

Effects of interventions on the demand for hospital services in an influenza pandemic: a sensitivity analysis

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Summary

Principles: The evaluation of the capacity of a country's public health system in case of an influenza pandemic is essential for preparedness planning. Only a few studies have compared existing medical resources with those required during a severe pandemic.

Methods: A sensitivity analysis was performed with the freely available simulation tool *InfluSim* to explore the expected number of outpatient visits and the hospital bed occupancy in an influenza pandemic in Switzerland. Plausible ranges were defined for unknown parameter values and random samples were taken from these ranges. A set of four simulations were run for each parameter constellation, considering no intervention, contact reduction, antiviral treatment or a combination of both interventions.

Results: It was found that the peak number of outpatient visits of influenza patients would still

be manageable with the current number of active physicians with practices in Switzerland, and that the demand of hospital beds would only be sustainable in the case of mild pandemics and a good compliance of the combined interventions. In a severe pandemic, the demand on intensive care unit beds would be unsustainably high.

Conclusions: The range of outcomes, resulting from parameter uncertainty, reaches from outpatient and hospitalization values which are half as high as the median to values which double the median. Pandemic preparedness plans would profit from having into account the severity of the outbreak and the efficacy of the interventions in their protocols.

Key words: influenza pandemic; preparedness planning; sensitivity analysis

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Introduction

The evaluation of the capacity of a country's public health system in case of an influenza pandemic is essential for preparedness planning. It has frequently been stated that an influenza pandemic may over-tax the health system's capacity for ambulant and stationary care of patients [1-3]. Some studies have compared existing medical resources with those required during a pandemic. These studies use static models which do not account for uncertainty in the parameter values, but consider a few fixed values for attack rates, hospitalization rates and mortality rates [4-10]. Only van Genugten & Heijnen (2004), Menon et al.

(2005) and Nap et al. (2007) consider therapeutic use of neuraminidase inhibitors. As pharmaceutical and non-pharmaceutical interventions influence the course of a pandemic wave, it must be evaluated whether they can lower the burden of the public health system to a supportable level. Such an evaluation is paramount for appropriate contingency planning. However, a major difficulty in this evaluation arises from the uncertainty of how contagious and pathogenic a yet unknown influenza strain will be. To address this problem, plausible ranges were defined for the yet unknown parameter values and normally distributed

random samples were taken from these ranges. For each combination of sampled parameter values, the course of the pandemic wave was simulated, using the freely available program *InfluSim* [11, 12]. Therefore a whole range of plausible influenza pandemics were generated, for which the

number of persons seeking medical help or needing hospitalization was evaluated. Simulations were performed with and without interventions and differences were calculated for each set of parameter values to evaluate the intervention effects.

Material and methods

The freely available simulation tool *InfluSim* version 2.1 (<http://www.influsim.info>) was used, a deterministic compartment model based on a system of over thousand differential equations which extends the classic SEIR model by clinical and demographic parameters relevant for pandemic preparedness planning. Details of the simulation and a discussion of the standard parameter values have been described previously [11, 12]. The simulation produces time courses and cumulative numbers of influenza cases, outpatient visits and hospitalizations. The analyses presented here employ demographic parameters from Switzerland (see Appendix). Using the standard set of *InfluSim* parameters, about one third of all infected individuals are expected to become severely ill and to seek medical care. Patients seeking medical care are referred to as “outpatients” throughout this paper. An exponential

distribution is used to model the delay between the onset of symptoms and seeking medical care; on average, patients visit a doctor after 24 hours. If a patient seeks medical care within 48 hours after onset of symptoms, he or she is given antiviral treatment. Antiviral treatment reduces the duration and degree of infectivity of the case and the number of hospitalizations [13].

As many parameters of future viruses or the effects of interventions and the population’s compliance to intervention measures are uncertain in advance, an uncertainty analysis was performed by randomly choosing values for key parameters such as the basic reproduction number R_0 and others listed in table 1 from realistic ranges. All random parameter samples were taken independently by assuming normal distributions with a mean value in the middle of the interval given in table 1. The standard deviation was chosen such that 99% of the samples lie within the interval (fig. 1b). A total of 100 000 different combinations of parameter values were sampled and a set of four deterministic simulations were performed for each parameter constellation, considering the following scenarios: no intervention, social distancing (contact reduction), antiviral treatment and a combination of both. Social distancing comprises contact reductions in the general population and of cases according to disease severity (table 1). Antiviral treatment is given on average 24 hours after onset of symptoms (but not later than 48 hours). It reduces the infectivity of patients and alleviates their course of disease, thus preventing a fraction of hospitalizations (table 1). From each simulation, the peak number of outpatients, the cumulative number of outpatients, the peak hospital bed occupancy and the cumulative number of hospitalizations were extracted. To evaluate the relative intervention effects, each simulation outcome was divided by the corresponding result of the no-intervention scenario. Finally, the results were related to the available (national average) number of hospital beds [14] and the number of physicians in practice (general medicine, internal medicine and pediatrics) [15]. The model also allows for HCW to be affected by disease but in the current study, the authors opted for a simplification and only considered national averages for the number of physicians and hospital beds. A more detailed analysis per canton, on the temporal evolution of the capacities could be done in the future.

Table 1
Stochastically sampled parameters and sampling intervals.

Randomly sampled parameter	99% sampling interval
<i>Infection and disease</i>	
Basic Reproduction Number R_0	1.5–3.5 ^a
Initial infectivity of infected individuals ¹	75–95% ^b
Fraction of infections remaining asymptomatic	25–50% ^c
Relative infectivity of asymptomatic ²	0–100% ^d
Hospitalization factor ³	0.5–1.5
<i>Antiviral treatment</i>	
Reduces infectivity of treated cases by	60–98% ^e
Prevents hospitalizations of treated cases by	49–69% ^f
<i>Social Distancing</i>	
Contact reduction in the general population	5–25%
Contact reduction of moderately sick cases	0–20%
Contact reduction of severely sick cases at home	10–30%
Contact reduction of hospitalized cases	20–40%

^a Chowell et al. 2006 [18]

^b Central value of 85%, equivalent to assumptions by Ferguson et al. 2005 [22]

^c 33% asymptomatic, cf. Longini et al. 2004 [13]

^d Central value of 50%, see Longini et al. 2004 [13]

^e Hayden et al. 1999, 2004, Kaiser et al. 2003, Longini et al. 2004 [13, 23, 24]

^f Kaiser et al. 2003 [24]

¹ “Initial infectivity” determines what fraction of potentially infectious contacts occur in the first half of the symptomatic period (50%: infections are equally likely on every day; 85% strong concentration during the first half of the symptomatic period).

² “Infectivity of asymptomatic” is used for the infectivity during the pre-symptomatic period as well as for the average infectivity of individuals with asymptomatic infection. A value of 100% refers to the infectivity of symptomatic cases.

³ “Hospitalization factor” is used to modify the standard parameter values which determine how many cases need hospitalization or die, depending on their age and risk group (cf. table A1 in the Appendix).

Results

For the no-intervention scenario, some epidemic curves are depicted in figure 1a, and the distribution of the total number of outpatient visits is given in figure 1c. Outbreaks tend to progress more slowly and lead to relatively small numbers of cases if the basic reproduction number R_0 is small. High epidemic peak values and large cumulative numbers of cases are reached if R_0 is high and if the infection is highly contagious at the beginning of symptoms (parameter x_{50}). Figure 1d shows the correlation of the total number of outpatients and the peak number of outpatients.

In the no-intervention scenario, a median number of 26 500 outpatients per 100 000 individuals would be expected, with a 99% region of tolerance ranging from 17 000 to 33 000 (fig. 2a). Antiviral treatment and social distancing can alleviate the public health situation as shown in figures 2a–d. Social distancing alone can reduce the cumulative number of outpatients by 17% (median); similarly, antiviral treatment alone can reduce it by about 14%. A combination of both interventions can even lead to a median reduction

of nearly 40%. In the no-intervention scenario, a median number of 630 hospitalizations per 100 000 individuals would be expected with a 99% region of tolerance ranging from 270 to 1050 hospitalizations. This number is reduced by a median fraction of 18% using social distancing, and by 58% using antiviral treatment. Combining both interventions reduces it by 70%. Note that uncertainty in the parameter values can imply considerable variation in the expected number of outpatients and hospitalizations (fig. 2a and c), as well as in the corresponding relative reductions.

Although cumulative numbers may be an important issue, the epidemic peak values determine whether a public health system is capable of dealing with a pandemic.

Therefore, the peak number of outpatient visits and the peak hospital occupancy were calculated and related to the available resources in Switzerland. Using the average Swiss values of 100 physicians and 390 hospital beds per 100 000 inhabitants, the no-intervention scenario yields a median peak number of 20 outpatient visits per doctor (99% range from 5 to 35) and a median peak demand for 60% of all available hospital beds (99% range from 15 to 115%; fig. 3a–b). Social distancing reduces these results to peak values of 13 outpatient visits per physician and 35% of the hospital bed capacity. Antiviral treatment alone reduces the results to 13 outpatient visits and 18% of the hospital bed capacity. Combining both interventions further reduces the peak numbers to 5 outpatient visits per physician (with an upper 99% reference limit of 17) and 6% of the total hospital bed capacity (with an upper 99% reference limit of 25%). Note that an effective intervention does not only reduce the peak percentage of hospital beds, but also reduces the uncertainty of the prediction, thus allowing for more precise planning of intervention effects.

These results are encouraging, but the available capacity of intensive care units (ICU) may become the most important pandemic bottleneck in hospital settings. Assuming that 15% of hospitalized influenza patients need intensive care [16] and using a total number of 6.4 ICU beds per 100 000 people, the capacity of Switzerland falls short of the median peak demand of 34 ICU beds in the no-intervention scenario, being 532% of what is currently available (fig. 3b, right axis); even the lowest value of its 99% region of tolerance exceeds the total available capacity 100%. Social distancing alone can reduce the median demand to 293% of the available capacity and antiviral treatment alone reduces the demand to 134%. Only a combination of both interventions leads to a median demand of 52% of the available resources, but the upper 99% reference limit is still more than twice the total ICU capacity of Switzerland.

Figure 1

Variability in the number of outpatients and their distribution originating from variability in the parameters under the no-intervention scenario (population size 100 000 individuals). (a) Epidemic curves for nine out of 100 000 realizations, representing the 10%, 20%, ..., 90% percentiles of all realizations, whereby ranking is based on the cumulative number of outpatients. (b) Parameter values for each realization are sampled independently from normal distributions (means given in bold, 99% of the values lie within the ranges specified by dotted lines, except b_A which is truncated). R_0 : basic reproduction number, x_{50} : cumulative infectivity during the first half of the symptomatic period, c_A : fraction of infections remaining asymptomatic, b_A : relative infectivity of asymptomatic compared to symptomatic cases, f_k : factor by which the *Influsim* default percentage of hospitalizations was varied (see table A1 in the Appendix). (c) Distribution of the cumulative number of outpatients. (d) Correlation between the cumulative number of outpatients and the number of outpatients at the peak day. Both values approach zero for very low values of R_0 .

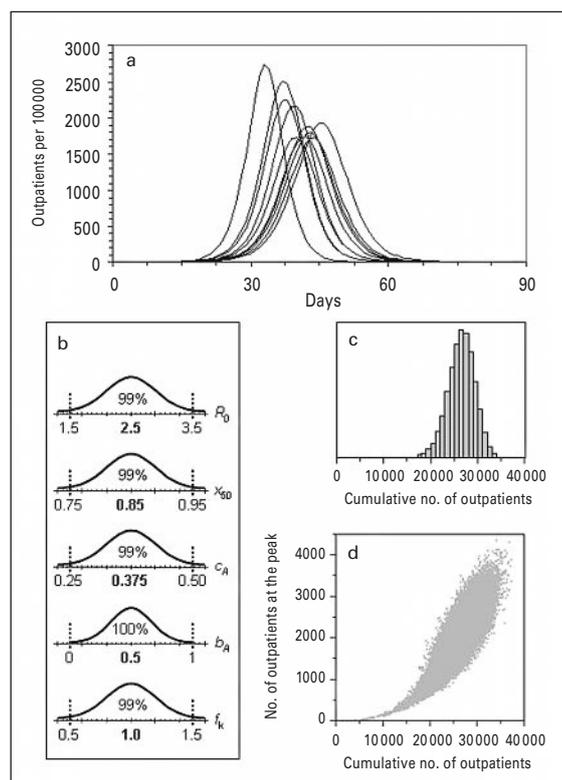
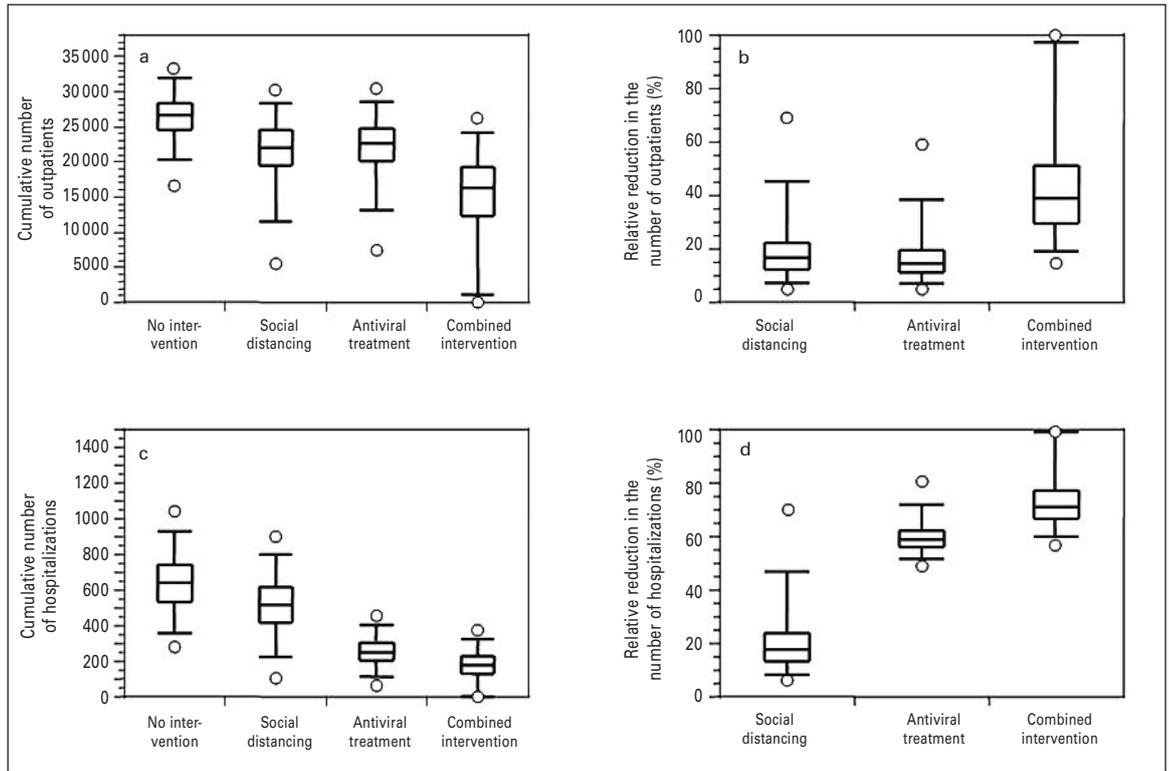


Figure 2

Effects of social distancing, antiviral treatment and a combination of both interventions compared to the no-intervention scenario. All results derive from 100 000 random parameter sets as explained in the text (population size 100 000 individuals). Box and whiskers plots show percentiles from bottom to top: 0.5, 2.5, 25, 50, 75, 97.5 and 99.5%, representing 99% of the simulation results between circles, 95% between whiskers and 50% within the box, respectively. Relative reductions (expressed as a percentage) are calculated by comparing pairs of simulations with and without intervention employing identical parameter values. (a) Total number of outpatient visits, (b) prevented outpatient visits as a percentage of the no-intervention scenario, (c) total number of hospitalizations, (d) prevented hospitalizations as a percentage of the no-intervention scenario.



To further elucidate this, it is necessary to take a closer look at the time course of the ICU demand during a pandemic wave (fig. 4a–b). If social distancing is the only intervention, the demand caused by flu patients exceeds the available capacity for three or four weeks even for mild pandemics (fig. 4a). If antiviral treatment is effective and combined with social distancing, the median curve has a peak demand of 61% of the total capacity, exceeding the level of 50% for two weeks (middle curve in fig. 4b). If it is generally

assumed that, at most, 50% of the total ICU capacity can be made available for flu patients, 5.5% of all flu patients with ICU demand will not be adequately treated in the median case of figure 4b, and 39.5% in the case of the more pessimistic 90% percentile. Mild pandemics (10% percentile, right) could be handled for with the available resources. The corresponding percentages for social distancing only are 77.6%, 66.3% and 39.0% for the 90%, 50% and 10% percentile, respectively (fig. 4a).

Discussion

Due to the uncertainties in parameter estimates for Influenza, it is important to consider ranges of parameter values. Sampling random values from reasonable intervals and using them in a

deterministic simulator allows translating input uncertainty into expected output variability. The wide regions of tolerance for the total number of outpatients and hospitalizations (fig. 1a–d) show

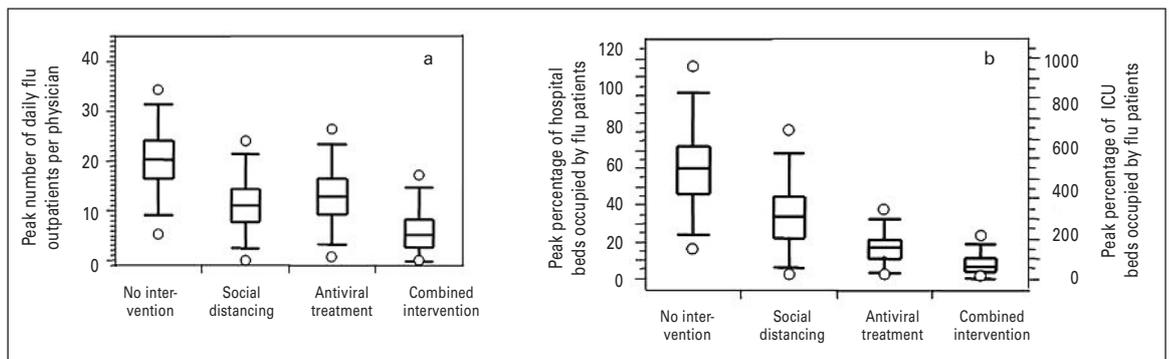


Figure 3

Simulation results of different intervention scenarios resulting from 100 000 random parameter sets as explained in the text (population size 100 000 individuals). Box and whiskers plots show percentiles from bottom to top: 0.5, 2.5, 25, 50, 75, 97.5 and 99.5%, representing 99% of the simulation results between circles, 95% between whiskers and 50% within the box, respectively. (a) Peak number of outpatient visits per physician in practice, (b) left axis: peak percentage of available hospital beds occupied by influenza patients, right axis: peak percentage of available ICU beds needed for influenza patients.

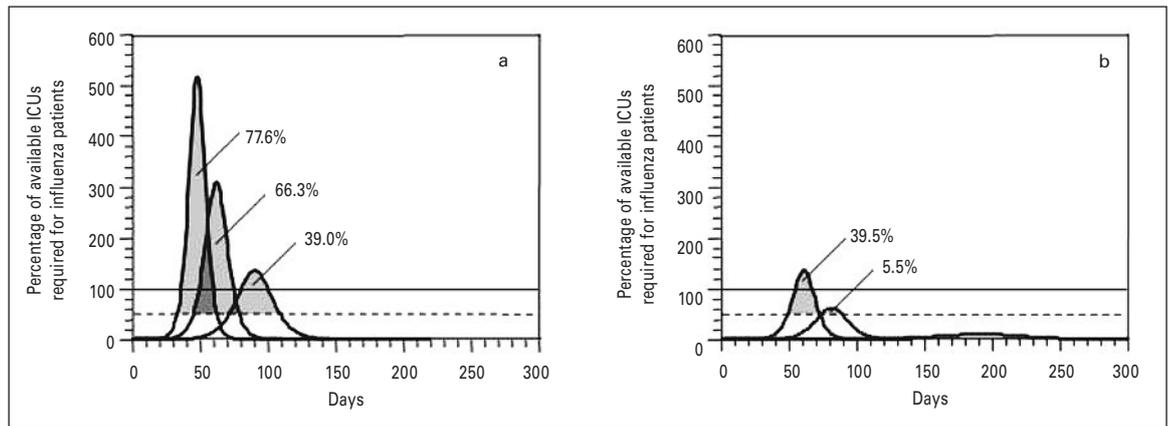


Figure 4

Demand of intensive care, representing (from left to right) 90%, 50% and 10% percentiles, respectively, of 100 000 random outcomes, ordered by the size of the peak of hospital bed occupancy. The curves show the percentage of the currently available ICU beds in Switzerland (6.4 per 100 000 inhabitants), assuming that 15% of hospitalized patients need intensive care. Horizontal lines indicate 50% and 100% level of the available ICU capacity. The gray areas under the curves indicate what percentage of cases with ICU demand cannot receive proper treatment if at most 50% of ICU beds can be made available for influenza patients. (a) Social distancing alone. (b) Social distancing combined with antiviral treatment.

that pandemic preparedness plans must not rely on expected or “mean” results only, but should also consider “best case” and “worst case” scenarios. The most important parameter which determines both the rapidity and the height of a pandemic wave, is summarized in the basic reproduction number R_0 . Even for previous pandemics and for seasonal influenza, considerable uncertainty in the estimation of this important parameter exists as is witnessed by the wide range of proposed values, ranging from 1.5 to 4 (for U.S. cities: [17], for Switzerland: [18, 19]). Longini [20] proposed “containment” with different strategies for low values of R_0 from 1.1 to 2.4 and since then many authors have only used these values in their studies. Ferguson [21] reviewed 1918 pandemic data and proposed $R_0 = 1.7$ as “moderate” and $R_0 = 2.0$ as “high” transmission scenarios, but these values should be regarded as effective reproduction numbers which also reflect the effect of interventions. In contrast with these studies, which focused on containment in terms of outpatient visits, a wider range of pandemics were explored (R_0 from 1.5 to 3.5) and also hospital bed occupancy and ICU demand were considered in the current study.

The population effects of antiviral treatment highly depend on the timing of the patients’ treatment and on whether they have been contagious before treatment. The success of social distancing measures depends on the compliance of the population. At the most pessimistic end of the simulations (high R_0 and strong concentration of contagiousness in the early phase of the infection, combined with low public health compliance and low treatment effects), the number of hospitalizations

can be 1.9 times higher than the mean, whereas at the most optimistic end, a major outbreak may be prevented (cf. 99% interval for combined intervention in fig. 2c).

This study confirms results of previous studies, which have used static models [5, 9] which point out ICU capacity as a bottleneck in hospital settings and which have stated that appropriate contingency planning must consider a rapid expansion of ICU capacity for severe pandemics. It has been shown that, in the most pessimistic case, a non-negligible percentage of hospitalized patients (ranging from 5.5 to 39.5%) would be at a higher risk of death during approximately 3–4 weeks, if 50% of the currently existing ICU beds could be made available at the peak of the epidemic (by cancellation of elective surgery and triaging of patients). As ICU capacity is difficult to expand and costly to maintain, additional and innovative measures are being considered and extensive preparation is needed. The current results support the view that hospitals and public health planners should take into account the severity of a pandemic and the efficacy of the interventions (such as antiviral treatment) in their protocols.

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Appendix

The full details of the model can be found in Duerr et al. 2007 and Eichner et al. 2007 [11, 12] (available from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17629919> and <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17355639>). Apart from varying some of the parameters, as given in table 1, we use the age distribution from Switzerland and other basic parameters listed in table A1.

Table A1

Age distribution of the Swiss population (per 100 000), contact matrix and risk of hospitalization and death from influenza by age class and risk group.

Age in years ¹	Children			Working adults		Elderly		
	0–5	6–12	13–19	20–39	40–59	60 or more		
Number per 100 000	5895	7701	8315	27 318	29 121	21 650		
Total number in class	21 911			56 439		21 650		
Contacts per week ²	0–5	6–12	13–19	20–39	40–59	60 or more		
with 0–5-year-old	169.14	31.47	17.76	34.5	15.83	11.47		
with 6–12-year-old	31.47	274.51	32.31	34.86	20.61	11.50		
with 13–19-year-old	17.76	32.31	224.25	50.75	37.52	14.96		
with 20–39-year-old	34.5	34.86	50.75	75.66	49.45	25.08		
with 40–59-year-old	15.83	20.61	37.52	49.45	61.26	32.99		
with ≥60-year-old	11.47	11.50	14.96	25.08	32.99	54.23		
Risk category	low risk		high risk	low risk		high risk	low risk	high risk
Fraction of age class ³	90%		10%	85%		15%	60%	40%
Fraction of infected who become severely sick ⁴	33%		33%	33%		33%	33%	33%
Fraction of severely sick who need hospitalization ³	0.187%		1.333%	2.339%		2.762%	3.56%	7.768%
Fraction of hospitalized patients who die ⁵	5.541%			16.531%			39.505%	

¹ Swiss Federal Statistical Office 2005 [14]; ² Wallinga et al. 2006 [25]; ³ Deutscher Nationaler Pandemieplan [26];

⁴ Longini et al. 2004 [13]; ⁵ Meltzer et al. 1999 [16]