Transmission Characteristics of Different Students during a School Outbreak of (H1N1) pdm09 Influenza in China, 2009

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Many outbreaks of A(H1N1)pdm09 influenza have occurred in schools with a high population density. Containment of school outbreaks is predicted to help mitigate pandemic influenza. Understanding disease transmission characteristics within the school setting is critical to implementing effective control measures. Based on a school outbreak survey, we found almost all (93.7%) disease transmission occurred within a single grade, only 6.3% crossed grades. Transmissions originating from freshmen exhibited a star-shaped network; other grades exhibited branch- or line-shaped networks, indicating freshmen have higher activity and are more likely to cause infection. R0 for freshmen, calculated as 2.04, estimated as 2.76, was greater than for other grades (P < 0.01). Without intervention, the estimated number of cases was much greater when the outbreak was initiated by freshmen than by other grades. Furthermore, the estimated number of cases required to be under quarantine and isolation for freshmen was less than that of equivalent other grades. So we concluded that different grades have different transmission mode. Freshmen were the main facilitators of the spread of A(H1N1)pdm09 influenza during this school outbreak, so control measures (e.g. close contact isolation) priority used for freshmen would likely have effectively reduced spread of influenza in school settings.

The 2009 H1N1 influenza virus pandemic (A(H1N1)pdm09) emerged in Mexico and rapidly spread globally, resulting in millions of cases and approximately 18,000 deaths in nearly 200 countries. Surveillance data from many countries have shown that school-aged children and young adults most likely to be infected by A(H1N1)pdm09 influenza. Many outbreaks occurred in schools, presumably because of a higher density of susceptible persons. Surveillance data on A(H1N1)pdm09 influenza in mainland China from May 7 to November 30, 2009 indicates that 39% (27,806/71,665) of reported A(H1N1)pdm09 cases were reported to be part of a recognized outbreak and 94% of those cases associated with an outbreak were 5–24 years of age. Based on surveillance data from Beijing city, 81% (47/58) of outbreaks with 10 or more laboratory-confirmed cases occurred in schools, and most of school outbreak was initiated by freshmen. Studies have also suggested that school-aged individuals facilitated the introduction and spread of A(H1N1)pdm09 influenza in households. Curbing school outbreaks would therefore help to mitigate pandemic influenza. Understanding disease transmission characteristics within school settings would therefore be helpful in defining effective control measures for A(H1N1)pdm09 influenza.

Compared to Western countries, there have been few descriptions of the transmission dynamics of A(H1N1)pdm09 influenza in school outbreaks in mainland China, where campus quarantines (fengxiao) rather than school closures represent the primary public health intervention. Studies have suggested that social networks and population structures affect the spread of communicable diseases and the selection of optimal control strategies. To identify optimal control interventions, we used an epidemiological survey and disease...
transmission dynamic model to explore the disease transmission characteristics among students in a school involved in an outbreak of A(H1N1)pdm09 influenza.

**Results**

**Epidemiological Features.** The epidemiological investigation showed that this outbreak was initiated by one infected freshman. A total of 226 confirmed cases were found, comprising 212 students and 14 teachers. Among confirmed cases, 198 were male (93.3%) and 14 were female (6.7%). This study focused on disease transmission among the student population, so 212 students data were used to analysis below. Of the 212 infected students, 24 (11%) were also excluded from the transmission chain analysis because they could not recall the source of their infection or contacts. Among 212 infected students, 118 (63%) were freshmen, 65 (35%) sophomores, 16 (9%) juniors, and 13 (7%) seniors (Figure 1). The infection rate was 6.8% among freshmen, 3.0% among sophomores, 0.9% among juniors and 0.95% seniors. Freshmen were the most affected group, with the highest infection rate among the four grades (Chi square test, p < 0.0001).

**Transmission Characteristics.** The transmission tree of A(H1N1)pdm09 influenza among the confirmed cases is shown in Figure 2a. A total of 142 transmission chains were identified, comprising 133 (93.7%) within-grade chains and 9 (6.3%) chains across grades (Figure 2b). Moreover, disease transmission with a freshman as the infection source exhibited star-shaped networks; and transmission with students from the other three grades as the infection source exhibited branch- or line-shaped networks (Figure 2a). This indicates that freshmen were the important determinant of social mixing among the students. An investigation of whether freshmen affected transmission dynamics of A(H1N1)pdm09 influenza in the school was performed by calculating reproductive numbers (R₀) from the different grades. The basic reproductive number of an infection, R₀, is defined as the expected number of secondary infectious cases generated by an average infectious case in an entirely susceptible population⁵⁹, and it was calculated from epidemiological data using the average number of individuals directly infected by a confirmed case during her or his entire infectious period⁵⁹. The R₀ values were 2.04, 1.18, 1.40, and 1.00 for freshmen, sophomores, juniors and seniors, respectively. The 95% confidence intervals of R₀ are [2.73, 2.77], [1.97, 2.04], [1.73, 1.79] and [1.72, 1.75] for freshmen, sophomores, juniors and seniors, respectively. The R₀ estimated value from model was higher than that from epidemiological investigation because the close contacts cannot be completely traced. The average goodness of fit between the simulation and observation data was 76.6% (Appendix figure 1). Also, the estimated R₀ value for freshmen was higher than those for the other grades.

**Estimated Transmission Dynamics.** Initial dynamics of disease transmission among the different grades were reproduced using the constructed model. The parameters were estimated using our model: \( \alpha_1 = 1.1, \alpha_2 = 0.8, \alpha_3 = 0.70, \alpha_4 = 0.69, \alpha_5 = 0.30 \) and \( C = 0.05 \). The estimated R₀ values determined by the model were 2.76, 2.01, 1.76, and 1.73 for freshmen, sophomores, juniors and seniors, respectively. The 95% confidence intervals of R₀ for freshmen, sophomores, juniors and seniors, respectively. The R₀ estimated value from model was higher than that from epidemiological investigation because the close contacts cannot be completely traced. The average goodness of fit between the simulation and observation data was 76.6% (Appendix figure 1). Also, the estimated R₀ value for freshmen was higher than those for the other grades.

**Effectiveness of Different Interventions.** By using the transmission dynamic model, it was estimated that a total of 2,035 cases would have resulted by the 20th day if no control measures were implemented if the outbreak was initiated by a freshman. The total number of cases estimated in the same day of the outbreak was greater when the outbreak was initiated by a freshman than if the outbreak was initiated by a student in any other grade (Figure 4).

The total number of cases infected by the 20th day of the outbreak under different quarantine and isolation situations was estimated using the constructed model (Table). Assuming that this outbreak was initiated by a freshman, the estimated number of freshmen cases under quarantine and isolation was less than the number under the quarantine and isolation of equal number of other grades, regardless of when quarantine and isolation occurred during the first to fifth days of the outbreak (Table; Figure 5). Assuming that this outbreak was initiated by a sophomore, the estimated number of cases under quarantine and isolation of sophomores was less than the number under the quarantine and isolation of equal number of other grades if quarantine and isolation occurred on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation occurred on the fourth or fifth day of the outbreak (Table; Appendix figure 2). Assuming that this outbreak was initiated by a junior, the estimated number of cases under quarantine and isolation of juniors was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation occurred on the fourth or fifth day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades, when the quarantine and isolation were performed on the first, second and third day of the outbreak.
under quarantine and isolation of equal number of other grades if quarantine and isolation occurred on the fourth or fifth day of the outbreak (Table; Appendix figure 3). Assuming that this outbreak was initiated by a senior, the estimated number of cases under quarantine and isolation of seniors was less than the number under quarantine and isolation of equal number of other grades, when the
quarantine and isolation were performed on the first, second and third day of the outbreak. However, the estimated number of cases under quarantine and isolation of freshmen was less than the number under quarantine and isolation of equal number of other grades if quarantine and isolation occurred on the fourth or fifth day of the outbreak (Table; Appendix figure 4).

**Discussion**

During the characterization of disease transmission among students in a college involved in an A(H1N1)pdm09 influenza virus outbreak, the data showed that most (93.7%) of the disease transmission chains constructed on the basis of laboratory-confirmed cases occurred within the same school grade. Cauchemez et al also found similar transmission dynamics when investigating an elementary school outbreak of A(H1N1)pdm09 influenza among a semirural population in the United States using Bayesian statistical methods. This transmission pattern may be caused by participation in more clustering activities among students of the same grade. Other school outbreak investigations showed that A(H1N1)pdm09 influenza spread in the school was likely facilitated by increased student interactions in the activities, including religious and club activities, close contact with friends, and lectures or laboratory work. Thus interventions to reduce transmission in collective activity may play a role in curbing and mitigating future school outbreaks.

Investigations at the country- or region-level indicated that seasonal changes in patterns of social contacts have a marked influence on the spread of A(H1N1)pdm09 influenza. In particular, the patterns of school terms and holidays affect the incidence. Our finding of star-shaped rather than branch- and line-shaped transmission trees with a freshman student as the infectious source showed that, even in a micro-environment like this school, patterns of social mixing also impacted disease transmission. Freshmen, as newcomers to the school and lacking stable social circles, are more likely to make new contacts by increasing their peer-to-peer activities thus creating their own social networks. The calculated R0 also indicated that freshmen facilitated the spread of A(H1N1)pdm09 influenza between the students. Therefore, infectious disease transmission modes in the school were established by social contacts of freshmen with other students.

Furthermore, the R0 value for freshmen calculated from the investigation data or estimated from a model, was greater than those for other grades. These findings indicate that freshmen are an important determinant of social mixing among students and disease transmission was increased by the degree of social mixing between freshmen and other students. This was further supported by the model estimation that many more cases were involved if the outbreak was initiated by a freshman than if the outbreak was initiated by a member of another grade. Studies using mathematical models also showed that patterns of social mixing played a key role in shaping disease transmission.

Studies have shown that many outbreaks of A(H1N1)pdm09 influenza occurred in schools and school-aged individuals were more likely to be infected. School-aged individuals facilitated the introduction and spread of A(H1N1)pdm09 influenza in households. It was inferred that the butterfly effect of disease transmission in A(H1N1)pdm09 influenza would be observed as the disease transmission pattern in school outbreaks; this is influenced by social mixing patterns of newcomers in schools.

During the early stage of A(H1N1)pdm09 influenza pandemic, fengxiao (campus quarantine), a reversal of the usual strategy of school closures adopted in many other countries, is usually implemented in mainland China to prevent movement of infected cases from the community. This measure was put in place to prevent explosive school outbreaks and decelerate disease spread. Studies have shown that the early implementation of fengxiao can delay the epidemic peak significantly and prevent the disease spread to the general population. Once a school outbreak has occurred, further quarantine and isolation of students is necessary to decrease the effect of outbreak without school closure. A key question that remains to be answered is how to implement the quarantine and isolation measures to effectively mitigate school outbreaks, especially in a situation when not all of the contacts can be traced due to complex mixing of students in many school activities.

By using a transmission dynamic model to estimate the case number involved in this outbreak under different quarantine and isolation methods, we found that the quarantine and isolation of freshmen more effectively mitigated the school outbreak, if the outbreak was initiated by a freshman and no matter when quarantine and isolation measures were conducted. The same model was used to estimate the number of cases if the outbreak was initiated by other students in other grades and if quarantine and isolation measures were conducted on days two through five of the outbreak. The model demonstrated that quarantine and isolation of freshmen without school closure can effectively contain a school outbreak when not all of the contacts can be traced. As mentioned above, school-aged individuals facilitated the introduction and spread of A(H1N1)pdm09 influenza in households. Therefore, the quarantine and isolation of freshmen without school closure is predicted to effectively reduce the spread and impact of pandemic influenza in the community. From another perspective, this finding suggested that freshmen were the key determinant shaping the disease transmission in this school outbreak.

In this study we ignored the heterogeneity of innate immunity to A(H1N1)pdm09 influenza among the students, since most people with a severe disease course.

![Figure 4](https://www.nature.com/scientificreports/images/2014/5982/figure04.png)
were expected to lack innate immunity to the novel strain of influenza. Additionally, the dynamic model assumed homogenous mixing of the students from the same grade. Although these limitations mean that the mathematical model used in this study represents a simplified version of a complex infectious disease system, they may provide insight into transmission characteristics of A(H1N1)pdm09 influenza among students in school outbreaks and serve as a tool for decision making when there is uncertainty. We conclude that, different grades have different transmission modes, and freshmen have higher activity and are more likely to cause infection. Freshmen were the main facilitators of the spread of influenza during this school outbreak, so control measures (e.g. close contact isolation) priority used for freshmen would likely have effectively reduced spread of influenza in school settings. It will provide the useful suggestions on making effective and economic control measures in future school outbreak of influenza or other respiratory infectious diseases.

**Methods**

**Ethics Statement.** The institutional review board of the Academy of Military Medical Sciences waived the need for written informed consent from the participants. This study is approved by the Academy of Military Medical Sciences Review Board. The study is entirely based on epidemiological survey data which is required by Chinese Ministry of Health to record during the epidemic control. There was no request for an ethical permission according to Chinese law. Even so, we took the following steps to protect our survey respondents and anyone mentioned in the survey. Firstly, we kept all completed questionnaires under strict anonymity and confidentiality, left no identifiable personal information (such as names of respondents or anyone listed in Table 1| Estimated number of cases involved on the 20th day of this outbreak under the quarantine and isolation of different proportional students from different grades on the first day, second day, third day, fourth day and fifth day of the outbreak, assuming the outbreak was initiated by different student grades respectively

| First case | Population intervened | Proportion intervened | Onset date of intervention: | Estimated number of cases |
|------------|-----------------------|-----------------------|-----------------------------|--------------------------|
|            |                       |                       | First day                   | Second day               | Third day                  | Fourth day                 | Fifth day |
| Freshman   | Freshmen              | 25%                   | 845                         | 981                      | 1025                      | 1090                      | 1136      |
|            | Sophomore             | 25%                   | 1903                        | 1916                     | 1931                      | 1942                      | 1992      |
|            | Juniors               | 25%                   | 1942                        | 1946                     | 1959                      | 1970                      | 2017      |
|            | Seniors               | 25%                   | 1966                        | 1971                     | 1976                      | 1982                      | 2026      |
|            | Freshmen              | 50%                   | 609                         | 744                      | 791                       | 868                       | 922       |
|            | Sophomore             | 50%                   | 1842                        | 1856                     | 1870                      | 1882                      | 1929      |
|            | Juniors               | 50%                   | 1903                        | 1909                     | 1923                      | 1934                      | 1981      |
|            | Seniors               | 50%                   | 1929                        | 1939                     | 1949                      | 1958                      | 2001      |
|            | Freshmen              | 75%                   | 366                         | 498                      | 549                       | 637                       | 701       |
|            | Sophomore             | 75%                   | 1776                        | 1790                     | 1804                      | 1815                      | 1861      |
|            | Juniors               | 75%                   | 1861                        | 1868                     | 1886                      | 1894                      | 1943      |
|            | Seniors               | 75%                   | 1910                        | 1921                     | 1927                      | 1932                      | 1975      |
| Sophomore  | Freshmen              | 25%                   | 988                         | 1011                     | 1045                      | 1109                      | 1156      |
|            | Sophomore             | 25%                   | 549                         | 749                      | 815                       | 916                       | 939       |
|            | Juniors               | 25%                   | 1211                        | 1218                     | 1229                      | 1280                      | 1282      |
|            | Seniors               | 25%                   | 1221                        | 1227                     | 1250                      | 1282                      | 1283      |
|            | Freshmen              | 50%                   | 880                         | 899                      | 927                       | 978                       | 1020      |
|            | Sophomore             | 50%                   | 469                         | 680                      | 751                       | 860                       | 988       |
|            | Juniors               | 50%                   | 1200                        | 1217                     | 1221                      | 1278                      | 1280      |
|            | Seniors               | 50%                   | 1220                        | 1221                     | 1247                      | 1280                      | 1282      |
|            | Freshmen              | 75%                   | 763                         | 777                      | 796                       | 833                       | 846       |
|            | Sophomore             | 75%                   | 388                         | 612                      | 687                       | 805                       | 858       |
|            | Juniors               | 75%                   | 1191                        | 1215                     | 1218                      | 1276                      | 1279      |
|            | Seniors               | 75%                   | 1214                        | 1220                     | 1244                      | 1278                      | 1280      |
| Junior     | Freshmen              | 25%                   | 818                         | 869                      | 912                       | 957                       | 982       |
|            | Sophomore             | 25%                   | 1018                        | 1025                     | 1060                      | 1102                      | 1107      |
|            | Juniors               | 25%                   | 488                         | 718                      | 786                       | 856                       | 1101      |
|            | Seniors               | 25%                   | 1075                        | 1076                     | 1089                      | 1126                      | 1129      |
|            | Freshmen              | 50%                   | 722                         | 765                      | 802                       | 829                       | 865       |
|            | Sophomore             | 50%                   | 994                         | 1003                     | 1043                      | 1089                      | 1093      |
|            | Juniors               | 50%                   | 440                         | 679                      | 752                       | 836                       | 881       |
|            | Seniors               | 50%                   | 1071                        | 1075                     | 1088                      | 1125                      | 1127      |
|            | Freshmen              | 75%                   | 619                         | 653                      | 680                       | 702                       | 739       |
|            | Sophomore             | 75%                   | 970                         | 981                      | 1026                      | 1075                      | 1080      |
|            | Juniors               | 75%                   | 394                         | 641                      | 721                       | 804                       | 842       |
|            | Seniors               | 75%                   | 1069                        | 1074                     | 1086                      | 1121                      | 1124      |
| Senior     | Freshmen              | 25%                   | 810                         | 826                      | 858                       | 863                       | 883       |
|            | Sophomore             | 25%                   | 985                         | 1003                     | 1005                      | 1021                      | 1081      |
|            | Juniors               | 25%                   | 1025                        | 1031                     | 1032                      | 1046                      | 1101      |
|            | Seniors               | 25%                   | 483                         | 636                      | 771                       | 874                       | 981       |
|            | Freshmen              | 50%                   | 715                         | 726                      | 752                       | 789                       | 856       |
|            | Sophomore             | 50%                   | 961                         | 981                      | 988                       | 1009                      | 1066      |
|            | Juniors               | 50%                   | 1019                        | 1029                     | 1031                      | 1044                      | 1100      |
|            | Seniors               | 50%                   | 437                         | 595                      | 743                       | 802                       | 861       |
|            | Freshmen              | 75%                   | 612                         | 617                      | 636                       | 673                       | 722       |
|            | Sophomore             | 75%                   | 937                         | 958                      | 971                       | 997                       | 1052      |
|            | Juniors               | 75%                   | 1015                        | 1028                     | 1030                      | 1040                      | 1099      |
|            | Seniors               | 75%                   | 391                         | 556                      | 718                       | 780                       | 837       |
the contact diaries) in our electronic data set, and destroyed the completed questionnaires after data cleaning. Secondly, we used the personal information from our sample list only to locate and identify our targeted respondents and then destroyed the name list after the interviews.

**Outbreak Survey.** The outbreak began on a college grounds near Beijing in northern China on August 27, 2009 and an epidemiological investigation was conducted by the team from the Institution of Disease Control and Prevention. The college awards a four-year degree; all students reside at the college with a total enrollment of 6721 students (1742 freshman, 1805 sophomores, 1808 juniors, 1366 seniors) ranging in age from 19 to 24. Influenza-like illness (ILI) was defined as the sudden onset of a fever of >38°C with cough or sore throat in the absence of other diagnoses; a confirmed case of influenza was defined as a case of ILI with laboratory-confirmed A(H1N1)pdm09 influenza virus infection using the polymerase chain reaction (PCR) according to WHO guidelines. We detected the antibody levels against seasonal influenza A (H1N1), H3N2 and influenza B, and found different grades had no difference. Each confirmed case was interviewed face-to-face to obtain demographic information, clinical symptoms, onset date of influenza-like symptoms and contacts. A close contact was defined as a person having cared for, lived with, or who had direct contact with respiratory secretions or body fluids of a probable or confirmed case, or

**Figure 5 | Estimated numbers of cases under quarantine and isolation of equal freshmen, sophomores, juniors, or seniors over the first 20 days of the outbreak, if the outbreak was initiated by freshman.** (a), quarantine and isolation of 25% freshmen, sophomores, juniors, or seniors on the first day of outbreak; (b), quarantine of 50% freshmen, sophomores, juniors, or seniors on the first day of outbreak; (c), quarantine of 75% freshmen, sophomores, juniors, or seniors on the first day of outbreak; (d), quarantine of 25% freshmen, sophomores, juniors, or seniors on the second day of outbreak; (e), quarantine of 50% freshmen, sophomores, juniors, or seniors on the second day of outbreak; (f), quarantine of 75% freshmen, sophomores, juniors, or seniors on the second day of outbreak; (g), quarantine of 25% freshmen, sophomores, juniors, or seniors on the third day of outbreak; (h), quarantine of 50% freshmen, sophomores, juniors, or seniors on the third day of outbreak; (i), quarantine of 75% freshmen, sophomores, juniors, or seniors on the third day of outbreak; (j), quarantine of 25% freshmen, sophomores, juniors, or seniors on the fourth day of outbreak; (k), quarantine of 50% freshmen, sophomores, juniors, or seniors on the fourth day of outbreak; (l), quarantine of 75% freshmen, sophomores, juniors, or seniors on the fifth day of outbreak; (m), quarantine of 25% freshmen, sophomores, juniors, or seniors on the fifth day of outbreak; (n), quarantine of 50% freshmen, sophomores, juniors, or seniors on the fifth day of outbreak; (o), quarantine of 75% freshmen, sophomores, juniors, or seniors on the fifth day of outbreak.
A number of recovered students from grade A prior to student B, we assume that student A infected student B. We used the expression "A → B" to show the transmission relationship between A and B. If there were several possible routes of transmission, we assumed the "earlier infector" is the "real infector". Disease transmission pathways were constructed using the program PAJEK. PAJEK is a Windows program for analysis and visualization of large networks having some thousands or millions of vertices.

Transmission Chains. We constructed disease transmission pathways among the confirmed A(H1N1)pdm09 influenza cases. If student A and student B are close contacts and symptom onset appeared in student A prior to student B, we assume that student A infected student B. We used the expression "A → B" to show the transmission relationship between A and B. If there were several possible routes of transmission, we assumed the "earlier infector" is the "real infector". Disease transmission pathways were constructed using the program PAJEK. PAJEK is a Windows program for analysis and visualization of large networks having some thousands or millions of vertices.

Transmission Dynamic Model. The susceptible-exposed-infected-removed (SEIR) model was used to simulate transmission dynamic processes. The SEIR model has been widely used in epidemic simulations. The SEIR model was used to simulate infectious diseases transmission dynamics, estimate epidemiological parameters and effectively evaluate interventions. The SEIR model separates the population of a region into four compartments, susceptible, exposed, infected, and removed, and simulates the time evolution of each of these subpopulations. We assumed the school to be a closed setting and the students from the same grade (e.g. freshmen, sophomores, juniors, seniors) to be homogenously mixed in school activities due to students from same grade with almost same age, and also they have same schedule, and ignored the heterogeneity of innate immunity to A(H1N1)pdm09 influenza between the students. Students from each grade were divided into four groups (Susceptible, Exposed, Infected and Removed). Under these circumstances, a transmission dynamic model was constructed (Figure 6).

There were Ni individuals in grade i, i = 1, 2, 3, 4. Therefore the number of susceptible students from grade i in the t day of outbreak; is defined as S(i, t), is the number of exposed students from grade i in the t day of outbreak; E(i, t); is the number of infected students from grade i in the t day of outbreak; and R(i, t); is the number of recovered students from grade i in the t day of outbreak. We also denoted xi (i = 1, 2, 3, 4), as the average number of secondary cases per primary case in a susceptible population from the same grade in the infectious period of primary cases per unit time, x0, as the average number of secondary cases per primary case in a susceptible population from the different grade in the infectious period of primary cases per unit time. Parameter (C) was set to control the change of xi (i = 1, 2, 3, 4, 5) under the control measures taken. The parameter C is equal to 1 when no interventions are taken, it is smaller than 1 when interventions are taken, and the more stringent the control measures, the smaller the C value. From the literature-derived parameter values of the infection and infectious periods, the incubation period was assumed to be 1/μ = 1.1 days and the infectious period was 1/γ = 2.5 days. The μ/γ is the R0 value of grade i (i = 1, 2, 3, 4). The newly infected cases per day were used to fit our model. The ANNEAL algorithm was used to optimize parameters of function, which is a stochastic method currently in wide use for difficult optimization problems.34,35. The model was constructed by using ordinary differential equations:34,35

\[
\frac{dS(i, t)}{dt} = -\frac{C \cdot N \cdot x_i \cdot t \cdot S(i, t)}{N \cdot C \cdot x_i \cdot t} + \sum \left( \frac{S(i, t) \cdot S(j, t)}{N} \right) \cdot S(i, t) \cdot N
\]

\[
\frac{dE(i, t)}{dt} = \frac{C \cdot N \cdot x_i \cdot t \cdot S(i, t)}{N \cdot C \cdot x_i \cdot t} - \sum \left( \frac{S(i, t) \cdot S(j, t)}{N} \right) \cdot S(i, t) \cdot N \cdot \beta 
\]

\[
\frac{dI(i, t)}{dt} = \beta \cdot E(i, t) \cdot \gamma
\]

\[
\frac{dR(i, t)}{dt} = \frac{N \cdot \gamma - \beta \cdot E(i, t)}{C \cdot 1 \cdot \gamma} \cdot \gamma
\]

Using the constructed model, the initial dynamics of disease transmission among the different grades were reproduced, and used to estimate Rc values for freshman, sophomores, juniors or seniors We simulated 100 times using the ANNEAL algorithm that minimizes a function using the method of simulated annealing.14 Simulated annealing (SA) is a generic probabilistic metaheuristic for the global optimization problem of locating a good approximation to the global optimum of a given function in a large search space. We simulate effectiveness of intervention through control numbers of four compartments (Susceptible, Exposed, Infected, and Removed).

Estimation of Transmission Effectiveness. By using the constructed model, estimates were derived for the total numbers of cases involved on the 20th day of the outbreak. Assuming that the first case of this outbreak was a freshman, estimates were made of the number of infected students involved in the outbreak on the 20th day, when 25%, 50%, or 75% of freshmen, sophomores, juniors, or seniors were quarantined and isolated on the first, second, third, fourth and fifth day of the outbreak. Similar estimates were made assuming the first case was a sophomore, junior, or senior, respectively. For these estimates, we applied the same stringent intervention measures to contain the epidemic of A(H1N1)pdm09 influenza, including isolation of confirmed cases and quarantining of contacts, which were recommended by the Chinese Ministry of Health on May 29, 2009.35 The susceptible students involved in this outbreak were assumed to be close contacts. Interventions were sustained through the whole epidemic in order to avoid creating a population of individuals who were protected from infection but would become infected after the intervention was stopped. The effectiveness of different quarantine methods under the different conditions were compared according to the estimated number of cases involved.

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Figure 6 The transmission dynamics model of A(H1N1)pdm09 influenza among students attending a college in northern China. † i = 1, 2, 3, 4, j = 1, 2, 3, 4, i ≠ j. Each grade was divided into four groups (Susceptible, Exposed, Infected and Removed).
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