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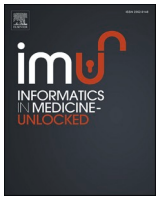

Agent-based model of measles epidemic development in small-group settings

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A B S T R A C T

Measles infection is a significant global public health concern, with one patient able to infect 12–18 people in a susceptible population. Mathematical modeling helps understand the factors influencing measles outbreaks, including vaccination levels, population density and movement patterns of the people who comprise it. Agent-based modeling, particularly useful in organized populations like hospitals or academic buildings, can predict the dynamics of infectious disease outbreaks. The aim of this work is to create an agent-based model of measles infection, which would predict the effectiveness of various anti-epidemic measures in small-group settings such as academic buildings. In this article, the effects of vaccination and isolation on the measles epidemic process were studied. The modeling found that combinations of vaccination and isolation measures are most effective, and these anti-epidemic measures allow to reduce the number of susceptible people that were infected from 199/199 (100 %) in the absence of measures to 73–80/199 (36.7–40.2 %).

1. Introduction

Measles infection is one of the world's most persistent and pressing public health problems. One measles patient can infect an average of 12–18 people in a fully susceptible population during normal social interactions [1]. Measles elimination is an achievable goal if vaccination coverage rates (VCR) of at least 95 % with two doses of a highly effective live attenuated measles-containing vaccine are achieved and maintained globally [1–3]. Meanwhile, since the pandemic of COVID-19, many regions of the world have experienced a meaningful rise in measles incidence [4].

Measles is a vaccine-preventable infection, vaccination against which contributes to a dramatic reduction in the spread of infection. The period of restrictive measures against COVID-19 has shown conclusively that non-specific measures aimed at preventing airborne infections also have an impact on the spread of measles [5]. The high infectiousness of the virus may contribute to the rapid development of a localized measles outbreak into an epidemic [6].

Frequently, measles outbreaks are reported in health care settings [7]. Healthcare workers, in the course of their professional activity, may encounter a measles patient at any period of the disease course (incubation period, period of early manifestations) [8]. Researchers have noted that lack of vaccination among healthcare workers may be a major cause of measles spread among susceptible patients [8–10]. Another organized population in which measles infection is spread is tertiary students [11,12], who share the same academic building, live in dormitories and have many social contacts.

Mathematical modeling of epidemic processes of vaccine-controlled infections has been used for many years to identify the influence of certain factors on the local or global epidemic process [13–15]. Many factors influence the outbreak of an infectious disease, including the level of vaccination or immunity, population density, and the age structure of the population. At the same time, the existence of under-immunized clusters can lead to the formation of large measles outbreaks [16,17].

An agent-based modeling is a method that can be used to better

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understand the dynamics of an infectious disease outbreak [18]. Agent-based models (ABMs) are particularly effective in predicting the deterioration of the epidemiological situation in organized groups within a single building, for example, among medical workers in a hospital setting or medical students within an academic building. The aim of this work is to create an agent-based model of measles infection, which would allow to study the effectiveness of various anti-epidemic measures in small-group settings such as academic buildings to provide a tool to better control and prevent measles in such populations, minimize the risks of outbreaks and eliminate them more quickly, in order to reduce the total number of cases.

2. Materials and methods

To write the model, the R programming language version 4.4.0 [19] was used, as well as the igraph 2.0.3 [20,21] and tidyverse 2.0.0 [22] libraries. For multi-threaded calculation of the model, the future 1.33.2 [23] and furrr 0.3.1 [24] libraries were used.

2.1. Agent parameters

In epidemiological ABMs, modeling occurs at the level of individual agents, that is, people who can move between different loci of the simulated space and change their state under certain conditions. In the proposed model, agents have properties such as ID (agent number), the state of the agent, indicating whether he is susceptible to the disease, is already sick, has recovered or has been vaccinated, the locus in which the agent is currently located, the end point of his route, as well as various auxiliary variables that perform the functions of counters, logical variables and show how long the agent has been in the current locus, how long he has been sick, whether various anti-epidemic measures have been applied to him, etc. These properties are shown in Table 1. All these variables are stored in the R dataframe.

The model implements three stages of the disease: I1 – incubation period, I2 – end of the incubation period and onset of the disease (prodromal period), I3 – disease period. From stage I2 onwards, the infected agent is capable of infecting other agents. At stage I3, the patient has obvious symptoms (in the case of measles, a rash) and is isolated (Fig. 1).

When the model is launched, a dataframe with agents is generated each time. In it, depending on the ratio of vaccinated and susceptible defined in the model parameters, agents are assigned a status (S or V, and the first agent is assigned I2 to be the patient zero). If infection is successful, the agent moves to stage I1, and then, as time passes, to stages I2 and I3. Moreover, if vaccination measures are turned on in the model, then in the case of successful vaccination, the agent can move to the V state from the S state.

In addition, from the vector of all rooms, each agent is randomly assigned the end point of his route. Agents are assigned a length of incubation period (time_incubation) and time until immunity occurs after vaccination (time_immunity). The values for each agent are taken from the corresponding distributions specified by the model parameters.

2.2. Model parameters

The model has various parameters that can be set before running the model (Table 2). These parameters include number of agents in population, proportion of vaccinated agents, duration of stage I1, I2 and I3 in minutes, the probability of transition from state S to I (i.e., the probability of infection) in 1 min, time before acquiring post-vaccination immunity (transition from state S to V), duration of isolation, introduction of anti-epidemic measures: isolation and vaccination on the scale of a room, floor or building.

Baseline vaccination rate and duration of isolation are designated in SanPiN 3.3686–21 ″Sanitary and epidemiological requirements for the prevention of infectious diseases" [25].

Table 1
Agent properties used in the model.

Variable name	Description	Value type
agent_id	Agent ID, denoted by a number in order.	Numeric, from 1 to number of all agents in population
state	The state of the agent, indicating whether he is susceptible to the disease, is already sick, has recovered or has been vaccinated.	S – susceptible I1, I2, I3 – infected (different stages of infection) R – recovered V – vaccinated
time_I	The counter for the time that the agent spent at the current stage of the disease. The agent progresses to the next stage when the counter exceeds the value specified in the parameters for the duration of this stage.	Numeric
time_incubation	Duration of the incubation period (I1) for each agent.	Numeric
locus	The name of the locus in which the agent is currently located.	String with name of locus from graph of possible transitions (see further)
time_locus	The counter for the time that the agent spent in the current locus. Used to determine the time before transition to the next locus in the route.	Numeric
number_locus	The number in order of the locus in the agent's route on which the agent is currently located.	Numeric, from 1 to length of agents route
vaccination	Whether the agent was vaccinated during anti-epidemic measures (in case the model is run with the vaccination).	Logical
time_vaccination	The counter for the time elapsed since vaccination. It is used so that after a certain time (time_immunity), the agent goes into state V, thus developing post-vaccination immunity.	Numeric
time_immunity	Determines the amount of time for susceptible (S) agent's transition to immunized state (V) after vaccination.	Numeric
isolation	Whether the agent was isolated during anti-epidemic measures (in case the model is run with the isolation).	Logical
time_isolation	The counter for the time elapsed since isolation.	Numeric
endpoint	The name of the final locus (room) to which the agent comes.	String with name of locus from graph of possible transitions (see further)

The value for the probability of infection in 1 min (S2I) was calculated from the basic reproduction number (R_0). The most commonly cited R_0 value range for measles is 12–18 [1]. For modeling, the average value from this range was chosen – 15. With a contact number of 15, a sick person in a non-immune population during his infectious period infects an average of 15 people [32,33]. Taking the infectious period for measles to be 8 days (4 days before through 4 days after rash onset) [27], we find that on average it infects $15/8 = 1.875$ people per day. Since not every successful delivery of the virus leads to infection, but only 90 % (one person infected by measles can infect 9 out of 10 of their unvaccinated close contacts) [34], then $1.875/0.9 \approx 2.083$ truly successful transmissions of the pathogen occur per day. In our model, the tick (iteration) time is 1 min, and there are 1440 min in a day. If we accept the model assumption of uniform every minute release of the pathogen, then 2.083 successful transmissions of the pathogen occur in 1440 min. Thus, the probability of successful transmission per minute is $2.083/1440 \approx 0.00145$.

The value for the time to achieve immunity after vaccination

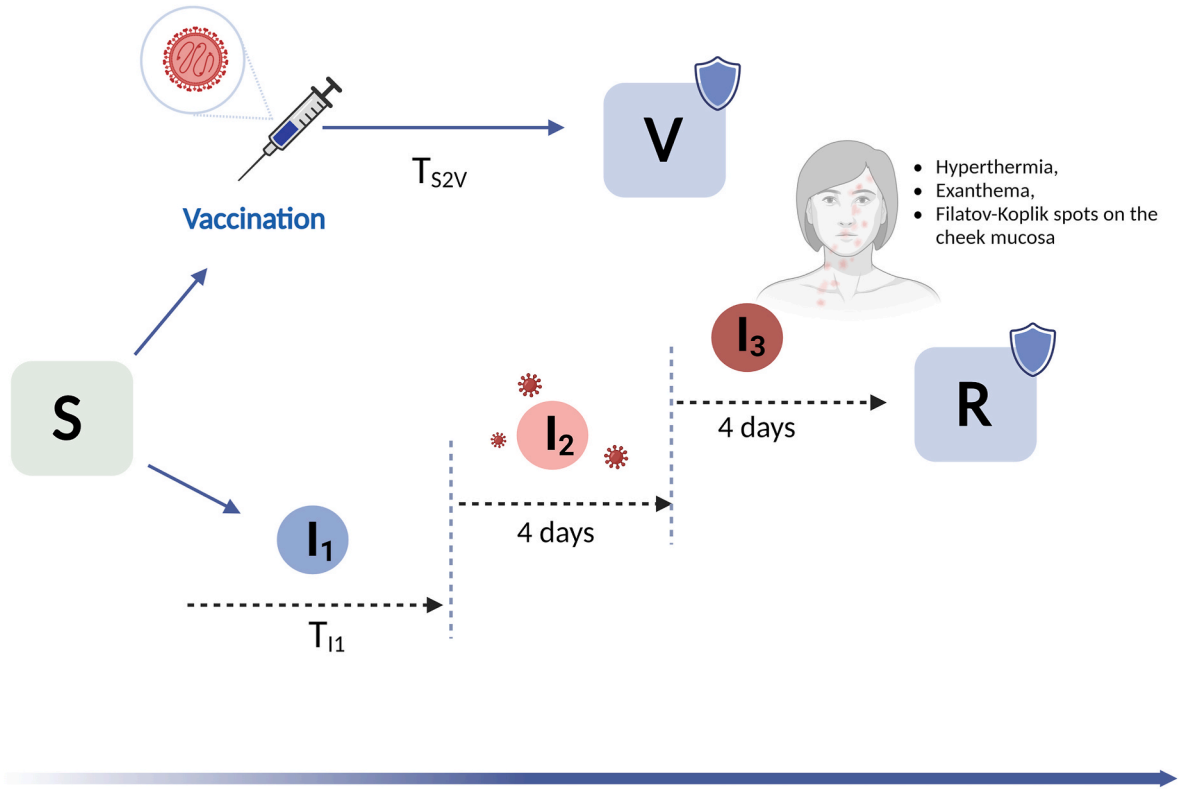

Fig. 1. The stages of disease used in the model. T_{I1} – length of incubation period. T_{S2V} – length of period to build up immunity.

individually for each agent in the model and is described by a normal distribution. Normal distribution parameters were calculated based on data from Ref. [28]. In this study the postvaccination IgM positivity rates were 2 % at 1 week, 61 % at 2 weeks from which the values for μ and σ were calculated.

Sources on the effectiveness of the MMR vaccine for post-exposure prophylaxis suggest different numerical values for this parameter [29–31]. For modeling purposes, the mean value was taken.

2.3. Model and simulation procedure

Time in the model is represented by so-called ticks. One tick is equivalent to 1 min of real time. The simulated space in the model is represented in the form of a dataframe with all possible transitions between loci, in which there are columns “source” and “target”. The value in the source column indicates the name of a specific locus, and the value in target is the locus to which agent can go from source. At the same time, transitions between loci are non-directed, i.e. transition is possible both from source locus to a target locus, and in the opposite direction (Fig. 2).

To determine agent routes, this dataframe is subsequently converted into a graph using the igraph library for R. In this case, the loci become the vertices of the graph, and the transitions between them become its edges. Agent routes are set in such a way that the agent from the initial locus O enters the building, visits the wardrobe, reaches the assigned room (endpoint), and then he would have done the same route in reverse and would have ended up in O locus. A route for each agent is generated before running the model according to its endpoint. All routes for each agent are stored in the list of vectors with the names of the vertices that the agent passes on its path in the order from the starting locus through the end point and back to the starting locus. Each agent has its own vector in this list.

To determine the time intervals that the agent will spend in each of the loci, another list is created in the model, but not with the names of the vertices, but with the corresponding number of ticks in minutes that the agent will be in the loci. At the same time, the amount of time for the entire agent’s route is 1440 min = 24 h = 1 day. In this model, the default is that the agent must arrive at the classroom at 8:15, the class time is 90 min, and he spends 5 min at each intermediate locus. Based on these conditions, as well as the length of the agent’s route, the time in each locus of the path is calculated, which is recorded in the vector for this agent in the corresponding place in the list. This list stores the default time, which corresponds to the time when the agent would arrive minute by minute at the start of the session. However, the model adds a random deviation delta, which determines within what limits (from -delta to delta) the agent can arrive early or late. By default, delta = 20 min. Also, if agents are more than 5 min late, they can speed up in each intermediate locus by 1 or 2 min to get to the endpoint room faster. If earlier by more than 5 min, they may linger in the intermediate locus from 0 to 2 min. After classes end 90 min later (at 9:45), they can also be delayed from 0 to 2 min. At the same time, the value of the time spent in O before and after classes is also adjusted according to random changes made to the time intervals. During the operation of the main cycle of the model, at the end of each day, according to a special condition, based on the default time in the loci for each agent, a new list is generated with the time in the loci with random changes for the next day.

The main cycle of the model corresponds to one tick, which corresponds to 1 min in the simulated world. The main cycle of the model continues as long as there are agents in the state I1, I2 or I3. This cycle includes the following operations: checking the infection, incrementing the counters for the time of infection, vaccination and isolation, and, if they are exceeded, making a corresponding change in the status of this agent/agents, checking the movement, checking the end of the day, as well as operations related to anti-epidemic measures.

The infection test for a specific agent works as follows: all loci except O are checked for the presence of agents with status I2 or I3. If such agents are present in a given locus, then all agents with S status located in the same locus are selected. They are being tested for infection

Table 2
Model parameters.

Parameter name	Description	Default value	References
n_pop	Number of agents in population	4000	–
VR	Baseline vaccination rate, proportion of vaccinated agents at the start of the model	0.95	[25]
I1_meanlog	Mean value μ of log-normal distribution describing duration of disease stage I1 in minutes. I1 duration selected individually for each agent.	2.3	[26]
I1_sdlog	Standard deviation σ of log-normal distribution describing duration of disease stage I1 in minutes. I1 duration selected individually for each agent.	0.2	[26]
I2	Duration of disease stage I2 in minutes	5760	[27]
I3	Duration of disease stage I3 in minutes	5760	[27]
S2I	The probability of transition from state S to I (i.e., the probability of infection) in 1 min	0.00145	[1]
S2V_mean	Mean value μ of normal distribution describing duration of period to build up immunity. S2V selected individually for each agent.	19050	[28]
S2V_sd	Standard deviation σ of normal distribution describing duration of the period to build up immunity. S2V selected individually for each agent.	4370	[28]
VE	Vaccination efficacy: the proportion of agents subject to vaccination in which the vaccine will work.	0.94	[29–31]
TI	Duration of isolation	30240	[25]
m_vaccination_all	Measures: vaccination of all agents in the building	FALSE	–
m_vaccination_floor	Measures: vaccination of all agents on the floor	FALSE	–
m_vaccination_room	Measures: vaccination of all agents in the room	FALSE	–
m_isolation_room	Measures: isolation of all agents in the room	FALSE	–
m_isolation_floor	Measures: isolation of all agents on the floor	FALSE	–
iters	Number of model runs	100	–

possibility. The condition for performing the check is that the value of a uniformly distributed random variable from 0 to 1 will be less than the S2I model parameter multiplied by the number of infecting agents (I2 or I3) in a given locus. If the condition is met, the agent becomes ill and is assigned the status I1.

The movement check condition tests all agents sequentially. If an agent's time spent in a locus is equal to that recorded in the list with times in all loci, the number of the locus in the agent's path is increased by 1. The time counter in the locus is reset to 0, and the name of the next locus (with an index increased by 1) from the routes list is written to the agent's current locus. Thus the agent moves to the next locus.

The end of day check is carried out when the number of ticks passed is equal to 1440 times the number of days that have passed since the model was launched. During this check, new timings are generated for the agents' route for the next day, and a status transition from I2 to I3 and I3 to R also occurs to allow agents to return to classes the next day after recovery. Also at the end of the day, the conditions for the action of measures are checked depending on the detection of agents with symptoms of the disease (in state I3), i.e., whether the agents will be vaccinated and/or whether they will be subject to isolation the next day.

In this model, vaccination measures are introduced when an agent is identified in state I3, and all agents with the same end room as I3 agent, or agents on the same floor where I3 agent's end room was, or all agents in the building will be vaccinated (depending from the choice of parameters). Isolation measures work the same way. When isolation or vaccination measures are applied to an agent, his corresponding logical variables are set to TRUE. In the case of vaccination, the time countdown is started using the time_vaccination variable, and when the value is greater than time_immunity, the agent's status changes from S to V (if he has not been infected before). When isolation is introduced, the agent does not leave the O locus the next day and spends there time indicated by the TI parameter.

3. Results

In order to determine the effectiveness of anti-epidemic measures, the model was run 100 times for each of the measures/combinations of measures. The effectiveness of measures was obtained by dividing the number of disease cases by the number of susceptible agents and subtracting from 1, i.e., the higher the value, the more cases of the infection were prevented (Fig. 3).

$$Effectiveness = 1 - \frac{N(R) - 1}{N_0(S)},$$

where N(R) is the final number of all recovered agents (from which one patient zero is subtracted) and $N_0(S)$ is the initial number of susceptible agents (was 199 in our model setup).

Median values for the duration of the infection outbreak (that is, the number of ticks until there are no agents left in I1, I2 and I3 states) are also presented (Table 3).

4. Discussion

The most effective of all options for anti-epidemic measures was the combination of vaccination for all agents in the building and isolation on the floors, where infected agents were identified. The median number of infection cases was 77.5 with 95 % CI [73, 80] from 199 susceptible agents.

This confirms the importance of measles vaccination, especially in the focus of infection, as stated by many researchers [35,36]. However, the long time required for immunity formation after vaccination, the non-100 % effectiveness of vaccines, and the long incubation period of measles (up to 21 days) reduce efficiency post-exposure vaccination, so measles outbreak may continue even after vaccination measures were applied. Isolation and quarantine measures for measles infection allow to immediately prevent the spread of infection without waiting for the formation of post-vaccination immunity in a sufficient proportion of the population. In addition, other studies confirm that isolation and separation measures not only for infected people and their contacts, but also for all unvaccinated people, are very effective in suppressing a measles outbreak, especially in undervaccinated populations [37]. According to our modeling, the most appropriate and rational intervention for measles infection outbreak is isolation and post-exposure vaccination.

In addition, the modeling results showed that if quarantine is introduced only for agents who were in the same room with the infected, the duration of the measles outbreak increases (median duration 74 days with room-by-room isolation versus 44 days with no measures). This is because insufficient containment measures result in the rate of spread of the virus decreasing, but all infected agents are not subject to isolation and the outbreak cannot be eliminated. A sign of this is that new cases of infection continue to appear after the peak has passed. In addition, it is noteworthy that the addition of vaccination in this case reduces the duration of the outbreak, as well as the incidence of disease (median duration 74 days versus 45 days with vaccination).

Highly contagious airborne infections (such as measles, flu, COVID-19 and other infections) require special attention from organizations

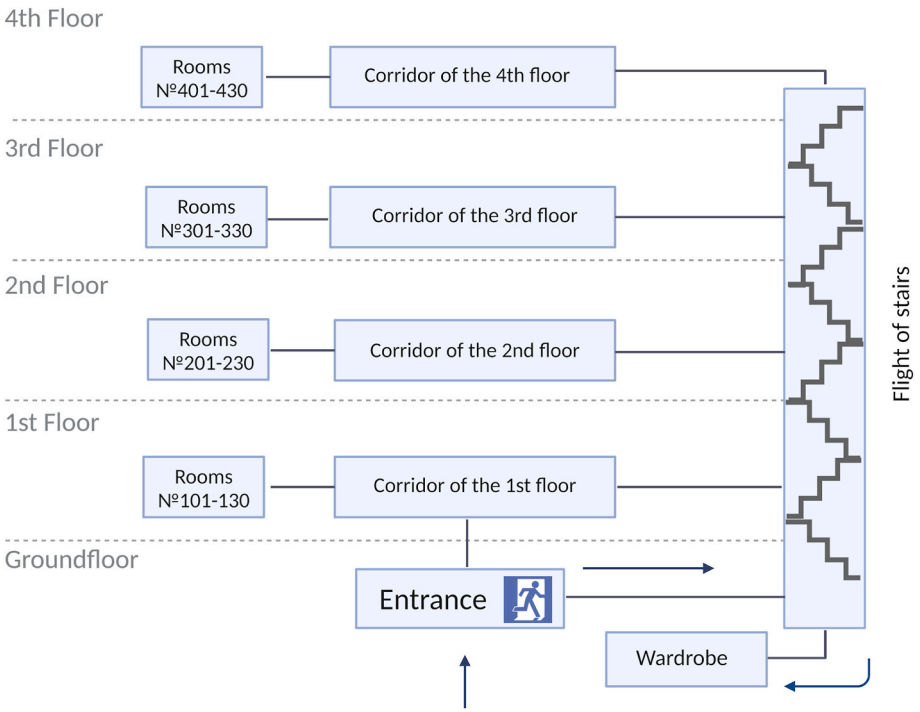

Fig. 2. The scheme of moving agents in the model.

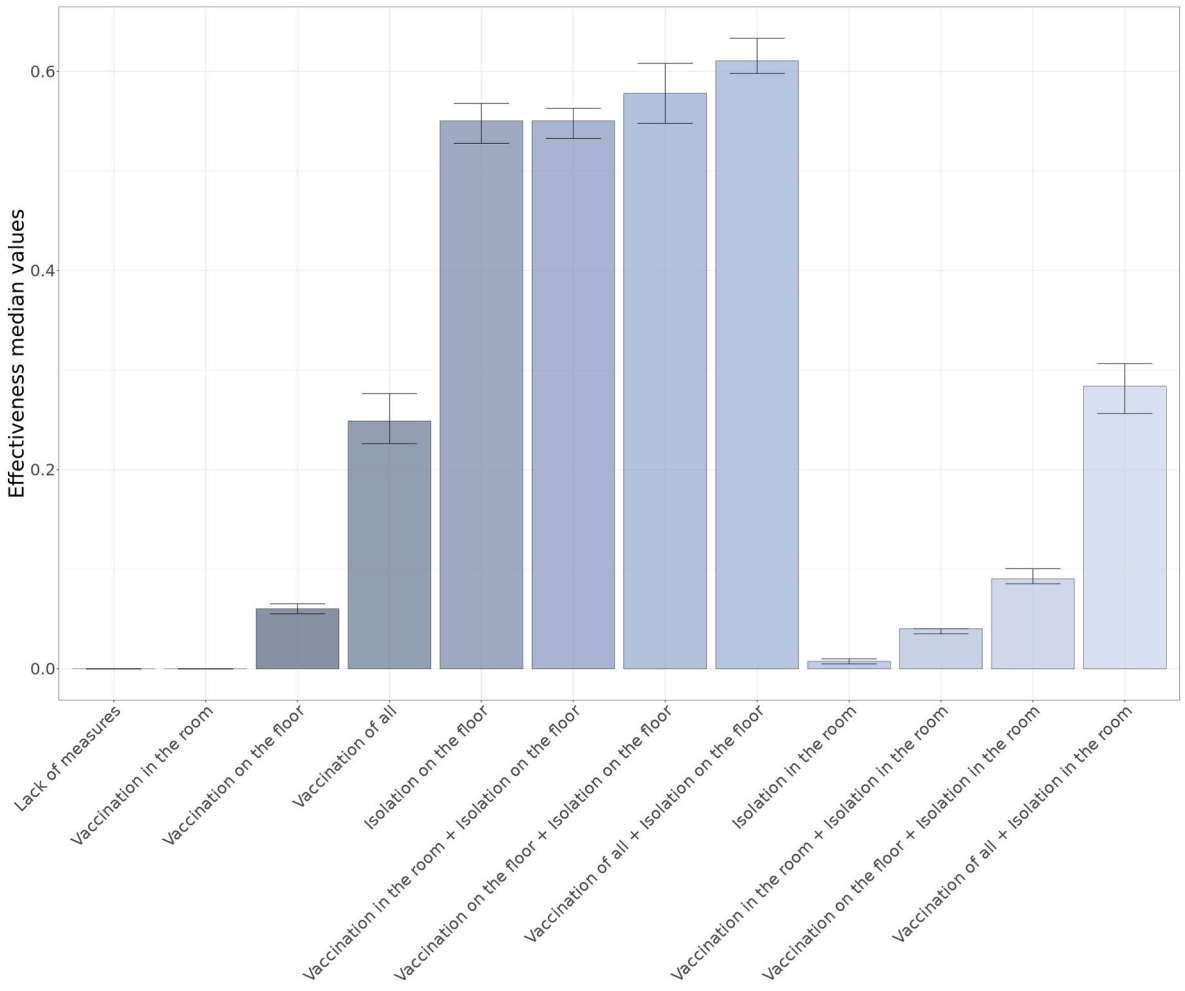

Fig. 3. Median values for effectiveness of anti-epidemic measures with 95 % confidence intervals.

Table 3
Modeling results for anti-epidemic measures.

Measure name	Median value of the anti-epidemic measures effectiveness	Lower 95 % CI	Upper 95 % CI	Duration of the infection outbreak; days
Lack of measures	0	0	0	44
Vaccination in the room	0	0	0	44
Vaccination on the floor	0.060	0.055	0.065	44
Vaccination of all	0.249	0.226	0.276	43
Isolation on the floor	0.550	0.528	0.568	38
Vaccination in the room + Isolation on the floor	0.550	0.533	0.563	38
Vaccination on the floor + Isolation on the floor	0.578	0.548	0.608	38
Vaccination of all + Isolation on the floor	0.611	0.598	0.633	38
Isolation in the room	0.008	0.005	0.010	74
Vaccination in the room + Isolation in the room	0.040	0.035	0.040	45
Vaccination on the floor + Isolation in the room	0.090	0.085	0.101	45
Vaccination of all + Isolation in the room	0.284	0.256	0.307	45

responsible for combating infectious diseases [38]. Local outbreaks of such infections, if there are a sufficient number of susceptible individuals, very quickly become widespread. Experience in combating epidemics shows that in countries with higher healthcare expenditures (medical technologies, human resources and the hospital admission capacity, the organization of vaccination campaigns, etc.), systemic vulnerability to crisis is reduced [39,40]. It should be emphasized that the main way to combat such infections was and remains high-quality, mass vaccination [41–47].

For measles infection, maintaining high annual vaccination coverage of those eligible for vaccination is extremely important. An increase in the proportion of susceptible individuals leads to an increase in the number of cases [16]. Duplicating vaccination with non-specific methods of combating infectious disease outbreaks (isolation, isolation) is an appropriate strategy, the effectiveness of which has been demonstrated in our model and in models of other researchers [37].

Mathematical modeling of infectious processes has been carried out by many authors [41,48,49], and different approaches were used and different variables were set. There are a number of ABMs of infectious diseases, which also, like the proposed model, allow us to simulate the infectious process in small groups and populations and, in addition, support the ability to study the effects of various anti-epidemic measures and interventions.

One notable example is the SIM-D model which simulates the spread of infectious diseases such as COVID-19, flu, malaria, dengue, mumps, and rubella [50]. This model captures human-to-human interactions, population dynamics, and disease transmissibility. SIM-D model is similar to that proposed in this article in the types of interventions it uses, which are also isolation and vaccination. However, the implementation of these measures in terms of the behavior and state of agents differs from our model. When isolated, agents in the SIM-D model reduced their activity outside the home and interaction with other agents, but not completely, up to 10 % of the time. When vaccination measures were introduced, 50 % of the population received the vaccine, and among those vaccinated, the susceptibility to infection decreased by 9 times. In the SIM-D model, unlike our model, there was no period between vaccination and the immunity appearance.

Another ABM that has common features with that described in this work is a model by Bonačić Marinović et al. that evaluates the effectiveness and timing of vaccination in a school setting during a measles outbreak [26]. Both models have a partially similar set of parameters for measles infection; in addition, both models simulate the effect of vaccination to control a measles outbreak in a small group setting. However, our model places more emphasis on understanding the spatial and temporal dynamics of infection spread within small groups with detailed spatial interactions and movement patterns of individuals, while the other model specifically aims to simulate different vaccination delay scenarios and their impacts on outbreak size. In our model, there is no delay in vaccination, and agents receive the vaccine the day after the case is identified. However, different scales of vaccination of contact persons have been implemented: in the same classroom with the sick person, on the same floor or in the entire building. In addition, our model implements the possibility of quarantine not only for a patient with obvious symptoms, but also for those in contact with him, which allows us to study a variety of anti-epidemic measures and their combinations.

Our study has several limitations that should be acknowledged. The model relies heavily on parameters obtained from existing publications rather than real-world data. This makes a model with this set of parameters suitable for a fairly general case of a measles outbreak, but may not be accurate enough to model an outbreak under specific conditions. However, calibrating the parameters and validating the model using outbreak data from specific settings would improve the accuracy of the proposed model for measles outbreak prediction.

In addition, to the limitations of the model can be added the fact that the movements of agents in the simulated space follow a certain route, and although they have random deviations in time, they do not allow a random change of route. Therefore, this model is more consistent with a setting with an organized population, where there is a certain schedule.

Modeling environmental and spatial factors also has certain conventions. It is known that the dynamics of the epidemic process will depend, among other things, on social and natural factors [51,52]. The minimum spatial unit in the model is a single room, and such granularity of spatial modeling may be insufficient to capture detailed local transmission dynamics, especially in heterogeneous environments.

In addition, a feature of this model is that transmission of infection occurs only inside the building, and in the O locus there is no spread of infection and any interaction of agents. Therefore, a description of the transmission of infection between agents from the model outside the building or to other persons outside the model population is not included in the model.

5. Conclusion

Our study demonstrated the feasibility of agent-based modeling of a measles outbreak in a small population of medical students. The study also predicts the effectiveness of basic anti-epidemic measures.

The modeling showed that a combination of quarantine measures, such as isolation of sick and contact persons, with post-exposure vaccination was the most efficient in reducing the number of people infected

and the duration of a measles outbreak.

In addition, according to our modeling, an insufficient scale of anti-epidemic measures reduces the rate of the virus spread in the group, but is not able to promptly eliminate an outbreak of infection.

The resulting model makes it possible to conduct scenario analysis to study various measles control strategies in small groups and predict the effectiveness of measures to prevent the spread of measles and reduce morbidity.

Ethical statement

Not provided.

CRediT authorship contribution statement

Sonya O. Vysochanskaya: Writing – original draft, Methodology. **S. Tatiana Saltykova:** Project administration. **Yury V. Zhernov:** Supervision. **Alexander M. Zatevalov:** Supervision. **Artyom A. Pozdnyakov:** Supervision, Methodology, Conceptualization. **Oleg V. Mitrokhin:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not provided.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2024.101574.

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