Transmission dynamics of novel influenza A/H1N1 2009 outbreak in a residential school in India

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Transmission dynamics of an outbreak of novel influenza A/H1N1 (2009) in June–July 2009 in a residential school in Maharashtra, India has been studied. A mathematical model of the type susceptible-exposed-infectious-asymptomatic-recovered has been adopted for the purpose. Analyses of epidemiological data revealed that close clustering within population resulted in high transmissibility with basic reproduction number $R_0 = 2.61$ and transmission rate (β) being 0.001566. Model has successfully described the dynamics of transmission in a residential school setting and helped in ascertaining the epidemiological parameters for asymptomatic cases and the effectiveness of the control measures. Our study presents a framework for studying similar outbreaks of influenza involving clustered populations.

Keywords: Influenza A/H1N1, outbreak, school, transmission dynamics.

IN spring 2009, the general public came to know about the outbreak of a new influenza virus strain, later named as the novel influenza A/H1N1 (2009), in Mexico. Since the first outbreak in Mexico in March 2009, the disease has spread rapidly to many countries mostly through travellers from the United States[1–3]. In June 2009, the World Health Organization (WHO) declared that a pandemic had begun. Although most of the cases reported outside Mexico in the early phase of the epidemic have been relatively mild, concerns remained about the potential impact of this new strain in the coming days.

The impact of any pandemic depends on the transmissibility of the causal pathogen (virus), irrespective of the severity of the symptoms. Hence, it is important to understand the dynamics of the infectious disease. Generating an effective response to any growing pandemic requires planning and resource mobilization. This necessitates estimation of the epidemiological parameters such as serial interval and basic reproductive number from the available data. The time and place of clinical onsets, and social connections of cases provide valuable information about the source of the outbreak, evidence of propagation in space and time and reflects the risk factors in the particular context. Considerable efforts have been made towards understanding the epidemiology of the novel Influenza A/H1N1 2009 outbreaks at community settings in various countries[2–5]. Mathematical modelling of the epidemics has great potential for better understanding the transmission pattern of diseases and predictions of outcome of different control strategies[6–9]. Kermack and McKendrick's[10] treatment of the Bombay plague of 1905–1906 has proved the capability of mathematical modelling in understanding and predicting epidemics. Subsequently, the modelling has been successfully applied to several studies which provided meaningful insights into the past epidemics and pandemics of influenza[11–18] and other diseases[19–20]. The model presented by Longini *et al.*[21] to describe the influenza (H2N2) pandemic of 1957–1958 provided discrete-time simulations based on detailed contact structure. However, there are limitations to modelling studies mostly due to changes in the network structure during the course of an epidemic or the inaccuracies in the simulations.

The present pandemic has affected populations of all age groups, with the highest attack rates among young people. High transmissibility has been observed in communities with close clustering of people such as village and schools[22–24]. Although several school outbreaks have been reported from various countries, it is difficult to find reports describing the outbreak with mathematical modelling and predictions.

The present work aims at development of a simple model framework to describe the transmission dynamics of an outbreak of novel influenza A/H1N1 (2009) in a residential school setting. Such models can be used to predict the pattern of disease propagation in the event of introduction of the virus in similar settings and to assess the effectiveness of control measures. A simple compartmental model of the type Susceptible-Exposed-Infectious-Asymptomatic-Recovered (SEIAR) has been developed to describe the dynamics of transmission of novel influenza A/H1N1 (2009) using the serological and epidemiological data collected from a residential school in Panchghani, Maharashtra, India. The details of mathematical formulations and specialized terminologies are given in the 'methodology' section.

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Methodology

Data set from school outbreak

On 21 July 2009, a residential school hosting a total population of 415 (362 students and 53 staff) in Panchgani (a hill station in western part of Maharashtra, India) reported a surge in influenza-like illness (ILI)[24] among students starting from mid-July 2009. Clinico-epidemiological studies were undertaken in the school by the Outbreak Response Group, National Institute of Virology (NIV) from 23 July 2009 and serological survey of the total school population completed by 28 July 2009. Outbreak due to the novel influenza A/H1N1 (2009) virus was confirmed and communicated to the school and the government authorities by 26 July 2009. Based on tracing of clinico-epidemiological data available from records of the school hospital, the index case has been identified to be a 10-year-old boy who had ILI onset on 24 June 2009. Thus, the estimated outbreak period extended from 24 June to 30 July 2009. Since the boy had no associated history of foreign travel or direct known contact with any confirmed case, probable source of infection might be a chance meeting with visitors to the school or tourists visiting Panchgani.

Fifty four per cent of the school population (227/415) was found positive for novel influenza A/H1N1 (2009) responsive antibodies by haemagglutination inhibitor (HI) test. Among these, 176 were symptomatic (had history of ILI within the outbreak period) and 51 asymptomatic. No fatalities were reported during the outbreak. The number of 'infectives' was highest on the 28th day (21 July 2009). Details of serologic survey protocols have been published elsewhere[25]. A brief description is given here.

Throat swabs from the students and staff members with ILI were collected in sterile viral transport medium and transported at 4°C and processed for detection of influenza A and B types and novel influenza A/H1N1 2009, seasonal H1N1 and H3N2 viruses by Real Time polymerase chain reaction (PCR) according to the Centres for Disease Control and Prevention (Atlanta) (CDC) protocol suggested by WHO[26]. For serologic studies, blood samples were collected from the total school population (415 individuals). HI assay was performed for detection of antibodies (Ab) according to the protocol established by WHO[27]. Antigens for influenza HI Ab titres $\geq 1:10$ were considered as positive for novel influenza A/H1N1 2009 and HI Ab titres $\geq 1:20$ were considered as positive for circulating seasonal influenza A and B viruses.

Individuals were classified as symptomatic, if they had clinical symptoms of ILI with laboratory confirmation of the novel influenza A/H1N1 (2009). Individuals, who did not have any history of ILI but had tested positive for the presence of antibodies to novel influenza A/H1N1 (2009) in serological tests (HI), were considered as asymptomatic. It should also be noted that the school authorities had implemented simple control measures starting from 21 July 2009 (28th day of the outbreak) resulting in decrease in cases and ending of the outbreak by 30 July.

The strain of the virus has been found to be the same as that in circulation in India in June–July 2009. The genetic characterization of whole genomes of the Indian isolates of novel influenza A/H1N1 2009 virus has been carried out at NIV, Pune. Sequence analyses of the whole genomes of isolates revealed >99% nucleotide identity with the California/04/2009(H1N1) strain in all the gene segments[28].

Case definitions

All case definitions and epidemiological terminologies used in the present study are in accordance with ref. 24. Some important terms are briefly described here.

The time interval between virus exposure (invasion by infectious agent) and onset of symptoms (appearance of first sign or symptom) in an individual is known as incubation period[29,30]. During this period, individuals are considered to be 'not infectious'. Such individuals have been referred to as 'exposed' in the present study.

The duration from the onset of symptoms to cessation (recovery) is known as the infectious period. This is the symptomatic state and individuals are capable of spreading infections through virus shedding. Such individuals have been referred to as 'infectives'.

The clinical attack rate is defined as the ratio of number of symptomatic individuals (confirmed cases) to the total study population (population at risk) during this outbreak[29].

The serial interval is the time period between successive clinical cases[31]. It is calculated as the sum of the incubation period and the time period from onset of symptoms to time of highest infectiousness in an affected individual. Although a range of values is possible, the average serial interval can be estimated as: average incubation period + half the average infectious (symptomatic) period, assuming that the maximum infectiousness occurs at the middle of the symptomatic period.

Mathematical formulation

Estimation of growth rate, basic reproduction number R_0 and transmission rate: During the initial phase of the outbreak, the numbers of secondary cases increased at an exponential rate. The growth rate of the epidemic (r) was calculated from the estimates of cumulative number of confirmed infections (y) and the estimated start date and size of the outbreak (t_0 and y_0) respectively and using the equation[2]

$$y = y_0 e^{r(t-t_0)}. \quad (1)$$

The basic reproduction number (R_0), defined as the number of secondary cases generated by the introduction of one infective into a wholly susceptible population over the course of infection of the infective, was computed using the formula

$$R_0 = \left(1+\frac{r}{\alpha}\right)\left(1+\frac{r}{k}\right), \quad (2)$$

with the mean infective period, $1/\alpha$ and mean incubation period, $1/k$. Since all types of influenza involve a definite incubation period in the host (exposed or latent state) and a definite infectious period for the symptomatic host (infectious state), effective modelling of such an epidemic should account for both these periods. Hence, the calculation of R_0 has been carried out based on the standard method for such diseases[32].

Transmission rate (β) was computed as: $R_0 = \beta N/\alpha$, N being the population size[5]. The value of p, the fraction of exposed population that becomes symptomatic, was estimated as

$$p = \frac{n_{\mathrm{I}}}{n_{\mathrm{I}} + n_{\mathrm{A}}}, \quad (3)$$

where n_{I} and n_{A} were the numbers of confirmed symptomatic and asymptomatic cases.

The doubling time (the time period in which the size of the outbreak doubles) is given by $t_{\mathrm{d}} = \ln(2/r)$, where r is the exponential growth rate of the epidemic[32].

An untreated SEIAR model: The transmission dynamics of the novel influenza A/H1N1 outbreak in a residential school setting was described using a compartmental model of the SEIAR type[6,33] with adaptations for untreated populations (no control measures and no antivirals such as oseltamivir). This adaptation was considered appropriate because of the fact that there was no treatment or interventions from the beginning of the outbreak. In this model, the individuals were classified as follows: susceptible (S) – those who did not have any immunity to the disease; exposed (E) or latent – those exposed to the virus and incubating it prior to the development of symptoms; 'infectives' (I) – symptomatic and infectious (laboratory confirmed cases of novel influenza A/H1N1 2009); asymptomatic (A) – those testing positive in serological tests for novel influenza A/H1N1 2009 virus and had no symptoms (but were assumed to be partially infectious); and recovered population (R). Following assumptions are made where S, E, I, A, R, denote the numbers of individuals in the susceptible, latent (or exposed), infective, asymptomatic and Recovered compartments, respectively, with the total population size at all times given by $N = S(t) + E(t) + I(t) + A(t) + R(t)$.

- Total population at the initial stage was susceptible with no members having immunity through vaccination or any previous exposure. One infective was introduced.
- There is no transmission from individuals at the latent (exposed) state.
- A fraction p of the latent (E) individuals proceed to infective (symptomatic) I compartment at the rate k. The remaining fraction $(1 - p)$ goes to the asymptomatic compartment A at the same rate k.
- Since the school population was residential and there were no fatalities or removal of infectives outside the campus, the study population was considered constant and no consideration has been made for the addition or removal of individuals.
- Asymptomatic individuals have a reduced capacity to transmit the disease. Let q be the factor that decides the reduction in transmissibility of the asymptomatic individuals ($0 < q < 1$) (ref. 22).
- Assuming homogeneous mixing within the population, the average member of the population made contact sufficient to transmit infection to βN others per unit time, where β is the transmission rate.
- A fraction α of the infective individuals and a fraction η of asymptomatic individuals moved to recovered class per unit time.

The transmission process is described by the set of ordinary differential equations (ODE)

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta S(I + qA),$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \beta S(I + qA) - kE,$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = pkE - \alpha I,$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = (1-p)kE - \eta A,$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \alpha I + \eta A$$

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \alpha I. \quad (4)$$

Here, C denotes the cumulative number of infectives. A flow diagram of the SEIAR model is given in Figure 1. Also, all variables are positive at all times ($0 < t < \infty$).

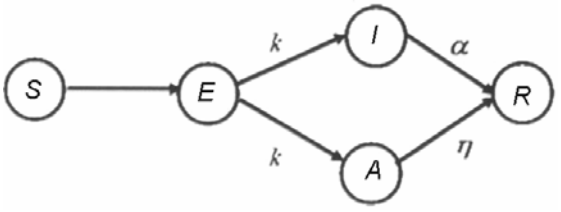

Figure 1. SEIAR compartmental model of disease transmission. Susceptible individuals (S) after being exposed to virus may, at the end of incubation period, proceed to become infective (I) (symptomatic) or asymptomatic (A) at the same rate (k). Infective (I) and asymptomatic (A) individuals proceed to become recovered (R) at rates α and η, respectively.

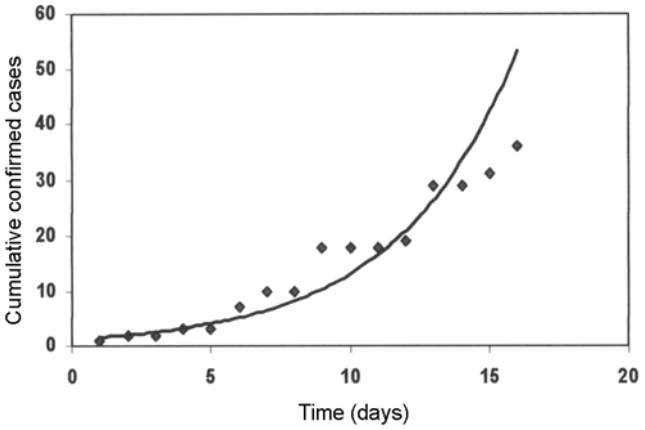

Figure 2. Growth of the cumulative confirmed cases during the initial 16 days. The exponential growth rate $r = 0.2341$ per day was obtained by curve fitting.

Model implementation: The epidemic growth rate has been estimated from the growth in the number of infectives during the initial phase of the outbreak (24 June–7 July 2009), as available from the clinico-epidemiological records. The basic reproduction number (R_0) has been estimated from eq. (2) using the estimated growth rate and assuming: (i) mean duration of symptoms (infectious period) as 4 days ($= 1/\alpha$; $\alpha = 0.25$) and (ii) mean latent period as 1.5 days ($1/k$; $k = 0.66$), both standard values for human infections of influenza[34–36]. Transmission rate (β) was calculated from the estimated value of R_0.

The numerical solution for the set of differential equations (eq. (4)) was obtained by using built-in differential equation solver ('ode45', 4th/5th order Runge–Kutta method) in MATLAB® software. Simulations were performed assuming various sets of values for parameters: α, k, q and η, varying one at a time. The number of cumulative infectives versus time, predicted from each run has been compared with that calculated from the actual data for the growth period of the epidemic (24 June–21 July 2009). The best fit solution has been considered as the final result and such a set of values for the parameters was considered appropriate for the outbreak under study.

The proportion of 'exposed' individuals actually developing symptoms was calculated using eq (3) with n_I and n_A as 176 and 51 respectively.

Results and discussion

Estimation of growth rate (r), R_0, β and doubling time (t_d)

The clinical attack rate of novel influenza A/H1N1 (2009) in the school population was 42% (176/415). Based on the growth of cumulative confirmed cases for the first 16 days (Figure 2), the intrinsic exponential growth rate (r) was calculated and the value was found to be 0.2341 per day. Assuming the mean incubation period as 1.5 days and mean infectious period (duration of symptomatic and infectious state) as 4 days, the basic reproduction number, R_0 was estimated to be 2.61. The transmission rate (β) was estimated as 1.566×10^{-3}, and the doubling time of the epidemic was found to be 2.14 days. The average serial interval was estimated as 3.5 days (1.5 days, incubation time + 0.5×4 days, infectious period).

Fifty-two per cent of the subjects had antibodies responsive to novel influenza A/H1N1 (2009) virus. This suggested intense transmission in the school setting. The higher risk of transmission could be attributed to close contacts between individuals for longer duration as well as monsoon weather, which has been known to favour influenza transmission in western India[37]. Outbreaks of seasonal influenza had been reported frequently in this school over the years (influenza surveillance data – NIV, Pune).

Intense transmission is reflected in the value of R_0 (= 2.61), which is higher than the average estimates from other outbreaks in schools[22,38] and in general population in various settings[39]. Calculation of R_0 using classical formula of the type $R_0 = (1 + r/\alpha)$, provided a lower estimation ~ 1.6 (ref. 2). Simulations using our model with such lower values of R_0 did not predict any outbreak in the school setting (data not shown). Also, some reports[40] speculate that the use of a low cutoff in the antibody titre levels (≥1 : 10) in HI assay may lead to an overestimation in the proportion of people who were immune at the start or the end of the epidemic wave by suggesting the existence of cross-reactive antibodies. Such pre-existing cross-reactive antibodies may bind to the novel influenza A/H1N1 virus (antigen) with low titre levels. However, in India the possibility of the population having such cross-reactive antibodies is very rare because of two reasons: first, the predominant circulating strain of seasonal influenza in India (prior to the introduction of the pandemic strain) was type H3N2 (80% cases) with co-circulation of type H1N1 (strain A/Brisbane/59/2007) (20% cases) (influenza surveillance data, WHO Influenza Surveillance Centre, NIV, Pune); and second, the study population has

not been vaccinated against influenza strains (H1N1, H3N2, etc.) previously. Also, it has reported that asymptomatic cases of novel influenza A/H1N1 2009 yielded low antibody titres[41]. Hence, the use of low antibody titre level ($\geq 1:10$) as cutoff in the serologic tests appeared justified. Our estimated value of R_0 (= 2.61) is comparable to the values of $R_0 \sim 2.8$ for novel influenza A/H1N1 (2009) outbreaks reported from Japan and elsewhere, which involved intense transmission driven by highly connected population clusters, mostly teenagers[5,18]. Higher values of R_0 were also reported for pandemic influenza of 1918 in various settings involving transmission in population clusters, mostly in military installations and barracks[11].

Model fitting and predictions

Figure 3 shows the transmission dynamics predictions (from the best solution) for this outbreak based on the applied untreated SEIAR model assuming a scenario of no interventions. Accordingly, the maximum number of infectives occurring on the 28th day (i.e. 21 July 2009), which matches with the actual data. The model also predicted that in the absence of control measures, the epidemic could have continued for 60 days generating a total of 281 symptomatic cases. The number of unaffected persons and asymptomatic persons at the end of this period (60 days) would have been 53 and 81 respectively (Figure 3).

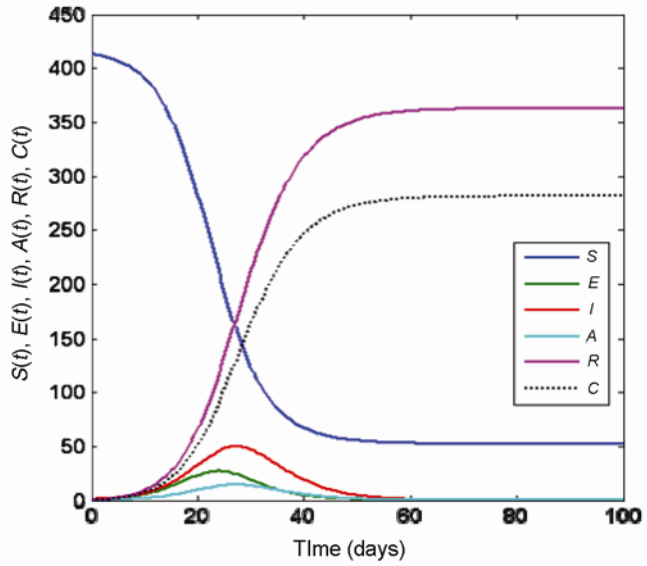

Figure 3. Numerical solutions of SEIAR model performed in MATLAB showing the transmission dynamics of novel influenza A/H1N1 2009 outbreak in a residential school in Panchgani, India (June–July 2009). *S*, *E*, *I*, *A*, *R* and *C* represent susceptible, exposed, infectives (symptomatic and infectious), asymptomatic (and partially infectious), recovered and cumulative confirmed infective populations respectively.

The cumulative number of infectives from the model prediction and that from actual data has been compared in Figure 4. The predicted growth followed the pattern computed from actual data in the initial phase up to the 29th day (22 July 2009). However, there was decline in the actual number of infectives from 23 July 2009 compared to the predicted values from SEIAR model as indicated by Figure 5. No new incidence was reported from 29 July 2009.

This decline in the growth pattern of actual cumulative infectives could be attributed to the implementation of simple control measures by the school authorities from

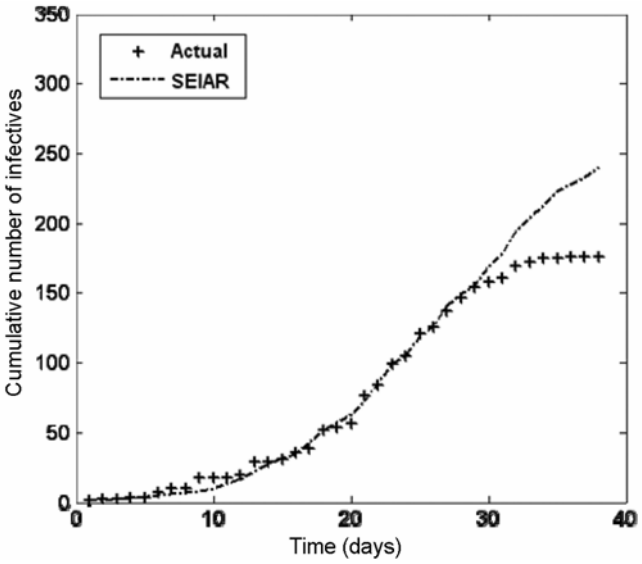

Figure 4. Growth of cumulative confirmed cases as predicted by model (dashed-dot line) and actual recordings ('+' symbol) during the period of study (24 June–30 July 2009).

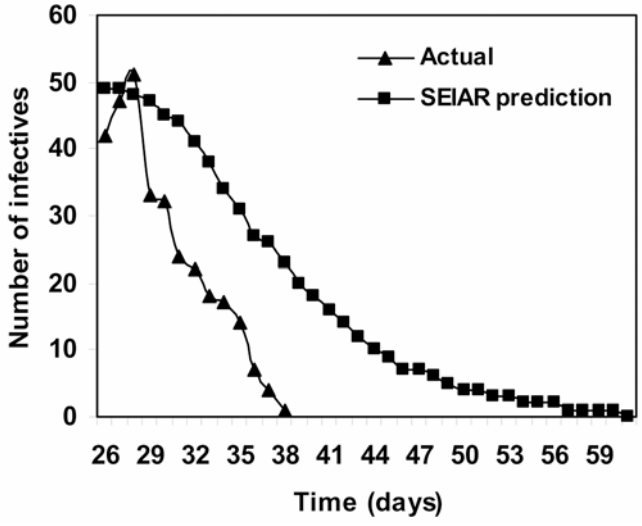

Figure 5. Change in the number of infectives–comparison of the actual and SEIAR prediction from 26th day (19 July 2009) onwards. Maximum number of infectives occur on the 28th day (21 July 2009).

21 July 2009 (28th day of the outbreak), which might have effectively lowered the contact rates. It should be noted that stringent measures, such as quarantine or removal of infectives from the school premises, etc. were not implemented. However, the simple control measures included: temporarily shifting students with high fever to the hospital wing within the school campus, discouraging students with cough and cold from attending classes and behavioural interventions aimed at social distancing (such as avoiding group activities and clustering, improved personal hygiene, etc.); (details to be found elsewhere[25]). Methods aimed at quantification for the evaluation of the effectiveness of control measures could not be undertaken for this outbreak. However, a qualitative assessment on the effect of interventions was obtained. Following the confirmation of outbreak, health officials initiated administration of Oseltamivir to the existing symptomatic cases and their contacts in the study population from 28 July 2009. However, by this time, the number of infectives had already reduced, due to the imposition of interventions by the school authorities.

Based on the best fit solution of the SEIAR model, the parameters for asymptomatic cases were ascertained. The duration of asymptomatic state was estimated as four days. Estimated value of q was 0.6, indicating that the transmissibility of the asymptomatic case would be ~ 60% similar to that of an infective case. The percentage of asymptomatic cases has been estimated to be 22.5 (51 out of 227 individuals confirmed with antibodies responsive to novel influenza A/H1N1 (2009) in serological tests), which appeared lower than that estimated for earlier pandemics. Earlier pandemics involved high percentage of asymptomatic infections[42]. The present findings reflect the earlier perceptions that asymptomatic infections played an important role in transmission of the influenza virus in various settings[43]. To the best of our knowledge, this article is the first report about the estimation of asymptomatic parameters for novel influenza A/H1N1 2009 pandemic. Although reports of disease outbreaks in Indian children exist[44,45], complete transmission dynamics studies on outbreak of influenza (novel influenza A/H1N1 or other strains) in residential school setting has not been reported from India so far.

The study was, however, not free from limitations. R_0 could also have been estimated using other advanced methods based on analyses of generation time data as in ref. 3. However, accurate estimation of the generation time at different phases of the outbreak could not be ascertained due to lack of effective contact tracing. This was primarily because of the fact that by the time NIV was intimated by the school authorities and studies were initiated, the outbreak had already reached its peak. We had to depend on the clinico-epidemiological records of the school hospital to estimate the start date and initial number of cases per day.

Conclusions

In short, a simple model framework has been developed successfully to describe the transmission dynamics of an outbreak of novel influenza A/H1N1 (2009) in a residential school setting. Such models can be used to predict the pattern of disease propagation in the event of introduction of the virus in similar school settings and may also be used to assess the effectiveness of control measures. The transmission dynamics study has provided estimates for various parameters for the outbreak such as the partial infectiousness and its duration in the asymptomatic cases. Such parameters were difficult to determine by clinical observations.

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