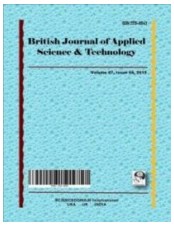

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Forecasting H1N1 Activity in India

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Authors' contributions

This work was carried out in collaboration between both authors. Authors DP and BNP designed the study, performed the statistical analysis, wrote the protocol and wrote the manuscript and managed literature searches. Both the authors read and approved the final manuscript.

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ABSTRACT

Aims: Dynamics of invariant influenza frequently defies intuition and qualitative forecasting. In view of the re-emergence of H1N1 infection in India, as well as the rise in H1N1 cases and associated fatalities in the current year (2015), quantitative forecasting of swine flu dynamics is performed here.
Methodology: Case fatality rates (CFR) are well established predictors of adverse human health outcomes, independent of overall disease status. To increase our understanding of the potential severity of outbreaks of H1N1 influenza in India, we study the pattern H1N1 infections since the outbreak of pandemic H1N1 in 2009 and derive both linear and non-linear trends for forecasting severity of infection based on CFR of H1N1 cases. Open access data available at different data bases WHO National Influenza Centre, www.who.inf/flunet; FluTrackers.com (flutrackers.com/forum/forum/india/seasonal flu-2009-2014; Press Information Bureau, Government of India, http://pib.nic.in/newsite/erelease. aspx?relid=107145; http://pib.nic.in/newsite/erelease.aspx?relid=115361) and media (http://www.tribuneindia.com/news/nat...jab/25608html), are utilised in this study. The trendline forecast were derived from Microsoft-Excel using scatter chart and trendline option.

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Results: Time series forecasting of H1N1 infection using smoothing methods reveal infection peaking during winter and rainy seasons of a year. Downward sloping polynomial curve (R^2=0.931) indicate declining trend of H1N1-infection over time. Polynomial forecasting the severity of H1N1 infection based on H1N1 case fatality rate (CFR), it is predicted to rise by ~20% in 2015 in comparison to 2014, and 30% in 2016 in comparison to 2015.
Conclusion: In the absence of effective control measures, the H1N1 fatalities are predicted to assume severe effect in the winter of 2015 and in 2016. Possibly, disproportionate control measures, loss of immunity and a possible antigenic drift in H1N1 virus underlie the re-emergence of viral onslaught in 2015 in India.

Keywords: H1N1 infection; swine-flu prediction.

1. INTRODUCTION

Swine Flu was described in the New England Journal of Medicine as Swine-origin influenza A (H1N1) virus (SOIV), differentiating it from the numerous swine viruses known to have existed in pigs for many years [1,2]. The unique feature of the novel swine flu is its ability to undergo person-to-person transmission, a feature not present in other swine viruses [1]. Transmission is thought to be via large particle respiratory droplet spread, such as coughing or sneezing [3].

Swine flu viruses do not normally infect humans; however, sporadic human infections with influenza viruses that normally infect swine have occurred. When this happens, these viruses are called “variant viruses”. H1N1 is a variant influenza virus. The 2009 pandemic influenza A (H1N1) virus, pH1N1 was first reported in India on May 16, 2009 from Hyderabad [4,5]. Globally influenza is responsible for 250,000 to 500,000 deaths annually [6]. India is seeing a rapid rise in swine flu deaths and cases this year, 2015. Between January 1 to 10 February 2015, the total number of confirmed H1N1 cases is 1025 based on WHO’s GIP records, while the number of H1N1 cases and deaths reported by the Press Information Bureau, Government of India are 5157 and 407 respectively [7]. Media reports suggest that till 18 February 2015, the variant virus has claimed about 663 lives and infected 10025 subjects in India [8]. Swine flu is now a national crisis not only because it has caused many deaths, but also because of the public attention and fears that has resulted from the uncertainty of the pandemic. As the virus is highly infectious and continues to infect and kill humans in India, a quantitative forecasting of swine flu dynamics is necessary to gauge the severity of the disease and help government implement strategies to mitigate and control the disease in the face of uncertainty. Epidemic processes are essentially stochastic in nature and proceeds by chance contacts with individuals [9]. Influenza in humans proceeds rapidly in a similar way and is the canonical example of an antigenically variable pathogen evolving rapidly in space and time. Hence, vaccines need to be updated every few years [10] and resistance to established treatments emerges regularly [11] and spreads rapidly. However, despite early progress [12,13], the representation of evolution at the global scale in a way that can be robustly tested with available data remains challenging [14]. In epidemiology, a key parameter for any novel infectious disease is the basic reproduction number (R_0), defined as the average number of secondary cases generated by a single primary case during its entire period of infectiousness in an otherwise uninfected population [15]. This metric is useful to a certain extent because it helps determine, whether or not, an infectious disease can spread through a population. It is simply a threshold value that determine whether a disease will die out (if R_0<1) or whether it may become epidemic (if R_0>1). This metric is, however, unsuitable for future forecast of a particular disease load during re-emergence of an infectious disease as the population in this situation is not completely susceptible. While forecasting tools are essential in estimating the forward prospects, no forecasting model can predict the future with complete certainty. Here we use the past numerical data on H1N1 infection and associated fatalities in India to derive both linear and non-linear trends for future infection in terms of variant H1N1 cases and case fatality rate (CFR).

2. METHODOLOGY

2.1 Source of Data

Raw data for deriving CFR of variant H1N1, available at the WHO National Influenza Centre (www.who.int/flunet),FluTrackers.com (flutrackers.com/forum/forum/india/seasonal flu-2009-2014), Press Information Bureau,

Government of India (http://pib.nic.in/newsite/erelease.aspx?relid=107145; http://pib.nic.in/newsite/erelease.aspx?relid=115361) and media (http://www.tribuneindia.com/news/nat...jab/25608html), are utilised in this study. The WHO's Global Influenza Programme (GIP) provides global standards for influenza surveillance. In addition, GIP collects and analyzes virological and epidemiological influenza surveillance data from around the world including India. The virological data entered into FluNet are critical for tracking the movement of viruses globally and interpreting the epidemiological data. The data is publically available and it is real-time. India lacks a comprehensive influenza surveillance, the study is based on WHO's GIP, FluTrackers.com and other media reports.

2.2 Estimation of CFR

The relative severity of an influenza virus has been estimated by the case fatality rate (CFR). It is expressed as the percentage of persons diagnosed as having a specified disease who die as a result of that illness within a given period. This term is most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths [16].

CFR = (Influenza death)/(Influenza cases) ×100

2.3 Statistical Analysis

Prediction of Disease severity is carried out on retrieved data from different sources by time series forecasting using the Scatter chart and trend line options. Since the data fluctuates, we performed Order 2 polynomial trendline forecast in addition to Linear forecast. The trendline forecast were derived from Microsoft-Excel with forecast level 2. The fitness of the trendline to the data is given by R^2. To determine the temporal wave of H1N1 activity since 2009 pandemic, a two period moving average trendline for the selected data is performed. The linear trendline provides a best fit straight line to display data set that increase or decrease at a steady rate. This type of trendline uses a linear equation to calculate the least squares fit for a line, y=mx + b, where m is the slope and b the intercept. Polynomial trendline applies a curved line to display fluctuating data values. To avoid hills and valleys in the data of H1N1 cases cumulative values are considered. This type of trendline uses the following equation to calculate the least squares fit through points:

$$y = b + c_1x + c_2x^2 + c_3x^3 + \ldots + c_6x^6$$

where *b* and $c_1 \ldots c_6$ are constants and x's are the dependent variables, in this case the time-series data.

3. RESULTS AND DISCUSSION

Influenza viruses belong to the family Orthomyxoviridae and have a single-stranded segmented RNA genome. These viruses are classified in to types A, B, and C on the basis of their core protein. Type A viruses are further subdivided according to their envelope glycoproteins with haemagglutinin (H) or neuraminidase (N) activity. H1N1 is influenza A virus. Ever since the first report of pandemic H1N1 (pH1N1) infection in 2009, India witnessed a high incidence of H1N1 influenza till the winter seasons of 2010-2011. However, in 2010, Centres for Disease Control and Prevention (CDC) reports that the overall flu activity due to 2009 H1N1 and seasonal influenza is low worldwide. In Asia, India remains the most active region for influenza transmission (predominantly 2009 H1N1); preliminary data suggests that the overall intensity and severity is lower than that observed during the first waves of 2009. Low levels of 2009 H1N1 activity are also being detected in several Southeast Asian countries, including Nepal and Bhutan [17]. Since the 2009 H1N1 outbreak in India, we observe that the pandemic was characterized by several distinct waves, with lower levels of activity that persisted between waves and through the end of December 2014 (Fig. 1). Each year was marked by two visible peaks corresponding to winter and monsoon season of the year. It is inferred that the H1N1 infection in India is linked to these seasons.

Despite sporadic influenza like illness in the year 2014, invariant influenza responsible for 2009 pandemic was low in India. Data retrieved from WHO on India Influenza cases from 2009 to 2014 are subjected to polynomial forecast trendline to study the severity and dimension of H1N1 case in the forthcoming years. A downward sloping polynomial trendline forecast a decreasing trend of H1N1 cases (Fig. 2). Despite monotonous increase in cumulative time series data, the quadratic curve predicts a parabola with a good fit (R^2= 0.93 and very close to 1) and a decreasing trend from 190 weeks onwards. Arguably, the cumulative time series data did not

fit a curve with increasing trend. For the same data, if we fit a linear regression curve, it shows increasing projection with a low R^2 (=0.78, not shown in the graph). Since R^2 is very close to 1, the polynomial model appears good. Data till the end of 2014 support the declining trend of H1N1 infection. With truth starring us in the face, we rule out the fitted parabola a mere coincidence. The decreasing trend of H1N1 cases from 190th week since the beginning of the pandemic, can arise due to acquiring of immunity among Indians and effective therapeutic, as well as preventive measures. However, the recent surge in H1N1 cases in 2015 is quite alarming. The quantum of H1N1 infection and associated fatalities in the first 5 weeks of year 2015 intuitively suggest that H1N1 will have severe impact ahead, though quantitative estimation of H1N1 infection kinetics is lacking. WHO data on India Influenza from January 1 – February 10, 2015 are subjected to linear and polynomial forecast trendline analysis; a steep upward trend (Fig. 3), oppose to pH1N1 trend since 2009, is observed. The polynomial trendline appears more reliable (R^2 = 0.962) than the linear forecast (R^2 = 0.695).

To validate the increasing trend of H1N1 cases in 2015, CFR measured from 2011 to 2014 based on mortality data and subjected to trendline analysis. A sharp rise in CFR in the year 2015 is indicative of susceptible health status and the absence of adequate control measure(s). It is predicted that H1N1-CFR will rise by ~20% in 2015 in comparison to 2014, and 30% in 2016 in comparison to 2015 (Fig. 4a). Notably, the acute respiratory infection induced CFR in 2015 is predicted to increase by > 2 folds (Fig. 4b). Hence, in the presence of existing control measures, the H1N1 fatalities are predicted to assume severe scenario in future.

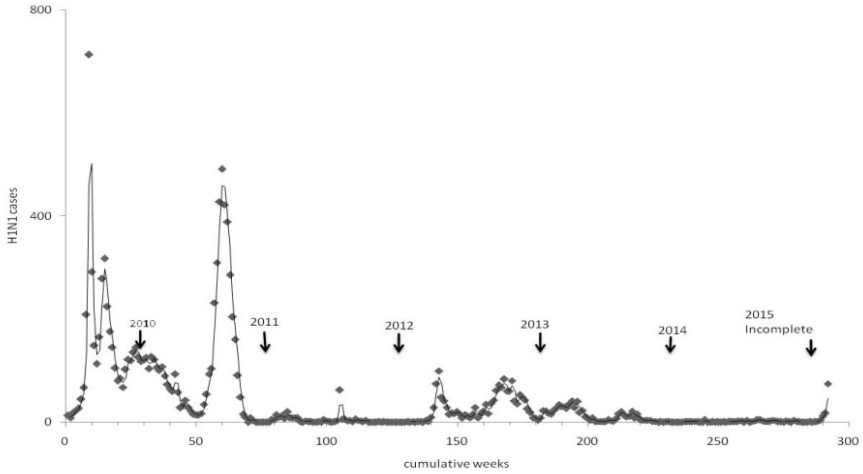

Fig. 1. A 2 point moving average trendline of H1N1 cases in India from June 2009 to first week of February 2015

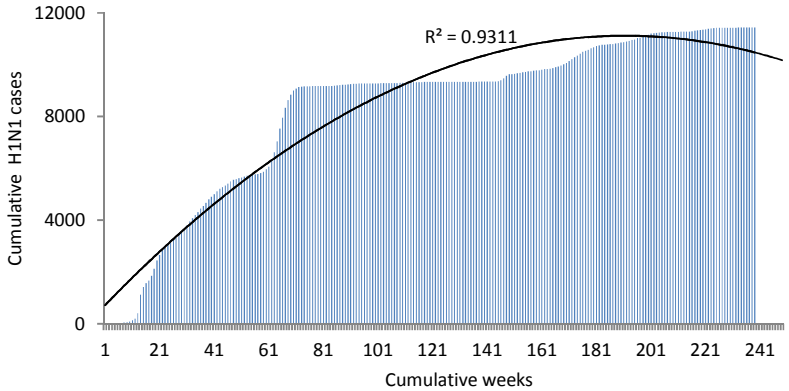

Fig. 2. Polynomial forecast trendline of H1N1 cases in India from 2009-14

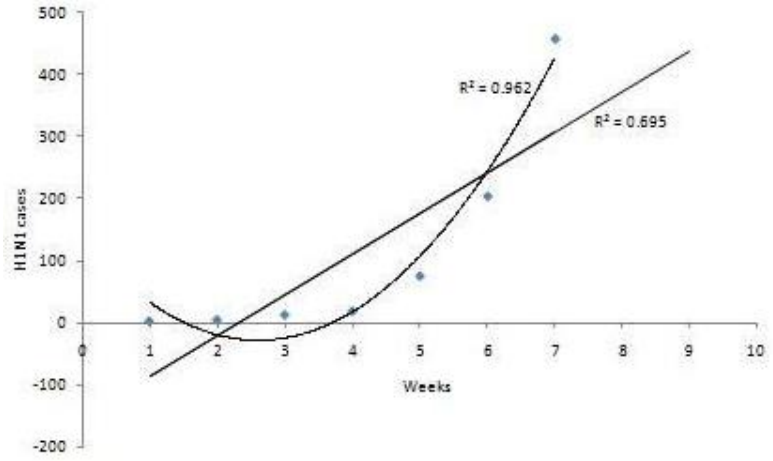

Fig. 3. Linear and polynomial forecast trendline of H1N1 cases in India in 2015

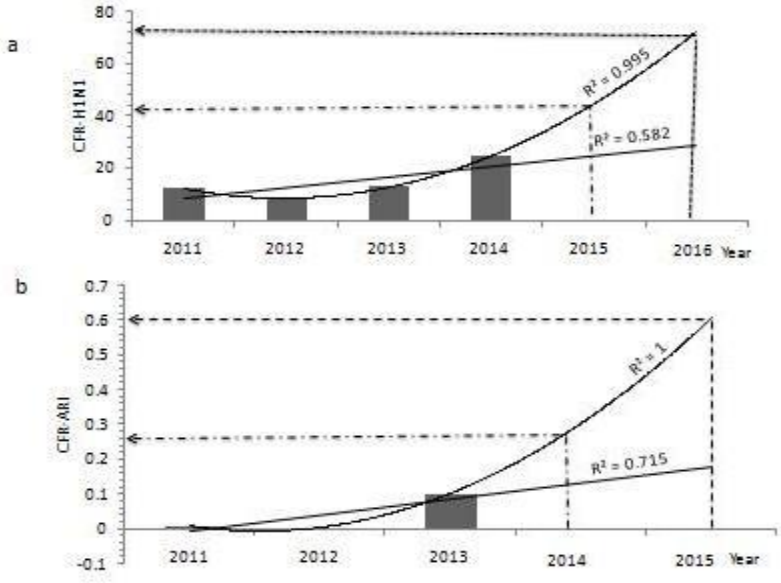

Fig. 4. Forecast of case fatality rate in India. a, H1N1 Influenza- CFR and b, acute respiratory infection induced CFR

Though it is ideal to have a polynomial fit from an infinite set of value, the present study is limited to 4 observed points only, a bare minimum according to the rule of thumb. This limitation may not make our model a true representations of reality, perhaps it provides a gross indication of useful reality. Notably, ~2233 H1N1 mortalities have been observed in the first 20 weeks of 2015 in India (www.flutrackers.com) (Fig. 5).

During the same period, 4962 H1N1 cases were observed (WHO's GIP). Hence, the derived CFR (~45) is in close approximation to predicted CFR. Despite, the use of minimum observed points, the polynomial model (Fig. 4a) seems to be a good predictor of H1N1 activity in India. Furthermore, presuming non-emergence of newer vacines against H1N1 and collateral increase in AIDS, Tuberculosis, sinusitis and respiratory disorders, as well as the virus undergoing mutation justify the extension of CFR trend to 2016. These findings raise concern over the management and containment of H1N1 epidemics in India. Statistical inference from these simple models may help nation to gauze the severity of H1N1 infection and implement tractable strategies to circumvent epidemics.

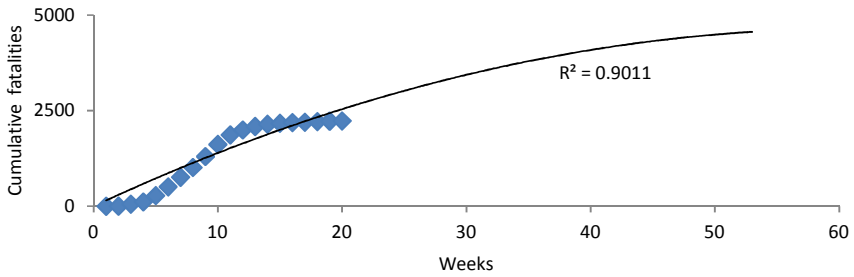

Fig. 5. Cumulative H1N1 fatalities in the first 20 weeks of 2015 (shown in blue). Black line represents polynomial forecast trendline of H1N1 fatalities in India in 2015

Seasonal epidemics caused by influenza virus are driven by antigenic changes (drift) in viral surface glycoproteins that allow evasion from pre-existing humoral immunity. Sandbulte and co-workers (2011) evaluated the antigenic evolution of different proteins in H1N1 and H3N2 viruses used in vaccine formulations during the last 15 years by analysis of hemagglutinin (H) and neuraminidase (N) inhibition titers and antigenic cartography. A discordant antigenic drift in both H and N are observed [18]. These small genetic changes can accumulate over time and result in viruses that are antigenically different and further away on the phylogenetic tree. In this situation, the body's immune system may not recognize these viruses.

Antigenic drift may also occur in response to suboptimal vaccination. In a study [19], sequential passaging of 2009 pH1N1 virus by contact transmission through two independent series of sub-optimally vaccinated ferrets result in the selection of variant viruses with an amino acid substitution (N156K, H1 numbering without signal peptide; N159K, H3 numbering without signal peptide; N173K, H1 numbering from first methionine) in a known antigenic site of the viral hemagglutinin. Thus, antigenic drift, a mechanism for variation in viruses that involves the accumulation of mutations within the genes that code for antibody-binding sites, is likely to occur in the future in response to increasing population immunity induced by vaccination. It is essential to review vaccination programme, as well as the quality of antivirals used in India. The latter assumes significance in the light of Tamiflu-resistant H1N1 reviewed elsewhere [20].

Despite comprehensive approach to forecast the impact of H1N1 infection in India, the present study depends on WHO H1N1 surveillance data, mortality data from Flutrackers.com and Press Information Bureau, Government of India; it does not take into consideration H1N1 deaths that have occurred without being recognised, and if recognised, not tested. It is to be noted that during the 2009-10 pandemic, confirmed fatalities in India represented only 2 to 3% of total fatalities. Nonetheless, it is hoped that the results of these effort will allow public health policy makers to better understand the impact of H1N1 Infection and prepare for the future events. In addition, the constant emergence of new influenza strains and the current risk of swine flu serve as warnings that influenza will remain a serious pathogen for the foreseeable future in India.

In the light of worst H1N1 resurgence in India, it is worth mentioning that practicing yoga can help improve pulmonary functions, quality of life, reduce airway hyper-reactivity and frequency of viral attacks, especially swine flu. Yogic meditations have demonstrated a significant effect on circulating immune cells, especially the lymphocyte subsets [21] and alleviate respiratory disorders [22,23]. Thus, Yoga lifestyle can supplement the existing preventive and therapeutic measures to curb H1N1 re-emergence in India.

4. CONCLUSION

In the absence of effective control measures, the H1N1 fatalities are predicted to be very severe in the winter of 2015 and in 2016. Possibly, disproportionate control measures, loss of immunity and a possible antigenic drift in H1N1 virus underlie the re-emergence viral onslaught in 2015 in India. Though not yet reported, the country is open to the emergence of Tami-flu resistant H1N1 in future.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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