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Stochastic Modelling: An Approach to Quantify the Transmission Intensity of Pandemic Influenza (H1N1) in Maharashtra

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ABSTRACT

In India, Maharashtra was one of the badly affected states during the influenza A/H1N1 2009 pandemic. We undertook the study to identify the disease dynamics and real time varying intensity of the strain in Maharashtra and to evaluate the internal heterogeneity under different epidemiological contours. Reproduction Number, the key epidemiological parameter, defined as average number of secondary infected individuals generated by a typical primary case in his/her entire infectious period, which being used to quantify the characteristic of the transmission intensity of pandemic. The aim of the paper is to estimate instantaneous reproduction number from daily case reported data considering the stochastic nature of generation time. We used the Kermack McKendrick transmission model (Time-Since-Infection model) applied to stochastic renewal process of disease outbreak. Our reliable estimate of reproduction number is 1.44 for the Influenza A/H1N1 pandemic in Maharashtra, comparatively higher than other part of India. Moreover, we examine that the effectiveness of interventions at the initial stage, and is found to have a significant role in reducing the contact rate, consequently the transmissibility.

Keywords: *Influenza, reproduction number, renewal process, mathematical models, Maharashtra*

INTRODUCTION

The novel influenza A/H1N1, a quadruple re-assorted virus, first detected in Mexico on 18th March 2009, and thereafter it has rapidly spread around the globe within a span of a couple of months[1]. Consequently, on 11th June World Health Organization (WHO) raised its pandemic alert from phase 5 to 6[2]. In India, the first exogenous case has been reported on 17th May, 2009 at Hyderabad and for Maharashtra on 13th June, 2009 at Pune[3]. Most of the cases reported subsequently were the travel related cases, immigrating to India from affected countries. In the beginning, the disease spread essentially through the south and western cities of India i.e. Hyderabad, Chennai, Bangalore, Mumbai and Pune. Maharashtra has experienced a strong wave (wave-1) of transmission during May-Oct, 2009 compare to the wave-2 during Nov 2009 – May 2010.On 17 May, 2010, Maharashtra alone has borne a brunt of pandemic with 461 (30% of national deaths) deaths out of 6283 (20% of national cases) lab confirmed cases, signifying the worst situation of disease spread compare to other states and union territories in India.

Thus the burden of this strain has highlighted the preparedness of the public health system against pandemic. The qualitative and quantitative case detection and treatment as per WHO guidelines was employed to reduce the mortality from influenza H1N1 virus, beside a intensive quantitative study has been demanded to assess the transmissibility of the strain, which might lead to design the optimal control strategies to be implemented.

Swine-flu, 2009 is a viral fever caused by newly emerging mutated strain influenza A virus subtype H1N1, which transmits human to human. This novel virus is a combination, derived from a reassortant swine-origin virus and two gene segments from the Eurasian influenza A (H1N1) swine virus lineage. Antigenic variation through antigenic-drift and antigenic-shift of hemagglutinin (HA) and neuraminidase (NA) proteins enable the virus to escape host immune responses. Antigenic drifts in the HA subtype are associated with seasonal epidemic whereas antigenic shifts in HA subtype are responsible for pandemic[4, 5].

The present study was carried out to quantify the disease intensity of pandemic Influenza A/H1N1 in Maharashtra and to evaluate the internal heterogeneity in transmission dynamics. To accomplish this noble job, we have calculated the real time-varying reproduction number (defined as the average number of secondary cases generated by a primary infectious case in his/her entire infectious period) from time series data on H1N1, through renewal theory applied to Kermack and McKendrick Time Since Infection model[6]. A comparative study has been made to enumerate the relative status among the several regions (cities) associated to different epidemiological profiles and interventions.

We estimate the reproduction number, 1.44 for Maharashtra and 1.45 for Pune, which is found to be little higher than that of India 1.32 at early stage of pandemic. Moreover, we quantify the effectiveness of interventions, taken up to control the pandemic in Maharashtra through different agencies and the several epidemiological events.

MATERIALS AND METHODS

Materials

We have analysed daily lab-confirmed case reports of pandemic H1N1 2009 for India, in particular Maharashtra considering its worst status on disease outbreak. This time series data obtained from Ministry of Health and Family Welfare (MoHFW) Government of India[3], Pune Municipal Corporation (PMC)[7]and Municipal Corporation of Greater Mumbai (MCM)[8]. The region-wise stratification on Indian scenario and city-wise stratification of the state Maharashtra has been used to study the comparative intensity of disease spread. To get insight on the variation of initial transmissibility in Maharashtra, we consider the urban areas mainly Pune and Mumbai.

Mathematical Model

Most often in epidemiological studies, reproduction number has been used to quantify the transmission intensity. We have made use of Kermack Mckedrick transmission model to estimate instantaneous reproduction number from the daily case reported data set, considering stochastic behaviour of generation time[9]. Here, we consider Time Since Infection model (a compartmental counterpart,i.e. SIR, SIS... etc.) which offers more inherent setting for modelling infectious disease transmission and importantly for its applications, providing advantages on typically easier approach to identify the model key parameters and its more readily adaptive nature to describe multi-level (within and between household) transmission[6, 10].

In reality, the report of new cases is rather uncertain. The variation in incidence rate, $\frac{d}{dt}I(t)$ can be treated as an arbitrary function of calendar time t and time since infection τ, in terms of the transmissibility, denoted by $\beta(t,\tau)$, which typically reflects pathogen load or pathogen shedding, pathogen growth followed by immune suppression or host death, effective contact rate between infectious and susceptible individuals (increases through coughing, sneezing etc. and decreases due to hospitalization, implementation of public health preventive measures etc.)[11, 12].

Statistically, transmission can be characterized as Poisson infection process, i.e. the probability that a person who has been infected at time t ago, will successfully infects someone else between time t and $t+\delta$, is $\beta(t,\tau)\delta$, where δ is a very small time interval. This assumption leads to the renewal equation of mean incidence $I(t)$ at time t as,

$$I(t) = \int_0^\infty \beta(t,\tau) I(t-\tau) d\tau \qquad (1)$$

The instantaneous reproduction number $R(t)$, which reflects the status of epidemic at time t and defined as the average number of secondary cases, generated by a typical primary case at time t under homogeneous conditions. It is given by

$$R(t) = \int_0^\infty \beta(t,\tau) d\tau \qquad (2)$$

On analytical simplification, the infectiousness can be decomposed as the product of the instantaneous reproduction number and the generation time distribution $w(t)$, as t and τ are independent. Therefore,

$$\beta(t,\tau) = R(t)w(\tau) \qquad (3)$$

The distribution $w(\tau)$ is really intended as a measure of infectiousness which will correspond to generation times for an index case in an ideal large closed setting where contact rates are constant. Inserting (3) into (1) yields a novel estimator for instantaneous reproduction number.

$$R(t) = \frac{I(t)}{\int_0^\infty I(t-\tau)w(\tau)d\tau} \qquad (4)$$

Usually, incidence is reported as a discrete time series in the form I_i, reported between time t_i and time $t_i + 1$, in which the generation time distribution should be appropriately discretised into the form w_i such that $\sum_{i=0}^{n} w_i = 1$.

Then the estimators for the reproduction numbers become,

$$R(t_i) = \frac{I_i}{\sum_{j=0}^{n} W_i I_{i-j}} \qquad (5)$$

Equation (5) was first used for analysing polio transmission in India[13].

Limitation
The method has its own inhabitable limitations on estimation of reproduction number through equation (5); firstly, we have to wait to get its first estimate until a complete generation time period to be exhausted, i.e. right censoring issue. Secondly, the null report of incidence in a day will return the reproduction number to be zero. To avoid this inadequacy, we have performed the statistical adjusted smoothening of the real time series data.

RESULTS AND DISCUSSION

The analysis of entire one year time series data (17th May 2009 to 17th May 2010) on pandemic Influenza A/ H1N1 in Maharashtra, has revealed the insight of our research questions. It has been reported that the novel influenza virus claimed 1525 deaths out of 31922 infected cases with Case Fatality Proportion (CFP) 4.78 in India [14]. The pandemic exhibited two distinct waves of transmission during the year in India as a whole. However, the national-level picture hides interesting regional heterogeneity. The outbreak mainly concentrated in North-West and South regions compare to other part of India. The state Maharashtra was noticed as one of the worst affected state in India (Figure 1) encouraged to investigate the disease dynamics pattern in Maharashtra.

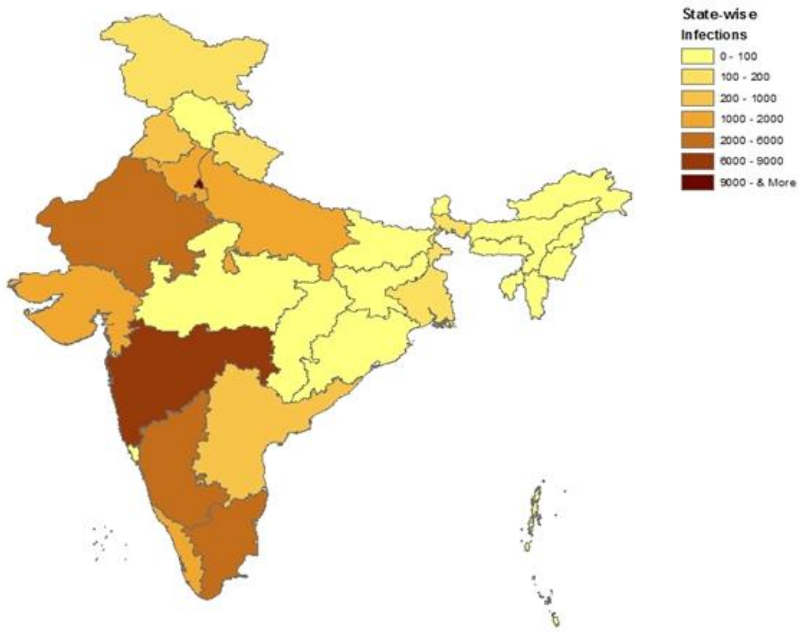

Figure 1 Spread of H1N1 virus (as on 17th May 2010)

The total number of 461 (30% of total national deaths) influenza deaths out of 6283 (20% of total national reports) infected cases has been reported in Maharashtra during the year with CFP of 7.34, much higher than that of India as a whole (4.78).

The wave-1 has higher burden than that of wave-2 for Maharashtra even for the South region (Table 1). In first wave, total of 3645 (25.50%) cases has been reported with 201 (44.86%) deaths in Maharashtra; where as it was 2638 (14.96%) infected case with 260 (24.14%) deaths in second wave.

Table 1 Region wise stratification of reported influenza cases, death cases with Case Fatality Proportion (CFP) for different waves

Regions	Wave 1 (17 May'09 - 31 oct'09)			Wave 2 (1 Nov'09 - 17 May'10)			Overall (17 May'09 - 17 May'10)		
	Infected cases	Deaths	CFP	Infected Cases	Deaths	CFP	Infected Cases	Deaths	CFP
Maharashtra	3645 (25.50%)	201 (44.86%)	5.51	2638 (14.96%)	260 (24.14%)	9.86	6283 (19.68%)	461 (30.22%)	7.34
South Region	8513 (59.56%)	399 (89.06%)	4.69	4664 (26.45%)	339 (31.47%)	7.27	13177 (41.27%)	738 (48.39%)	5.60
India	14292	448	3.13	17630	1077	6.11	31922	1525	4.78

Interestingly, it has been noticed at the very beginning of outbreak (till mid of August) that the dynamics of pandemic influenza for Maharashtra was representing almost 60% of the whole India status (Figure 2).

Before the report of first Indian H1N1 pandemic death in Pune on 3rd Aug, 2009, the total number of influenza cases was 131 (22.66%) for Maharashtra, out of which Pune has reported 108 (82.44%) and Mumbai 22 (16.79%), showing the pandemic-focus in urban areas at beginning. This unexpected death has increased the public awareness and massive exposure of the disease outbreak to common people, consequently the report rate in urban area of Maharashtra has amplified within a couple of weeks. We found that during 4th Aug to 21st Aug, 2009, the reported influenza cases has raised to 1196 (51.23%), where in Pune alone reported 650 (57.12%) and Mumbai 395 (31.42%); which exhibit the 88.37% increment in influenza report rate in Maharashtra (see, red vertical line in Figure 2). During this period, an exhaustive number of awareness programs have been implemented by Central/State Governments and Non-government agencies through pharmaceutical and non-pharmaceutical interventions.The decline in the daily report cases after 21st August, 2009 was probably a consequence of these interventions, particularly for Maharashtra. It has been noticed that the transmission again a little ascend up during Sep-Oct, 2009 indicating the natural dynamics of the disease, accounting the contact pattern in rural population, who were comparatively less conscious about the strain.

The city-wise stratifications of the time series daily reported data have unveiled the interesting heterogeneity in the transmission of novel virus. Till the end of Aug, 2009, the transmission of H1N1 Virus in Maharashtra was concentrated in urban areas especially in Pune and Mumbai (see Figure 3). On detection of first indigenous case on 11th July, 2009 at Pune, the disease spread over the other main cities of the state rapidly within a month, accelerating the contact rate between susceptible and infective.

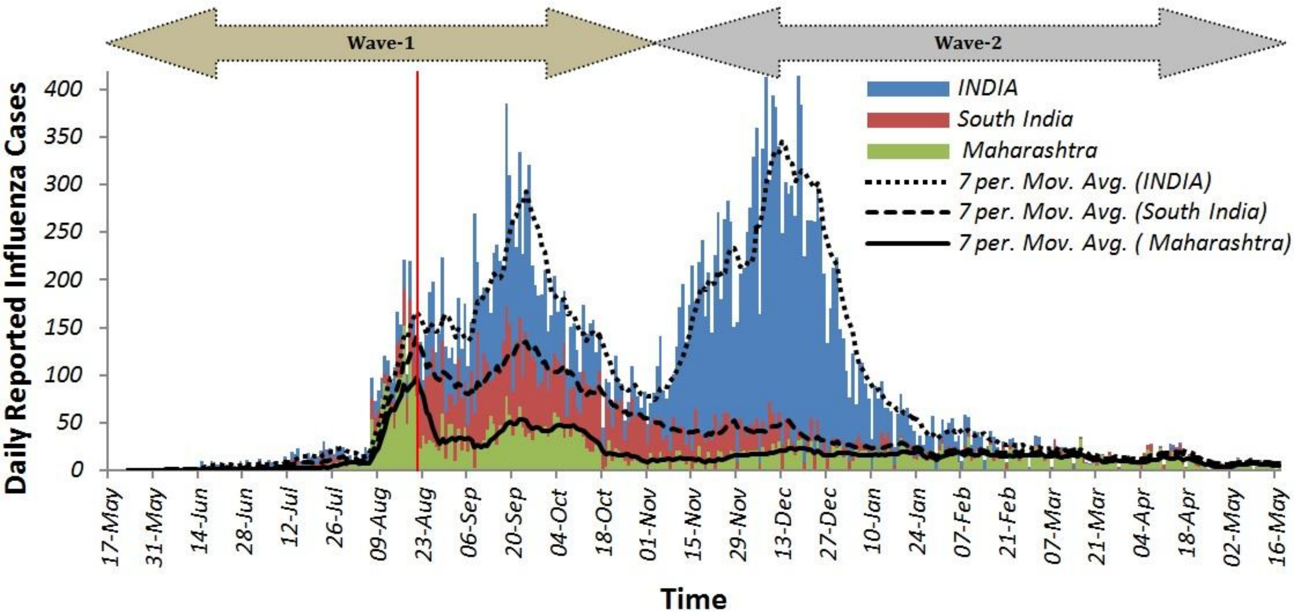

Figure 2 Daily reported influenza cases for India, South region and Maharashtra with their statistical smoothening. ** The vertical red line indicates the first peak of wave-1 and coincides with the best length of initial exponential growth phase*

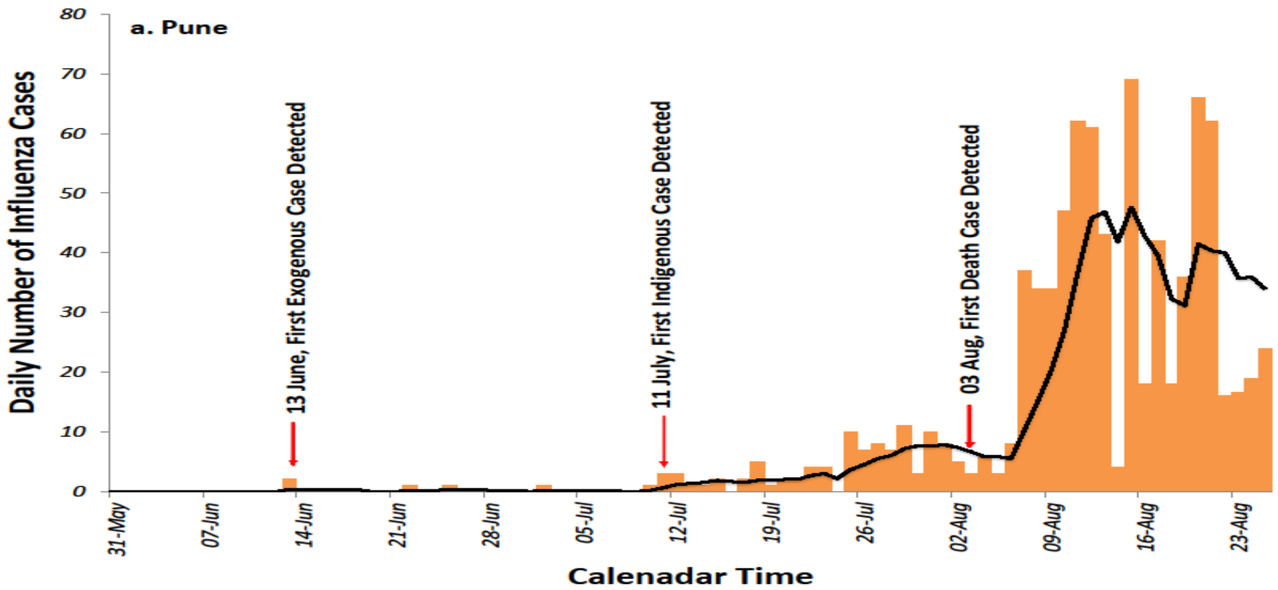

Figure 3a The initial dynamics of influenza pandemic in Pune with epidemiological events

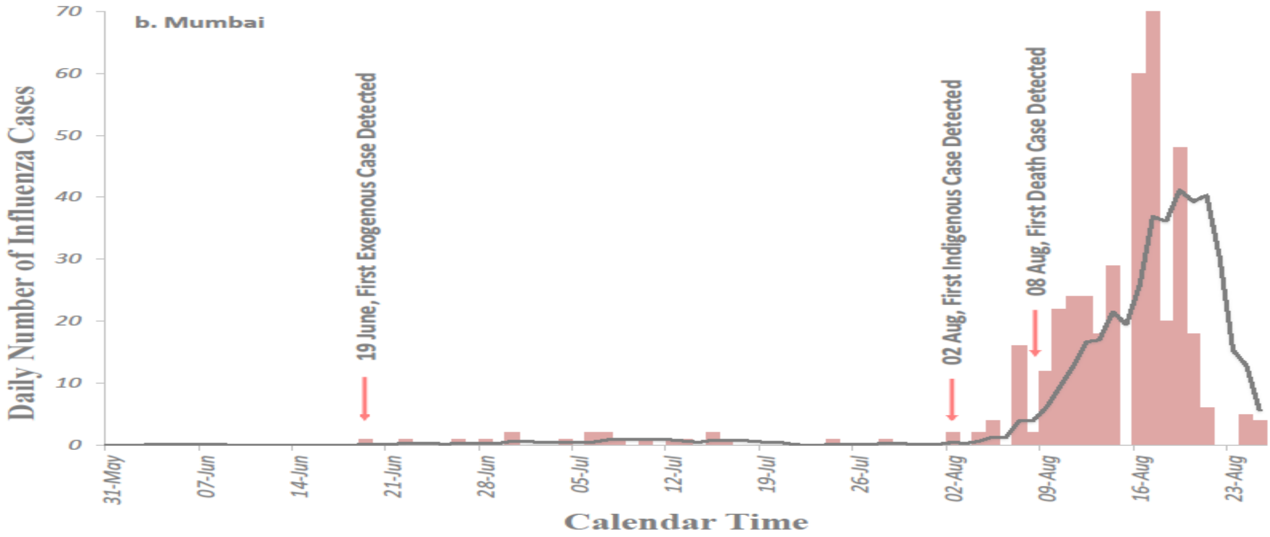

Figure 3b The initial dynamics of influenza pandemic in Mumbai with epidemiological events

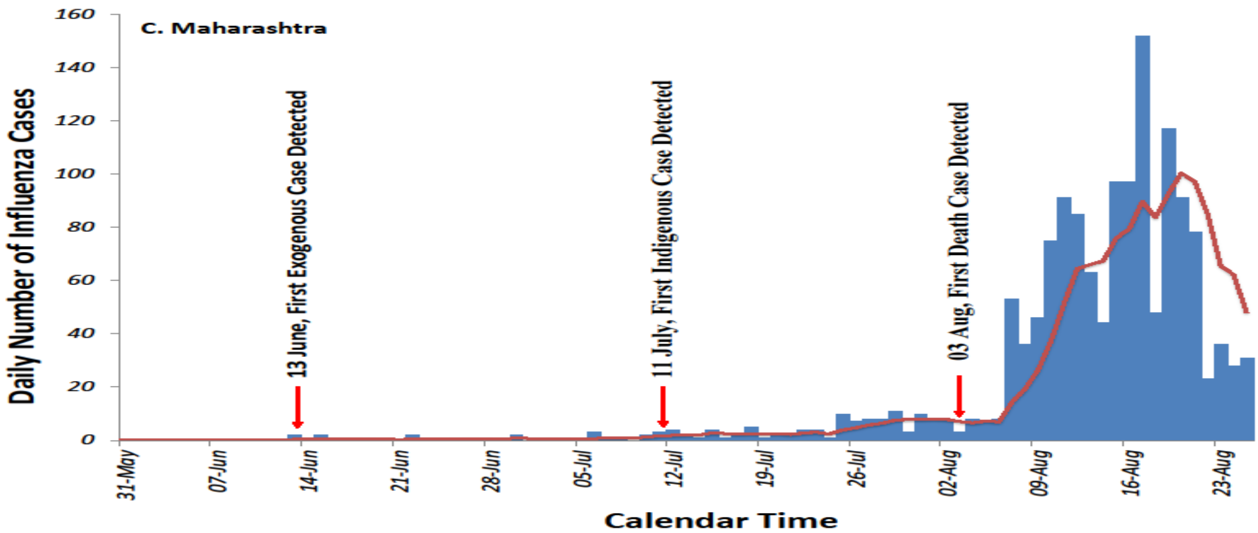

Figure 3c The initial dynamics of influenza pandemic in Maharashtra with epidemiological events

To address the main objective of our present study, we have assessed the real time estimates of reproduction number to quantify the intensity of pandemic transmission (Figure 4a & b). Our estimate of average reproduction number for Maharashtra is 1.44, which off course indicating the worst situation among the other parts of India (see, Table 2). Our estimate varies from 0.80 to 1.75 for Maharashtra and 0.53 to 1.60 for Pune, which was the most affected city in Maharashtra with average reproduction number 1.45 at the early phase of pandemic.

Before the report of first death on 3rd Aug, we estimate the reproduction number as 1.33 for Maharashtra and 1.40 for Pune. It was noticed that the detection of this maiden death of H1N1 has accelerated the public awareness on pandemic alert resulting the rapid report of influenza cases within next couple of week. In the post-death-period, we observe that the reproduction number increased to 1.75 for Maharashtra and 1.60 for Pune, which indicate the fact of sudden jump in transmission as well as reporting rate. The effect has been seen in the neighbouring states, concluding the relatively highest estimate of transmissibility as 1.95 for south region (see Table

2). Although, some study suggests this variation of sudden increment in transmission as a consequence of seasonal fluctuation in temperature, rainfall and humidity etc.[15].

Table 2 Instantaneous Reproduction Number and Percentage of Variation in Transmissibility (in parenthesis +'ve shows increment and –'ve implies decline)

Regions	Before First Death Detected (Till 3 Aug '09)	After First Death Detected (4Aug - 17Aug'09)	On Intervention Phase (22 Aug -31Aug'09)	Average Reproduction Number*
India	1.21	1.77 (+ 32%)	1.01 (- 43%)	1.32
South Region	1.28	1.95 (+ 34%)	0.94 (- 52%)	1.37
Maharashtra	1.33	1.75 (+ 24%)	0.80 (- 54%)	1.44
Pune	1.40	1.60 (+ 13%)	0.53 (- 67%)	1.45

**Reproduction numbers are calculated considering the natural exponential growth length (21st August, 2009)*

Following the first pandemic death case, during the month August, 2009, an extensive effort of control measures has been implemented by Government of Maharashtra along with Central agenises: starting with the instructions on local school closure, shutting down the cinema halls/ malls/ multiplexes, discouraging mass gathering (Dahi Handi and Ganesh Chaturthi) and large congregations, suggesting to avoid redundant national or international travels and organizing several workshops and media programs etc. during the 2nd week of August, as the non-pharmaceutical measures, whereas the dispatching Tamiflu tablets to the affected cities, distribution of masks, providing guidelines to the hospitals on the treatment of swine flu and allowing the retail sale of Tamiflu during the late August etc. as pharmaceutical interventions. We notice that this preparedness has reduced the transmissions in Maharashtra significantly with almost 54% fall in reproduction number, estimated as 0.80 and in Pune the estimate is 0.53, lessening the 67% in transmission. Notably, in the south region, the estimates fall below 1 ($R(t) < 1$), indicating effective control over pandemic. But the second peak (Sep-Oct) of wave-1 in Maharashtra (see Figure 2) indicates the reverse picture, accounting the relatively uncontrolled rural spread of the virus.

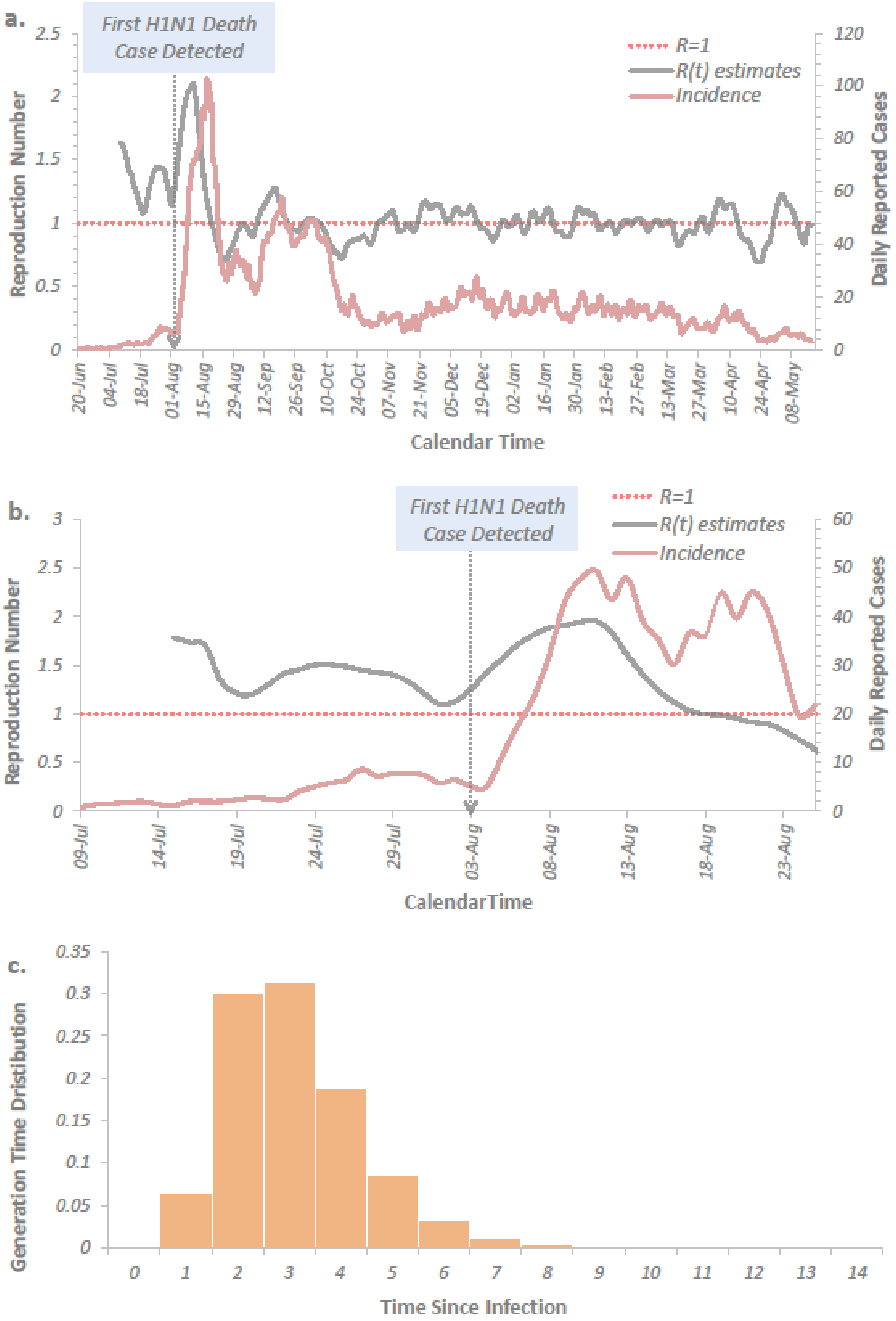

Figure 4 Estimation of real time varying instantaneous reproduction number for a. Maharashtra, b. Pune and c. generation time distribution (discretized Gamma with mean 4.2 and standard deviation 1.27) used for evaluation.

CONCLUSION

We conclude that the intensity of influenza A/H1N1 pandemic in Maharashtra was comparatively higher at initial phase and was condensed in urban areas. In the case of Maharashtra even in South region, the wave-2 is found to have less affect of the strain where as the significant burden of wave-1 has been noticed, resulting its worst situation alone. The intense preparedness through non-pharmaceutical interventions when pharmaceutical one is not even available against the strain was found to have important role in reduction of transmissibility, lessening the contact rate. Apart from the inhabitable limitation, the method under the present study has a benefit of forecasting nature on quantification of transmission dynamics, which can anticipate the pandemic situation in advance of the natural epidemic curve. This is off course an advantage to the public health researchers or professionals in designing the control strategies. One may be encouraged to characterize the likelihood and stochastic estimate of reproduction number, considering its uncertainty behaviour for the further development.

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