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Original Article

Modelling of H1N1 Flu in Iran

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Background: This year's new H1N1 flu strain has rapidly become a serious threat worldwide. This pandemic calls for urgent preparedness to mitigate its impact as much as possible. Employing this knowledge, we simulated a model of the outbreak of H1N1 in two cities of Iran (middle size: Kerman and metropolitan: Tehran).

Methods: We developed a compartmental model to predict the expected number of patients who might develop severe (S), very severe (VS) disease or die (D). We assumed that, in winter, the Basic Reproductive Number (R_{0w}) would reach 1.6 in Kerman and 1.8 in Tehran, respectively. Corresponding figures in summer varied from 1.2 (R_{0sMin}) to 1.4 (R_{0sMax}) in Kerman and from 1.3 to 1.5 in Tehran. Moreover, we checked the effect of the number of imported infectious cases at the beginning of the outbreak based on predictions.

Results: A minimum lag of six months was observed between introduction of the virus (June 2009) and beginning of the outbreak (December 2009). The lag was sensitive to the number of infectious cases and the R_0: a lower R_0 postponed the peak. In Kerman, with R_{0sMax} of 1.4, the number of S, VS, and D were 2,728, 546 and 468 respectively. Corresponding numbers in Tehran with R_{0sMax} of 1.5 were 83,363, 16,673, and 14,291.

Conclusion: Since the number of S and VS cases would be crowded over a short period of time, the health care system most probably would not be able to provide appropriate services unless special measures are taken in advance. By reduction of R_0 and the number of introduced infectious cases the peak of the outbreak might be postponed to the end of 2010. This would provide a golden opportunity to vaccinate a considerable proportion of the population.

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Keywords: Compartmental models • flu • influenza • outbreak • pandemic • prediction

Introduction

Influenza, a respiratory infection caused by the influenza virus, occurs as an annual outbreak. Seasonal flu causes an average of 36,000 direct and indirect deaths each year in the USA. Therefore, it is a major public health threat which increases demands on both in and outpatient care providers.[1,2] The disease can become a pandemic when a particular strain of the virus spreads rapidly amongst humans and causes intermittent worldwide outbreaks. Major pandemics have caused the loss of millions of lives, for example, the 1918 – 1919 Spanish flu caused claimed at least 20 million lives worldwide, while the 1957 and 1968 pandemics led to nearly one million deaths.[1]

The H1N1 strain of influenza virus (known as the swine flu) is a highly contagious strain with the capacity to create a new worldwide pandemic. Within a few days the virus was spread far from its country of origin (Mexico) into different continents.[3] On July 11, 2009 the World Health Organization (WHO) declared a global pandemic of influenza[4] and regarding its fast expansion, announced the current phase of pandemic alert as six.[5]

People of all age groups are susceptible to this new virus. In addition, considering the virus' high contagiousity, it is transmitted rapidly from an infected to a susceptible person.[6] Although the case fatality rate of this strain is not higher than

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seasonal variants, considering its high attack rate it can potentially cause a disaster. Therefore, the total number of hospitalized patients, those needing intensive care and overall mortality is expected to be high as a result of the high numbers of people becoming infected.

Since October 4, 2009, the deaths of 4,525 people from this strain has been confirmed worldwide.[7] Under these circumstances, policy-makers face the difficult task of making appropriate and timely decisions to mitigate the serious adverse effects over a short period of time. Emergency decision making could be rather difficult because of the very rapid surge in the numbers of severe and very severe patients and the completely different situation as compared to the per-epidemic phase.[3]

While prediction of the features of influenza pandemics is difficult, preparedness against such pandemics is highly recommended by the WHO[8] and many countries have pandemic preparedness plans.[9] Furthermore, surveillance on both local and global scales enables policymakers to act during the early phase of a pandemic.[3]

Based on the above explanation, it is very important for health policy makers to have access to outbreak models in different scenarios to predict the speed of expansion under different circumstances. In addition, such models forecast how many general and intensive care hospital beds may be needed in the event of a disease outbreak.

Here we describe models of the new influenza pandemic in two different populations: a city with a population of 500,000 (almost the size of Kerman, the centre of Kerman province in south-east Iran) and a metropolitan, large city with a population of 10,000,000 (almost the size of Tehran, the capital of Iran) in order to sketch the outlines of what may be the impact of such a pandemic on health care systems in such cities.

Materials and Methods

At first we created a simple but comprehensive compartment model. To do this, we have extended the classic SEIR model (Susceptible, Exposed, Infected/Infectious, and Recovered). Our model shows how a susceptible person moves along different states and experiences different outcomes (Figure 1).

Susceptible people contract the virus through contact with infectious people (recovered subjects or cases with mild, severe, or very severe flu). However, the contact rate of these groups with

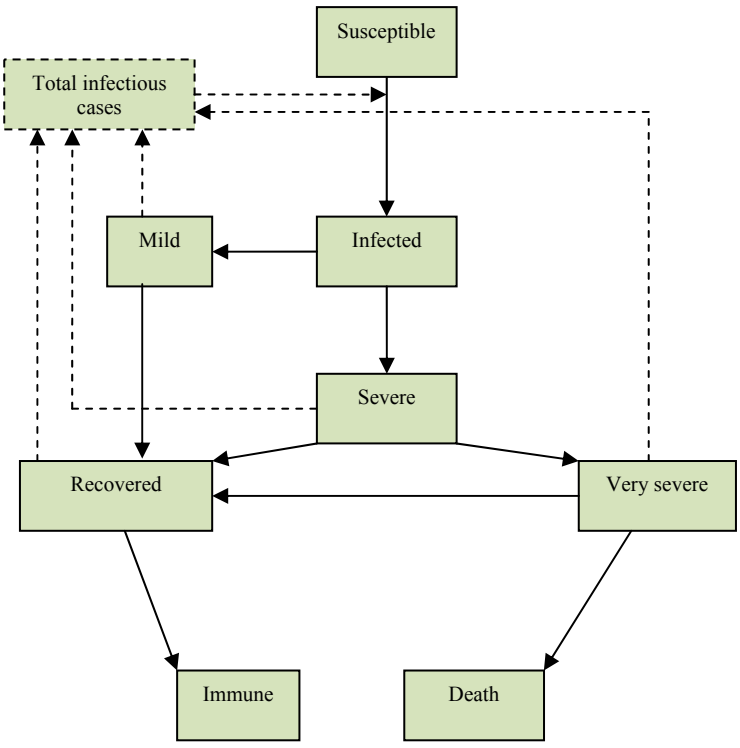


Figure 1. Conceptual framework for influenza transmission within a human population

susceptible individuals would not be the same. We assumed that the effective contacts of severe and very severe cases with susceptible subjects were half that of the asymptomatic/mild cases.[10] Moreover, we supposed that the risk of transmission during the recovery phase is around 70% less than that during the active disease phase because of their partial acquired immunity and also more caution would be exerted with their contacts. It should be noted that since almost all of the infectious cases (97%) have a mild presentation (Table 1), the contact rates of severe and very severe cases do not change the final results.

Infected subjects may present a mild form of the disease or severe symptoms which call for hospitalization. Patients with severe disease might then recover or develop very severe conditions and need ICU care. We assumed that only ICU patients might die.

In the next step we parameterized the model based on information available in the literature. We presented the parameters in Table 1; these parameters were extracted from published papers and the information presented by WHO.[1,3,11-17] Basic Reproductive Number (R_0) is defined as the average number of new infections that an index case generates in a susceptible population.[18] This indicates that severe and mild outbreaks are associated with high and low R_0 values.[17] The innovative aspect of our model was the seasonal variation of R_0. This statistic is estimated to vary from 1.4 to 2.4[1,19] in the US and from 1.28 to 2[3] in the UK. As summarized in Table 1, in our model, R_0 peaks around the end of December in winter (R_{0w}; 1.6 for Kerman and 1.8 for Tehran); while in different scenarios its value in summer varies from 1.2 (R_{0sMin}) up to 1.4 (R_{0sMax}) for Kerman, and 1.3 up to 1.5 for Tehran during the end of July[13] (Mathematical equations are given in the Appendix). To run our models, we assumed that ten infected cases were introduced to each of these two cities in July 2009 which is very close to the date that the first positive H1N1 case was detected in Iran in mid-June.

In the next part of our modeling, we checked the impact of the number of imported infectious people at the beginning of the outbreak. In these models, only the maximum summer R_0 statistics (1.4 for Kerman and 1.5 for Tehran) were applied. We compared the number of deaths, hospitalized patients and those who need ICUs in different scenarios assuming that 1, 20, and 100 infectious cases entered Kerman or Tehran.

In all analyses, we assumed that individuals were mixed at random, the population size was constant over time (no birth or death rates were taken into account), the transition rates would remain invariant over time, and no intervention (such as vaccination) was applied during the outbreak time. A recent study showed that simple models are very likely to be sufficient for these types of policy making.[20] We also ignored the fact that, in response to the outbreak, the community might change its behavior.

The models were run in Model-Maker version 4. In our models, each time click was one day and we ran the models for 1000 days (around 3 years). We present the number of predicted severe (hospitalized) and very severe cases (who need ICU) as well deaths in line curves. The death line presents the cumulative number of those who would lose their lives due to this infection between

Table 1. Parameters used in the conceptual framework of influenza model

Parameter	Value used	Reference
Latent period	2 days	1, 3
Duration of infectivity	7 days	22
Duration of moderate disease	4 days	1
Duration of severe disease	7 days	11, 12
Duration of recovery	5 days	23
Percentages of asymptomatic or mild patients	97%	6, 12 – 13
Percentages of severe patients	3%	6, 12 – 13
Percentages of severe patients who needs ICU care	20%	6, 12 – 13
Percentage of death among patients in ICU	60%	6, 12 – 13
R_0 (in summer)	1.2 (R_{0sMin}) up to 1.4 (R_{0sMax}) for Kerman 1.3 (R_{0sMin}) up to 1.5 (R_{0sMax}) for Tehran	3, 13, 14, 16, 24, 25
R_0 (in winter)	1.6 for Kerman 1.8 for Tehran	3, 13, 14,16, 26, 27

Having reviewed the latest statistics about R_0 around the world, based on the results of an expert panel, theR_0 values, during winter and summer, for Kerman and Tehran were defined

days 0 and 1000. However, the lines of severe and very severe curves present the number of people who need in-hospital and ICU care on each day (t_i), respectively. This allows us to check the distribution of subjects with severe disease so as to predict the outbreak peak.

Results

To predict the peak of the outbreak, the numbers of patients who might develop severe and very severe disease daily are plotted in Figure 2. In addition, to estimate the total number of patients

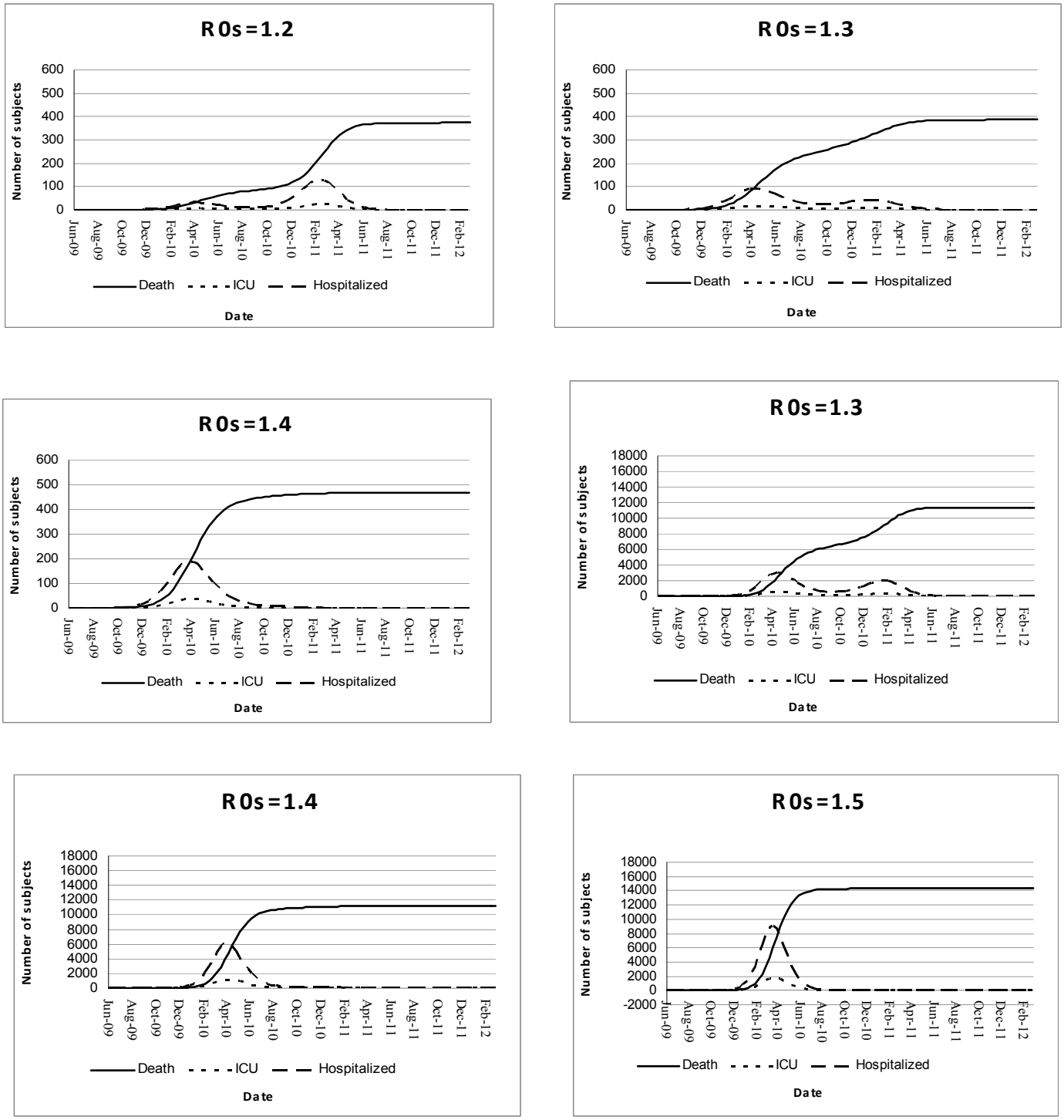


Figure 2. Cumulative number of deaths and the number of people who need in-hospital and ICU care on each day in Kerman (top panels) and Tehran (bottom panels) with different R_0s during summer

who might die during the epidemic course, the cumulative number of deaths is plotted.

Based on Figure 2, the date of outbreak peak depends highly on the R_0 during the summer. In Kerman, with an R_{0sMin} of 1.2, the maximum number of hospitalized cases would be expected around Feb 2011. However, with an R_{0sMax} of 1.4, the outbreak peak might happen up to ten months earlier (April 2010). This means that a reduction in the R_0 may postpone the outbreak. Furthermore, this leads to a 20% reduction in the total number of individuals who would become sick during the course of the outbreak (104,018 for R_{0sMin} of 1.2 versus 129,877 for R_{0sMax} of 1.4).

In Tehran, applying the R_{0sMin} of 1.3, the number of hospitalized patients followed a bi-modal distribution with a dominant peak in May 2010 and another less prominent peak in February 2011. It seems that higher R_0 values during summer (1.4 and 1.5) would not change the outbreak peaks but influence the number of hospital beds required (65,415 versus 83,363, respectively). Furthermore, reduction in the R_0 from maximum to the minimum (1.5 to 1.3) lead to a 20% reduction in the number of cases that might develop the disease (3,969,650 versus 3,161,360).

The Kerman model predicts that, with R_{0sMin} of 1.2, 2,185 patients will need hospitalization, 437 might need intensive care, and 375 deaths would be expected (Figure 2). With an R_{0sMax} of 1.4, the comparable numbers would rise to 2,728, 546, and 468 respectively (Figure 2).

In Tehran, with an R_{0sMin} of 1.3, a total of 66,389 patients would need in-hospital care, 13,278 will need intensive care and 11,381 might die. If we assume an R_{0sMax} of 1.5, more than 80,000 cases would be hospitalized, of whom more than 16,000 would need intensive care and more than 14,000 would die.

The impact of the number of infectious patients at time zero

We then evaluated the impact of the number of imported infectious cases (1, 20, and 100) at time zero. In the Kerman model, with R_{0sMax} of 1.4, the maximum estimated number of required hospital beds during the outbreak varies between 105 and 283 (in one and one hundred infectious cases, respectively). When only one infectious case exists, the outbreak would happen between October and December 2010 (Figure 3, top left panel). In the case of 20 and 100 infectious cases, the outbreak might happen 9 and 11 months earlier, respectively (March and January 2010). Corresponding curves are given in Figure 3, top middle and top right panels.

In Tehran, applying an R_{0sMax} of 1.5, if we modeled with one infectious case at time zero, the outbreak peak would be in May 2010 (six months earlier than that in Kerman) where 5,393 hospital beds for that single day would be required (Figure 3 bottom left panel). If 20 or 100 infectious cases are introduced at time zero, the outbreak would happen two to four months earlier (in March or January 2010, respectively, Figure 3, bottom middle and bottom right panels).

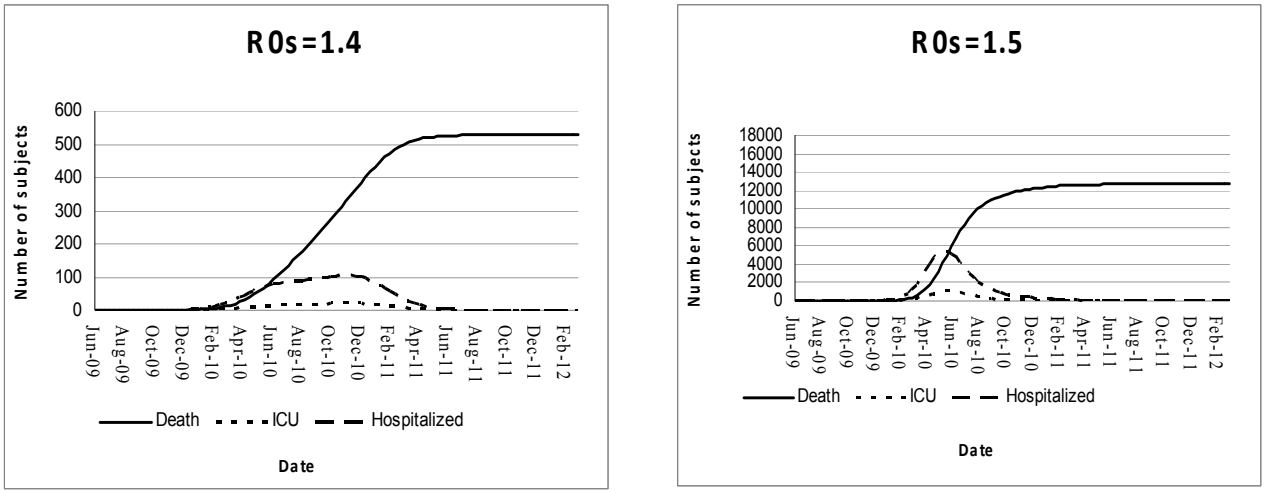
Discussion

Our models showed that the shape of H1N1 outbreaks in Kerman and Tehran are different. Their shapes were dependent on the minimum value of R_0 during summer and also the number of infectious cases imported at time zero. Generally, our data shows that the peak of outbreak in Tehran is much sharper and occurs earlier.

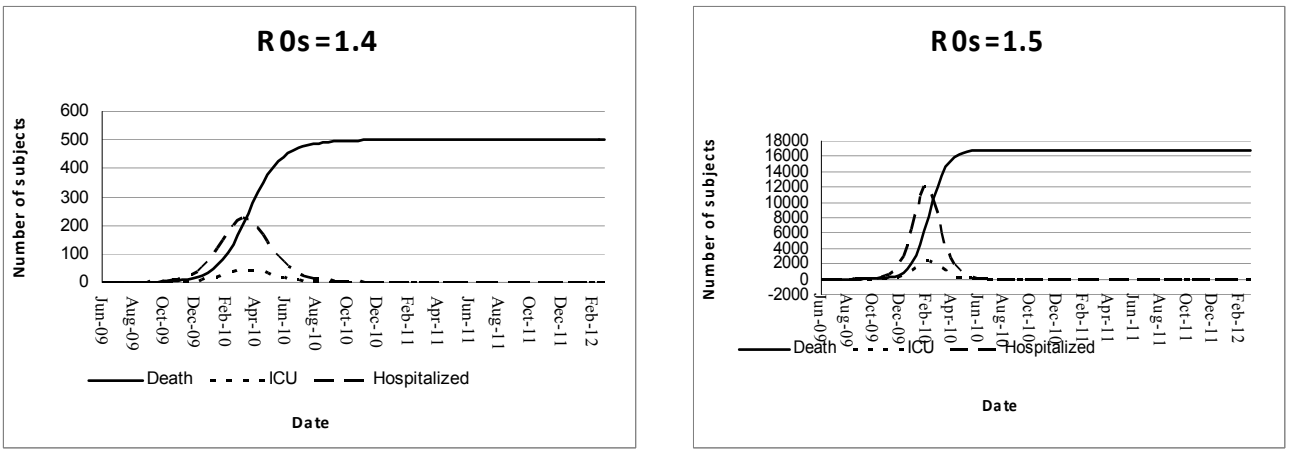
Extending the basic SEIR model, our model reveals the number of hospital beds required in the outbreak course as well as the number of expected deaths. This information should be important to policy-makers who are responsible for providing both out and in-patient care services to the community. This helps them to make efficient decisions based on the best available evidence, not just according to their personal judgments or their experience in non-emergency situations.

Generally speaking, our model shows that the burden of disease would considerable. Providing appropriate out and in-patient hospital care as well as providing intensive care facilities to such a large number of those in urgent need over a very short period of time is undoubtedly a wearisome and serious task. It seems that the number of required hospital and ICU beds is more than the available capacity in both Kerman and Tehran during the peak of the outbreak. Therefore, the health care system is expected to have special and efficient plans to prepare for that difficult time. The surge in the number of severe and very severe cases and deaths are very sharp at this peak and without adequate preparedness, the whole community will face a real disaster and turmoil. Without any doubt, in the current situation, the health care system would not be able to provide enough inpatient services during the peak of outbreak. Lack of services would increase the complications of

10 infectious case



20 infectious case



100 infectious case

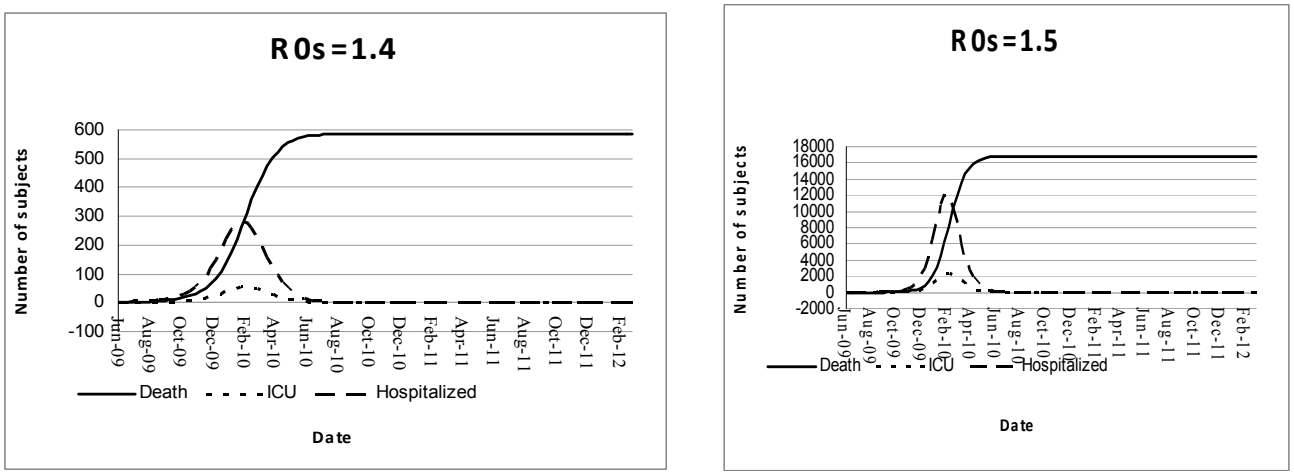


Figure 3. Impact of the number of imported infectious cases at time zero on outbreak peak in Kerman (top panels) and Tehran (bottom panels.

disease and death. However, it is not easy to predict the number of deaths as a result of this shortage. To address this question, we have to have some information about the clinical sequence of disease without special care, which is beyond the scope of this paper.

Nearly all of our models showed a six month or longer lag between the introduction of the virus into the population (June 2009) and the beginning of the outbreak (December 2009). This is a golden time for the community to prepare itself to face the outbreak. More importantly, we showed how much the shape of the outbreak depends on the transmission capacity in the lag phase.

Decreasing the minimum R_0 not only decreased the number of hospitalized patients and mortality, but it also postponed the peak. This means that if we increase our protective measures during the pre-outbreak phase, we can considerably decrease the burden of disease in 2009 and based on the current situation we most likely have access to an efficient vaccine in 2010 to suppress the second outbreak peak under real circumstances. In other words, any delay in outbreak time provides a golden opportunity for the health care system to optimize its resources, for researchers to find an effective vaccine, and for the community to be trained to control and decrease the burden of the outbreak. This can noticeably reduce the sinister consequences of this outbreak.

Our findings have also revealed that the shape of outbreaks is highly dependent on the number of imported cases. Therefore, any measures that can restrict the number of imported cases should be undertaken in order to decrease the burden of the unavoidable epidemic. Educating people, responsible authorities and the involved bodies in this regard is of utmost importance.

When reliable data is available, it is important to take into account in the modeling, the fraction of susceptible patients who will be at low and high risk of acquiring influenza, so as to develop an age-structured model.[23,24] However, due to the lack of information, or reliable data and as the first movement, we decided to avoid complex models. This is because it has been recommended that, due to uncertainty in parameters, it would be better to use a general compartmental model with relatively few parameters.[20]

R_0 was the most important parameter in our models. There is a huge variability in the estimation of this statistic. This is due to specific location, pandemic wave, the spatial aggregation of the data, or estimation method applied.[17] As an example, an estimation of the R_0 for 1918 Spanish flu for different regions of the world varies from 1.5 to 5.4.[25–29] Moreover, the transmissibility of seasonal influenza where a fraction of the population is vaccinated is estimated to be 1.3 with year-to-year variability.[30] In another study, to develop the Canadian pandemic plan for the heath sector, R_0 value is estimated to be between 1.4 and 1.8.[16] In the US and UK estimates varies from 1.4 to 2.4 (with an average of 1.68)[1,19]and from 1.28 to 2,[3] respectively. Corresponding figures for the Netherlands was 1.68 to 1.89.[14,15]

Main factors that affect R_0 are pathogenecity of the virus and network size (the number of effective contacts of people per day). Therefore, for the same virus, the higher the network size, the larger the R_0. Following this argument, we assumed that the R_0 for Tehran would be slightly larger than that in Kerman.

Similar to any other predictions, our models were made based on assumptions.[31] Our knowledge about the new H1N1 virus is limited and all of the parameters used in our models were extracted based on limited data available from outbreaks around the world. Although these assumptions may be subject to change as epidemiology of the virus is better known, but according to the available evidence we do not expect dramatic alterations in our estimations. Most of the estimated parameters are comparable with the values of the seasonal flu virus as well as the experience of different countries.

In addition, in order to fulfill the research questions, we fixed many other influential parameters. However, under real circumstances, most of these parameters may change simultaneously. In other words, in our predictions we ignored the impact of some of the main factors such as the changes in behavior of the community in response to the outbreak. There is a very long list of such influential factors with a great uncertainly around each of them. In nearly all models, we have to explore the impact of only a few parameters and evaluate how much the results are sensitive to changes of these variables.

For a well-developed model, sensitivity analysis and consideration of uncertainty in parameter values is very important. In our future analysis and hopefully in the next papers, we will explore the influence of changing main parameters using sensitivity analysis. However, with this limitation, the impacts of changes in R_{0s} were very

obvious and there is less concern about the low validity of our final conclusions.

It should be noted that differences between the results applying different R_{0s} does not necessarily mean that changes observed was the direct impact of change in R_{0s}. However, based on our best knowledge, there is no solution to explore this issue.

In conclusion, we showed that the risk of H1N1 flu is considerable and without appropriate preparedness, we may face a national disaster with paralyzing consequences in the months to follow. However, a slight reduction in transmission in the pre-outbreak phase and restriction of the number of imported infectious cases can postpone the peak of the outbreak from winter 2009 to winter 2010.

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Appendix[1]

Beta (summer) = R_{0s}/ (duration of infectivity)
Beta (winter) = R_{0w}/ (duration of infectivity)
Seasonal beta = ((((Sin ((t+273.5) * 2 *3.1415 /366) + 1) / 2) * (Beta (winter) – Beta (summer)) + Beta (summer))
Adjusted number of infectious cases (t) = (Mild (t) + 0.5 Severe (t) + 0.5 Very severe (t) + 0.3 (Recovered (t))
Susceptible (t+1) = Susceptible (t) – Susceptible (t) (adjusted number of infectious cases) (seasonal beta)
Infected (t+1) = Infected (t) + Susceptible (t) (adjusted number of infectious cases) (seasonal beta) – Mild (t) (0.97) – Severe (t) (0.03)
Mild (t+1) = Mild (t) + Infected (t) (0.97) – Recovered (t) (0.2)
Severe (t+1) = Severe (t) + Infected (t) (0.03) – Recovered (t) (0.8) – Very severe (t) (0.2)
Recovered (t+1) = Recovered (t) + Mild (t) (0.2) + Very severe (t) (0.4) – Immune (t) (0.2)
Very severe (t+1) = Very severe (t) + Severe (t) (0.2) – Recovered (t) (0.4) – Death (t) (0.6)

[1]Constants applied are derived from literature (see Table 1)