An artificially simulated outbreak of a respiratory infectious disease

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Abstract

Background Outbreaks of respiratory infectious diseases often take place in crowded places. To understand the spreading pattern of an outbreak of a respiratory infectious disease and provide a theoretical basis for the targeted implementation of scientific prevention and control, we attempted to establish a stochastic model to simulate an outbreak of a respiratory infectious disease at a military camp. This model fits the general pattern of disease transmission and further enriches theories on the transmission dynamics of infectious diseases.

Methods We established an enclosed system of 500 people exposed to adenovirus type 7 (ADV 7) in a military camp. During the infection period, the patients transmitted the virus randomly to susceptible people. The spread of the epidemic under militarized management mode was simulated using a computer model named “the random collision model”, and the effects of factors such as the basic reproductive number (R0), time of isolation of the patients (TOI), interval between the onset and isolation (IOI), and immunization rates (IR) on the developmental trend of the epidemic were quantitatively analysed. Results Once the R0 exceeds 1.5, the median attack rate increases sharply; when R0=3, with a delay in the TOI, the attack rate increases gradually and eventually remains stable. If the IOI exceeds 2.3 days, the median attack rate will also increase dramatically. If the IR exceeds 0.5, the median of the attack rate nears zero. The median generation time was 8.26 days (95% CI: 7.84-8.69 days). The partial rank correlation coefficients between the attack rate of the epidemic and the R0, TOI, IOI, and IR were 0.61, 0.17, 0.45, and -0.27, respectively. Conclusion The random collision model not only simulates how an epidemic spreads with superior precision but also allows more flexibility in the settings of the exposure population’s activities and different types of infectious diseases, which is conducive to furthering the exploration of the epidemiological characteristics of epidemic outbreaks.
Background

Respiratory infectious diseases, especially influenza A and ADV, such as H1N1, H7N9, ADV 7, and ADV 55, among others, often lead to worldwide spread and seriously endanger human health. For example, from late April to the end of 2009, the peak of the local H1N1 flu epidemic had passed in most countries, and approximately 70,000 lab-confirmed hospitalized patients and 2,500 fatal cases were observed in 19 countries or administrative regions [1,2]. Epidemics of ADV infection often occur in healthy children or adults in closed or crowded settings (particularly in the community, military recruit training centres, hospitals, and chronic care facilities) worldwide [3-6]. Fatality rates for untreated severe adenovirus-associated pneumonia or disseminated disease may exceed 50% [7].

ADV 7 outbreaks are very common among military trainees in many countries [8-13]. This commonality is thought to be due to the trainees’ close living quarters, as infectious agents from epidemic areas enter the camp, adenoviruses persist in the environment, the general population is susceptible to some variants [14], and vaccine coverages are low [15]. These diseases can spread to a large scale in a very short period of time. Some viral strains can cause serious intrapulmonary infections and even lead to death. Therefore, determining the precise timing for disease control and adopting comprehensive scientific measures to control the spread of an epidemic are demanding challenges facing the public health systems of every country. To achieve the objectives discussed above, we need to perform theoretical research on the dynamics of epidemic transmission and to quantitatively analyse the time of control and the impact of measures on the attack rate. Mathematical models of infectious diseases can help to deepen our understanding of the epidemiological distribution of infectious diseases. At present, the most commonly used model is the Susceptible-Exposed-Infectious-Recovered (SEIR) model, from which many
models have been derived and widely adopted to analyse infectious outbreaks of Ebola, tuberculosis, influenza, etc. [16-18]. Indeed, the SEIR model has proven to be critical for revealing the epidemiological characteristics of infectious diseases. However, this model has some limitations in the analysis of outbreaks of respiratory infectious diseases. For example, SEIR-based models assume that contacts between the infectors and others are continuous over time, that is, that infectors transmit the virus continuously, whereas in reality, these contacts occur randomly, and time intervals do exist between infection events. Furthermore, according to the SEIR model, as long as someone within the population is infected, and the effective contact rate (the number of people infected by one infecter within the time unit when all the exposed persons are susceptible) is greater than 0, the outbreak will be triggered, and the disease will spread continuously. However, again, in reality, even if someone in the population becomes infected, it still may not cause an epidemic outbreak, and on many occasions, even without human intervention, outbreaks usually end before all the susceptible people become infected. Additionally, the SEIR model assumes that all infectors display the same epidemiological characteristics in their effective contact rates, incubation periods, symptom duration, and treatment duration, whereas in fact, these factors vary randomly from patient to patient. Another fact to consider is that the activities of exposure population are not constant. For example, soldiers in military camps train together during the day, and at night, they rest in the dormitory with their squad unit. Thus, the close contacts of the infectors change over time, but the SEIR model fails to reflect this element.

To overcome the limitations of the SEIR model, we tried to establish an individual-level stochastic research model to simulate the spread dynamics of epidemic outbreaks in the real environment. Currently, such models have been used in teaching and research related to the epidemiology of infectious diseases. For example, Eichner M used stochastic
computer simulations to examine how case isolation, contact tracing, and surveillance impede the spread of smallpox in a highly susceptible population [19]. Salathe M modelled the spread of an infection in a "small-world" network, based on computer simulations, to assess how a personal opinion about vaccination affects the probability of disease outbreak [20]. Williams A employed a discrete time simulation environment to model a virtual town that experiences a bioterrorist attack of pneumonic plague and assessed the attack rate under the influence of the mass treatment centre and home isolation [21]. In addition, Cremin I et al presented a teaching exercise in which an infectious disease outbreak is simulated over a five-day period and subsequently analysed [22]. Although these studies used the concept of individual-level and random contact among people, they did not fully account for some factors such as the difference in patients’ contact behaviour during the day and night, the time of isolation, and the duration from onset to isolation, which influences morbidity. Therefore, a stochastic model for the prevention and control of outbreaks of respiratory infectious diseases in a military camp is still lacking.

We chose to use ADV 7, which has a high incidence and poses serious health threats in the army, to establish a random collision model to simulate the complete process of the occurrence and development of an ADV 7 outbreak, with effective intervention measures. Therefore, with this model, we not only set the scope of the population’s activities with greater flexibility and depict the outbreak’s transmission network, but we also quantitatively analyse the impact of intervention measure to provide a scientific basis for the targeted prevention and control of the outbreak.

Methods

Data sources

Firstly, we needed to acquire parameters necessary for the model, which were derived from a real outbreak in a boot camp. In November 2018, we conducted an epidemiological
investigation and analysis with prevention and control management of an ADV 7 outbreak in northeastern China. The probability distributions and the parameters of the incubation period (the interval from infection to the onset of the disease), the generation period (the interval between successive onsets of symptoms in a chain of transmission), the symptom duration (the duration of a patient's clinical symptoms), and the isolation treatment duration (the duration of isolation treatment for a patient) were calculated (Table 1). These parameters were applied directly to the model, and their source and the method of calculation are provided in the supplemental material.

Model establishment

Secondly, we established the model according to the following disposal method of respiratory infectious disease outbreak in Chinese military camps. At the early stage of an outbreak, patients are often treated for the common cold at a clinic in the camp and are still in normal contact with other exposed individuals during treatment, which leads to a delayed opportunity for timely isolation and control of the epidemic. When the outbreak reaches a certain level, the CDC will participate in disease control. Patients whose symptoms appeared before the TOI but are still within the durations of symptoms are quickly sent to the hospital. The body temperatures of the exposed individuals are monitored several times daily, and those who develop fevers are also quickly sent to the hospital. Patients return to the camp once they recover. The relationships among the time of attack, time of recovery, and TOI of the patients are shown in Figure 1. Based on the above description, two enclosed and interconnected systems were simulated in the outbreaks. The former was the military camp where the disease transmission originated. Each patient in the model is considered a mass point that walks randomly during the infection period. When patients have contact with other susceptible people, they too become infected. After an incubation period, the infected individuals become
patients and transform into new mass points. Such collisions continue until no new mass points are generated. Patients are considered infectious only when clinical symptoms begin to appear, and thus the infection period is equivalent to the symptom duration. Each patient transmits the virus at a certain rate through close contact with susceptible people, and the time intervals between infected individuals infected successively by one patient successively are independent of each other and are exponentially distributed at the same time.

The latter was the hospital where the isolation treatments were performed. Since medical personnel at the hospital take strict protective measures to prevent nosocomial infections, patients should not transmit the disease to other susceptible people during the treatment duration. Once patients have recovered, they are sent back to the camp to continue their activities with other exposed people. Since recovered individuals have already produced specific antibodies, they will not become infected again.

**Disease transmission network**

In addition, we analysed the transmission network of ADV 7 and mapped it using Gephi 0.9.2 under the assumption that the entire exposed population was susceptible and that patients could transmit viruses to susceptible individuals without isolation treatment.

**Factors affecting the outbreak**

The model we envisaged was simulated on a computer and was based on a description of the epidemic. In our model, we set up a total of 50 squad units with 10 people in each unit. Military drills are from 06:00 to 18:00 hours daily; during these times, all subjects gather to participate in training or learning, and the virus is freely spread among the crowd. In contrast, during non-military drill periods, the subjects rest in the dormitory with their squad unit, and the virus will spread only within the dormitory. Since all soldiers are male, they are nearly 20-years-old, and their physical fitness has reached the unified
standard, we consider that the population characteristics were homogeneous. The effective contact rate, incubation period, symptom duration, and treatment duration for each patient are randomly sampled according to the probability distributions presented in Table 1. In addition, immunization of the exposed population can have an impact on the development of the outbreak. We pre-established that a portion of the exposed population gained immunity to the virus through vaccination and that these individuals are randomly distributed among the population.

**Generation period**

The generation period was also calculated. According to the literature, the generation period is consistent with the Weibull distribution [23]. Therefore, we estimated this index directly on the basis of the probabilistic characteristic using a bootstrap method (1000 iterations of random sampling). The specific calculation methods are described in the supplemental material.

**Sensitivity analyses**

Finally, we performed sensitivity analyses of four significant parameters to assess the impact on the attack rate. Partial rank correlation coefficients (PRCC) and Latin hypercube sampling (LHS) were used to conduct sensitivity analyses. PRCC-LHS is an efficient and reliable sampling-based sensitivity analysis method that provides a measure of monotonicity between a set of parameters and the model output after the removal of the linear effects of all parameters except the parameter of interest [24,25]. Each parameter interval (from 0.5 to 1.5 times the average value of the parameters) was divided into $N$ smaller and equal intervals, and one sample was selected randomly from each interval [24,25]. A standard coefficient denoting the correlation between the parameter and the model output was calculated. All analyses were conducted using MATLAB R2019a (MathWorks, USA, 2019).
Results

**Disease transmission network**

The transmission network is shown in Figure 2. The black dots with connecting lines represent patients with infectious connections (as either an infector or an infected individual), totalling 328 people; the dispersed dots around the edge of the graph represent individuals who are exposed but uninfected. The first patient is marked in red; he infected a total of 3 susceptible people during the infection period.

**Factors affecting the outbreak**

$R_0$ As demonstrated in Figure 3A, when the $R_0$ increases, the attack rate increases correspondingly. The maximum attack rate increased continuously from 0.3 to 0.96. The median attack rate remained close to 0 when the $R_0$ was between 1 and 1.5 but then increased sharply as the $R_0$ increased, reaching a maximum value of 0.93 when the $R_0$ reached 3. When the number of patients reaches 3 or more, the disease is considered an outbreak. We calculated the probability of an outbreak under different $R_0$ values and found that it rose from close to 0.5 to 0.93. Figure 4A shows that when the $R_0$ was equal to 3, 3.5, and 4, the peak values of the median growth rate (the number of new patients per day) were achieved on the 50th day (13 patients), the 46th day (16 patients), and the 41st day (19 patients), respectively, while the median cumulative numbers of patients on the 120th day at those $R_0$ values were 464, 479, and 488 people, respectively. We defined the day that the first patient was detected as the 1st day.

**TOI** Figure 3B shows that under the condition of $R_0=3$, the probability of an outbreak increased slightly, from 0.85 to 0.9, and consistently stayed near 0.9. When the TOI was on the 10th day, the probability of having more than 10 patients was only 0.2, indicating
that the outbreak was well under control. With the delay in the TOI, the probability of having more than 10, 20, 40, or 80 patients increased. When the TOI was later than the 25th day, the outbreak scenario in which more than 80 people were infected began to emerge, indicating that a later TOI leads to the infection of more patients and, consequently, to greater outbreaks. From the 50th day onwards, the attack rate of the epidemic stabilized and remained at a high level. As demonstrated in Figure 4B, when the TOIs were the 40th day and 50th day, the median growth rate reached peak values after 4 day (11 patients and 15 patients, respectively) and then dropped rapidly, with the corresponding median cumulative numbers of patients reaching 157 and 300, respectively. When the TOI was on the 60th day, the median cumulative number of patients reached 418 people.

**IOI** Figure 3C shows that when $R_0=3$, the probability of an outbreak rose from 0.32 to 0.92. The maximum attack rate increased from 0.16 to approximately 0.95, and the 75% quantile, median, and 25% quantile of the attack rate began to increase drastically on the 1.5th day, 2.3rd day, and 3.8th day, respectively, with all three approaching 0.9 on the 6th day. This result suggests that when the IOI is below a certain threshold, the attack rate of the disease can be controlled at a low level; however, once the IOI exceeds the threshold, the attack rate will increase very quickly. Figure 4C shows that when the TOIs were on the 3rd day, 3.5th day, and 4th day, the growth rate of patients peaked on the 63rd day (5 patients), 58th day (7 patients), and 57th day (9 patients) correspondingly, while the medians of the cumulative patient numbers reached 357, 400, and 423, respectively.

**IR** Again, when $R_0=3$, the probability of outbreak showed a continuous reduction from 0.92 to 0.56, as shown in Figure 3D. At the same time, the maximum attack rate was reduced from 0.96 to 0.2, and the 75% quantile, median, and 25% quantiles of attack rate
all dropped from the original value of 0.92. When the IR exceeded 0.5, the median of the attack rate became close to zero. As Figure 4D shows, when the IR was 0.1, 0.15, and 0.2, the growth rates for patient numbers peaked at the 56th day (10 patients), the 57th day (8 patients), and the 60th day (7 patients), and the cumulative patient numbers were at 402, 370, and 336 patients, respectively.

**Generation period**

We obtained an average value of 8.28 days, with a standard deviation of 2.78 days. Figure 5 shows that the median was estimated to be 8.26 days (95% CI: 7.84-8.69 days).

**Sensitivity analyses**

Sensitivity analyses were performed to assess the relationship between four indexes (TOI, IOI, IR) and one output (attack rate). We obtained 500 samples from a uniform distribution for each parameter range, and the PRCCs were 0.61, 0.17, 0.45, and -0.27, respectively. A value greater than 0 indicates a positive correlation, and a value less than 0 indicates a negative correlation. Values near -1 or +1 indicate that the parameter has a strong impact on the output, whereas those closer to 0 indicate less effect on the output result.

**Discussion**

In our study, we used a completely different idea from the SEIR model. The random collision model has the following specific advantages: 1. The model can more precisely describe the process of epidemic transmission. We used the individual subject as the study unit, and in the program, each patient’s file contains a record of the time of infection, attack, isolation, rehabilitation, susceptible persons he might have infected, as well as whether his range of activities was restricted during the day and night. Not only is it conducive to inquire about the disease development process of each patient, but the transmission chain of the infection can be drawn, and therefore, an in-depth analysis of
the transmission path of infectious diseases in a crowd is valuable. 2. Randomization is in greater agreement with the transmission characteristics of an infectious disease. Contact between patients and susceptible persons is random rather than continuous. The effective contact rate, incubation period, treatment duration, and immunity of the patients are also in accordance with random distribution. We randomly sampled from the probability distributions, which are shown in Table 1, that were obtained from the actual epidemic situation and distributed to each patient. This sampling can ensure the authenticity and scientific integrity of the research. 3. This method can be extended to other infectious diseases and their occurrence scenarios, e.g., tuberculosis outbreaks in schools or the spread of HIV among gay men; we can also set patient activities in programs, such as in a school, where students attend classes during the day, return home at night, or board at the school. Furthermore, more complex factors affecting epidemic transmission can be designed as part of the program, which has the flexibility and diversity that the traditional SEIR model cannot achieve.

Additionally, in the following four paragraphs, we discuss the impact of four indicators, $R_0$, TOI, IOI, and IR, on the attack rate in the outbreak.

Overall, $R_0$ was positively correlated with the attack rate at a PRCC of 0.61, which was the highest absolute value among the four parameters included in the comparison, indicating that $R_0$ has the strongest influence on attack rate. It is worth noting that the median attack rate does not continue to increase with the increase in $R_0$, which differs from the traditional theory that an epidemic will be triggered once $R_0 > 1$ [26]; rather, it starts to increase dramatically at a certain critical point. The reason for this dramatic increase is because when the value of $R_0$ is small, even when a source of infection is present within the crowd, the patient’s ability to spread the disease is weak, and he will recover before
the disease is transmitted to other susceptible people. As the $R_0$ increases, the speed of disease transmission increases with it, and the cumulative effect is amplified in a manner that corresponds to the increase in the number of disease generations. This phenomenon reminds us that as long as appropriate preventive measures (such as health education, active circulation of indoor air, etc.) are taken to keep the $R_0$ at a low level, serious disease outbreaks can be prevented.

The timely isolation of patients after an outbreak can very effectively control further outbreaks of an epidemic. Our results showed that when the $R_0$ stays constant, with a delay of the TOI, the probability of a total patient number that exceeds 80 people remains very low initially; then, it rises sharply; and finally, it reaches a high level and remains there, differing from the traditional theory that the attack rate continues to rise as TOI is delayed. This pattern reveals that when isolation treatment is carried out at the early/beginning stage of an outbreak, the attack rate can be controlled at a lower level; however, with postponed isolation measures, the total number of patients will increase very quickly, and if isolation is initiated too late, outbreaks of the epidemic become extremely difficult to control. When the TOI occurs before the growth rate peaks, the growth rate displays a phased trend of an initial increase, followed by a rapid decrease and a final slow decrease. This trend is observed because many people became infected before being isolated; although those who became sick after the TOI were isolated within 1 day of the onset of illness, those patients may have had contact with others and thus could have transmitted the virus. A small number of the individuals infected during this period will become new patients after an incubation period, which averages approximately 5 days.

The timely diagnosis and treatment of patients following the early onset of the disease
can reduce the number of susceptible people who are infected. The PRCC for the IOI is 0.45, indicating a strong positive correlation. Under a constant $R_0$, the probability of an outbreak gradually increases as the IOI is extended. The median attack rate stays at a very low level at first; when the IOI reaches a threshold, the attack rate increases rapidly but then slows down. According to the traditional theory, however, no such threshold exists. This trend suggests that we can effectively reduce the risk of an outbreak by taking isolation measures within a certain time frame. The earlier that detection, diagnosis, and isolation can be performed, the greater the possibility that the disease attack rate will remain low.

Immunization is an effective approach for preventing infectious diseases. The PRCC between the IR and attack rate is -0.27, indicating that the higher the IR among the population, and lower the attack rate will be. The results section shows that as the IR increases gradually from 0, the probability of outbreaks decreases steadily. In addition, the median attack rate continues to decrease rapidly until it reaches a critical point, after which it remains at an extremely low level; this outcome is convergent from the SEIR model in which the epidemic will not occur once the IR increases to . This outcome occurs because when the IR increases to a certain extent, patients will not be able to continue to infect more susceptible people. This trend indicates that the outbreak of an epidemic can be efficiently restricted if the IR reaches a critical point. However, if it does not reach that critical point, disease prevention will be limited. The relationships between the attack rate and the above four parameters are similar to each other in general, all of which display a sharp rise in attack rate after that parameter reaches a certain critical value, meaning that the risk of an epidemic outbreak is manageable; nonetheless, if the measures taken are not effective, difficulty in controlling the outbreak will increase rapidly.

Although we present some original findings, our study has some limitations. For example,
the suitability of the random collision model for some diseases that have a more chronic prevalence among the population (such as tuberculosis and AIDS, among others) still requires further discussion where the SEIR model has been proven valuable. Because cluster outbreaks have fewer influencing factors and shorter durations, it is relatively easy to establish a random collision model. However, for some other chronic diseases, modelling requires the consideration of various factors, including population migration, age structures, and government interventions. In addition, we calculated only the PRCCs between the attack rate and each parameter in the sensitivity analyses; we did not investigate the compounding effects of multiple parameters acting together on the attack rate, a topic that needs to be addressed in future studies.

Conclusion

In summary, When the $R_0$, TOI, and IOI exceed certain thresholds, the disease attack rate increases very quickly, whereas when the immunization rate of the population exceeds the threshold, the disease attack rate declines rapidly. The random collision model is suitable for the simulation and epidemiological analysis of outbreaks of respiratory infectious diseases. This model is an extension of the dynamics model of infectious diseases, which provides a theoretical basis for individuals to grasp the opportunity to control the outbreak more precisely and to allocate public health resources in a more rational manner.

List Of Abbreviations

Adenovirus type 7 (ADV 7)

Time of isolation of the patients (TOI),

Interval between the onset and isolation (IOI),

Immunization rates (IR)
Susceptible-Exposed–Infectious-Recovered (SEIR)
Partial rank correlation coefficients (PRCC)
Latin hypercube sampling (LHS)

Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent to publish**
Not applicable.

**Availability of data and materials**
The source of the simulated dataset and analysed the model are available in the supplemental material.

**Competing interests**
The authors declare that they have no competing interests.

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**Author contributions:**
Guo ZY designed the study, analysed the data, and wrote the manuscript; Xu S, Tong LB, and Dai BT conducted the literature review; Liu YD and Xiao D reviewed the manuscript, and provided commentaries.

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Tables

Table 1. Parameters related to the outbreak characteristics of ADV 7
| Types                          | Probability distribution | Parameters |
|-------------------------------|--------------------------|------------|
| Incubation period             | Lognormal distribution   |            |
| Generation period             | Weibull distribution     |            |
| Symptom duration              | Log-logistic distribution|            |
| Isolation treatment duration  | Log-logistic distribution|            |
| Basic reproductive number     | Normal distribution      |            |

**Figures**
Schematic diagram of the relationship among the time of attack, time of recovery, and TOI Legend: A. When a patient's time of attack is earlier than the TOI, if he recovers before isolation, he will not be isolated; B. When a patient's time of attack is earlier than the TOI, if he does not recover before isolation is instated, he will be isolated at the TOI; C. When a patient's time of attack is later than the TOI but he recovers before isolation is instated, he will not be isolated; D. When a patient's time of attack is later than the TOI, if isolation is instated before the patient recovers, he will be isolated.
Figure 2

The transmission network of the epidemic outbreak Legend: Black dots indicate exposed individuals; the red dot indicates the first infector; and the lines represent connections between the infector-infected pairs.
The impact of the four factors on the outbreak Legend: A. The impact of $R_0$ on the attack rate; B. The effect of TOI on the number of patients; C. The effect of IOI on the attack rate; and D. The impact of IR on the attack rate.
Figure 4

Effect of the four factors on the growth rate of patients and on the cumulative number of patients

Legend: The solid lines represent the growth rate of patients; scales are indicated on the left axis of the coordinate. The dotted lines represent the cumulative number of patients; scales are indicated on the right axis of the coordinate plane. The 25%-75% quantiles are indicated by grey shading. A, B, C, and D represent the respective effects of R0, TOI, IOI, and IR on the outbreak,
respectively. The above analyses were performed under the following conditions: the total number of individuals exposed in the population was 500; the R0 for B, C, and D was 3; and the computer simulation was carried out 500 times.

Figure 5

Generation period Legend: The black curve represents the point estimate for the generation period, and the blue shades area represents the estimated interval calculated using the bootstrap method. The median was 8.26 days (95% CI: 7.84-8.69 days), with 3.72 days representing the 5% quantile (95% CI: 3.15-4.35 days) and 12.96 days representing the 95% quantile (11.71-14.36 days).
Supplementary Files

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