Transmission dynamics of the 2009 influenza A (H1N1) pandemic in India: The impact of holiday-related school closure

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ABSTRACT

The role of social-distancing measures, such as school closures, is a controversial aspect of pandemic mitigation planning. However, the timing of 2009 pandemic provides a natural experiment for evaluating the impact of school closure during holidays on influenza transmission.

To quantify the transmission intensity of the influenza A (H1N1) pdm'09 in India, by estimating the time varying reproduction number (R_t) and correlating the temporal changes in the estimates of R_t for different regions of India with the timing of school holidays. We used daily lab-confirmed case reports of influenza A (H1N1) pdm'09 in India (during 17 May'09 to 17 May'10), stratified by regions. We estimated the transmissibility of the pandemic for different regions from these time-series, using Bayesian methods applied to a branching process model of disease spread and correlated the resulting estimates with the timing of school holidays in each region.

The North-west region experienced two notable waves, with the peak of the first wave coinciding with the start of a 4 week school holiday (September–October'09). In the southern region the two waves were less clear cut, though again the first peak of the first wave coincided with the start of school holidays – albeit of less than 2 weeks duration (August'09). Our analysis suggests that the school holidays had a significant influence on the epidemiology of the 2009 pandemic in India. We estimate that school holidays reduced the reproduction number by 14–27% in different regions of India, relative to levels seen outside holiday periods. The estimates of the reproduction number obtained (with peak R values below 1.5) are compatible with those reported from other regions of the world. This work reinforces past studies showing the significant impact of school holidays on spread of 2009 pandemic virus, and by inference the role of contact patterns in children on transmission.

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Introduction

The first case of the 2009 pandemic H1N1 influenza A virus was detected in California on April 15th 2009, with infection rapidly traced back to Mexico. By late April 2009, multiple cases being detected in the United States, Canada and several European countries. On April 29, 2009, the World Health Organisation (WHO) raised the pandemic alert from phase 4 to phase 5 indicating widespread human infection (WHO, update 29 Apr. 2009), raising to phase 6 on June 11, 2009 (WHO, press conference 11 June 2009). On August 10, 2010, WHO declared that the world had entered the post pandemic period (WHO, press conference 10 Aug. 2010).

In light of the initially uncharacterised threat posed by the new pandemic virus, the Government of India instituted a series of preventive actions on April 27, 2009 that included surveillance at International Ports, Borders and Airports, inspection through Integrated Disease Surveillance Project (IDSP) units in the States and District level, and the issuing of a travel advisory to defer non-essential travel to affected countries. Initially, the Ministry of Health and Family Welfare (MoHFW) implemented an aggressive containment strategy based on the national pandemic preparedness plan, including isolation of all suspected case-patients in designated hospitals, contact tracing, medical observation of persons exposed to patients with confirmed cases, and international entry/exit screening. On May 17, 2009 the first case of A (H1N1) pdm'09 in India was detected at Hyderabad airport, in a 23 year old passenger who travelled from the USA (MoHFW India, update 17 May 2009).

Although pre-pandemic vaccines and antiviral drugs might significantly reduce illness rates (Ferguson et al., 2006), their stockpiling is too expensive to be practical for many developing countries. Consequently, alternative non-pharmaceutical control strategies represent a more feasible and potentially attractive policy option. One commonly considered social distancing measure is school closure or class dismissal (Cauchemez et al., 2009b).

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But due to the socio-economic costs, closing schools for long period is challenging and controversial (Dawood et al., 2012). The rationale for school closure as a policy is that children are key transmitters of influenza, with contact rates being particularly high in the school context (Cauchemez et al., 2009b). Several early analyses of the 2009 pandemic highlighted children as the age group with highest attack rate (Fraser et al., 2009; Cauchemez et al., 2009a), with similar patterns being seen in retrospective analyses of serological and case data from a wide variety of countries (Chowell et al., 2011). However, data from developing countries is more limited, with little have been published on the epidemiology of the pandemic in India in particular.

In this study, we analyse the transmission patterns of the 2009 pandemic in different regions of India for a period of one year (from 17th May 2009 to 17th May 2010) and examine the effectiveness of holiday-related school closures on transmission using daily reported case data. We examine how the timing of school holidays correlates it with the instantaneous reproduction number (R_t), which characterises transmission intensity at a point in time and is defined as the average number of secondary infections generated by a person infected at time t in his entire infectious period.

Material and methods

Pandemic surveillance in India

Prior to the pandemic, influenza surveillance in India occurred through two separate hospital-based sentinel networks run by The National Institute of Communicable Diseases (NICD) and The Indian Council of Medical Research (ICMR), with virological isolation and identification largely occurring in one of three National Influenza Centres in different regions.

As a result of the initial pandemic alert, on April 27, 2009, the Government of India instituted a series of preventive actions that include surveillance at International Ports, Borders and Airports, observation through Integrated Disease Surveillance Project (IDSP) units. Once WHO raised the influenza pandemic alert level to phase 5, health screening of passengers coming from affected countries was implemented at airports in Delhi, Mumbai, Kolkata, Chennai, Hyderabad and Bangalore.

More generally, from phase 5, India took substantial action at the national, state and district level, coordinated by the National Disaster Management Authority (NDMA) and the Ministry of Health and Family Welfare (MoHFW). The response included strengthening surveillance and early detection, and clarifying policies on the use of pharmaceutical and non-pharmaceutical interventions, clinical management and risk communication. The surveillance of influenza was strengthened by integrating the existing separate networks under the auspices of IDSP units. The existing sentinel sites and laboratories continued to routinely test samples while the IDSP units ran call centres for the reporting of clusters of community cases of influenza-like-illness (ILI). Upon report of a case cluster, the rapid response teams (RRT) of the States and the Districts investigated the outbreak. Public health measures were instituted as per the district plan and micro planning, done for the affected area. Following the pandemic, the Indian National Influenza Surveillance Network was created, integrating the structures in use during the pandemic (MoHFW India, update 17 May 2009).

In this paper, we analyse incidence data on confirmed pandemic H1N1 cases – people with an acute febrile respiratory illness with novel influenza A (H1N1) virus infection confirmed at a WHO approved laboratory. Dates of symptom onset were not available, so day of testing was used.
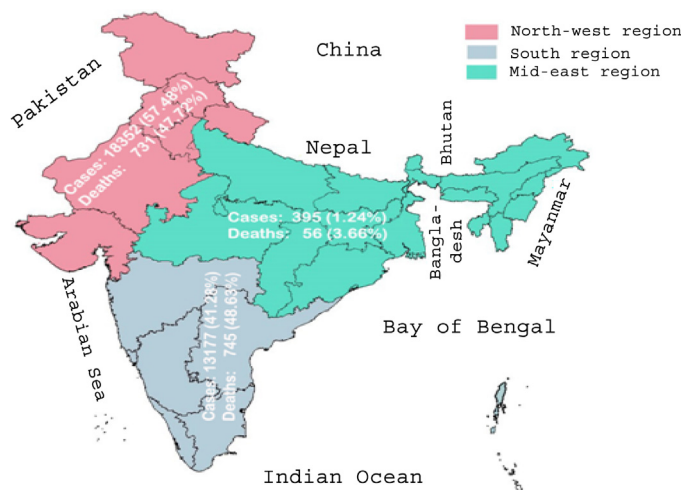

Fig. 1. Boundaries of regions used in this paper.

Data stratification and holidays

In order to examine geographic heterogeneity in transmission patterns, we stratified the case data into three regions (Fig. 1): (a) the North-west, consisting of Gujarat, Rajasthan, Haryana, Delhi, Punjab, Chandigarh, Himachal Pradesh, Uttaranchal, Uttar Pradesh, Jammu & Kashmir; (b) South, consisting of Maharashtra, Andhra Pradesh, Tamil Nadu, Karnataka, Kerala, Goa, Pondicherry, Lakshadweep, Andaman Nicobar Island, Daman & Diu and Dadra Nagar Haveli; (c) Mid-east, consisting of Madhya Pradesh, Chhattisgarh, Orissa, Jharkhand, Bihar, West Bengal, Sikkim, Assam, Meghalaya, Arunachal Pradesh, Tripura, Manipur, Nagaland and Mizoram. This choice of stratification was informed by the timing of school holidays across India. Holiday timing is not uniform at a national scale, but is relatively consistent within each of the regions with the definitions given above (Table 1).

We did not estimate transmission intensity for the Mid-east region due to the very limited number of cases detected (only 395, 1.24% of total confirmed cases).

Mathematical model

We use a simple branching process model of epidemic spread to estimate the intensity of pandemic transmission (quantified by the reproduction number) during the pandemic in India, focussing on comparing transmission rates during and outside school terms.

Fraser (2007) estimated the time varying reproduction number, R_t from the deterministic renewal equation for an epidemic as:

$$R_t = \frac{I_t}{\sum_{k=0}^{n} w_k I_{t-k}} \tag{1}$$

Here I_t is the number of incident symptomatic cases between time t and time $t+1$, and w_k is the proportion of secondary infections which first show symptoms between time k and $k+1$ after a primary case becomes symptomatic (the serial interval distribution), such that $\sum_{k=0}^{n} w_k = 1$ This formulation assumes that the serial interval distribution is constant during the epidemic. New work (Cori et al., 2013) has developed a Bayesian framework to generalise this inferential approach and to account for the stochasticity of the transmission process. From (1) the expected incidence at time t is $R_t \sum_{k=0}^{n} w_k I_{t-k}$, a Poisson-distributed count.

Assuming the transmissibility is constant over a time period $[t-\tau, t]$, as quantified by the reproduction number $R_{[t-\tau,t]}$, the likelihood of the incidence $I_{t-\tau}, \ldots\ldots\ldots, I_t$ during this time period,

Table 1
Regional variation in school vacation timing. Shaded cells indicate vacations applying to each region.

	Ganesh puja and Onam festival vacation: 23rd Aug–2nd Sept 2009	Mid-term vacation: 20th Sept–4th Oct 2009	Mid-term plus Dashera and Diwali vacation: 20th Sept–19th Oct 2009	Year-end vacation (Mid-east): 20th Dec 2009–20th Jan 2010	Year-end vacation: 20th Dec 2009–24th Jan 2010
North-west			▓▓▓		▓▓▓
Mid-east			▓▓▓	▓▓▓	
South	▓▓▓				▓▓▓

given the reproduction number $R_{[t-\tau,t]}$ and conditional on the previous incidences $I_0, \ldots\ldots, I_{t-\tau-1}$ is given by a product of Poisson probabilities:

$$P(I_{t-\tau}, \ldots\ldots, I_t | I_0, \ldots\ldots, I_{t-\tau-1}, \ w, \ R_{[t-\tau,t]})$$

$$= \prod_{s=t-\tau}^{t} \left\{ \frac{(R_{[t-\tau,t]}\Lambda_s)^{I_s} e^{-R_{[t-\tau,t]}\Lambda_s}}{I_s!} \right\} \quad (2)$$

where, $\Lambda_t = \Sigma_{k=0}^{n} w_k I_{t-k}$.

Assuming a Gamma distributed prior with parameters (a,b) for, $R_{[t-\tau,t]}$ the posterior joint distribution of $R_{[t-\tau,t]}$ is proportional to:

$$R_{[t-\tau,t]}^{a+\sum_{s=t-\tau}^{t} I_s - 1} e^{-R_{[t-\tau,t]}(\sum_{s=t-\tau}^{t}\Lambda_s + 1/b)} \prod_{s=t-\tau}^{t} \left\{ \frac{\Lambda_s^{I_s}}{I_s!} \right\} \quad (3)$$

Therefore, the posterior distribution of $R_{[t-\tau,t]}$ is a Gamma distribution with parameters $(a + \Sigma_{s=t-\tau}^{t} I_s, \ 1/(\Sigma_{s=t-\tau}^{t}\Lambda_s + 1/b))$. In particular, the posterior mean of $R_{[t-\tau,t]}$ is $(a + \Sigma_{s=t-\tau}^{t} I_s)/(\Sigma_{s=t-\tau}^{t}\Lambda_s + 1/b)$, and the posterior coefficient of variation of $R_{[t-\tau,t]}$ is $(a + \Sigma_{s=t-\tau}^{t} I_s)^{-1/2}$.

We assumed a Gamma distribution with mean 5 and standard deviation 5 as the prior on the $R_{[t-\tau,t]}$ (i.e. $a = 1$, $b = 5$). The choice of smoothing window τ is determined by a trade-off between temporal resolution and credible interval width around the resulting estimates; we explore $\tau = 7$ and 14 days here. We use a discretised gamma distribution for the serial interval (Fig. 2a) with a mean of 2.6 days and a standard deviation (SD) of 1.5 days (Cauchemez et al., 2009a; Ferguson et al., 2005). Uncertainty in these estimates of the mean and standard deviation of the serial interval distribution were accounted for by integrating over truncated normal prior distributions for both (Fig. 2b and c), without attempting to infer either. We assumed the mean of the normal prior for the mean serial interval to be 2.6 days, the standard deviation of the prior to be 1.5 days, with the prior distribution being truncated at a minimum of 1 day and a maximum of 4.2 days (Fig. 2c). Similarly the normal prior on the standard deviation of serial interval had an assumed mean and SD of 1.5 days and was truncated below at 1 day and above at 2.5 days.

Results

Following detection of the first indigenous case of the new pandemic virus on June 6th 2009 (Fig. 3a), spread occurred rapidly across India affecting all regions within 2–3 months. At a national scale, the pandemic exhibited two distinct waves of transmission, but at a regional level interesting heterogeneity was seen (Figs. 3 and 4). The North-west region experienced two notable waves whereas in the South region, the two waves were less clear cut. Comparatively, the Mid-east and North-east regions reported much lower numbers of cases (only 1.24% of all cases in India), though this may reflect the limitations of surveillance more than true incidence. Given the low numbers of cases reported in the Mid-east and North-east regions, we restrict the rest of our analysis to the all-India dataset and the North-west and South region data. In addition, due to the abrupt jump in case numbers on 7th August 2009 (due to surveillance system enhancements in the
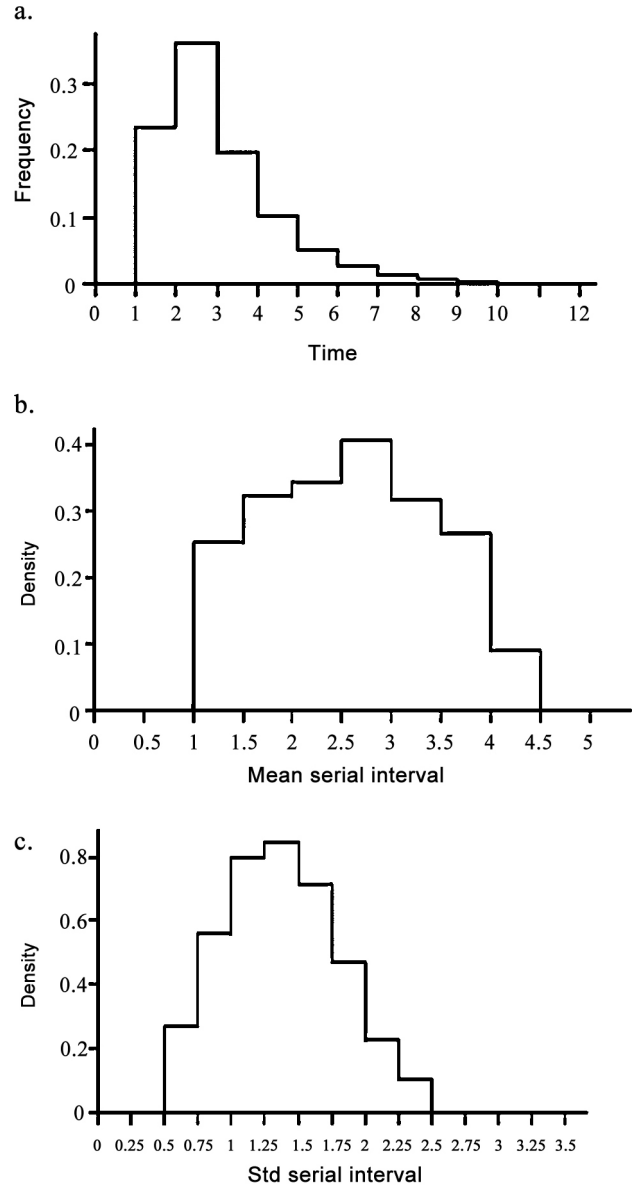

Fig. 2. (a) Assumed discretised serial interval distribution (mean = 2.6 days, SD = 1.5 days); (b) and (c). Assumed prior distributions for the serial interval distribution mean and standard deviation, respectively.

South region), we restrict out analysis of transmission intensity to the period from 7th August on.

We estimated the time varying reproduction number $R_{[t-\tau,t]}$ for these three datasets, with results for a $\tau = 14$ day smoothing window being shown in Fig. 5. Since case incidence in the South region (Fig. 3c) showed a step change in early August, coincident with improvements in surveillance following the first reported H1N1pdm death in India, we only report reproduction number estimates calculated from case reports from that time on.
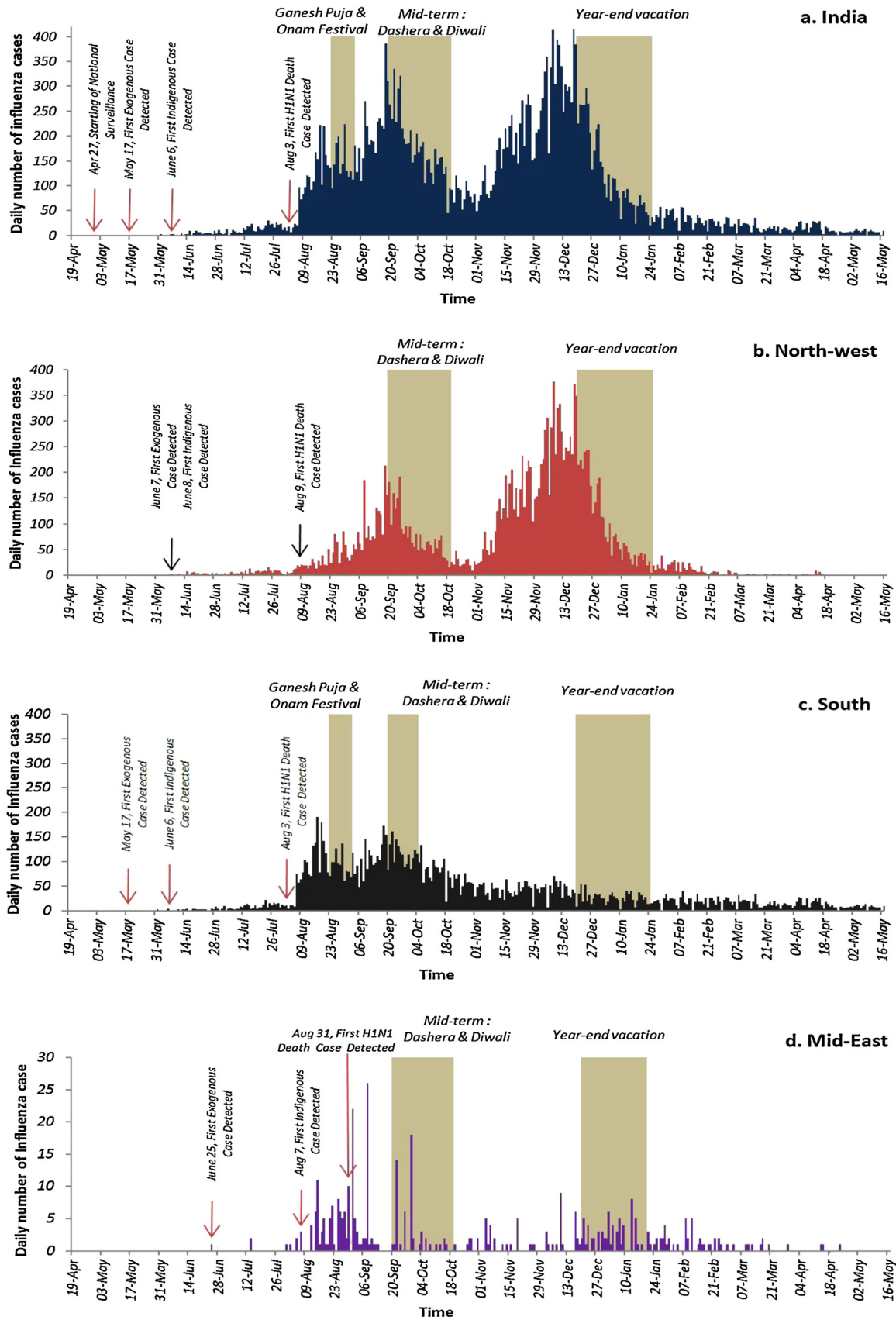
Fig. 3. Daily reported confirmed daily cases of H1N1 pandemic influenza in different regions of India in 2009–2010 by region. Shaded areas indicate school holidays. (a) India as a whole; (b) North-west region; (c) South region; d. Mid-East region.

Table 2
Estimated instantaneous reproduction numbers (with 95% CrI) for India and the North-west and South regions before and after the start of school holidays. Period of data used to estimate *R* shown in square bracket.

	Before Ganesh puja and onam holiday starts [7 Aug–22 Aug'09]	During Ganesh puja & onam holiday [23 Aug–2 Sep'09][a]	Before mid-term dashera and diwali vacation starts [3 Sep–19 Sep'09]	During mid-term dashera & diwali vacation [20 Sep–19 Oct'09][b]	Before year end vacation starts [20 Oct–19 Dec'09]	During year end vacation [20 Dec'09–24 Jan'10]
India	1.19 (1.06, 1.37)	0.96 (0.91, 1.02)	1.15 (1.06, 1.22)	0.91 (0.87, 0.97)	1.06 (1.03, 1.09)	0.85 (0.78, 0.93)
North-west	1.21 (1.06, 1.39)	1.15 (0.99, 1.33)	1.21 (1.07, 1.34)	0.88 (0.83, 0.95)	1.08 (1.04, 1.12)	0.81 (0.75, 0.91)
South	1.19 (1.04, 1.38)	0.92 (0.83, 1.01)	1.11 (1.03, 1.19)	0.95 (0.90, 1.00)	0.96 (0.89, 1.03)	0.95 (0.89, 1.02)

[a] Ganesh Puja and Onam were not much practiced in North-west region.
[b] In South region the Mid-term Dashera and Diwali vacation was shorter (20 Sep–4 Oct'09) than in other regions (see Table 1).

Table 2 compares estimates of the mean reproduction number before and after the start of school vacations. For India as whole, before the start of Ganesh Puja & Onam holidays (in August 2009), we estimated mean *R* as 1.19 (95% CrI: 1.06, 1.37), but during the vacation the estimate dropped to 0.96 (95% CrI: 0.91, 1.02), a 19% (95% CrI: 14–26%) reduction in transmission rate. These festivals are not practiced in the North-west region, and in that region less evidence of a slowing of transmission was seen at that time. Conversely, the reproduction number estimates for the South fell substantially during this holiday.

Coming up to the Mid-term Dashera and Diwali holidays in September, the estimated mean reproduction number for India was 1.15 (95% CrI: 1.06, 1.22), falling to 0.91 (95% CrI: 0.87, 0.97) in the vacation, a 21% (95% CrI: 18–20%) reduction in the transmission rate. In North-west region the start of that vacation coincided with the peak of the first wave of the pandemic. In the 3 weeks before the start of that vacation, the estimated reproduction number in the North-west was 1.21 (95% CrI: 1.07, 1.34), dropping to 0.88 (95% CrI: 0.83, 0.95) during the vacation, a reduction of 27% (95% CrI: 22–29%). In case of the South region, this holiday was shorter but a reduction in transmission rates was still seen, from 1.11 (95% CrI: 1.03, 1.19) to 0.95 (95% CrI: 0.90, 1.00), a reduction of 14% (95% CrI: 13–16%).

Similarly, in the second wave, prior to the year-end vacation (December–January) we estimate R_t for India to be 1.06 (95% CrI: 1.03, 1.09), falling to 0.85 (95% CrI: 0.78, 0.93) in the holidays; a 20% (95% CrI: 24–15%) reduction in transmission rate. For the North-west region, R_t was 1.08 (95% CrI: 1.04, 1.12) before the start of year-end vacation, but dropped to 0.81 (95% CrI: 0.75, 0.91) during the vacation, a 25% (95% CrI: 28–19%) reduction. Indeed in the North-west, the start of the year-end vacation coincided with the peak of the
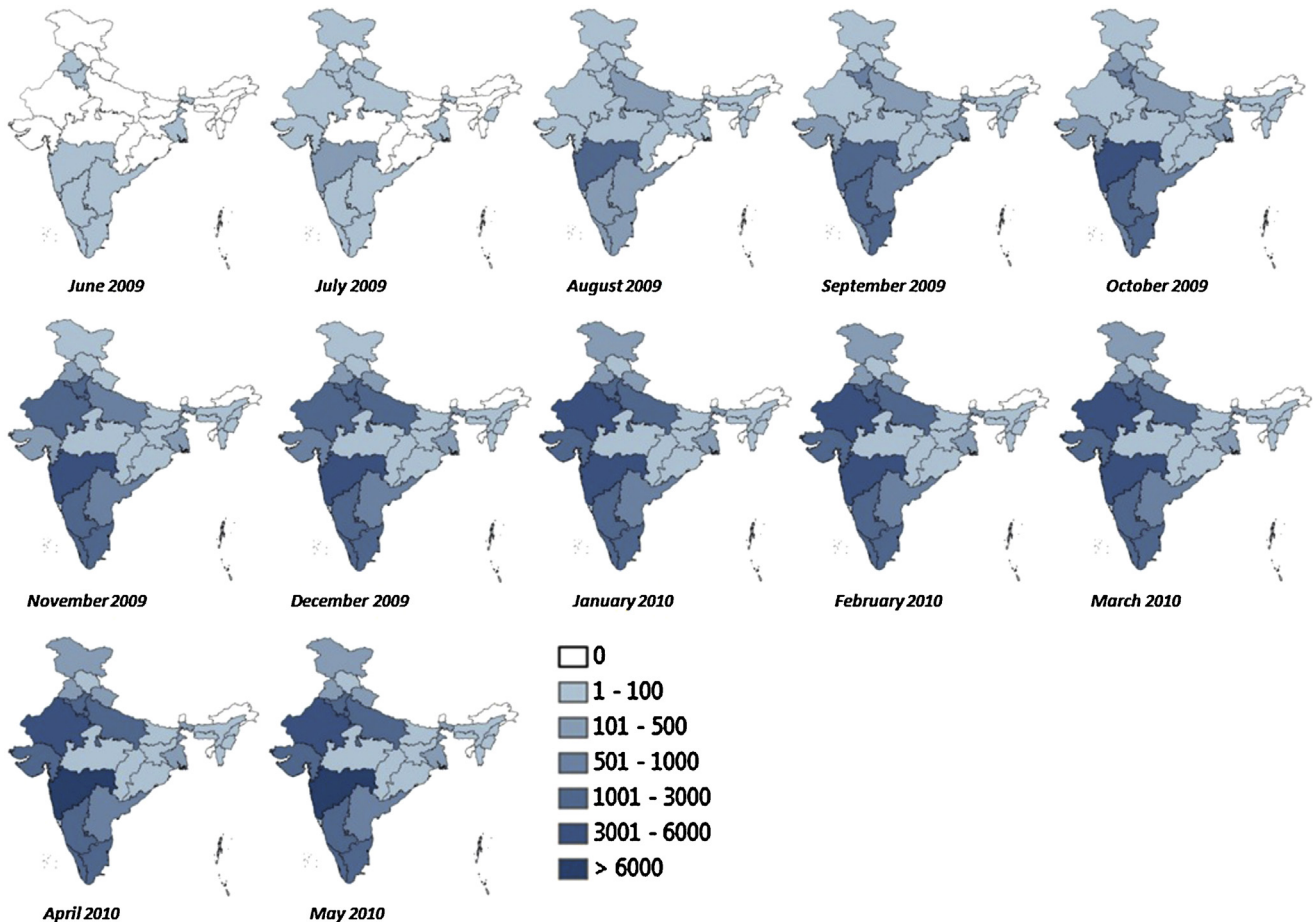

Fig. 4. Cumulative absolute incidence of confirmed cases of influenza A (H1N1)pdm'09 virus infection, by month and different states & union territories of India during June'09–May'10 (till 17th May).
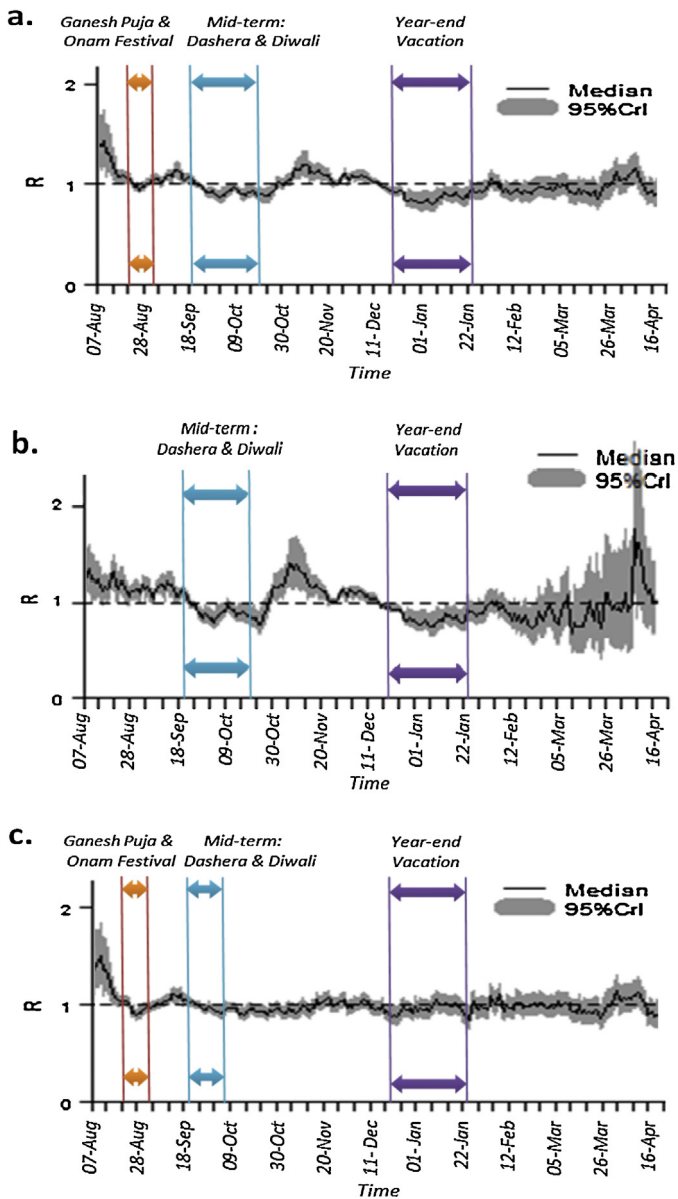
Fig. 5. Estimated reproduction number R_t (posterior median in black line) with 95% CrI (grey zone) for different regions of India: (a) India as a whole, (b) North-west region and (c) South region. A smoothing window of $\tau = 14$ days was used.

second major wave of the pandemic in that area. However, in the South region, incidence had started to decline substantially earlier by that time (Fig. 3), and the effect of this vacation was found to be slight – a non-significant reduction of 1% in the reproduction number.

Conclusions

As seen in a number of other countries (Baguelin et al., 2010; Yu et al., 2012; Merler et al., 2011; Reed et al., 2012), India experienced multiple waves of transmission of the 2009 H1N1 pandemic virus, with considerable variation between regions (Figs. 3 and 4). Our analysis demonstrates that some (but not all) of the geographic heterogeneity seen may be explained by differences in the timing and duration of school holidays. In the growth phase of the first pandemic wave in India, we estimate the reproduction number to be in the range 1.1–1.3, comparable with values estimated for several other countries (Baguelin et al., 2010; Yu et al., 2012;

Opatowski et al., 2011), albeit on the lower end of the range of estimates from prior studies. It is interesting to note that the highest reproduction estimates were seen in the North-west (Table 2), the most arid region of India, suggestive of a correlation between transmission intensity and humidity (Shaman et al., 2010). Exploring the relationship between climate and influenza transmissibility across India

In the North-west region during the first wave, we estimated that the Mid-term Dashera and Diwali school vacation was associated with a 27% reduction in the rate of transmission. Likewise, in the second wave, the year-end vacation was associated with a 25% reduction in the reproduction number. In the South region, the peak of the first wave coincided with the start of school holidays in August, and a 23% reduction in transmission rate. While a number of other factors (such as seasonality and depletion of susceptibles) may have contributed to these reductions, these values are comparable to those seen in the UK, US, Mexico and China, other countries with sizeable waves of transmission in the late spring and early summer of 2009 (Baguelin et al., 2010; Yu et al., 2012; Merler et al., 2011; Wu et al., 2010). The reduction in transmission seen in school holidays is likely to have been dominated by reductions in contact rates between children (Eames et al., 2012), but it should also be noted that official advice in India during the pandemic was to avoid traditional mass-gatherings and travel during vacations (MoHFW India, update 17 May 2009).

Methodologically, our analysis benefitted from using a flexible and robust Bayesian inferential framework for estimating time varying reproduction numbers from case incidence time-series data (Cori et al., 2013). The method used generalises past work (Fraser, 2007; Wallinga and Teunis, 2004) and provides a computationally efficient (and largely analytically tractable) means of estimating credible intervals around reproduction number estimates, while accounting for uncertainty in the serial interval distribution.

Our study has several largely inevitable limitations. Principal among these is the potential frailty of the surveillance data used. Virologically confirmed cases of influenza at best represent a tiny proportion of underlying infections, and rarely represent an unbiased sample of community cases. Capacity limits on outbreak investigation, sample collection and laboratory diagnostics also tend to mean that confirmed case incidence is a declining fraction of true incidence as the incidence of infection grows, potentially leading to epidemic growth rates being underestimated. In addition, the propensity of cases to seek healthcare (and therefore be tested) may have declined over time as concern over the pandemic virus waned. Case detection may also be lower during vacations than outside them; however, we would emphasise that such an effect would only affect reproduction number estimates transiently at the start and end of each vacation and have only a minor impact on average estimates across the whole period of a vacation. Furthermore, in a country as large and diverse as India, there is substantial geographic variability in surveillance and laboratory capacity. Passive sentinel surveillance recording cases seen in primary care or hospitals can be substantially affected by variation in healthcare seeking behaviour over time or by region.

Second, while our study demonstrates an association between the timing of school holidays in India and transmission rates, such a correlative analysis cannot demonstrate causality or determine the precise changes in contact patterns which are responsible for the observed changes in transmission. Behavioural studies can give some insight into the latter (Eames et al., 2012), but short of a randomised trial, cohort studies of influenza transmission which also collect contact data perhaps offer the best opportunity to understand the relationship between individual contact patterns and infection/transmission risk. Information on the age-distribution of cases over time and how this was affected by school holidays might

also allow a signature of reduced contact rates between children during vacations to be resolved; however, we did not have data on the ages of confirmed cases.

Finally, our study adds to the already extensive body of evidence informing the ongoing debate around the potential use of deliberate school closure as a non-pharmaceutical intervention during a moderate to severe influenza pandemic (Cauchemez et al., 2009b; Sadique et al., 2008). In this context, it is important to note that school holidays appear to have had a particularly substantial impact on transmission in the 2009 pandemic due to the primary role children played in the transmission of the H1N1pdm virus. However the 1918 H1N1, 1957 H2N2 and 1968 H3N2 pandemics (Stuart-Harris, 1970; Brundage, 2006) showed much less pronounced trends for clinical attack rates to decline with age than was seen in 2009; with more uniform susceptibility by age, it would be expected that the impact of school closure on transmission would be more limited than the 2009 experience might suggest (Ferguson et al., 2006; Cauchemez et al., 2008, 2009b). Any use of school closure as an intervention measure in a future pandemic needs to weigh the expected benefit against the high economic and social cost (Cauchemez et al., 2009b; Sadique et al., 2008) against the potential benefits in transmission reduction. Mathematical modelling coupled with statistical analysis of available epidemiological data will be critical to a rigorous assessment of this trade-off.

Acknowledgments

References

Baguelin, M., Hoek, A.J., Jit, M., Flasche, S., White, P.J., Edmunds, W.J., 2010. Vaccination against pandemic influenza A/H1N1v in England: a real-time economic evaluation. Vaccine 28, 2370–2384.

Brundage, J.F., 2006. Cases and deaths during influenza pandemics in the United States. Am. J. Prev. Med. 31, 252–256.

Cauchemez, S., Donnelly, C.A., Reed, C., Ghani, A.C., Fraser, C., Kent, C.K., Finelli, L., Ferguson, N.M., 2009a. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. N. Engl. J. Med. 361, 2619–2627.

Cauchemez, S., Ferguson, N.M., Wachtel, C., Tegnell, A., Saour, G., Duncan, B., Nicoll, A., 2009b. Closure of schools during an influenza pandemic. Lancet Infect. Dis. 9, 473–481.

Cauchemez, S., Valleron, A.J., Boelle, P.Y., Flahault, A., Ferguson, N.M., 2008. Estimating the impact of school closure on influenza transmission from sentinel data. Nature 452, 750–754.

Chowell, G., Echevarri'a-Zuno, S., Viboud, C., Simonsen, L., Tamerius, J., Miller, M.A., Borja-Aburto, V.H., 2011. Characterizing the epidemiology of the 2009 influenza A/H1N1 pandemic in Mexico. PLoS Med. 8 (5), e1000436.

Cori, A., Fraser, C., Ferguson, N.M., Cauchemez, S., 2013. A new framework and software to estimate time-varying reproduction numbers during epidemics. Am. J. Epidemiol (in press).

Dawood, F.S., Iuliano, A.D., Reed, C., Meltzer, M.I., Shay, D.K., Cheng, P.Y., Bandaranayake, D., Breiman, R.F., Brooks, W.A., Buchy, P., Feikin, D.R., Fowler, K.B., Gordon, A., Hien, N.T., Horby, P., Huang, Q.S., Katz, M.A., Krishnan, A., Lal, R., Montgomery, J.M., Mølbak, K., Pebody, R., Presanis, A.M., Razuri, H., Steens, A., Tinoco, Y.O., Wallinga, J., Yu, H., Vong, S., Bresee, J., Widdowson, M.A., 2012. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect. Dis. 12 (9), 687–695.

Eames, K.T.D., Tilston, N.L., Brooks-Pollock, E., Edmunds, W.J., 2012. Measured dynamic social contact patterns explain the spread of H1N1v influenza. PLoS Comput. Biol. 8 (3), e1002425.

Ferguson, N.M., Cummings, D.A., Cauchemez, S., Fraser, C., Riley, S., Meeyai, A., Iamsirithaworn, S., Burke, D.S., 2005. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature 437, 209–214.

Ferguson, N.M., Cummings, D.A., Fraser, C., Cajka, J.C., Cooley, P.C., Burke, D.S., 2006. Strategies for mitigating an influenza pandemic. Nature 442, 448–452.

Fraser, C., 2007. Estimating individual and household reproduction numbers in an emerging epidemic. PLoS ONE 2, e758.

Fraser, C., Donnelly, C.A., Cauchemez, S., Hanage, W.P., Van Kerkhove, M.D., Hollingsworth, T.D., Griffin, J., Baggaley, R.F., Jenkins, H.E., Lyons, E.J., Jombart, T., Hinsley, W.R., Grassly, N.C., Balloux, F., Ghani, A.C., Ferguson, N.M., Rambaut, A., Pybus, O.G., Lopez-Gatell, H., Alpuche-Aranda, C.M., Chapela, I.B., Zavala, E.P., Guevara, D.M., Checchi, F., Garcia, E., Hugonnet, S., Roth, C., WHO Rapid Pandemic Assessment Collaboration, 2009. Pandemic potential of a strain of influenza A (H1N1): early findings. Science 324, 1557–1561.

Merler, S., Ajelli, M., Pugliese, A., Ferguson, N.M., 2011. Determinants of the spatiotemporal dynamics of the 2009 H1N1 pandemic in Europe: implications for real-time modelling. PLoS Comput. Biol. 7 (9), e1002205.

2009. Ministry of Health and Family Welfare, Ministry of Health and Family Welfare, Government of India; Situation update, Press release: http://www.mohfw-h1n1. nic.in/documents/PDF/SituationalUpdatesArchives/may/Situational Updates on 17.05.2009.pdf (last access: Mar 08.03.12).

Opatowski, L., Fraser, C., Griffin, J., De Silva, E., Van Kerkhove, M.D., Lyons, E.J., Cauchemez, S., Ferguson, N.M., 2011. Transmission characteristics of the 2009 H1N1 influenza pandemic: comparison of 8 southern hemisphere countries. PLoS Pathogens 7 (9), e1002225.

Reed, C., Katz, J.M., Hancock, K., Amanda, B., Fry, A.M., for the H1N1 Serosurvey Working Group, 2012. Prevalence of seropositivity to pandemic influenza A/H1N1 virus in the United States following the 2009 pandemic. PLoS One 7 (10), e48187.

Sadique, M.Z., Adams, E.J., Edmunds, W.J., 2008. Estimating the costs of school closure for mitigating an influenza pandemic. BMC Public Health 8, 135, http://dx.doi.org/10.1186/1471-2458-8-135.

Shaman, J., Pitzer, V.E., Viboud, C., Grenfell, B.T., Lipsitch, M., 2010. Absolute humidity and the seasonal onset of influenza in the continental United States. PLoS Biol. 8 (2), e1000316.

Stuart-Harris, C.H., 1970. Pandemic influenza: an unresolved problem in prevention. J. Infect. Dis. 122, 108–115.

Wallinga, J., Teunis, P., 2004. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am. J. Epidemiol. 160 (6), 509–516.

World Health Organization, 2009a. Influenza A(H1N1), Director-General, Dr Margaret Chan 29 April 2009, http://www.who.int/mediacentre/news/statements/ 2009/h1n1_20090429/en/ (last access: 08.03.12).

World Health Organization, 2009b. Influenza Pandemic Alert Raised to Level 6, Director-General's Statement at Press Conference. June 11, 2009, http://www. who.int/pmnch/media/news/2009/20090611_who/en/ (last access: 08.03.12).

World Health Organization, 2010. H1N1 in post-pandemic period, Director-General's statement at press conference. August 10, 2010, http://www.who.int/ mediacentre/news/statements/2010/h1n1_vpc_20100810/en/index.html (last access: 08.03.12).

Wu, J.T., Cowling, B.J., Lau, E.H.Y., Ip, D.K.M., Ho, L.M., Tsang, T., Chuang, S.K., Leung, P.Y., Lo, S.V., Liu, S.H., Riley, S., 2010. School closure and mitigation of pandemic (H1N1) 2009, Hong Kong. Emerg. Infect. Dis. 16 (3), 538–541.

Yu, H., Cauchemez, S., Donnelly, C.A., Zhou, L., Feng, L., Xiang, N., Zheng, J., Ye, M., Huai, Y., Liao, Q., Peng, Z., Feng, Y., Jiang, H., Yang, W., Wang, Y., Ferguson, N.M., Feng, Z., 2012. Transmission dynamics, border entry screening, and school holidays during the 2009 influenza A (H1N1) pandemic, China. Emerg. Infect. Dis. 18, 758–766.