Modeling co–circulation of influenza strains in heterogeneous urban populations: the role of herd immunity and uncertainty factors *

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Abstract. In this research, we aimed to assess the influence of herd immunity levels on the process of co-circulation of influenza strains in urban populations and to establish how the stochastic nature of epidemic processes might affect this influence. A spatially explicit individual-based model of multistrain epidemic dynamics was developed and simulations were performed using a 2010 synthetic population of Saint Petersburg, Russia. According to the simulation results, the largest influenza outbreaks are associated with low immunity levels to the virus strains which caused by these strains. At the same time, high immunity levels per se do not prevent outbreaks, although they might affect the resulting levels of disease prevalence. The results of the study will be used in the research of long-term immunity formation dynamics to influenza strains in Russian cities.

Keywords: Seasonal influenza · Herd immunity · Multiagent modeling · Stochastic processes · Strain co-circulation.

1 Introduction

Outbreaks of influenza, one of the most widely spread human infectious diseases, result in 3 to 5 million cases of severe illness annually worldwide, and the mortality rate is from 250 to 640 thousand individuals per year [6]. One of the directions of influenza propagation studies, which help better understand the mechanics of disease dynamics and thus diminish its negative effects, is related to co-circulation of different influenza strains and its interplay with the levels of herd immunity to these strains. It is generally known that immunity level dynamics and disease incidence dynamics in the population are intertwined, but there are still open questions related to the quantification of their connection. In a conventional deterministic SEIR model, the population immunity level directly influences the outbreak size, and the onset of an outbreak is guaranteed

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when the number of susceptible and initially infected people are non-zero. At the same time, is it known that in real life the arrival of the infected individual in the population does not necessarily start an outbreak due to stochastic effects inherent to the initial stages of the epidemic onset [4], [3]. These effects might significantly alter the properties of the outbreak, allowing it to gain momentum even if the level of population protection to the virus strain is high, or, alternatively, to make it die out in seemingly favorable conditions. As a result, it seems fair to ask to what extent the dominance of a particular influenza strain during the fixed epidemic season is defined by a mere effect of chance rather than by initial conditions, such as variation in immunity levels to different influenza strains. In the current study, we addressed this question by creating a spatially explicit individual-based model and examining the properties of artificial outbreaks caused by the introduction of several influenza strains into a synthetic population.

2 Experimental setup

"Synthetic population" is an artificial spatially explicit human agent database representing the population of a city, a region or a country [2]. In this study, we have used a 2010 synthetic population of St Petersburg which was introduced in [9]. To simulate the circulation of multiple influenza strains, we employed a modified multiagent modeling framework first introduced in [8]. We do not take into account simultaneous co-infection, thus, if various strains are instantaneously transmitted to an individual at the place of contact, one of them is selected at random as the one causing the infection. Each agent in the population potentially interacts with other agents if they attend the same school (for schoolchildren), workplace (for working adults), or lives in the same household. The contacts in public transport are not considered. We take a simplifying assumption that the infection transmission coefficients are not dependent on the strain[1]. The infectivity of each individual is defined by a piecewise constant function g_τ which reflects the change of individual infectiousness over time from the moment of acquiring influenza [1]. Since, according to [7], a slight variation of g_τ values does not affect much the epidemic dynamics, we assumed the values of g_τ the same for all strains. Individuals recovered from the disease are considered immune to the particular influenza strain, that caused it, until the end of the simulation. Cross-immunity is not considered, i.e. the mentioned recovered individuals do not acquire immunity to other influenza strains.

3 Simulations

In the course of simulations, we analyzed how different factors influence epidemic outbreaks. As a defining property of an outbreak, we used disease prevalence at

[1] According to the published modeling results of other research groups, the virulence of A(H1N1) and A(H3N2) is almost similar, while the virulence of B strain might be slightly lower [5].

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day 15 (corresponds to two weeks after the virus introduction in the population). We assumed that zero prevalence at day 15 of the simulation run signifies the absence of an outbreak (a stable transmission chain was not formed and the disease died out).

Dependence on initial number of infected and herd immunity level. In this set of simulations, we considered that α_m, the fraction of individuals susceptible to the virus strain m, is equal for all the strains. Firstly, we tested the effect of changing the number of initially infected, taking $I_0^{(m)} = 1$, $I_0^{(m)} = 100$, and $I_0^{(m)} = 100$ for each strain $m \in \overline{1,3}$ (Fig. 1, left). Secondly, in the same way we tested the effect of changing $\alpha^{(m)}$ (Fig. 1, right). It can be seen that disease prevalence levels are largely defined by the values of $I_0^{(m)}$. The experiment demonstrated that the epidemics started from a single 'patient zero' have higher chances of dying out compared to the larger quantities of initially infected persons. The leftmost group of bars shows that the chance of an epidemic decline till day 15 is around 50% for the case of $I_0^{(m)} = 1$ and around 30% for the $I_0^{(m)} = 100$. As to the influence of herd immunity, its high level reduces the number of the occurred epidemic surges (although due to the stochastic nature of the outbreaks the dependency between the two variables might be not monotonic). The highest level of herd immunity, which corresponds to the smallest level of $\alpha^{(m)}$, prevented large outbreaks from happening (e.g., with $\alpha^{(m)} = 0.05$ no outbreaks with prevalence > 50000 were detected).

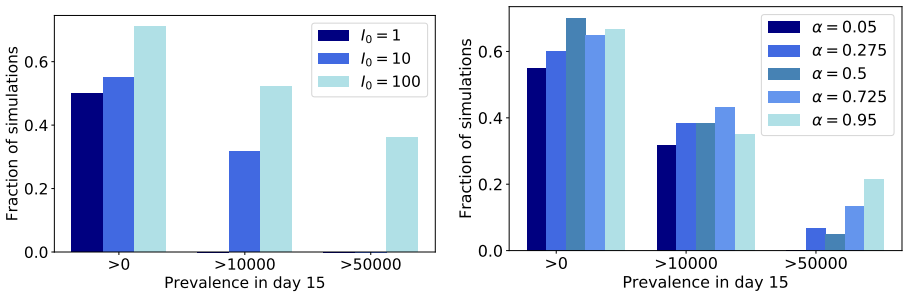

Fig. 1. Distribution of disease prevalence levels on day 15 depending on the fraction of initially susceptible individuals (left graph) and on the fraction of susceptible individuals (right graph)

Simulating multistrain outbreaks. The second set of experiments with the model was dedicated to the simulation of co-circulation of three influenza strains, A(H1N1), A(H3N2), and B, in the synthetic population with strain-specific herd immunity levels. Unfortunately, the information on seroprevalence levels registered in the population of Saint Petersburg was not available to the author

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at the time of the study. Two sets of corresponding values for the beginning of 2010-2011 epidemic season in Moscow and Voronezh were taken for the experiments, as these two cities are situated not far from Saint Petersburg and have the fullest seroprevalence records. We assumed that the fraction of samples seropositive to the virus strain m from the provided dataset (Table 2) is equal to $1 - \alpha_m$, which made it possible to calculate α_m. The resulting values of α_m for the three strains were 0.57, 0.13, 0.1 for 'Voronezh' simulation and 0.78, 0.74, 0.6 for 'Moscow' simulation. According to the data, 'Voronezh' synthetic population possesses rather low susceptibility levels to A(H3N2) and B strains and has slightly higher vulnerability to A(H1N1) strain. At the same time, 'Moscow' population is considerably less protected from the possible outbreak caused by any of the three strains. The obtained distribution of the registered disease prevalence is demonstrated in Fig. 2. As one can see, high levels of population protection in 'Voronezh' experiment did not prevent the occurrence of epidemic outbreaks of the strains A(H3N2) and B, and, moreover, their number is bigger than the number of A(H1N1) outbreaks which have a larger reservoir of susceptible individuals. Nevertheless, the single case of considerably high disease prevalence (>50000 cases at day 15) is attributed to A(H1N1). The results conform to the previous experiment, where the value of $\alpha_m = 0.05$ (twice as low as the lowest susceptibility level in this setting) still permitted full-fledged outbreaks in the population. In the case of 'Moscow' experiment, the distribution of the number of outbreaks of considerable sizes better conforms to the differences in levels of susceptibility. The biggest registered outbreak is caused by the A(H3N2) strain, which is also in fair agreement with the predefined values of α_m.

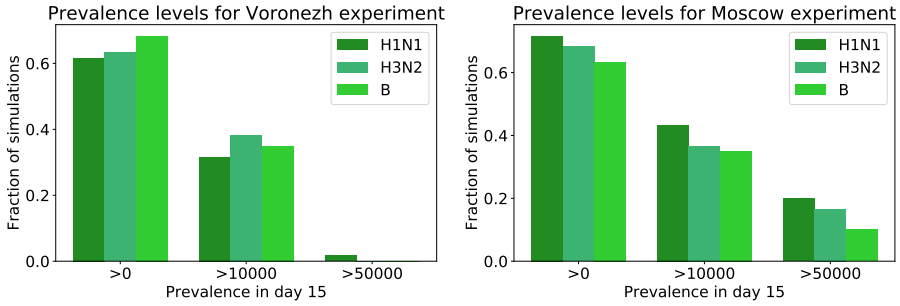

Fig. 2. Distribution of disease prevalence levels on day 15 for the immunity levels set according to seroprevalence tests for Voronezh (left) and Moscow (right)

To assess the interrelation between the herd immunity to the particular virus strain and the possible chance that an epidemic caused by that strain will die out before getting the chance to gain momentum, we listed the corresponding data in Table 1. The numbers show that there might be a correlation between the immunity levels and percentage of 'failed' outbreaks in 'Moscow' experiment,

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whereas the data for Voronezh is contradictory. In the latter setting, high levels of immunity do not seem to negatively affect the probability of A(H3N3) and B strain–related outbreaks, as it was also shown in the above-mentioned Fig. 2.

	A(H1N1)	**A(H3N3)**	**B**
Voronezh, seropositives before the epidemic season	43%	87%	90%
'Voronezh' simulation, halted outbreaks	38.3%	36.7 %	31.7 %
Moscow, seropositives before the epidemic season	28.9%	37.4%	46%
'Moscow' simulation, halted outbreaks	28.3%	31.7%	36.7%

Table 1. Percentage of samples seropositive to particular strains and number of epidemics with zero prevalence on day 15 in the simulations 'Voronezh' and 'Moscow'

4 Results

In this research, we aimed at assessing the role of herd immunity in the epidemic progression through the population. The conclusion we can draw is the following: the actual influenza dynamics in the population, reproduced by stochastic models, is indeed influenced by herd immunity, but the factor of uncertainty inherent to the disease transmission process might somewhat reduce this influence. On one hand, we can see that the increased level of herd immunity apparently lessens the probability of a full-fledged outbreak, as well as lowers the prevalence of the outbreaks occurred. On the other hand, this impact is apparent only when we compare the experiments with dramatically different herd immunity levels. The change of the fraction of susceptible individuals from 0.95 to 0.05 resulted in the chance of an outbreak occurrence decreased only by 11% (from 66% to 55%). Also, as Fig 1 demonstrates, the dependency between the mentioned two values is not monotonic.

A similar conclusion might be drawn from the experiment dedicated to the co–circulation of viruses in the population with the strain-specific levels of herd immunity. In both experimental settings, a single largest outbreak (prevalence level $>$ 50000 for 'Voronezh' setting and $>$ 100000 for 'Moscow' setting) was caused by the virus strain which was favored among the others due to decreased corresponding population protection. At the same time, the distribution of smaller outbreaks by strain types does not conform well to the levels of $\alpha^{(m)}$, nor is the proportion of 'successful' outbreaks in general (Fig. 2, Table 1).

What is more defining in the 'success' of the outbreak is the number of initially infected individuals introduced at the beginning of the simulation. It is known that in SEIR-type deterministic models the introduction of infection is often modeled by one person, i.e. $I_0 = 1$, since in these types of models the initial surge of disease prevalence caused by a single individual is guaranteed, if the selected parameter values allow the infection propagation. At the same time, in the stochastic models starting the simulation from one 'patient zero' might

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lead to the infection dying out rapidly. In our case, for the population with 5% of susceptible individuals, a half of the started outbreaks dies out till day 15 (Fig. 1). In the author's opinion, this type of dynamics is more adequate, comparing with the output of mean-field approximations. A large number of the initially infected individuals introduced at once reduces the possibility of transmission chains being broken, but this way of initializing the simulations affects the final outbreak size and, besides that, seems unrealistic. The better option might be to allow an influx of infected individuals in the course of simulation [11]. In this case, the model will be able to demonstrate a time delay between the moment of the first introduction of the infected person in the population and the actual outbreak surge. This time delay takes place in real epidemic outbreaks — for instance, it was detected during the first wave of COVID-19 in Russia in spring of 2020. The surge of prevalence in deterministic SEIR models always starts at day 0, which might partially explain big biases in assessing the influenza outbreak peaks demonstrated by these models [10]. Additionally, as it is clear from the data, the surges of outbreaks of different strains are separated in time, so the reintroduction hypothesis is supported by this evidence as well.

5 Discussion

To conclude, the performed research showed that the percentage of individuals in the population who are immune to particular influenza strains might somewhat affect the properties of the forthcoming outbreaks — particularly, it might define the resulting dominant virus strain. At the same time, the data on immunity levels might be not enough to determine whether the outbreak itself will take place, because this largely depends on the external factors (possibly, on the dynamics of reintroduction of the infected people in the population with the migration influx). Also, a high level of registered immunity to a particular strain does not guarantee a total absence of disease cases caused by that strain. It might be still circulating in the population, although without causing a major outbreak. The obtained results might be sensitive to the structure of the regarded synthetic population, — particularly, to contact network structure defined by the population and the assumed rules of individual behavior, — and this matter should be considered thoroughly in separate research.

One of the drawbacks of the study is that we considered the seroprevalence levels obtained by laboratory testing of biological samples to be equal to the fraction of individuals in the population not vulnerable to influenza, which is, strictly speaking, not the case. The role of indirect protection of the individuals, which is also responsible for the herd immunity, was not considered and remains an aim for subsequent studies. Also, we plan to perform simulation runs with the increased modeling period ($T = 100$ instead of $T = 15$) to assess how the immunity levels affect the outbreak sizes, which at this point was not possible due to the limitations of the algorithm performance. The modeling framework developed in the course of the study will be used in the research of the long-term immunity formation dynamics to influenza strains in Russian cities. Besides

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that, it might be utilized to assess the effects of targeted vaccination campaigns and to simulate a co-circulation of different acute respiratory diseases in the populations, particularly, the co-circulation of influenza and COVID, which now draws wide attention of various research teams.

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