Simulation Modelling Practice and Theory 103 (2020) 102091

Contents lists available at ScienceDirect

Simulation Modelling Practice and Theory

journal homepage: www.elsevier.com/locate/simpat

Enhancing response preparedness to influenza epidemics: Agent-based study of 2050 influenza season in Switzerland

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ARTICLE INFO

Keywords:
Agent-based modeling
Demographics
Influenza epidemic
Traffic simulation
Public transport

ABSTRACT

Incidences of seasonal influenza are increasing in severity with significant impacts on human health and on economy, due to missed working hours. As transmission of influenza is highest in spaces where persons are in close proximity, public transport networks are increasingly vulnerable in strategies to manage potential influenza epidemics. In this work, we integrate into an agent-based framework, a stochastic model that simulates, on a sub-hourly timescale, the different daily activities of all individuals in a population. Thus, the contact patterns of individuals are accurately modeled, and with the use of agent-based epidemic and mobility models, individual-level transmission of influenza, and its subsequent spread, are accurately modeled. We demonstrate this novel approach in an assessment of seasonal influenza in Switzerland for the year 2050, when Switzerland's population will exceed 11 million. In the absence of interventions, we show that, although of shorter duration, future influenza epidemics will be significantly more severe and infect more of the population. The incidence of influenza is larger during leisure and needs activities, rather than at home, school or work. We demonstrate also that influenza-transmission preventive measures are effective: the intensity of the epidemic and the total number of infections are reduced; however, there is little impact of different preventive measures on the duration of the epidemic. This work demonstrates therefore an accurate tool that can predict the spatiotemporal characteristics of an influenza epidemic, and that can be used to assess the most effective measures to mitigate the epidemic.

1. Introduction

Every year, seasonal influenza affects about 5–10% of the global adult population, and 20–30% of the global young population [34]. The World Health Organization attributes to seasonal influenza 3–5 million annual cases of severe illness worldwide, which lead to 9–13% deaths [31]. Amongst those with a higher risk of developing severe illness are the 0–5 and 65+ demographics, and pregnant women [32]. The impacts of seasonal influenza are not only limited to human health, but also lead to significant economic impacts: in 2017, approximately 2.8% of total working hours were missed because of influenza [28]. In order to limit the spread of influenza, every year the Federal Office of Public Health produces a series of strategies and measures, for example the National Strategy to Prevent the Seasonal Influenza [2], in order to prepare for a possible influenza pandemic in Switzerland. Fig. 1 shows the impact of population density on the spread of influenza in Switzerland from the 2013/2014 influenza season to the 2017/2018 influenza season. It is evident that as the population increases so too does the duration and spread of seasonal influenza [33,8].

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https://doi.org/10.1016/j.simpat.2020.102091
Received 1 November 2019; Received in revised form 28 January 2020; Accepted 6 March 2020
Available online 07 March 2020
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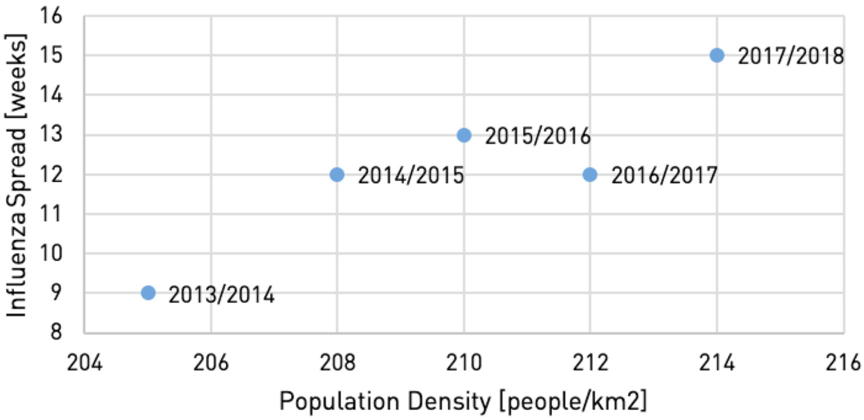


Fig. 1.. Impact of population density on spread of in Switzerland from the 2013/2014 season to the 2017/2018 season.

Indeed in Switzerland, the 2017/2018 influenza season is considered to be one of the longest ever recorded [21]."

Amongst the reasons for this trend, is the increase in population density, which favors the spread of infectious diseases [8]. Switzerland's population is expected to increase to 11.3 million by 2050 [29], a 39% increase over the 2014 population. Thus, in the future it will be imperative to have accurate tools to predict and mitigate epidemics.

Seasonal influenza is transmitted by different means including via droplets or aerosols disseminated by coughing and sneezing [18], and hand contamination followed by mucosal inoculation [34]. Currently, the measures to reduce the number of influenza infections include vaccinations, as well as preventing transmission through basic actions such as sneezing into one's hand or elbow, washing one's hands before meals, or staying at home if one feels ill. Hand sanitizers, placed in public institutions or in places where people frequently come into contact with the same surfaces, as used in hospitals or in nursing homes, are another common way of preventing infections. Aside from the mode of transmission of influenza, it is clear that the likelihood of transmission is highest in crowded spaces; public transport vehicles are amongst the spaces where the contact rate between people and holding surfaces is highest, but rarely are specific countermeasures related to public transport applied in Swiss cities. As Switzerland's population grows and undergoes demographic aging, the Swiss public transport network will become more crowded and will increase exposure to infection of high-risk demographics.

Predictive models are widely used to investigate the spread of diseases. These models are often agent-based SEIR models, in which susceptible (S), exposed (E), infectious (I) or recovered (R) agents are modeled [4]. Typically, compartmental models are used to define the contact between agents over scales with relatively coarse spatial and temporal resolutions. As contact between the agents is not explicitly modeled, only the large scale behavior of the spreading of an infectious disease can be analyzed. Smieszek and co-authors [18,9] used historical data to generate contact patterns in the context of assessing historical epidemics using agent-based models. In contrast, Eichner et al. [5] looked at future epidemics using extrapolations of historical data. Balcan et al. [1] integrated empirical human mobility data into their simulation of global disease dynamics, but did not model disease transmission at level of individuals. More recently, Cliff et al. [3] integrated an agent-based model for individual-to-individual contacts in an agent-based framework to assess the nationwide spread of disease. The model of Cliff et al. [3], specifically designed for Australia, generates a synthetic population based on census data and simulates, with a 12-h temporal resolution, social mixing groups, within which the transmission of a disease through contact between agents can occur. It is evident from the prior works, that an accurate modeling of the contact pattern is crucial in order to be able to capture the spatial-temporal spread of a disease, and that further improvements in terms of temporal resolution are needed in order to capture the transmissivity of diseases related to the dynamics of population movement, such as transmission on public transport. The outcomes from this more accurate modeling will help policy makers plan possible preventive measures that can be applied in locations, such as airports and train stations, which have a high transit of people, and where contact between large numbers of people occurs within a relatively short time period. The more accurate modeling is accomplished in large part by the improved temporal resolution. Another limitation of existing models is that these models are mostly based on past statistics and census, and thus these models do not account for the future evolutions of population, demographics, and behavioral patterns, that will have an influence on spread of disease. On the otherhand, agent-based models allow for the simulation of detailed contact patterns with very high spatial and temporal resolutions. Agent-based models also allow that events that never happened in the past can be simulated, since agents can react to abrupt changes in their environment. Nevertheless, the main disadvantage of agent-based models is that large amounts of data and time are required to develop and calibrate the models; it is primarily for this reason that in the present work the agent-based framework has been extended, developed and validated in order to allow for the simulation of the spread of epidemics. Thus, the novelty of the present work can be summarized as follows:

- An extension relative to prior studies by integrating into an agent-based population development framework a stochastic model that simulates the different daily activities, on a sub-hourly timescale, of all individuals in a population; further, this daily activity model is linked to an agent-based disease transmissivity model.
- The daily activity model takes inputs from an agent-based population model, which simulates both the whole life-cycle of all geo-

localized individuals, as well as the future evolutions of population and demographics.

- An agent-based, multi-modal, mobility model is used to simulate, with one-second temporal resolution, the mobility of individuals between their locations of activities, including their selection of a means of transport.
- Both the daily activity model and the mobility model include outcomes from a mesoscale weather model to determine the execution of certain daily activities, and the selection of the means of transport.

Thus, possible contact patterns are accurately modeled, and with the use of an agent-based epidemic model, the individual-level transmission of infectious diseases, and the subsequent spread of the disease, are modeled. We demonstrate this novel approach in an assessment of seasonal influenza in Switzerland for the year 2050; further, we investigate what interventions could be most effective in managing an influenza epidemic in Switzerland in 2050, focusing on the sensitivity in relation to measures aimed toward public transport. Thus, the paper is structured as follows. In the next section, the methodology is described. Then, a validation of the novel approach is presented, and outcomes of the study of 2050 influenza season in Switzerland are discussed. The paper concludes with a summary of the main findings of this work.

2. Methodology

2.1. Agent-based simulation framework

In the present work, we integrate into our in-house developed agent-based simulation framework, EnerPol, (i) a daily activity model that simulates the daily activities of individual agents on a sub-hourly scale, and (ii) an epidemic model that simulates at an individual level the transmission of a contagious disease to a susceptible agent in a population. The former models in detail the possible occurrences in which individuals may interact; the latter models the possible person-to-person transmission. Our agent-based simulation framework has been demonstrated in previous works as being well suited for large-scale, national level, scenario-based assessments to support decision-making in a number of fields, including: urban planning, Marini et al. [10,12]; finance, Marini et al. [11]; electric mobility, Pagani et al. [16]; and, transportation, Saprykin et al. [17]. Thus, the framework developed in this work is suited to investigate epidemics at the national scale with the very fine resolution that is required to assess the effectiveness of measures of prevention and control. The sequence of simulations applied in the present work consists of: (i) population simulation; (ii) daily activities planning; (iii) mobility simulation; and (iv) disease spread. Thus, while more complete details of the existent agent-based population and mobility models can be found elsewhere, Marini et al. [11], Saprykin et al. [17], both the existent and novel models are described below.

The simulations are run on a single CPU core (Intel(R) Xeon(R) CPU E5-2620 v4 clocked at 2.10 GHz.) with 128GB of RAM. The GPU-accelerated population model runs on a single NVIDIA P100 with 16GB RAM.

2.1.1. Agent-based population model

In the agent-based population model, Marini et al. [11], a synthetic population of 8.24 million individual agents is generated from the 2014 population statistics, Swiss Federal Office for Statistics [26], which include, at the resolution of each of Switzerland's 2′356 municipalities, characteristics such as total population, age distribution, income distribution, household structure, employment status, etc. Using highly detailed databases of housing stock – including features such as the location, structure and build year of the building, etc. – and activities – examples of which are the locations of activities include office workplaces, shops, schools, etc. – the population model links each individual agent of the synthetic population to a household, which is assigned a dwelling, and, if relevant, each individual agent is assigned a workplace. Thus, an activity-based demand for transportation is generated, and subsequently used in the agent-based mobility model as described below. The databases employed in the agent-based population model are from several sources including the Swiss Federal Registries of Residential Buildings and Dwellings [23,27], and the Swiss Federal Registry of Economic Activities [25].

With a temporal resolution of one-year, the population model simulates, as a function of the characteristics of agents and households, the complete life-cycle of each individual agent, including: birth, aging, and death; the evolution of households (that is coupling, uncoupling, and leaving a parental household); the relocation of households; and the job changes of agents. Exogenous factors such as immigration into Switzerland, which accounts for 80% of the annual population growth, are included in the life-cycle simulation; thus, the 2014 synthetic population is evolved to a future year.

2.1.2. Agent-based daily activity model

The agent-based daily activity model computes, with 15-min temporal resolution for each individual agent of the synthetic population, the daily activities of working and nonworking days. With a transportation mode for each agent, that is known from the agent-based mobility model, routine activities comprised of (i) a main activity (for example job, education, etc., ii) sleeping and (iii) eating are first determined, and then needs and leisure activities, which fill the remainder of the day, are determined. The determination of the hierarchical importance of routine activities of sleeping and eating, and of needs and leisure activities is based on the theory of Maslow, Maslow [13]. The need for an agent to perform a certain activity in order that the agent satisfies a certain need in the hierarchy is described by multiple reservoirs; each reservoir has a level of balance that decreases either over time or by performing an activity. The levels of the balances define the need of an agent to execute a particular activity, with the goal of improving the associated level of balance. The rates of increase or decrease of a level of balance depend on the characteristics of an agent (for example, age, gender, job status etc.). Furthermore, statistical noise is added to the rates of increase or decrease in order to

Table 1
: Description of the parameters used in the vehicle choice model.

Vehicle Choice	Independent variable, x	Midpoint, x0	Maximum, value, L	Steepness, k
Bike	Age,	average age,	1	age elasticity,
	travel distance	average distance	1	distance elasticity
e-Bike	Age,	average age,	1	age elasticity,
	travel distance,	average distance,	1	distance elasticity,
	Income	average income	1	income elasticity
Car	Age,	average age,	1	age elasticity,
	travel distance,	average distance,	1	distance elasticity,
	income	average income	1	income elasticity
Public Transport	income	average income	1	income elasticity

mimic differences across agents having similar characteristics. For all activities, a score is computed, using either a sigmoid function (Eq. (1))

$$S(x, x_0, L, k) = \frac{L}{1 + e^{-k(x-x_0)}} \tag{1}$$

(where x is the independent variable, x_0 is the sigmoid's midpoint, L is the maximum value, and k the steepness), or a probability density function (Eq. (2))

$$PDF(x, \mu, \sigma) = e^{-\frac{(x-\mu)^2}{2\sigma^2}} \tag{2}$$

(where the parameters of the function are the independent variable, mean value, and standard deviation). An agent performs the activity with the highest score.

A sigmoid function (Eq. (1)) is used to describe the tendency towards a saturation, when no specific cumulative density function could be derived to describe this tendency. Specifically, the sigmoid function is applied in the choice of vehicle as a function of income, age, and distance of travel. Table 1 provides a description of the different parameters used in the vehicle choice model. The parameters are derived from statistics of the micro census [24].

A probability density function (PDF) (Eq. (2)) is used to describe the inherent spread around an intended or mean value, if no other probability distribution function could be derived. Specifically, the PDF is applied where a dependence to a parameter is known; the probability of doing a given activity, as a function of time of day, sex, or age, is derived from statistics, and from the state of the related reservoir balances.

In the present work, three types of balances are employed: (a) main balances, which are sub-divided into a food reservoir and a fatigue reservoir, and which are evaluated at each time step; (b) daily balances consisting of a fitness reservoir, a health reservoir, a mood reservoir, religious needs, and other needs, all of which are updated once a day; and (c) household balances, which are comprised of a fridge reservoir, a social reservoir, a disposable income, and a value of time, and which are evaluated on the occurrence of an event. For example, if the score of the grocery activity is highest, then an agent will go to buy groceries, thereby refilling the fridge reservoir. In addition to the aforementioned databases that are used in the agent-based population model, Switzerland's 2010 micro census data [24], are employed in the agent-based daily activity model. Furthermore, predictions of weather are used in the daily activity model as these impact possible daily activities; the weather predictions are generated from the mesoscale weather model that is integrated into the EnerPol simulation framework. The mesoscale weather model is adapted from the Weather Research and Forecasting model developed by Skamarock et al. [19], and used to predict precipitation and ambient temperature. The weather simulations cover a whole year with temporal and spatial resolutions of 1 h and 10 km, respectively. The predicted precipitation and temperature influence an agent's choice of means of transport (public transport, car, or bike), as the fractions of agents using each mode of transport are dependent on precipitation and temperature, Fig. 2. For example, in very cold or rainy weather, an agent who normally uses a bicycle may instead use public transport. The functional variations are based on micro census data [24].

It is evident from above that our agent-based daily activity model provides a sufficiently high spatial resolution of possible person-to-person interactions, such that there is a basis for an accurate modeling of person-to-person transmission of a viral infections described below in the agent-based epidemic model. In order that the computational time for the simulation of the daily activities of a whole country's population is reasonable, similar to the existent agent-based population and mobility models, the agent-based daily activity model is fully parallelized and optimized to run on GPUs.

2.1.3. Agent-based mobility model

The agent-based mobility model, Saprykin et al. [17], uses the activity-based demand generated in the agent-based population model as the basis for a mobility simulation. This mesoscopic, queue-based, multi-modal, mobility model simulates, with one second temporal resolution, both private and public modes of transportation. The choice of mode of transport depends on the agent's characteristics, such as age, as well as the accessibility to the given means of transport at the agent's location. In a mobility simulation, the agents perform their daily activities, as specified in the agent-based daily activity model, and travel between the locations of activities. Switzerland's road network comprised of 513’770 nodes and 1’127’775 road links obtained from OpenStreetMap [14] is

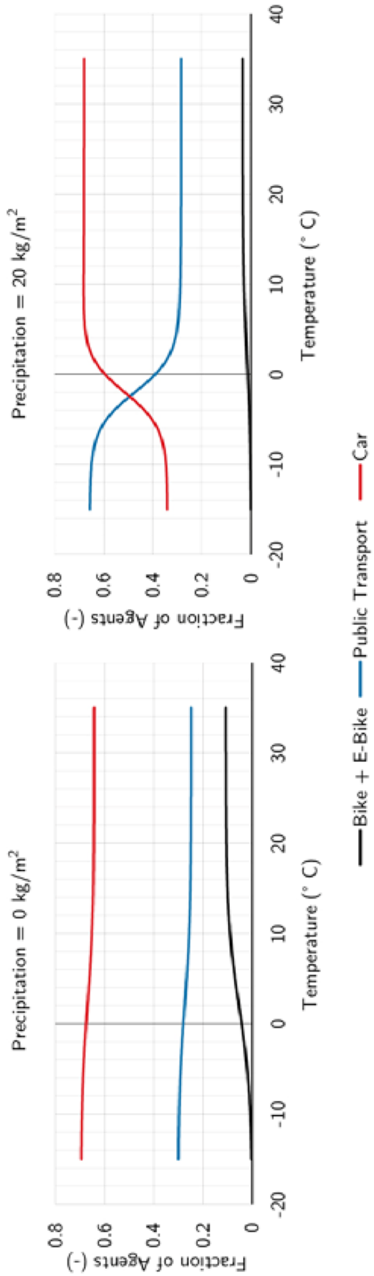


Fig. 2.. Variation in choice of mean of transport as a function of the temperature and precipitation.

Table 2
: Five stages of viral infection, adapted from Ge et al. [7], Wang et al. [30], and Longini et al. [9].

Stage	Duration (h)	Infectious	Agent Shows Symptoms	Description
0	–	–	No	Healthy agent
1	48	No	No	Incubation period
2	24	Yes	No	Incubation period
3	72	Yes	Yes	Sick, stays at home
4	168	No	Yes	Sick, stays at home
5	–	–	No	Recovered and immune

used; each link is described in terms of, length, number of lanes, flow capacity, free speed, and transportation modes. The public transit schedule of the year 2018 that contains 27′873 stops and 21′847 routes for trains, buses, tramways, metro and all other modes of public transit in Switzerland is extracted from the data platform of the Swiss Federal Railways [15].

2.1.4. Agent-based epidemic model

The agent-based epidemic model simulates, as a function of the daily activities, the mode of transport, and the characteristics of agents, the likelihood of a viral infection and the subsequent transmission of the infection. At each timestep, based on the locations of agents, possible contact patterns are generated. If an agent is sick, healthy agents within an infectious proximity distance x_p have a likelihood of becoming sick; this likelihood is expressed in terms of the infectivity R_q, where *d* is the distance between a healthy agent and an infected agent:

$$LikelihoodOfInfection(d) = \begin{cases} 0\, if\ d > x_p \\ R_q\ if\ d \leq x_p \end{cases} \tag{3}$$

The infectivity and infectious proximity distance are $R_q = 1E\text{-}4$ and $x_p = 2$ m, respectively. The infectivity R_q is calibrated to match the cumulative incidence between the years 2008 and 2015 [21]. Since the spatial resolution in the simulation framework is 1 m and the locations of public stops, activities, and vehicles are approximated as points with 1 m diameter, the agents who come into contact are assumed to be at distances less 2 m apart. If an agent is infected, the disease progresses in stages that mimic the different effects on the host agent and his/her fellow agents. The stages of the influenza type viral disease that is considered in this work, Table 2, are based on Ge et al. [7], Wang et al. [30], and Longini et al. [9]. Depending on the stage of progression, each sick agent has the ability to infect other agents, who simultaneously are within the infectious proximity distance of the sick agent. The probability of infection increases in proportion to the number of present hosts; based on historical influenza cycles in Switzerland [21], the maximum probability of infection is five times the single infectivity, as there is a limited number of people that can be in close proximity to the sick agent, and also there is a subsequent dilatation of virus within inhaled air.

In the present work, we make several simplifying assumptions: (i) the infectivity is assumed to not vary over time, and all infected agents get sick, showing symptoms in stages 3 and 4; (ii) it is assumed that there is no variation of the duration of each stage of the viral infection, and the duration of each stage is assumed to be independent of the characteristics of the agents; (iii) the transition from one stage to a next stage is assumed to be discrete; and, (iv) no agents are vaccinated, and all agents recover fully from illness.

2.2. Scenarios

In this work we evaluate scenarios in the year 2050 whereby a passenger aircraft, which carries agents hosting the influenza virus, lands at Zurich Airport, the largest in Switzerland, and the spread of the virus occurs largely through the use of public transport. Zurich Airport is served by around 350 rail connections and over 700 bus and 400 tram departures a day, that are used by approximately 70,000 public transport users daily. The initial number of sick (stage 2) agents is a fraction, 4E-5, of the population. Using the agent-based population model, the synthetic population of 8.24 million individual agents in 2014 was used to generate Switzerland's population of 11.3 million agents in 2050. Over the period 2014 to 2050, fertility and life expectancy rates were assumed to be the same as in 2016 [20], and the assumed migration rate (71′030 people per year) is consistent with the most recent trends [29]. New dwellings and jobs are generated such that the levels of vacancy are the same as in 2016. The countrywide timetable of the public transportation network is kept the same as the schedule of 2017. To allow for comparison between future scenarios and present data, transportation technologies, transportation modal choices, and rate of population remotely working from home are assumed to be the same as in 2016. Three scenarios with different effectiveness of influenza-transmission preventive measures in public transport are assessed. In the first scenario, 2050–0% PT, no preventive measures are applied; in the second scenario, 2050–50% PT, preventive measures are effective in 50% of cases; and in the third scenario, 2050–100% PT, preventive measures are considered to be 100% effective. The transportation capacity and network has been maintained the same as of today, based on the data provided by Swiss Federal Office of Transport [[15]TransportData (2019]).

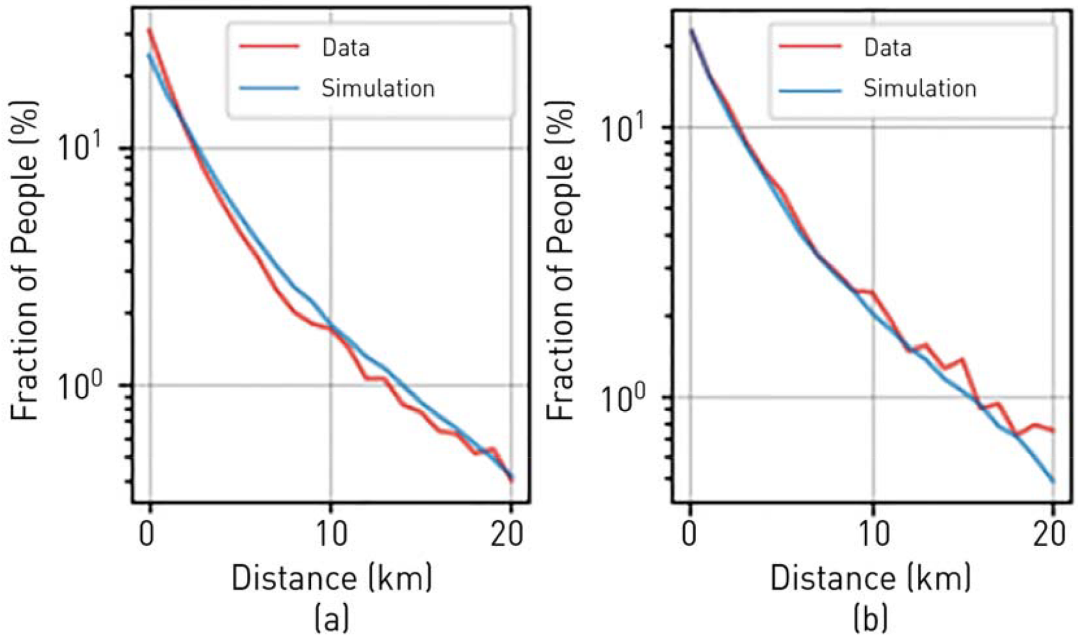


Fig. 3.. Comparison of the predicted and actual daily sum of the travelled distances for weekday activities of (a) grocery shopping, and (b) leisure.

3. Results and discussion

3.1. Validation

Fig. 3 compares the predicted and actual daily sum of the travelled distances for two weekday activities: grocery shopping and leisure. The actual data are from the 2010 micro census [24]. It can be seen that the agreement between predictions and data, over the range of distances, are very good, highlighting the spatial accuracy of the agent-based daily activity model.

Boxplots of the predicted and actual weekday daily travel distances by demographic are compared in Fig. 4. It is evident that the predictions capture very well the variability that is seen in the data across all demographic groups.

The temporal distributions of the predicted and actual number of agents on a weekday journey to work or do groceries are shown in Fig. 5. The agent-based daily activity model is seen capture well both the magnitudes of peaks and the trends showing thus the good temporal accuracy of the model.

Fig. 6 compares the predicted and actual weekly incidence and cumulative incidence of influenza in Switzerland. The actual data

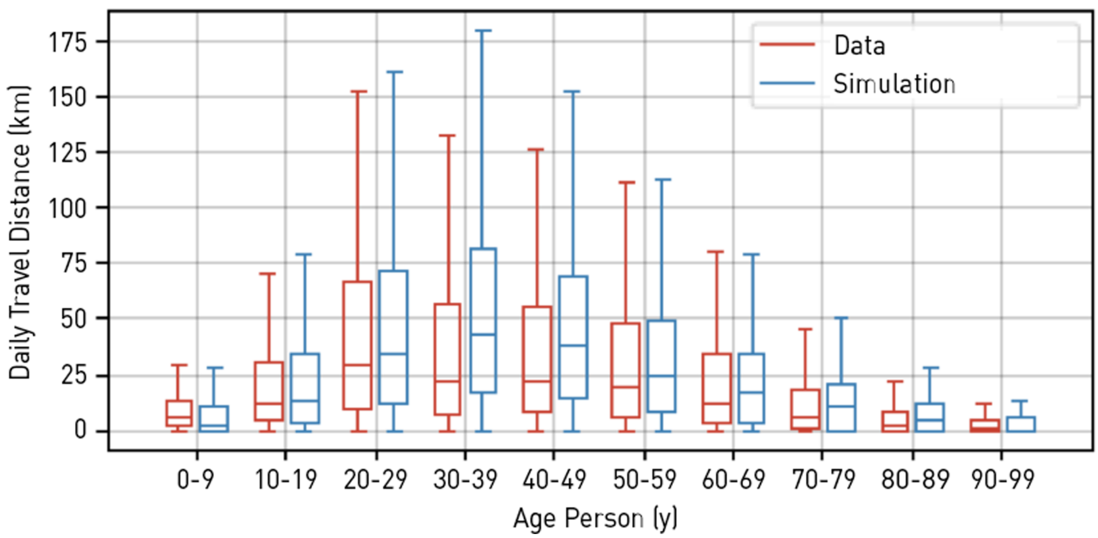
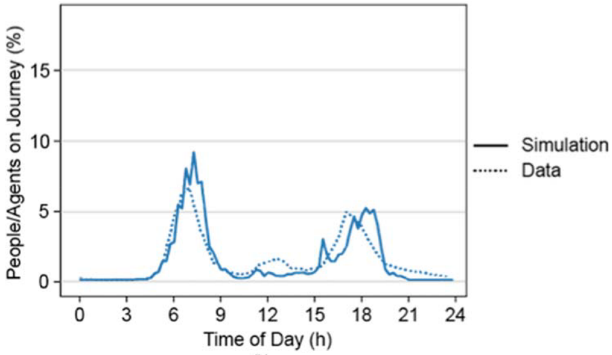
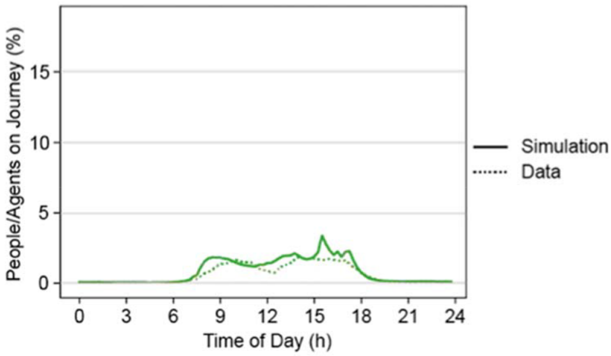


Fig. 4.. Comparison of the predicted and actual weekday daily travel distances by demographic.



(b)



(a)

Fig. 5.. Comparison of the predicted and actual number of agents on weekday journeys (a) to work and (b) do groceries.

are for the influenza seasons of 2015/2016, 2016/2017 and 2017/2018, as reported by the Federal Office of Public Health [21], and show interseason variability that arises from differences in climate and size of population, amongst other factors. In order to facilitate comparison, the predictions and data are shifted to match at the time when a weekly incidence of 0.68‰, which corresponds to the threshold of classification as a national epidemic event [22], is first reached. The time between surpassing and then returning below the 0.68‰ threshold is 12.6 weeks on average for the data, and is 12.7 weeks for the simulation. The predicted maximum weekly incidence is 3.2‰, which is in very good agreement with the maximum weekly incidence of 3.15‰ in the influenza season 2015/2016, and relatively good agreement with the other two seasons (3.68‰ and 3.58‰ in the 2016/2017 and 2017/2018 influenza seasons, respectively). The predicted fraction of infected agents is 26.8‰, which compares very favorably with 29.6‰ and 27.9‰ in the 2015/2016 and 2016/2017 influenza seasons, and less well with 40.2‰ in the 2017/2018 influenza season. The overall good agreement between prediction and validates the approach that is used in the agent-based epidemic model.

3.2. Population increase leads to substantial increase in incidence

Fig. 7 compares, for the 2014 and 2050 populations, the daily incidence and the cumulative incidence of influenza. The threshold of influenza being classified as a national epidemic is 26 and 21 days after onset for the 2014 and 2050 populations, respectively, and the respective durations of the epidemic are 91 and 82 days. Whereas, the maximum daily incidence of 3.2‰ in the 2014 population is reached 42 days after onset, a 2.9 times larger maximum daily incidence of 9.2‰ is reached 54 days after onset in the 2050 population; it should be noted that the latter population is 39% larger than the 2014 population. Fig. 7(b) compares the cumulative incidence in the two populations. The influenza virus infects 57‰ of the population in 2050 influenza season, compared to 26‰ of the population in the 2014 influenza season. Thus, although the 2050 influenza season, is shorter, it is more intense than the 2014 influenza season, and the 2050 influenza season impacts a substantially larger portion of the population. Indeed, it can be seen that in the 2014 influenza season, there are two peaks in the temporal evolution of the daily incidence, whereas in the 2050 influenza season, there is only one peak. We attribute this coalescence of peaks to the higher population density in the 2050 population, that enhances a more rapid spread of the influenza virus. However, due to the duration of the viral infection, 84 days after onset, the incidence in the 2014 population is more than the incidence in the 2050 population. Nevertheless, it is expected that future influenza epidemics will be significantly more severe.

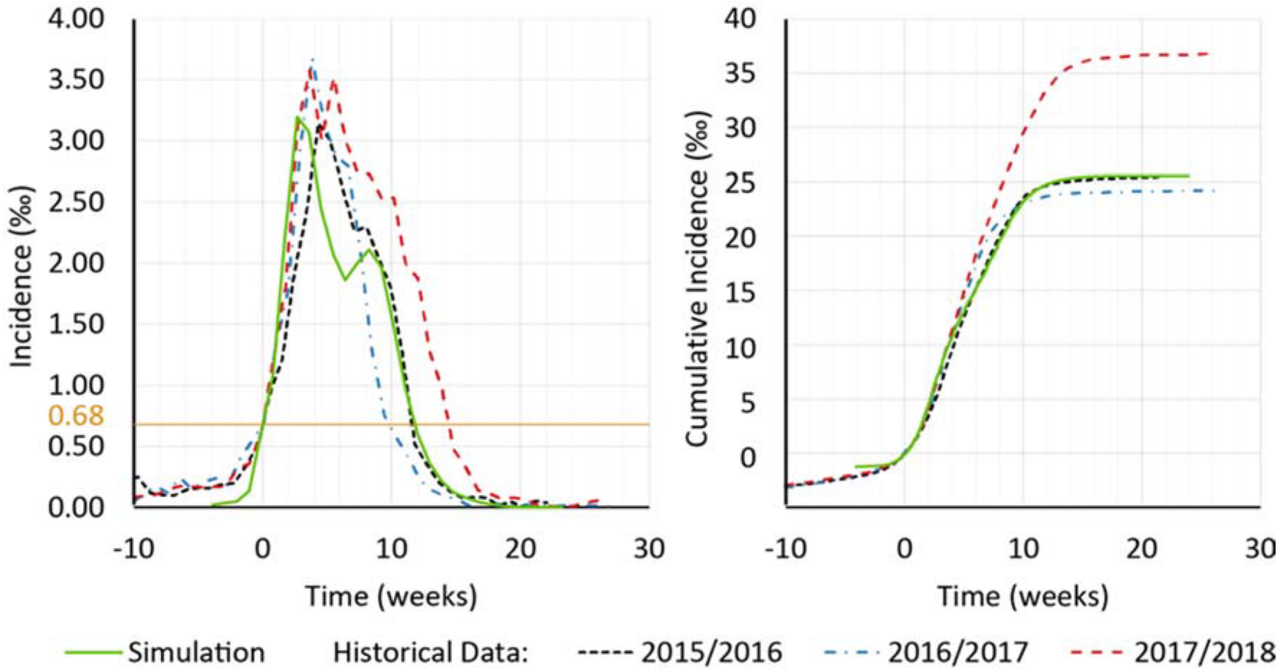


Fig. 6.. Comparison of the predicted and actual weekly influenza incidence and seasonal cumulative incidence. The actual data are for are for the influenza seasons of 2015/2016, 2016/2017 and 2017/2018. The prediction and data are shifted to match the time at which the threshold of weekly incidence is 0.68‰.

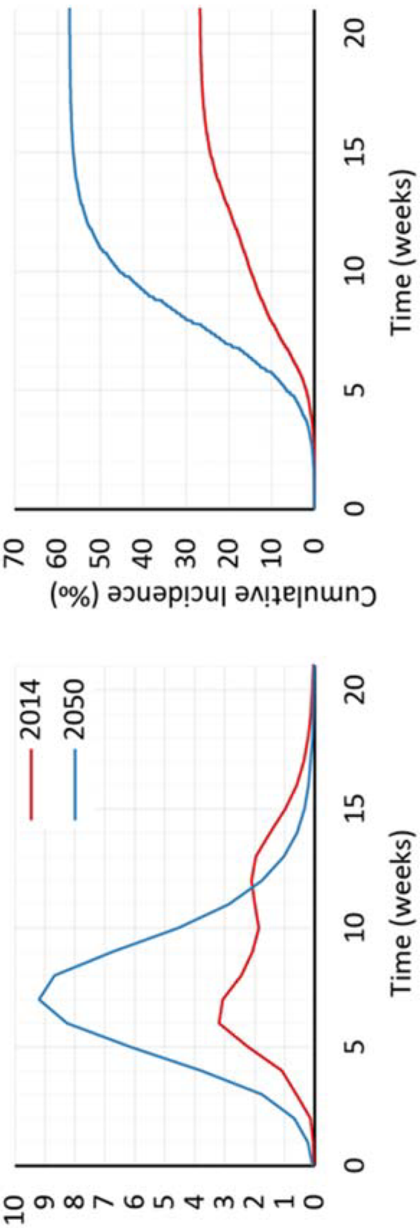


Fig. 7.. Comparison of (a) daily incidence and (b) cumulative incidence in 2014 and 2050.

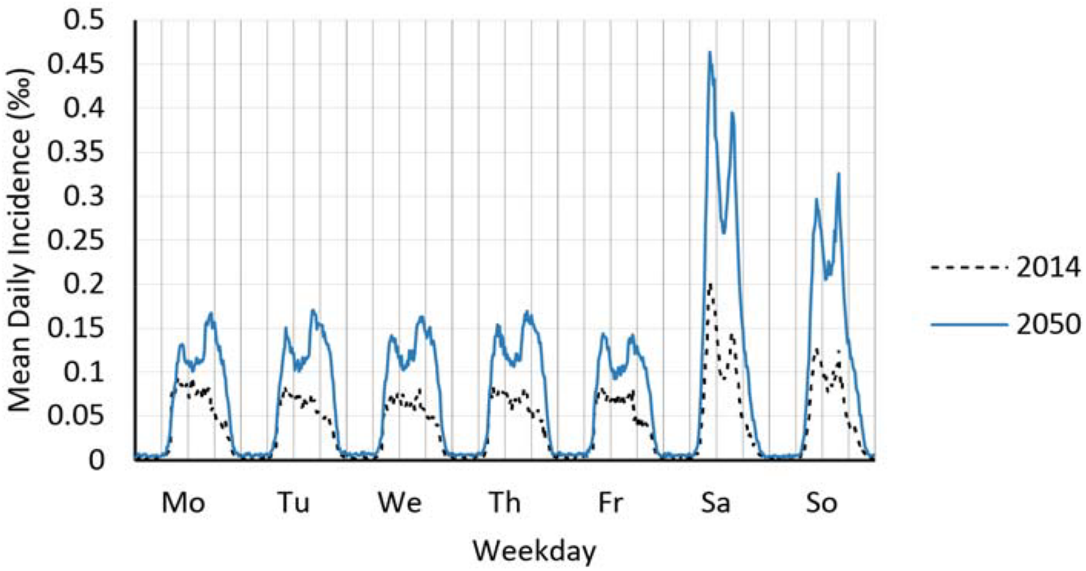


Fig. 8.. Comparison of weekly profiles of daily incidence averaged over the influenza in 2014 and 2050.

3.3. Disease incidence is larger during leisure and needs activities

Fig. 8 compares, for the 2014 and 2050 influenza seasons, the mean daily incidence. In the 2014 season, there are 42% more infections on Saturdays than any weekday, while Sundays have only a 13% higher incidence compared to weekdays. For the 2050 season, this trend is more pronounced with a 91% increase in infections on Saturdays and a 48% increase on Sundays. The outcomes of the simulations show that 42% of infections in 2014 occur during leisure and needs activities. As Sunday shopping is restricted in Switzerland, a large share of needs activities is undertaken on a Saturday, thus, leading to the highest rate of infections on Saturdays. Infections at work or at home only account for 21% of infections, and 24% occur during educational activities. Thus in the case of a pandemic, a more effective approach to curb spread of the influenza virus is to limit leisure and needs activities rather than to limit work-related activities.

3.4. High density, highly accessible areas are at most risk

Fig. 9 shows for the 2050 influenza season the spatial distribution of the season-end cumulative incidence. The spatial distribution is on the resolution of municipalities. Also shown in Fig. 9 is the population density in the municipalities. As expected, larger proportions of the population are infected in municipalities with a high population density. In municipalities with more than 2000 agents/km^2, the mean season-end cumulative incidence is 41.9‰ and 97.6‰ for the 2014 and 2050 influenza seasons, respectively. By comparison, the mean national season-end cumulative incidences are, respectively, 22.4‰ and 46.3‰. It can also be seen in Fig. 9 that less accessible areas, especially in the region of the southern Alps, have substantially smaller portions of the population that are infected by the viral infection that originates in Zurich.

3.5. Interventions in public transport can be effective

Fig. 10 compares the effectiveness of influenza-transmission preventive measures in public transport in the 2050 influenza season in terms of the daily incidence and the cumulative incidence of influenza. As can be seen the maximum daily incidence is more reduced with the more effective preventive measures. However, although the intensity of the epidemic is reduced, there is little impact of the different preventive measures on the duration of the epidemic. Nevertheless, it is evident from the cumulative incidence of influenza that with improved effectiveness of transmission preventive measures, the total number of infections are reduced. As Switzerland's modal split of passenger transport is the highest in Europe, 19.6% compared to the European average of 7.8% [6], the effectiveness of transmission preventive measures in public transport is key to curbing the spread of influenza. Indeed, countries such as Luxembourg, Germany and Austria which have medical and hygienic standards, demographic structures and population density similar to Switzerland, have on average 4.7 times smaller total prevalence of seasonal influenza than Switzerland [32].

As a comparison, Fig. 11 shows the variation of incidence as a function of influenza-transmission preventive measures on public transport for the year 2014. Since the population density in 2014 is lower than in 2050, there is a less pronounced effectiveness of measures than in 2050.

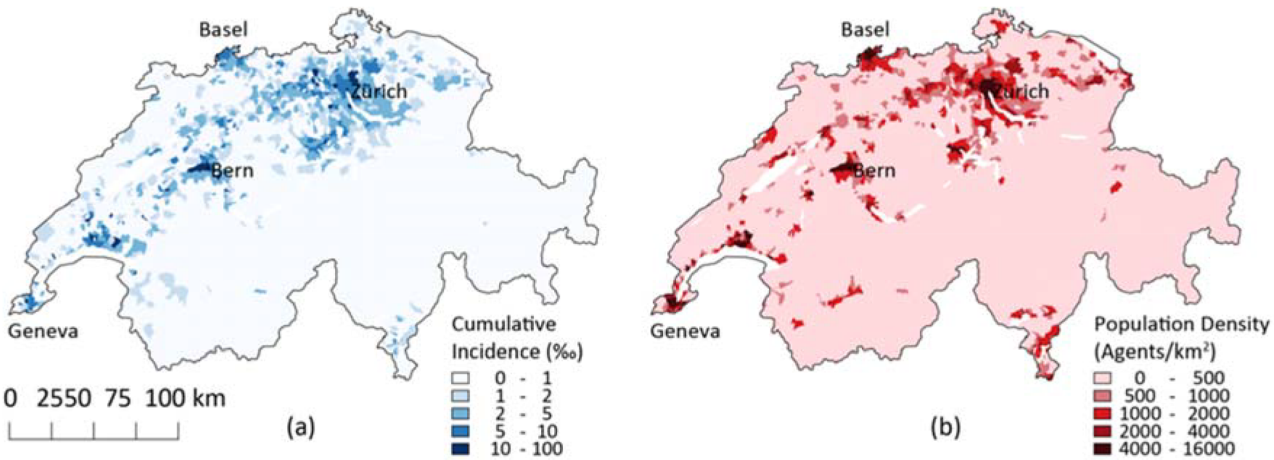


Fig. 9.. (a) The geographical distribution of the cumulative incidence as a fraction of the population living in a municipality. (b) The population density of the Swiss municipalities.

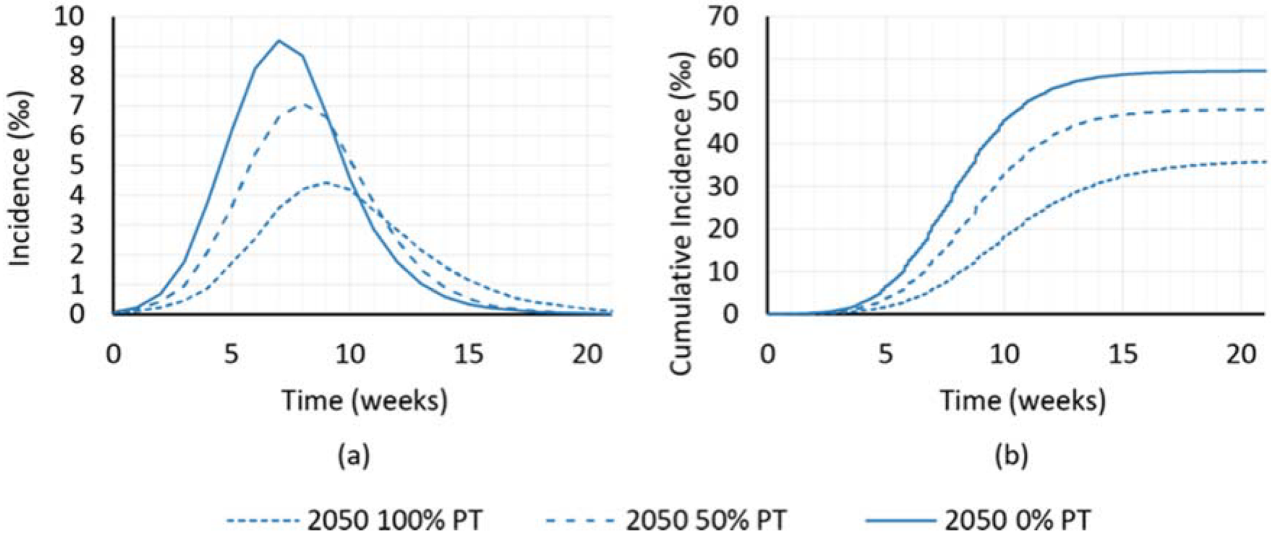


Fig. 10.. Comparison of the effectiveness of influenza-transmission preventive measures in public transport in the 2050 influenza season. (a) Weekly incidence of influenza epidemic and (b) cumulative incidence. The effectivenes in public transport is full (100%), half (50%) or none (0%) of all infections in public transport.

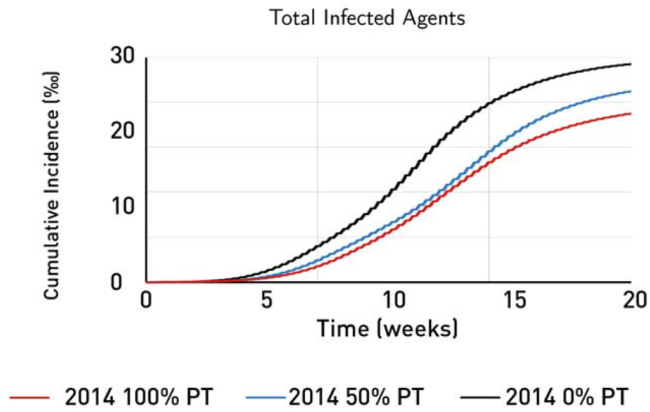


Fig. 11.. Comparison of the effectiveness of influenza-transmission preventive measures in public transport in the 2014 influenza season. The effectiveness in public transport is full (100%), half (50%) or none (0%) of all infections in public transport.

3.6. Young demographic benefits most from interventions on public transport

Fig. 12 compares the decrease in the incidence of the influenza endemic for the 50% and 100% effective influenza-transmission preventive measures in public transport in the 2050 influenza season. The decrease in the incidence is evaluated relative to the incidence in the case where there is no effectiveness of the preventive measures. It is evident that the 0–17 demographic benefits the most from the preventive measures. It is also noteworthy that the 65+ demographic is the second most beneficial from the effectiveness of preventive measures on public transport.

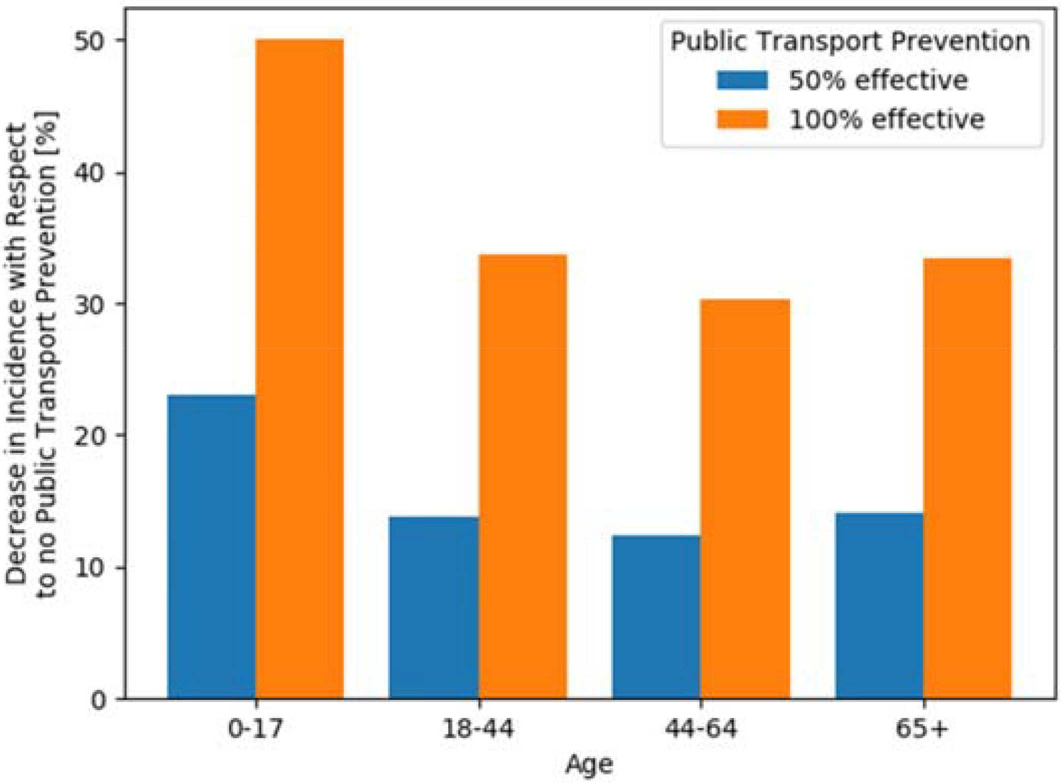


Fig. 12.. Comparison of the decrease in incidence for the 50% and 100% effective influenza-transmission preventive measures in public transport in the 2050 influenza season. The decrease is relative to the incidence with no effectiveness in the preventive measure.

3.7. Simulation performance

The population model takes 12 h to simulate the evolution of the population from year 2014 to year 2050. For the simulation of one day, the generation of the individual daily plans and the mobility of the whole population takes approximately 17 h. The simulation of an epidemic, including the contact patterns between agents, takes approximately 12 h. Up to 8 days are simulated in parallel, and thus the total time to complete one scenario is about 14 days.

4. Conclusions

This work demonstrates an accurate tool that can be used to predict the spatio-temporal characteristics of an influenza epidemic, and that can be used to assess the most effective measures to mitigate the epidemic. We have integrated into our in-house developed, agent-based simulation framework (i) a stochastic model that simulates, on a sub-hourly timescale, the different daily activities of all individuals in a population, and (ii) an epidemic model that simulates, at an individual-level, the transmission of influenza from an infected agent to a susceptible agent in the population. The agent-based daily activity model simulates routine activities, including a main activity (for example job, education, etc.), sleeping and eating, needs activities, and leisure activities, which fill the remainder of the day, are determined. Sleeping, eating, needs and leisure activities are modeled on the basis of reservoirs, whose levels of balance decrease either over time or by performing an activity, the levels of which are increased by the execution of a particular activity. Within the simulation framework, an agent-based population model is used to generate, from population statistics, a synthetic population of individual agents, each of whom has his/her own characteristics; further, using highly detailed databases, each individual agent is linked to a household, a dwelling, and a workplace. Furthermore, an agent-based multi-modal, mobility model is used to simulate, with one second temporal resolution, both private and public modes of transportation. Thus, with this novel agent-based simulation framework, the contact patterns between individuals, the individual-level transmission of influenza, and the subsequent spread of influenza are accurately modeled. We have demonstrated the utility of this novel approach in predictions of the spatiotemporal characteristics of an influenza epidemic in Switzerland, and an assessment of measures to mitigate the epidemic.

Validations show that predictions of the spatio-temporal characteristics of the daily activities of the Swiss population are in very good agreement with micro census data. Further, the post-dictions of weekly incidence and cumulative incidence of influenza in Switzerland, show good agreement in regards to the peak incidence, the duration of the influenza season, and the total number of infected agents.

In the year 2050, Switzerland's population will exceed 11 million, an increase of 39% over the 2014 population. We assess a scenario, whereby a passenger aircraft, which carries agents hosting the influenza virus, lands at Switzerland's largest airport, and the spread of the virus occurs largely through the use of public transport, as approximately 70,000 public transport users daily use the airport's multiple rail, bus and tram connections. In the absence of interventions that prevent or reduce the transmission of influenza, we show that due to the increased population density and the relatively high usage of public transport, future influenza epidemics will be significantly more severe and will infect more of the population; however, the influenza seasons will be of shorter duration than the historical average. Furthermore, the simulations show that the incidence of influenza is larger due to leisure and needs activities, rather than activities at home, school, or at work. In regards to measures to prevent the transmission of influenza, measures that are effective reduce both the intensity of the epidemic and the total number of infections; specifically, a 50% reduction of the infectivity on public transport will reduce the total number of infections by 16%. However, there is little impact of different preventive measures on the duration of influenza epidemics.

Declaration of Competing Interest

The authors whose names are certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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