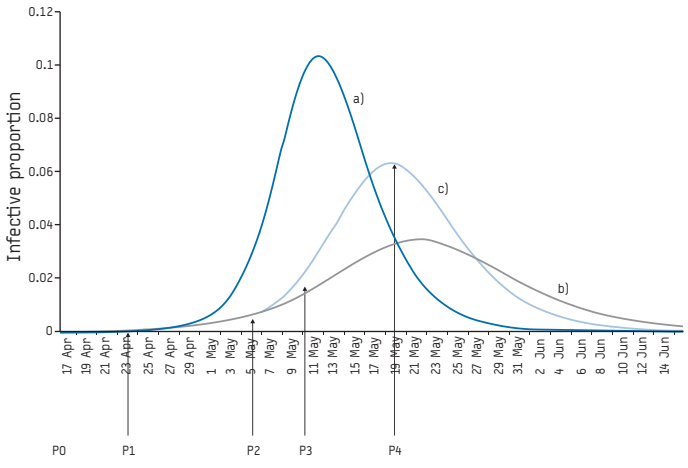
In order to have a preliminary estimate of the effect of the relaxation of the controls, we calculated the prevalence curve i (t). According to the model, a natural time to partially relax the controls would be close to the inflection point P2 of curve a), which corresponds to 6 May. Indeed, the health authorities announced relaxation of the measures near that date, on 1 May. At this date, the contact rate βN increased due to the continuation of normal activities. We assume that it increased from 0.44 to 0.5. We calculated the evolution of the epidemic shown in P3 of curve c). We observed an increase in the maximal prevalence, but no substantial change of the time of arrival of the peak compared to curve b). This calculation predicted the maximum prevalence at P4 on 20 May, which is the maximum of curve c) and corresponds to zero incidence. We remark that these calculations were available on 30 April and we assumed an instantaneous response of the contact rate for these preliminary estimations. Next, we examined in detail with the new available data how a more precise fitting of the model explains in simple terms the observed evolution of the epidemic.

To fit the evolution of the incidence we considered the data shown in Figure 2, and used the probable cases to determine the time evolution of the contact rate as a result of the controls. We start by remarking that when this work was under revision, the Mexican Secretariat of Health reported on 2 June 126 new cases in Mexico City without giving the dates of their occurrence; these cases were therefore not included in the calculations in the paper. Looking at the incidence data for the whole country for 26 May and 2 June, it is obvious that some cases take up to 30 days to be reported [3].

There is a clinical estimate of about five days as the relaxation time of the contact rate βN after sanitary measures are taken. We noticed that a better fit of the incidence data was obtained when a relaxation time of six days was used. We assumed a linear decrease of the contact rate βN between 24 and 30 April, from its original value 0.57 to 0.42. The latter value gave an Ro of 1.27 which was

Figure 1

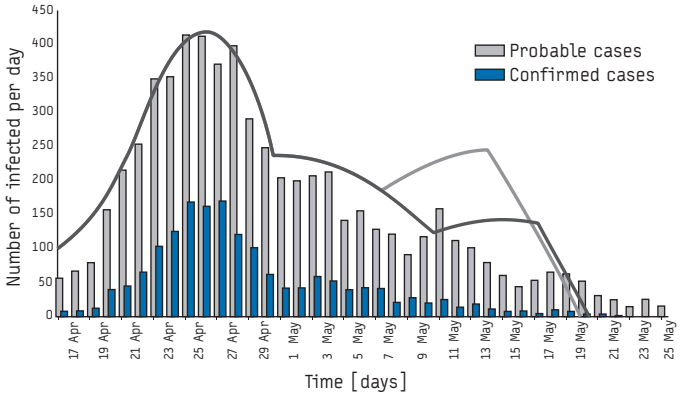
Modelling the evolution of the influenza A(H1N1)v outbreak in the metropolitan area of Mexico City, 17 April - 17 June 2009



P0=17 April, P1=24 April, P2=6 May, P3=11 May, P4=20 May.
a) The evolution of the outbreak with no control starting at April 17.
b) The evolution of the outbreak with control measures starting on April 24.
c) The evolution of the outbreak with the measures relaxed on May 6.
Note the peak of the epidemic at P4 on 20 May.

Figure 2

Incidence curve of the influenza A(H1N1)v outbreak in Mexico City, 17 April – 26 May 2009 (n= 6,114 probable cases and 1,752 confirmed cases)



The bars indicate the incidence in Mexico City. The light gray curve gives the results of the model for a recovery of the contact rate to 0.46 starting on 7 May. The dark gray curve gives the results of the model for a recovery of the contact rate to 0.46 starting on 10 May.

slightly below the value Ro=1.3 given by the Mexican Secretariat of Health. The contact rate βN=0.42 was kept constant for the rest of the period under sanitary measures. With these values, we obtained a good fit to the actual evolution of the epidemic up to 10 May. On 6 and 7 May, universities and senior high schools reopened in Mexico City. Elementary schools and junior high schools reopened on 11 May, but on 10 May was Mother's Day and there was much activity in the city.

The data for May is still incomplete, therefore we present two possible scenarios. In Figure 2, the green curve shows a linear increase of the contact rate βN for six days, starting on 7 May, increasing to the value 0.46 and keeping this constant value until the incidence curve reaches zero on 20 May. The purple curve shows a linear increase of the contact rate for six days starting on 10 May, increasing to the value 0.46 and keeping this constant value until 20 May. The available data seem to indicate that the increase of the contact rate did not start until 10 May, suggesting that the reopening of universities and senior high schools in Mexico City did not have a big impact on the contact rate. However, as we remarked above, the data for this period are incomplete and therefore, we will only be able to see which scenario is more likely to have occurred once these data become available.

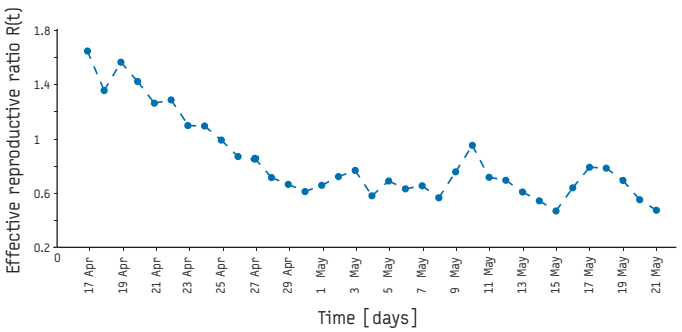
Finally, we note that the curves in the final phase are similar to straight lines and indicate 20 May as the time of zero incidence which corresponds to maximal prevalence. The straight line behaviour is due to the short duration of the peak as seen in the prevalence curves in Figure 1. We therefore propose a closer examination of the data, when available, to understand the duration of the peak in detail.

Figure 3 shows the reproductive ratio R(t) computed with the data from the Mexican Secretariat of Health shown in Figure 2 and using the method of Wallinga and Lipsitch [5] and the mean and standard deviation for the distribution intervals from Carrat et al. and Boëlle et al. [6,7]. This ratio determines the current growth rate relative to its weighted average in the past. It reaches one at the maximum incidence.

The reproductive ratio R(t) was >1 at the onset of the outbreak and decreased slowly until 7 May, crossing the value 1 on 25 April. This behaviour is consistent with the results shown in Figure 2, where the maximum incidence occurred on 26 April, which was the same day when R(t) was 1. After 26 April, both curves descended until 7 May. After this, R(t) showed larger oscillations, which are another indication of a change in the progression of the epidemic due to the relaxation of the sanitary measures. This is the region for which we give two possible scenarios. We observed that both methods complement very well each other.

Figure 3

Effective reproductive ratio R(t), influenza A(H1N1)v outbreak in Mexico City, 17 April – 21 May 2009



Discussion

We have shown how a time dependent modification of a classical model can be used to make reliable predictions on the evolution of the influenza A(HIN1)v epidemic, using only preliminary estimates of the life time of the virus and the initial growth of the incidence curve at the onset of the outbreak. Usually, these are the only available data when an outbreak of a new virus starts. The effect of the sanitary measures was studied modelling the decrease and increase of the contact rate using linear functions of time. The fitting shows a time of relaxation of the contact rate of around six days. The model shows that the sanitary measures had a long lasting effect in that it kept the contact rate low in the period when these measures were in place. Once the sanitary measures were lifted, the contact rate remained much lower than at the onset of the outbreak. The use of antivirals as a prophylactic measure requires an independent study. However antiviral drugs were not used in Mexico during the outbreak.

The time scale of the response to controls and their relaxation show that the present model together with real-time monitoring of the incidence curve can provide reliable forecasts of the evolution of the outbreak, providing another tool for a decision regarding the epidemic alert level during a future outbreak.

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The emerging influenza pandemic: estimating the case fatality ratio

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To determine appropriate influenza pandemic containment and mitigation measures, health authorities need to know the approximate case fatality ratio (CFR) for this new infection. We present four different methods for very provisionally estimating the plausible range of the CFR for symptomatic infection by this pandemic strain in developed countries. All of the methods produce substantially lower values (range 0.06% to 0.0004%) than a previously published estimate for Mexico (0.4%). As these results have many limitations, improved surveillance and serological surveys are needed in both developed and developing countries to produce more accurate estimates.

Introduction

The first published estimate of the case fatality ratio (CFR) for those infected by the influenza A(H1N1)v pandemic strain was based on data from Mexico [1]. This work estimated the CFR to be 0.4% (range 0.3% to 1.5%) based on confirmed and suspected influenza A(H1N1)v-related deaths reported up to late April 2009. Since that date, the new pandemic strain has spread globally and new impact data are available, but we were unable to identify new estimates of the CFR in the literature. Yet this figure is critical if health authorities are to produce reasonable estimates of the likely impact of the pandemic in their particular countries. The estimated mortality burden is particularly useful for calibrating appropriate containment and mitigation measures that balance the likely health gains from interventions against their social and economic costs.

Methods

We considered four different ways to provide provisional estimates for plausible ranges of CFRs in developed countries for this pandemic.

Multiplier method

This method used confirmed deaths and cases reported to the World Health Organization (WHO), but with a range of multipliers for the latter to adjust for under-ascertainment. These multipliers were based on expert judgement that most symptomatic cases of the new pandemic involve relatively mild symptoms and that the great majority of cases were not being identified and reported. For example, spokespeople from the United States (US) Centers for Disease Control and Prevention (CDC) have announced "hundreds of thousands of cases that have occurred in the US" in late May and mid-June 2009 [2,3]. Similarly, one estimate for the United Kingdom was 30,000 cases in the community in May 2009 [4]. Regarding the choice of a multiplier to adjust data on laboratory-confirmed cases of pandemic influenza, we considered the above assessments, which are specific to the current pandemic, to be more informative than past experience with seasonal influenza, which only provides very broad estimates of a potential multiplier. For example, it has been estimated for seasonal influenza in the US that there are 2.3 influenza cases in the community for every outpatient consultation, and 84.1 for every case that is hospitalised (derived from Molinari et al. [5]). But during a pandemic, patients are encouraged to remain at home unless they have "severe illness" or are "at high risk for influenza complications". Additionally, laboratory testing capacity can be quickly saturated in a pandemic and priority is given to those who require hospitalisation or are at high risk for severe disease [6]. These processes will tend to push the ratio of community cases to laboratory-confirmed cases upwards to the multiplier in the range of 10-30 that we judged reasonable for this analysis.

In the calculations we used WHO data for cumulative cases and deaths as of 26 June 2009 [7] for all member countries of the Organisation for Economic Cooperation and Development (OECD), but excluding data from Mexico. The reason for this exclusion was that the epidemic appeared to have started in Mexico and we were concerned about the quality and sensitivity of numerator data in the early stages of the epidemic there, i.e. when it was not recognised that the new pandemic strain was spreading.

Community survey method

This method used an estimate for community cases from a telephone survey done by the New York City Department of Health [8]. It reported that 6.9% of New Yorkers had symptoms of influenza-like illness (ILI) between 1 and 20 May 2009. The report on this survey did not publish confidence intervals, so we calculated these to be 5.6% to 8.5% (for the survey of 1,005 households). Furthermore, at the time of this survey, only 90% of the influenza samples tested in the city were of the current pandemic strain [9], and so we adjusted the CFR estimate accordingly by this proportion. We conservatively used the cumulative death toll for New York City at three weeks after the time period used in this survey (when it was n=12) to allow for a lag in illness progression and then in reporting fatalities to health authorities [10]. We identified that there were no pandemic influenza deaths prior to May [11] and the New York City population of 8,274,500 used in our calculations was that for 2007 [12].

Method extrapolating from seasonal influenza mortality

This method was based on evidence that the elderly population appear to have a relatively low mortality rate compared to other age

groups in this pandemic. Data from Canada on hospitalisations and deaths [13] and US data indicate a median age of hospitalisation at 19 years and of death at 37 years [14]. Hence, we assumed that a CFR for seasonal influenza in the age group of under 65 year-olds could provide a crude approximation for the CFR of the new pandemic strain. To obtain this value we used the full range estimates that could be derived from a detailed US study [15] that used seven models for determining excess mortality attributable to influenza (Table 1).

Method extrapolating from a more 'mature' epidemic

This method was restricted to data from Canada and assumed that the epidemic there was relatively advanced in that the trend data for cases and hospitalisations were suggestive of a peak in early June with a subsequent waning of the epidemic in the following three weeks [17]. To calculate the CFR, we assumed that the epidemic in Canada was half complete in terms of cumulative deaths (with n=21 deaths confirmed as of 26 June [17]), which is possibly a conservative assumption given the low level of new hospitalisations in late June. We also assumed that the cumulative total of symptomatic cases would ultimately reach between 5% of the total population (which is within the range of seasonal influenza) and around 30% (which is approximately the value predicted by modelling for a pandemic with an R0 value of 1.5 [18] as estimated for the current pandemic using the Mexican data [1]).

Results

The four different methods produced a wide range of estimates for the CFR in developed countries, from 0.0004% to 0.06%, a range of 150-fold (Table 2). The ranges for each model overlapped with at least one other model. When these CFR estimates were applied to a country with a population of 10 million, that ultimately experienced a cumulative incidence of symptomatic infection with the pandemic strain of 30%, the total number of deaths would range from 12 to 1,800 (Table 2).

Discussion

All these estimated CFRs are substantially lower than the previously published estimate (0.4% for Mexico). They also differ markedly from the simplistic estimate that would be derived from using surveillance data available only for confirmed cases reported to WHO (i.e. of CFR = 0.29%, based on 110 deaths in 38,409 cases for the 29 OECD countries used in this analysis [7]). A low CFR would be consistent with the mild first wave seen in previous pandemics which caused widespread infection but low mortality [19]. It could also be related to the relatively young age of the

Table 1

Estimates of annual seasonal influenza-associated deaths in the <65 year-old population with average results for the 1976-7 season through to the 2002-3 season* and calculated case fatality ratios

Model	Number of deaths	CFR (5% AIR)*	CFR (10% AIR)*
Summer season rate difference model (10% threshold)	6,574	**0.060%**	0.030%
Summer season rate difference model (15% threshold)	4,509	0.041%	0.021%
Peri-season rate difference model (10% threshold)	3,819	0.035%	0.018%
Serfling-Poisson regression model	2,680	0.025%	0.012%
Peri-season rate difference model (15% threshold)	2,507	0.023%	0.012%
Serfling least squares cyclical regression model	1,475	0.014%	0.007%
Autoregressive integrated moving average (ARIMA) model	809	0.007%	**0.004%**

AIR: annual incidence rates, CFR: case fatality ratio.
Bold figures represent the extremes of the range and are the values used in our calculations for the range of CFRs in Table 2.
* Data from: Thompson et al. [15]
** CFR calculated using the 1990 census data for the US population (n=217,468,042 under the age of 65 years [16]), and assuming 5% and 10% AIR for infection resulting in symptomatic illness.

Table 2

Case fatality ratio for symptomatic infection with influenza A(H1N1)v pandemic strain in developed countries, estimated by four different methods

Method used	Estimated range of CFR	Projected number of deaths in a developed country with 10 million inhabitants where 30% experience symptomatic infection with the pandemic strain*
Extrapolating from seasonal influenza mortality method (US data for <65 year age group)	0.004% – 0.06%	120 – 1,800
Multiplier method (10x to 30x WHO-reported cases)	0.01% – 0.03%	300 – 900
Community survey method (New York City data)	0.002% – 0.003%	60 – 90
Extrapolating from a "mature" epidemic method (Canadian data)	0.0004% – 0.003%	12 – 90

CFR: case fatality ratio.
* Initial estimates suggested the pandemic virus has a reproductive number of around 1.5 [1], so it could be expected to infect around 40% of the population [18] and to cause symptomatic illness in about 30% of people.

majority of cases and the use of highly effective modern treatment for those who are seriously ill.

Although based on the most current data possible, all the methods used still have substantial limitations. The multiplier method merely relied on the judgement (from other experts as well as ours) of widespread and relatively mild disease that is not being reported. Nevertheless, the suggestion of widespread community spread in the US is broadly consistent with the community survey in New York City and another community survey in the US with around 6% cumulative incidence of ILI [14].

The New York City survey was limited by asking only about ILI that occurred during a 20-day period in May and by ignoring illness in April even though there were hospitalisations in New York City in that month. Therefore the method using this survey could have overestimated the CFR, although the opposite could have occurred if some of the reported ILI symptoms were due to other respiratory infections and allergic conditions such as hay fever.

The method that extrapolated from seasonal influenza mortality data in under 65 year-olds was limited in that it effectively considered no aspects of the epidemiology of the new pandemic influenza virus other than the age distribution, i.e. that it seems to affect younger age groups more than older age groups. Yet there is little information comparing the current pandemic strain with seasonal influenza strains in terms of mortality risk in this younger age group. Furthermore, the data from which the estimated range was derived may be outdated in that modern medical care has progressed since the early part of the period used in the particular US study [15] that the estimates were based on.

Although the Canadian epidemic appears to be waning, the method using the crude extrapolation of the course of this epidemic was very simplistic. Indeed, rather than being half complete, this epidemic wave could continue throughout the northern hemisphere summer and beyond.

These methods tended to focus on correcting for under-ascertainment of the denominator, yet there is also a potential bias from under-ascertainment of the numerator of the CFR. Particularly in the early stages of an epidemic there will be a lag in reported deaths and other severe outcomes. Sophisticated statistical methods have been proposed for obtaining adjusted CFR estimates using data from the early phase of an epidemic [20], and these result in adjustment for various time lags and an upward shift of the CFR. However, such adjustments would probably have little effect on the estimates presented in this article which are based on data from country epidemics which have progressed well beyond their early stages (e.g. the Canadian data). There is also the potential for under-recognition of deaths attributable to influenza in those with serious co-morbidities, but this can only be addressed by careful research studies and post-epidemic modelling to determine total excess deaths. Nevertheless, this bias might be relatively smaller in this pandemic where more deaths involve young people. Also, once the new influenza A(H1N1)v strain was recognised there is likely to have been increased sensitivity for diagnosing influenza-related deaths (at least in developed countries where hospitalisation is likely to precede influenza-related death).

All of the presented methods have limitations and could be refined using additional data to provide more robust estimates. Ultimately, such estimates require enhanced surveillance, outbreak investigations in a range of settings, and carefully designed population studies, ideally with serological testing [21]. Additionally, the ranges of CFRs for disadvantaged populations in developed countries and for most of the population in developing countries are likely to be much higher than those estimated here, given likely differences in disease transmission, co-morbidity, access to antivirals and standards of medical care.

Conclusion

We present several methods for provisionally estimating the plausible range for the CFR of the emerging influenza pandemic in developed countries. All methods used have significant limitations, but they collectively suggest that infection with this particular pandemic strain is likely to cause illness with a relatively low CFR compared to an earlier estimate and also to historical standards. A further reason for presenting this range of methods is to encourage data collection that can start to reduce the uncertainty around this important pandemic parameter.

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StatFlu - a static modelling tool for pandemic influenza hospital load for decision makers

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The emergence of a new influenza virus strain setting off a global epidemic can put considerable strain on the current hospital capacity. The task of estimating hospital load during an influenza pandemic event remains difficult, despite a number of tools that are publicly available for decision makers today. The estimate depends on a multitude of parameters, each with associated uncertainties. We provide a new tool, StatFlu, combining advances in static modelling using historic influenza data with a pedagogical interface designed to highlight propagation of parameter settings and uncertaintiesin the output. StatFlu provides graphs of the load on hospital wards as well as primary care units as a function of time, aiding the user in decision making. Here we present the model and software. We also demonstrate it with an example and compare the results with a similar tool.

Introduction

Many successful models using dynamic simulations to estimate the effect of an influenza pandemic have been presented and have been essential in providing the knowledge needed for pandemic preparedness [1-9]. All models have their inherent ailments and there is always a great deal of uncertainty in the estimates they are able to produce. This depends on the data used to calibrate the model as well as the assumptions made by the model itself. The virulence of a new viral strain can only be guessed at. Contact patterns and other social dynamics contribute a similar uncertainty. Conveying the difficulties of modelling and the effect of the many uncertainties in the estimates provided should be a primary objective for modellers.

From the attack rate estimates that dynamic models produce it is possible to estimate the hospital load, using assumptions of how many of the clinically ill are expected to seek medical care. This could be done by extrapolation from historic data on past epidemics or pandemics. It is this last step that is the focus of many static models.

Many publicly available software applications use static modelling. Whether using simulation output or presumed attack rate scenarios, these models translate outbreak data into variables of interest, such as hospital load, cost of treatment or loss of lives. Static models have the advantage that assumptions about social networks and similar factors are already implicit in the data, which makes them very reliable. Generally, fewer assumptions are made which need to be accounted for and the results are more transparent. The two main sources of uncertainty in static models are in the parameters of the extrapolation and in how historic data from a particular region and time is relevant and plausible in another region and another time. The first of these uncertainties can be handled using statistical methods. All models described in this paper have this in common.

A notable example of a static modelling approach available on the internet is FluSurge [10], released by the United States (US) Centers for Disease Control and Prevention (CDC), which can be used to project the total hospital load over the duration of the pandemic. This software, its predecessor without time projection – FluAid [11], as well as slightly adapted versions thereof, have been used by authors in published articles predicting hospital load in several regions and countries [12-17].

The StatFlu project was initiated to bridge the gap between researcher and decision maker and to replace FluSurge, amending several of its flaws, to be detailed below. StatFlu is currently in use at the National Board of Health and Welfare in Sweden. The excess hospital and primary care load due to a pandemic is calculated without intermediate steps using a closed formula, at a resolution of one day. The full variance of the possible scenarios generated by the uncertainties in the input is displayed using a colour gradient in the plots. We have built our model with a bottom-up approach, incorporating the time-distribution from the start. We also allow the user to specify the age-dependent risk of contracting infection, relative to the other age groups, rather than a distribution of the attack rate among age groups, making the model independent of differences in age distribution.

Using StatFlu, the user can immediately see the effects that changing assumptions in attack rate, average susceptibility of age groups, duration of the pandemic and length of hospital stay will have on the hospital load and primary care visit frequency. The uncertainties of other parameters in the model, in particular the risk of hospitalisation of infected individuals, are taken into account by use of a Monte Carlo-type sensitivity analysis [18-20]. The output estimates of 10,000 such simulations are collected and presented so that probable and less probable outcomes are apparent. The objective is for the user to acquire an intuitive understanding for the assumptions behind the estimates.

StatFlu can be downloaded and used freely from www.s-gem.se/statflu.

Previous research

Meltzer *et al.* used Monte Carlo methods to express the uncertainty in a study to evaluate the economic impact of a pandemic influenza outbreak in the US [21]. Using predefined probability distributions they could model a range of estimates. Essential parameters for age group-specific attack rates were collected from various studies of outbreaks of seasonal and pandemic influenza. Parameters were assumed to be either triangular or uniform in their uncertainty distributions. The distributions were randomly sampled and used to calculate mean economic impact. Mean hospital admittance and mortality was calculated with 90% confidence bounds. They also compared results with and without the use of vaccination.

A similar setup was used in France by Doyle *et al.* with slightly different background variables and with a focus on hospital admittance and mortality [22]. Many parameters were taken from the study by Meltzer et al. Also in this study the authors compared scenarios with and without the use of intervention programmes, in this case both vaccination and antiviral pharmaceuticals.

Van Genugten *et al.* used detailed national data collected from seasonal influenzas [23]. Their approach was a scenario analysis. This approach is more pedagogical and the results are more readily applicable. The lack of sensitivity analysis means that only the expected outcome is shown of each scenario. Information on the variability of the output is not provided. This may or may not be problematic depending on the parameter values used.

A missing piece in the first two studies mentioned above is how the hospital load varies over time. It is important to point out that the predicted increase in patient load during a pandemic, whatever the degree of uncertainty, will not happen in one day. The frequency of visits will follow the epidemic incidence curve, which means that the estimated total increase cannot directly be translated into a required capacity.

Reasonable adjustments have been made to amend this. Bonmarin *et al.* [24] published a follow-up calculation to the French study, assuming the shape of the time function would be similar to that of previous seasonal influenza outbreaks as gathered from sentinel data. Van Genugten et al. included a time plot in the original study where the estimated attack rate was distributed along a Gaussian (normal) curve [23]. FluSurge also plots the output on a time axis, although it is not clear what the rationale behind their choice of algorithm is.

In the Results section of this paper, we compare output from StatFlu and FluSurge. In our opinion, the latter is flawed. We are concerned about the appearance of the admissions plot as well as some of the calculations concerning the death rate described in the manual [25]. Most importantly, however, FluSurge will give unexpected results unless the age group proportions in the target country or region matches those of the United States. Both Doyle *et al.* [22] and van Genugten *et al.* [23] have used data from Meltzer *et al.* without the flaw.

It should also be noted that the contribution of static models to understanding the effect of vaccination and antiviral pharmaceuticals is questionable. Usually, the effectiveness of the drug is quoted and used simply as a reduction factor on final outcome [21-23]. However, as with any intervention strategy, antiviral drugs (as prophylaxis or therapy) as well as vaccination, can at best completely halt the spread, but may also have an insignificant impact. The end result is in part due to chance, but more specifically, each prevented case will not spread the disease further and one dose can have a wide-reaching effect in the transmission chain. At the very least a pharmaceutical effect should be used, covering both the effectiveness of the drug and the dynamic effects. Due to the difficulty in this, we decided not to include the feature in the currently available release of StatFlu. However, users should be cautioned against the assumption that antiviral drugs and vaccines are not effective.

Table 1

Variables used in StatFlu, their sources and implementation

Variable	Description	Source	Uncertainty	Implementation/treatment
Gross attack rate	Fraction of population infected	User-specified	Hypothetical	User-specified 5-50%
Duration of epidemic	From first infected to last	User-specified	Hypothetical	User-specified 10-150 days
Population	Population in age groups 0-19, 20-64, >64, by region	Population register [37]	High certainty	Fixed, specified in text file
Duration of hospital visit	Average length of treatment at hospital	User-specified	Attainable, partly hypothetical	User-specified for all ages 1-14 days
Age group-dependent relative risk of infection		User-specified	Hypothetical	Specified for age group relative to the other age groups
Size of risk group	Fraction of age group at elevated risk for complications	Provided by [35]	Definition-dependent, attainable in theory	ca. 2% for the whole population; specified in text file
Risk of hospitalisation	Risk per age and risk group of hospitalisation given infection	Provided by [30,32,33,38] and expert opinion, see Table 3 in [38]	Uncertain, dependent on risk group definition	Sampled from beta-distribution; hard-coded
For primary care load only				
Primary care visits	Yearly primary care visits per region under normal circumstances	Provided by [39]	High certainty	Fixed, editable in text file
Hospitalisations associated with influenza-like illness	Hospital patients coded with influenza	Provided by [35]	Highly uncertain, coding-dependent	Fixed, editable in text file
Risk of primary care visit	Risk per age and risk group of hospitalisation given infection	Provided by [21,32,40] and expert opinion, see Table 3 in [38]	Uncertain, dependent on risk group definition	Sampled from beta-distribution, hard-coded
Fear factor	Deterrence from primary care due to pandemic	User-specified	Hypothetical	User-specified 0-40%

Both Meltzer *et al.* and Doyle *et al.* provide estimates of incidence reduction following either vaccination or antiviral drugs. Wallinga *et al.* [26] have developed the model by van Genugten *et al.* with a dynamic model approach, further developed by Mylius *et al.* [27].

Aims of the StatFlu project

Our priorities in developing StatFlu were:

1. Pedagogical input and output,
2. Full time resolution,
3. Transparency,
4. Visualised variance/uncertainty combined with scenarios analasys,
5. Independence from age distribution.

In our opinion, this work represents an improvement over previous attempts in terms of presentation and, in some aspects, of validity. It should be pointed out that the outcome is still highly uncertain and the intention with StatFlu is to highlight the uncertainty, not conceal it. There is still a danger that the user over-interprets the results. StatFlu is a tool for aiding intelligent decision-making, and the results must always be interpreted by the user based on input and experience.

In a recent version of the model an addition was made to provide figures for primary care load whereby we also explored the possibility of a decrease in load due to public awareness of transmission risk within the health care system. We call this the *fear factor*. Studies conducted during the epidemic of severe acute respiratory syndrome (SARS) support such assumptions [28,29]. A reduction in visits as large as 35% was seen in Taiwan during following the peak of the epidemic.

Methods

A detailed description of the model is given in a separate section at the end of the article.

Data and input

As much of the required epidemiological data is not available in Sweden, as far as we know, we have incorporated many of the figures found in Meltzer *et al.* [21], and references therein, into StatFlu, as we regarded this paper to be the standard in the field [30-34]. Results can therefore be compared with that of other studies based on the same parameters, differences resulting primarily from differences in demographics and less from differences in epidemiological assumptions. A summary of the variables used in StatFlu is given in Table 1.

Regarding the size of the risk groups in Sweden, we used the Swedish Hospital Discharge Diagnosis Register [35] for a rough estimate of the prevalence of certain chronic diseases including heart, kidney and lung disease that increase the risk of developing complications and being hospitalised subsequent to an influenza infection. These data are stratified by age, county and the number of distinct diagnoses. Our results may be considered low compared to estimates in other countries.

In the estimation of the number of primary care visits we used data from the Swedish Hospital Discharge Diagnosis Register on influenza diagnosis in each county during a normal influenza season. We also included estimates on the total primary care visits, taken from Otterblad Olausson [36].

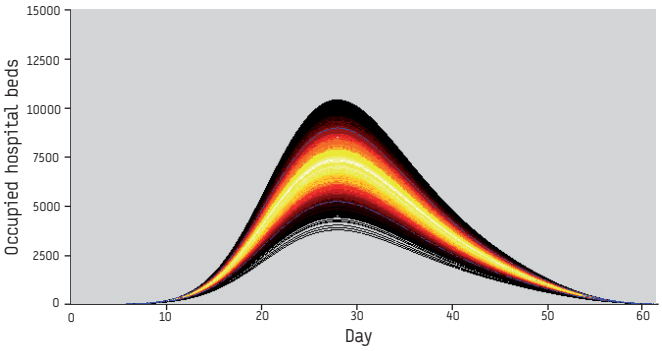
Estimates from Meltzer *et al.* used in our model included the risk of being hospitalised and visiting primary care depending on age group and risk group. We use the estimated lower and upper bounds including the conversion factor used to convert from population risk to risk among afflicted [21].

The users themselves enter the population size and demographics by selecting one of the predefined counties or the whole country. It is also possible to customize the demographics with data from other countries or regions by editing a text file. The user also sets the duration of the pandemic, the average duration of a hospital visit, the fear factor, and, as discussed in the introduction, the age group-dependent relative risk of infection. The user has at their disposal a flexible graphical user interface functional under the Windows operating system.

Table 1 shows the input variables used in the model, the details of which are described below in the Model section.

FIGURE 1

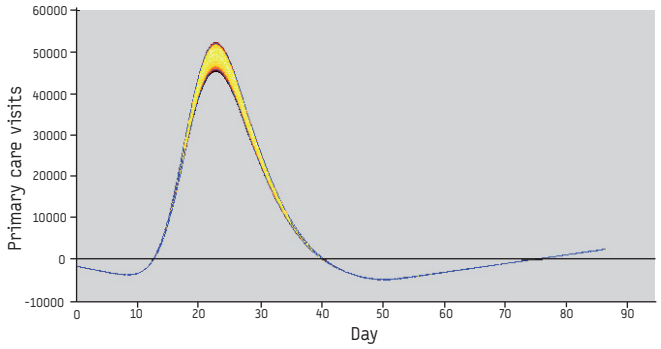
Example of hospital load output from StatFlu, i.e. simultaneously occupied hospital beds



We used Swedish risk group estimates. Blue lines indicate 95% confidence intervals.

FIGURE 2

Example of primary care load output from StatFlu, i.e. visit frequency per day



We used Swedish risk group estimates. Depending of the fear factor, in this case 20%, the curve may initially decrease due to deterrence of visiting the facilities for other reasons than severe influenza illness.

Results

Output of StatFlu and comparison with FluSurge

We provide here (Figure 1) sample outputs from StatFlu based on the whole Swedish population, using Swedish values for risk group distribution as described above, an attack rate of 25%, a duration of 90 days of the epidemic, and 10 days average time in hospital (full colour figures are available from the StatFlu website, www.s-gem.se/statflu). We also used the values from Meltzer *et al.* for age group-dependent relative risk of infection [21]. The most probable scenario estimates the number of simultaneously occupied beds to about 7,500 at the peak of the outbreak, at 28 days.

Figure 2 shows the primary care visit load, i.e. the number of visitors per day. We set the fear factor to 20%, resulting in an initial decrease in the patient rate. 23 days into the outbreak, the increased rate of patients is just short of 50,000 in the most probable scenario.

For comparison with FluSurge we chose the same settings between the two applications as far as was possible. This included population size, attack rate, hospital visit duration and duration of pandemic. In StatFlu, we used values from Meltzer *et al.* for age group-dependent relative risk of infection [21]. We also used the risk group partition from Meltzer *et al.* In FluSurge we set the probability for intensive care unit and ventilator requirements to =0, because the types of care are not differentiated in the current version of StatFlu. The results are slightly higher than in the previous scenarios modelled for Sweden, probably due to the size of the risk groups (see Discussion).

Table 2 shows the weekly admission rate as modelled in FluSurge. The last row shows the number of patients in hospital, and these values can be compared to the plotted output from StatFlu in Figure 2.

The two applications give similar estimates, as is to be expected in this comparison scenario. The daily distribution of admissions given by FluSurge is the interpolated curve in Figure 3.

Figure 4 shows the corresponding plot from StatFlu accomplished by setting the duration of stay =1.

The results provided by StatFlu represent an improvement over FluSurge in terms of graphic display of the load and the uncertainty, the daily resolution of the results and the robustness of the calculations.

Discussion

Regarding the size of the risk groups in Sweden, we used the Swedish Hospital Discharge Diagnosis Register [35] for a rough estimate of people inflicted with certain chronic diseases including heart, kidney and lung disease. Persons so diagnosed were assumed to have an increased risk of developing complications and being hospitalised subsequent to an influenza infection. We calculated that roughly 2% of the population belong to the high-risk group. This in contrast to 15% in Meltzer *et al.* and 10% in van Genugten et al. [21,23]. The difference has to do with limiting the number of diseases included in the query, including persons over the age of 64 years based only on the discharge data in the high-risk group and not including pregnant women, infants and institutionalised persons. Meltzer *et al.*, for example, included by default 40% of the population above the age of 65 years.

All individuals registered at a Swedish hospital during 2006 with one or more of a predetermined set of symptoms or diseases were counted. Ultimately, our goal was to sample the entire population that had at one point in time carried such disease, i.e. the prevalence. The prevalence is generally very hard to estimate accurately without conducting a large scale study. We restricted our method to taking hospital discharge frequency to be an estimate of the prevalence. The sample period of one year was chosen arbitrarily. An extension of the sampling period would probably yield a higher number of cases but would also make it likely that a significant number is lost due to death during the sampling period.

It might be considered a flaw that we used many epidemiological parameters from an American study, as the relevant figures should reflect conditions for the nation in which they are applied. But the figures in Meltzer *et al.* [21] are boundary values reflecting a range of possible values. Based on these values we performed an uncertainty analysis as described above. As a benefit we have the opportunity to compare results with Meltzer *et al.* and all others using the same values.

Model

Occupancy

We postulated that the pandemic incidence is normally (Gaussian) distributed over time, adopted from [23]. Notation is according to.

$$Ae^{-(t-\mu)^2/2\sigma^2}$$

This gives a symmetrical distribution with thin tails at either end. Adjusting the appearance to a more recognisable form can be accomplished by time substitution with a cubic spline, as

Table 2

Tabular weekly output data from FluSurge

Weeks	1	2	3	4	5	6	7	8	Total
Weekly admissions	2,027	3,379	5,068	6,420	6,420	5,068	3,379	2,027	33,789
Minimum scenario	893	1,489	2,233	2,829	2,829	2,233	1,489	893	14,889
Maximum scenario	2,667	4,446	6,669	8,447	8,447	6,669	4,446	2,667	44,458
Peak admissions/day				1,000	1,000				
No. of influenza patients in hospital	2,027	4,299	6,602	8,721	9,438	9,182	7,296	5,038	

The row "Number of patients in hospital", corresponds to the curve from StatFlu plotted in Figure 2.

explained below. As the incidence is normally distributed, so is the number of daily admissions. The procedure gives the curves a more recognisable form but may give false confidence in the output.

As the incidence is normally distributed, so is the number of daily admissions. We have complete control of the mean and standard deviation of this distribution. The mean m is the point in time when the pandemic is expected to reach its peak. μ is the standard deviation and controls the horizontal distribution over the duration of the outbreak. A is a normalising constant. The duration of the pandemic, the average length of each hospitalisation and the risk of admission, given symptoms, are assumed independent of the attack rate. All these parameters are assumed given at the start and can be altered by the user.

The number of admissions during the period t_1 till t_2 is normally distributed according to

(1)

$$S(t_1,t_2) = A\int_{t_1}^{t_2} e^{\frac{(t-\mu)^2}{2\sigma^2}}\,dt$$

The total admittance during the pandemic, S, is the integral taken over the whole time axis which is shown to be .

$$S = \sqrt{2\pi}\sigma A$$

The Gaussian is defined on an infinite axis in both directions, but we took the end of the epidemic t_e to be the point in time when the number of remaining admissions drops <1, i.e.

(2)

$$1 = A\int_{t_e}^{\infty} e^{\frac{(t-\mu)^2}{2\sigma^2}}\,dt.$$

Symmetry similarly defines the start of the pandemic t_0. Setting the peak of the epidemic to $\mu = t_e/2$ and $t_0=0$, σ can be extracted by solving the integral.

The hospital load was considered by introducing the average duration of each hospital visit into the model and calculating the number of simultaneously occupied hospital beds, the occupancy. Let τ be the average duration of each hospital visit. The number of simultaneously occupied hospital beds, the occupancy B(t), is then given by

(3)

$$B(t) = A\int_{t-\tau}^{t} e^{\frac{(t-\mu)^2}{2\sigma^2}}\,dt.$$

Time substitution

The Gaussian distribution, though a good starting point and easy to manipulate mathematically, is decidedly not realistic enough with its symmetric shape. Epidemics are not symmetric. The most familiar shape is one that climbs quickly, almost exponentially, and reaches a peak before declining with a long tail. This is the shape that is generated by the standard SIR (Susceptible – Infectious – Recovered) model [41]. To accommodate the user's expectations, we choose to manipulate the form to resemble something recognised from classical epidemic models, using a one-to-one function $t = g(t)$ on the interval $[t_0,t_e]$. This function must obey

$g(t_0) = 0$
$g(t_e) = t_e$
$g'(t) = 1$, $t \leq 0$ and $t > t_e$

in order not to change the tail values. The definite solution to the integral (1) now must carry with it a correction e. We chose a piecewise continuous spline:

Figure 3

Hospital load in comparison scenario from StatFlu, to be compared to the output from FluSurge in Table 2

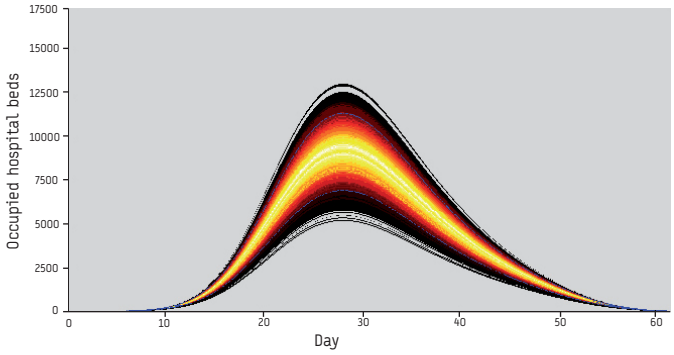


Figure 4

Daily admission rate in StatFlu along a more realistic epidemic curve, to be compared with Figure 3

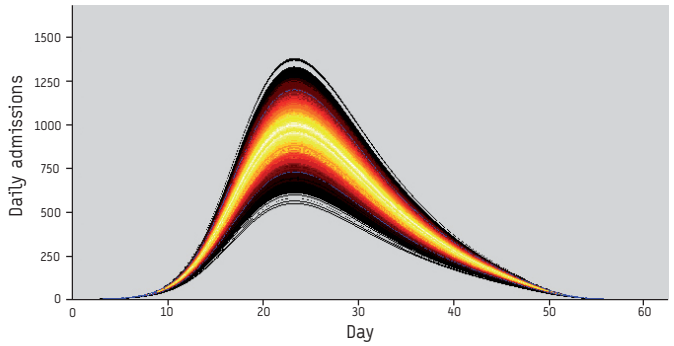
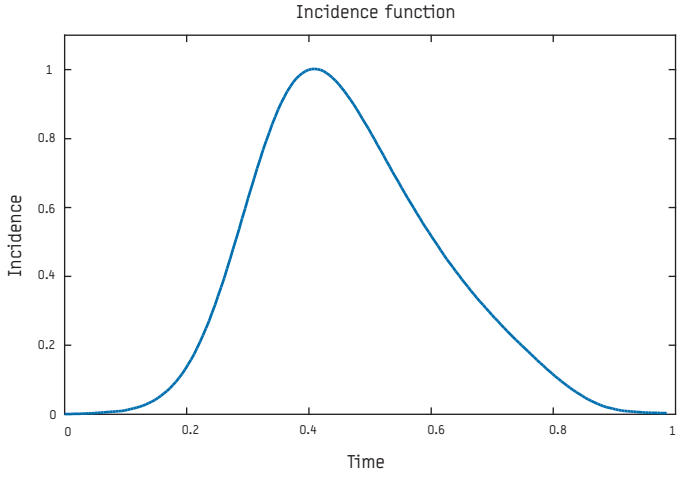


Figure 5

The new incidence curve, a normal distribution with time substitution $t=g(t)$.



$g(t) = t$, $t \leq t_0$ and $t \geq t_e$
$g(t) = -2.9t^3 + 1.8t2 + t$, $t_0 < t \leq .4t_e$
$g(t) = 1.9t^3 - 1.7t2 + t + .50$, $.4t_e < t \leq .74t_e$
$g(t) = 8.2t^3 + .21t2 + .53t + .73$, $.74t_e < t \leq .94t_e$
$g(t) = -112t^3 + .5.1t2 + 1.6t + .91$, $.94t_e < t \leq t_e$

A correction was calculated numerically for feasible integer values of t_e ensuring that the total number of cases remains constant. The resulting distribution is depicted in Figure 5.

The other definitions in the previous sections were redefined by replacing t with $\tilde{t}$.

The time substitution is implemented in the current release of StatFlu without the possibility to turn it off. This possibility will be an important amendment to upcoming releases, to make sure the user recognises the artificiality of this approach. Otherwise, there is a danger of too much confidence in the graph.

Monte Carlo simulation

The uncertainty in the risk of succumbing to illness upon infection and being admitted to hospital is modelled using a beta-distribution over a given uncertainty interval (see introduction). The beta-distribution was chosen for its applications in Bayesian sensitivity analyses [42], opening the possibility of creating a distribution based on point value estimates of risks from an expert panel. The intervals are specific for each combination of age group and risk group, six in total. 10,000 random values are picked from each distribution producing a value for the total admittance, S, according to equation (1). This value in turn is used to calculate according to equation (2).

It should be noted that the values from the size distributions are coupled, i.e. not considered independent. More specifically this entails that a single value is picked randomly from a uniform distribution and then transformed to each of the six beta-distributions, giving rise to six different value of risk for admission. The admittance is calculated separately and then added. The purpose of the coupling is done to minimise the variance and is justified by the fact that the uncertainty in the risk of admission originates in our ignorance. It is less probable that we overestimate the risk for one group and at the same time underestimate it for another [18-20,42].

Numerical model

A number of measures have been taken to maximise the speed of calculation, making StatFlu quite efficient. Despite the complexity of the numerical calculations, it is the graphic output that proves to be the major bottle neck.

σ is calculated for 10,000 values of admittance originating from a beta-distribution. First the attendance values are sorted. A large repository of random beta distributed values comes pre-calculated for each age/risk group and σ according to equation (2) is solved numerically by StatFlu using binary search. A standardised normal distribution is read from file as a lookup table with a resolution of 10^{-4} for parameter t<10. The table is searched using binary search down to the two closest t values and then linearly interpolated between them. The s values are calculated from both ends of the sorted list. The results of the previous calculation can thereby be exploited to narrow even further the binary search interval.

The σ values are then binned to desired resolution. The central values in the bins are what produces the plotted curves, in other words the integration in equation (3) is made for these central values only. The integrations are carried out with Simpson's formula with a resolution of hospital visit length τ =1 day. By saving intermediate partial results, all the integrations can be carried out in a single sweep.

Primary care and fear factor

StatFlu also outputs the expected increase in primary care visits during an influenza pandemic. These calculations work along the same lines as hospital load. The main difference is that a visit to a primary care unit does not have duration as such. We have also included the concept of deterrence from approaching the health care system as a consequence of a pandemic scare, the so called *fear factor,* $\tilde{\alpha}$. Studies conducted during the SARS-epidemic support such assumptions [28,29]. A reduction in visits as large as 35% was seen in Taiwan following the peak of the epidemic. The effect of the fear factor is to attenuate the increase of primary care visits. The fear factor is set by the user, between 0% and 40%. The total resulting reduction is distributed over the whole duration, linearly increasing up to the peak of the pandemic and then decreasing to zero again.

If μ_0 is the probability of visiting a primary care unit given disease, excluding those with influenza, μ_{i0} is the same risk including influenza, and N and N_i is the population at risk of disease including and excluding influenza, the total number of primary care visits can be expressed as:

(4) $$n_0 = (N - N_i)\,\mu_0 + Ni\mu_{i0}.$$

We might as well assume that the whole population is at risk for disease, thereby setting N to the population size. We also know the frequency of primary care visits [36]. The frequency of primary care visits due to symptoms of influenza-like illness (ILI) is estimated using the number of admitted with ILI symptoms and the associated risk given in Meltzer et al. [21]. The unknown risk mi0 can now be extracted from the above expression (4).

During a pandemic we assume that m0 and indeed also mi0 are valid, modified by the fear factor a:

(5) $$n_p = (N - N_{ip})\,\mu_0\alpha + N_{ip}\mu_{i0}\alpha.$$

As detailed in the section on Monte Carlo simulation, we form a beta-distribution for the uncertainties in m0 and mi0. The difference in primary care visits in the pandemic versus non-pandemic case is np - n0. This value will be different for all combinations of age group and risk group. We calculate, as before, each of these separately and then sum them up. The result is treated in the same way as the total admittance S in the subsection on occupancy, including time substitution and distribution over time. The difference is that the visit does not have duration in time in the sense that the value on the graph should be interpreted as *visits per day*. Hospital visit duration τ is always set =1.

What remains to be explained is how the fear factor a is treated over time. To assume a constant fear factor would merely offset the output curve downwards – a clearly unrealistic immediate cut in primary care visit frequency from the first day of the pandemic. We have opted for a model where the reduction is increases linearly to peak at the same time as the incidence, and then decreases to zero again. To this end we calculate the total reduction due to the fear factor and distribute it accordingly over time. Finally we subtract this function from the output number of primary care visits. The fear factor model makes it possible for the curve to increase initially, but to decrease, even below zero, towards the epidemic peak.

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ECDC guidance on chlamydia control in Europe: next steps

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On 30 June 2009, the European Centre for Disease Prevention and Control (ECDC) launched the guidance on chlamydia control in Europe [1]. This guidance document aims to support the European Union Member States in developing and improving their national chlamydia control strategies. Such strategies need to take into consideration not only the clinical and epidemiological factors (such as the prevalence of chlamydia in the population), but also the healthcare systems, infrastructure and resourcing. The ECDC guidance on chlamydia control proposes a step-by-step approach which should ensure the presence of prevention systems for sexually transmitted infections (STI) and of patient management systems before considering complex population-based interventions such as screening. It takes into account the current heterogeneity with respect to control activities across Europe as demonstrated in the review of chlamydia control in 2006-2007 [2].

Evaluation of the guidance and subsequent activities include enhanced surveillance of chlamydia and a repeated survey on chlamydia control activities in the European Union (EU) and in the European Economic Area and European Free Trade Association (EEA/EFTA) Member States. At European level, the target is to reduce the proportion of countries reporting no (or less) organised activity (currently 45% of EU and EAA/EFTA countries). A second goal would be an increase in the evidence on which recommendations for screening should be based, as the current evidence is insufficient. In order to collect comparable data on chlamydia case reports at international level, enhanced chlamydia surveillance at European level needs to be implemented. For a better interpretation of the data across Europe, chlamydia experts suggested collecting also information on the chlamydia testing volumes across countries. These activities will contribute to the evaluation of the outcome and impact of chlamydia control programmes.

In achieving these objectives, the role of the ECDC will be to collect data on chlamydia as part of the enhanced surveillance of sexually transmitted infections (STI) that is starting this year. Following the transfer of the European Surveillance for Sexually Transmitted Infections (ESSTI) network to ECDC, STI data will be collected at EU level in the European Surveillance System (TESSy). In addition, the ECDC plans to update the results of Screening for Chlamydia Review in Europe (SCREen) project [3] in individual Member States in 2010-2011.

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