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Seasonal Influenza Incidence in India: A Retrospective Study Based on Multiple Indian Hospital and Diagnostic Laboratory Centre

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The objective of the study is to understand the seasonal variation in influenza incidence across multiple Indian states by using diagnostic laboratories data of influenza.

Materials and Methods: Diagnostic laboratory-based data of subjects who were tested for influenza between 1st January April 2014 to December 2017 across seven Indian states were analysed. In diagnostic laboratories of Maharashtra, Delhi, Uttar Pradesh, Haryana, and Rajasthan RT-PCR was used for detection of H1N1 and laboratories of Tamil Nadu used GeneXpert along with RT-PCR. A total sample size of 10,755 was used in the descriptive observational retrospective study.

Results: In case of H1N1, sample population had almost equal male and female proportion (5172) with 36.5 years mean age. In majority of states, >3-5 years age group had the highest positivity rate. Paediatric age group (0-18 years) contributed 25% of total H1N1 burden, while older adults (>60 years) contributed 15% of the total sample. The yearly trends showed a higher incidence rate of H1N1 in 2015, followed by a decline during 2016 and a surge in 2017. Monthly trends showed

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consistent rise in H1N1 positivity rate during early months (January, February, and March) of 2015, 2016 and 2017. For influenza B, paediatric age group (0-18 years) showed the highest positivity rate and contributed almost 40% of total influenza 'B' burden.

Conclusion: This study highlights the importance of big data-based analytics and its use in understanding the epidemiological behaviour of diseases like influenza. Insight by leveraging laboratories data, like in the case of current research study, gives demographic patterns of influenza in terms of age, gender, seasons, and regions/states.

Keywords: Seasonal influenza; H1N1; influenza B; infectious respiratory disease.

1. INTRODUCTION

Influenza is a highly infectious respiratory disease of viral origin. Influenza virus undergoes antigenic mutation and causes periodic epidemics and pandemics. It is a single-stranded RNA virus with four antigen types: A, B, C and D [1]. Type A has subtypes determined by surface antigens Haemagglutinin (H) and neuraminidase (N). Influenza A and B cause moderate-to-severe illness and seasonal epidemics. Influenza C causes mild illness, while D does not cause disease in humans.

Influenza illness causes asymptomatic-to-severe disease. The features of disease [2] include abrupt onset of fever, myalgia, cough, headache, and sore throat etc. Pulmonary complications include pneumonia, croup, and bronchitis. Other complications include myocarditis, worsening of chronic pulmonary diseases, and Reye syndrome.

Influenza is a global public health problem, causing considerable mortality and morbidity, and incurring significant costs to nations. A systematic review [3] reported that worldwide in 2008, 90 million new cases of influenza, 20 million cases of influenza related acute lower respiratory infections (ALRI) and 1 million cases of influenza related severe ALRI occurred in children younger than five years. This study attributed 28,000-1,11,500 deaths to influenza-related ALRI in 2008, and 99% of these deaths occurred in developing countries. According to Chadha et al. [4] adjusted annual incidence of influenza hospitalizations was 46.8 of 10,000 during the pandemic in 2009, and 40.5 of 10,000 during post-pandemic period.

The annual attack rate of influenza is estimated at 5-10% in adults and 20-30% in children [5]. Worldwide annual epidemics of influenza results in 3-5 million cases of severe illness and 250,000-500,000 deaths [1].

The World Health Organization (WHO) estimated that the total annual cost of influenza is between US$1 million and US$6 million per 100,000 population.[6] Another study [7] investigating the cost of influenza in 2003 calculated US$10.4 billion annually in direct medical costs and U$16.3 billion in indirect costs, associated with lost earnings and loss of life. The total economic burden of the flu in the United States is $87.1 billion.

Surveillance is the part and parcel of any preventive strategy for influenza. There are multiple epidemiological factors, which determine the seasonal trends of influenza in any geographical area. A broader understanding of the complex relationship between influenza epidemiology and seasonal variations is essential for the planning of epidemic management and deciding on vaccination timings for influenza. India being a vast country, comprises differsent climates ranging from tropical rainy to sub-tropical humid climate and alpine climate in Himalayan states. There is a wide variation in India in terms of seasonal factors like amount of rainfall, humidity, sunlight, and temperature. Various research studies across the globe have highlighted the relation between seasons and peak in influenza activity. Seasonal factors like absolute humidity [8] affect both influenza virus transmission and its survival in the environment.

This study will provide insights into seasonal patterns of influenza in Indian cities and states in most recent time with the help of diagnostic laboratories data of influenza. Therefore, this study was set up to assess seasonal variation in the influenza incidence and analyse trends of influenza across multiple Indian states by using diagnostic laboratories data of influenza.

1.1 Objectives

Assessment of seasonal variation in the influenza incidence across multiple Indian states by using diagnostic laboratories data of influenza.

To analyse trends of influenza, across age, gender, and states in India.

2. METHODS

To study the seasonal variation in influenza from retrospective diagnostic laboratories data. The methodology was adapted from the existing US influenza surveillance system that includes both public health and clinical laboratories [9]. The surveillance system reports variables such as total number of respiratory specimens tested for influenza, number positive for influenza by virus type (A and B), and age of the persons from whom the specimens were collected.

2.1 Study Design

This retrospective and observational study was designed to understand the seasonal variation in the incidence of influenza by using diagnostic laboratories data. The Technology Healthcare and Big data analytics (THB) is a digital healthcare company and provides an information technology support for patient engagement. The THB has created a multi centric influenza surveillance system by collaborating with multiple diagnostic laboratories across India. The data has been collected from multiple laboratories across various Indian states.

2.2 Sampling and Sample Population

The study included all subjects who got tested for influenza (H1N1 and B) in multiple diagnostic laboratories between April 2014 to December 2017 across major Indian cities in states of Maharashtra, Uttar Pradesh, Tamil Nadu, Uttarakhand, Delhi, Haryana, and Rajasthan. The overall sample size was 10755, with a female proportion of 48.1%. These diagnostic laboratories were situated in major cities including Mumbai, Navi Mumbai, Thane, and Pune in Maharashtra, Noida in Uttar Pradesh, Dehradun in Uttarakhand, Chennai in Tamil Nadu, and Jaipur in Rajasthan.

2.3 Diagnostic Tests

The GeneXpert (Cepheid Xpert® Flu) and RT-PCR were used for H1N1 detection in diagnostic laboratories of Tamil Nadu for different samples. Whereas, Maharashtra, Delhi, Uttar Pradesh, Haryana, and Rajasthan laboratories used RT-PCR only. Total samples 10,755 were tested for H1N1, while out of these 5310 samples were also tested for influenza type B.

2.4 Statistical Analysis

We used big data technology to extract and transform data and finally to create a master data repository. Data analysis was done by using MS Excel and R. Monthly positive rates were calculated as the proportion of positive cases out of total laboratories test done for influenza in that month. Positivity rates were plotted across age, sex, and states. An overall burden in different categories had been estimated by calculating percentage contribution in total incidence burden of influenza.

3. RESULTS

The total sample size was 10,755 with 48.1% female proportion. The biggest proportion of sample population was from Maharashtra (60.3%), followed by Delhi (20.4%) and Tamil Nadu (10.9%), as shown in Table 1.

Table 1. Descriptive statistics of sample population

Variables	Values
Total sample population	10,755
Sample population - Influenza B	5,310
Mean age (years)	36.5
Standard deviation	24.0
Age range (years)	<1 year – 100
Female proportion	5172 (48.1%)
Time interval	April 2014 – December 2017
State wise sample mix	Maharashtra: 6483 (60.3%)
	Delhi: 2,192 (20.4%)
	Tamil Nadu: 1,169 (10.9%)
	Uttar Pradesh (UP) / Uttarakhand (UK): 558 (5.2%)
	Haryana: 313 (2.9%)
	Rajasthan: 40 (0.4%)

Table 2. Region and state-wise positivity of influenza (H1N1 and B)

Zone	States	H1N1 tests done	H1N1 positive	Percent positivity	Influenza B test done	Influenza B positive	Percent Positivity
South	Tamil Nadu	1169	112	9.6	79	0	0
West	Maharashtra	6483	894	13.8	5044	119	2.36
North	New Delhi	2192	434	19.8	187	0	0
	Rajasthan	40	8	20.0	-	-	-
	UP / UK	558	100	17.9	-	-	-
	Haryana	313	49	15.7	-	-	-
	Total	**10755**	**1597**	**14.8**	**5310**	**119**	**2.24**

3.1 Positivity Rate and Burden of Influenza (H1n1 and B)

The Table 2 shows the positivity rate of H1N1 and influenza type B across seven states. In Delhi, 2192 samples tested for H1N1 and 19.8% were found to be positive but no sample was found positive for type 'B', out of 187 samples tested.

Table 3 shows H1N1 positivity rate across states and age categories. In the paediatric population, >3-5 years age group had the highest positivity rate in most of the states. Haryana and Maharashtra showed very high positivity rate in >30-50 years age category along with >3-5 years age category. The paediatric age group (0-18 years) contributed 25% of the total H1N1 burden, while population above 60 years contributed 15% (Table 3). The adults aged 30-50 years were the major contributor (almost one third) of the total H1N1 burden.

In 0-5 year age group, positivity was the highest among children between 3 to 5 years of age (Fig. 1).

Females showed a slightly higher positivity rate for H1N1 and slightly lower for influenza 'B', although the gender-wise differences were not statistically significant (Table 4).

The incidence rate of H1N1 was high in 2015, followed by a dip during 2016 and a rise again in 2017 (Fig. 2). On the contrary, incidence rate of Influenza 'B' peaked during 2016 and shown a dip in 2015 and 2017. Other states also showed a similar decline in the number of reported H1N1 cases in 2016.

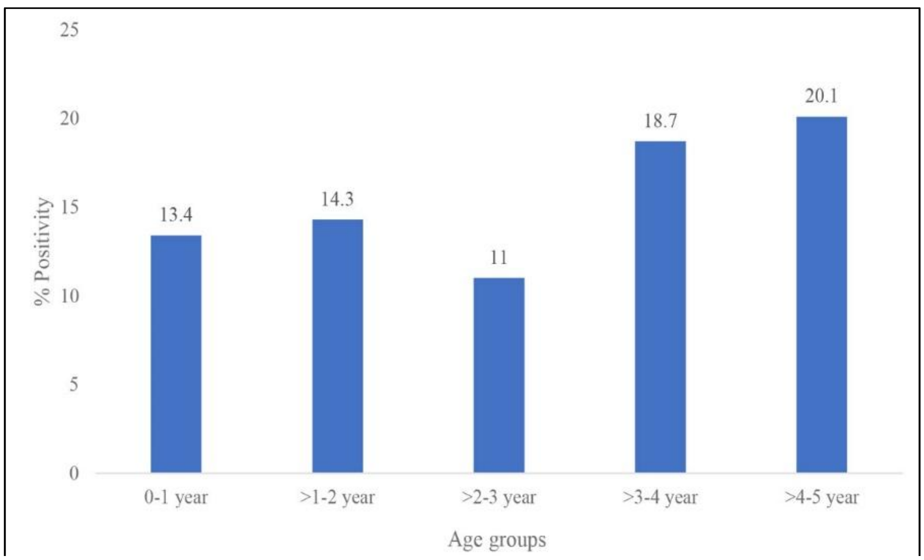


Fig. 1. Positivity rates of H1N1 among children (0-5 years)

Table 3. H1N1 positivity across age categories and states

Age category (Years)	New Delhi (%)	UP / UK* (%)	Haryana (%)	Rajasthan (%)	Maharashtra (%)	Tamil Nadu (%)
0-3	27.1	17.6	21.4	50.0	11.0	9.9
>3-5	43.6	33.3	25.0	-	16.1	13.4
>5-18	19.9	16.7	0.0	0	10.4	8.3
>18 - 30	18.2	21.3	21.6	16.7	12.6	6.9
>30 -50	24.1	20.6	26.5	50.0	17.8	9.8
>50 -60	20.7	25.9	18.9	9.1	16.9	12.2
>60-70	13.9	14.0	10.6	20.0	13.0	9.8
>70	14.4	7.3	7.0	0	7.6	9.9

UP / UK – Uttar Pradesh / Uttarakhand*

Table 4. Gender-wise positivity rate

Gender	H1N1 - Samples tested percent positivity	Influenza 'B' - Samples tested percent positivity
Male	5584 (14.6)	2714 (2.4)
Female	5171 (15.1)	2596 (2.0)
Total	**10755 (14.8)**	**5130 (2.2)**

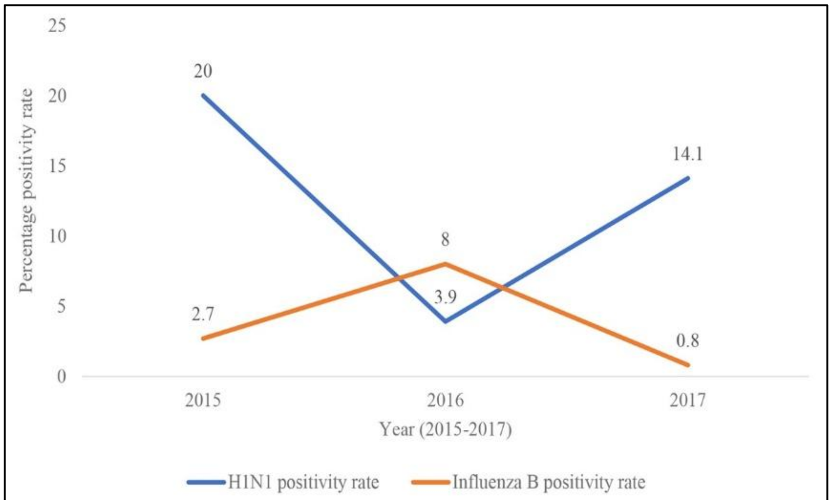


Fig. 2. Yearly trend of HINI and Influenza B (2014-2017)

The monthly trend showed a consistent rise in H1N1 positivity rate during early months (January, February, and March) of 2015, 2016 and 2017 (Fig 3). The positivity rate started declining from April onwards, followed by a second peak during monsoon months (June, July, and August), and then a subsequent drop in post-monsoon months (October and November).

The North Indian (Delhi, Haryana, Uttar Pradesh, Uttarakhand, and Rajasthan) states showed a peak between January and March, followed by a slope during summer months (Fig. 4 a). The 2015 data showed a second peak starting from October (post-monsoon), which sustained during the winter season (January and February 2016). The year 2017 showed a second peak during the monsoon season (June, July, and August). There was no peak reported during monsoon season of 2016. In contrast to North India, West India (comprising of Maharashtra) showed prominent peaks primarily during the monsoon season (Fig. 4 b).

The Fig. 4 c depicts that Tamil Nadu had high peaks of H1N1 during February and March, and comparatively smaller peaks during September and October which are rainy season in Tamil Nadu.

The Fig. 5 further shows that there was a marked difference in timings of peaks for H1N1 across different regions, i.e., winter and monsoon in north India, monsoon in West India, and early summer in South India.

3.2 Influenza 'B' Epidemiology

The analysis of 5310 samples showed overall Influenza 'B' positivity rate as 2.24%. In Delhi (Table 2), there was not a single positive case reported, out of 187 samples tested. These 5310 cases were tested for Influenza B and H1N1 as well. Out of total positive cases (1058), 88.75% (939) were positive for H1N1 while 11.25% (119) for Influenza B.

The paediatric age group (0-18 years) showed the highest positivity rate (7.52%) for Influenza B (shown in Table 5). Paediatric age group (0-18 years) contributed almost 40% of total influenza 'B' burden (Fig. 6).

Young (18-30 years) and middle-aged (30-50 years) adults together reported ~45% of positive cases. In comparison to these categories, older adults and geriatric population showed less influenza 'B' infection. Adults showed a consistent decline in positivity rate with age.

The Fig. 7 showed seasonal variations of H1N1 and Influenza B incidence. The H1N1 showed peaks from January to March (winter), and June to September (monsoon). Influenza 'B' positivity rate showed a peak during post-monsoon months (October and November).

4. DISCUSSION

Influenza is a complex disease because of its dynamic patterns and ever-evolving capacity to affect humans. Close monitoring of patterns of influenza is essential to prevent it. Diagnostic laboratories can be a great platform in building real-time surveillance and help in understanding regional epidemiological differences across India. Our study also demonstrates that diagnostic laboratories data can be used not only to understand seasonal variation of influenza but to know populations which are at more risk. A detailed understanding of seasonal variation can help in ascertaining timings of influenza vaccination.

A research study [10] on surveillance report from Puducherry, estimated H1N1 positivity rate as 12.7% for the period of 2009-2013 among patients with influenza-like illness. In our study positivity rate for H1N1 in Tamil Nadu was 9.6%. In our study, Haryana and Maharashtra showed very high positivity rate in >30-50 and >3-5 years age category. A population-based surveillance study [11] in a rural community

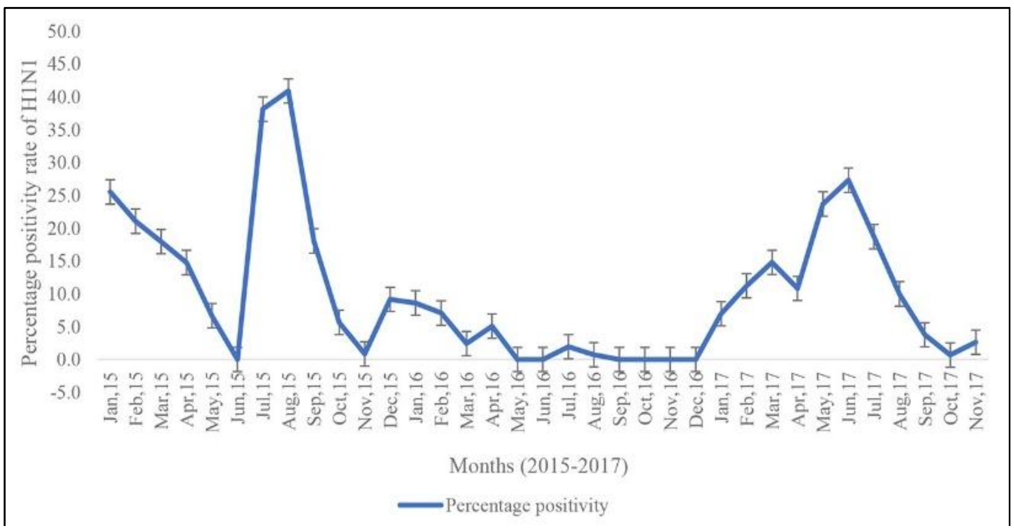
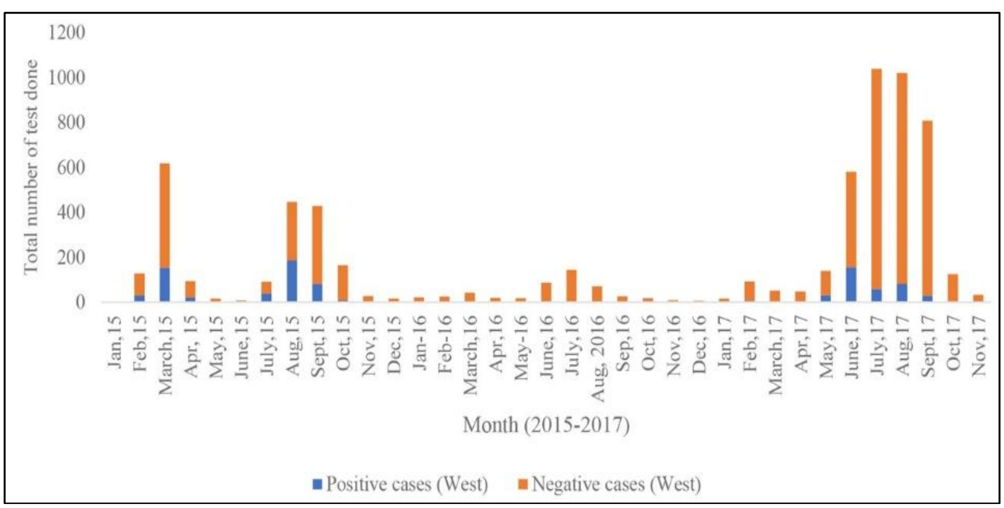
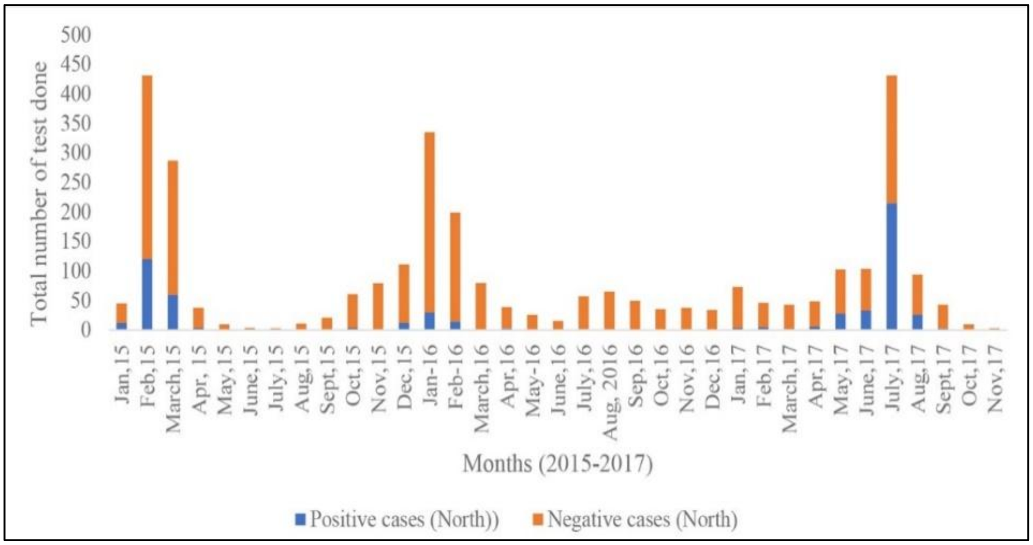


Fig. 3. Monthly positivity rate of H1N1 from 2015-2017 (collectively for all six states)



(a)



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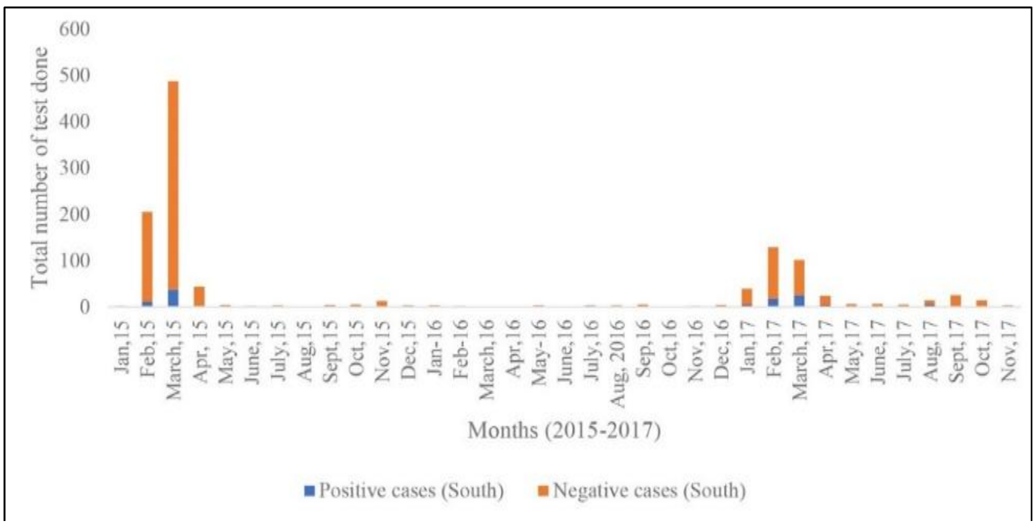

C)

Fig. 4. Seasonal patterns of H1N1 (2015-2017) in a) Northern India, b) Maharashtra, and c) Tamil Nadu

of Ballabgarh in Haryana, gives insight into seasonality, age distribution, and magnitude of the influenza post 2009 pandemic. This study highlighted the highest positivity rate among under 5 years children. The same surveillance study found distinct peaks of influenza during November – December of 2009 (winter season) and August – October of 2010 (post-monsoon).

Our study also reported the highest positivity rate in 3-5 years age category. A study [12] conducted in Saurashtra showed highest proportional burden (38.7% of total H1N1 case burden) attributed by adults. The incidence rate of H1N1 was high in 2015 and 2017 and a drop during 2016. Whereas, incidence rate of Influenza 'B' peaked during 2016 and shown a dip in 2015 and 2017. The integrated disease surveillance program (IDSP) reports [13] showed a similar annual trend of H1N1 in Delhi and other states. As per the IDSP reports, Delhi reported 4307 cases of H1N1 in 2015, 2835 cases in 2017 but only 193 cases in 2016. IDSP reports for the period of 2015-2017 report high burden of influenza disease across other states, like Gujarat, Karnataka, Madhya Pradesh, and Telangana. In our study, no peak was reported during monsoon season of 2016. The IDSP reports also show a fewer number of cases during 2016.

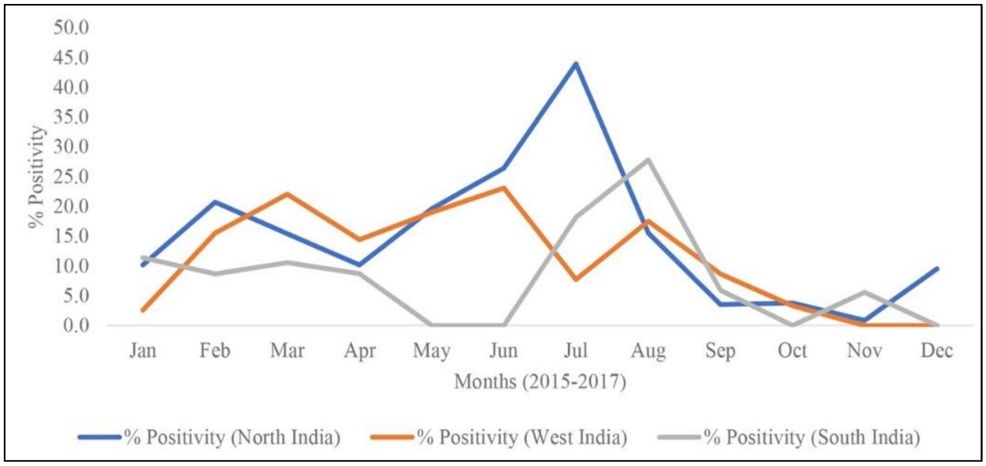

Fig. 5. The monthly positivity rate of H1N1 across Indian regions

Table 5. Age-wise Influenza 'B' positivity rate

Age category (years)	Test done 'B'	Total positive	Percent positivity
0-3	657	6	0.91
>3- 5	267	8	2.99
>5-18	885	32	3.62
>18- 30	862	23	2.67
>30- 50	1423	29	2.04
>50- 60	556	11	1.98
>60 -70	402	7	1.74
>70	258	3	1.16
Total	**5310**	**119**	**2.24**

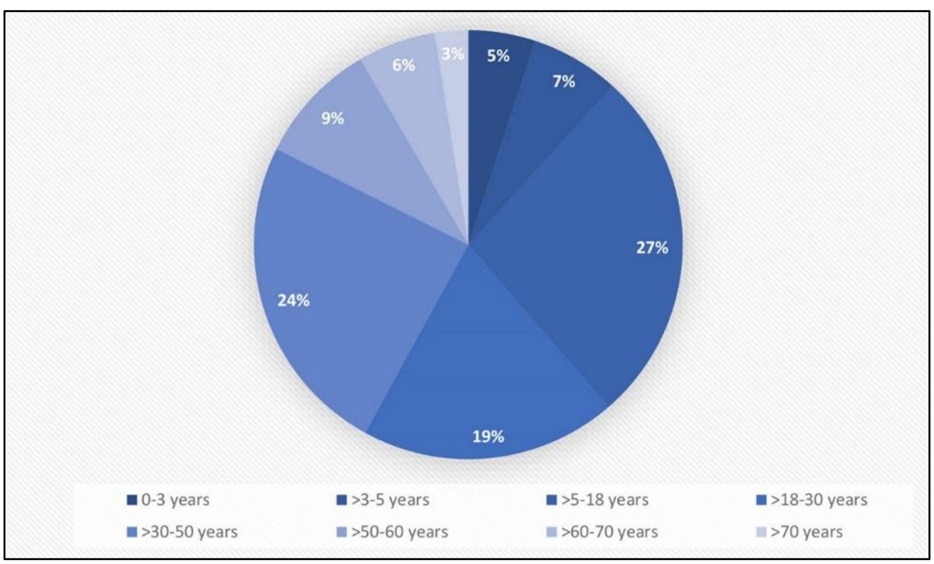

Fig. 6. The burden of influenza B across age categories

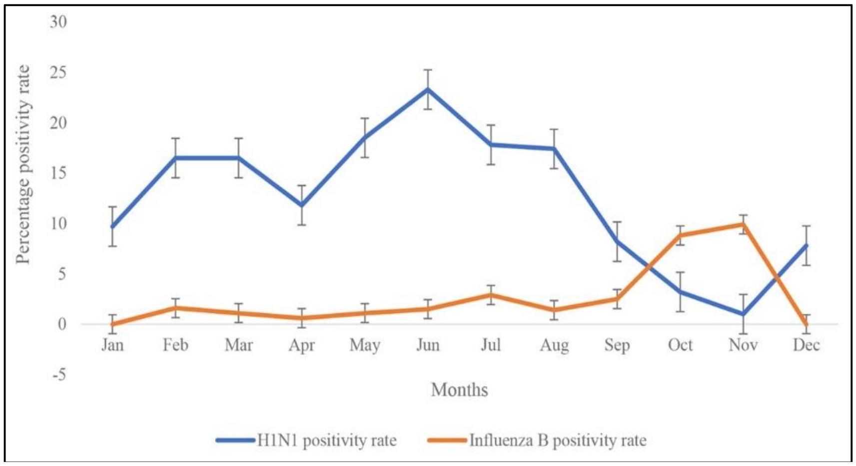

Fig. 7. Percentage positivity for different strains of influenza across months

Our study reported positivity rate of Influenza 'B' as 2.24%. In Delhi, there was not a single positive case reported, out of 187 samples tested. A North Indian community-based surveillance for febrile acute respiratory infection (FARI),[14] estimated 17% positivity for influenza, and out of total positive cases, 45% were found to have influenza 'B'.

Similar to this study, a study by Chadha MS et al*.,* [15] demonstrates seasonal variation at sub-regional level in India. Though both studies represent different time periods. This study showed peak activity of influenza in Delhi (2009-2013) and Lucknow (2011-2013) during July to September, November to December in Chennai and Vellore and July to August in Nagpur and Pune. Our study (2014-2017) showed higher influenza activity during winter months of 2015 and 2016, while in 2017, incidence rate was higher from May to August in North Indian cities. In Chennai, our study showed a peak during February and March and in Mumbai June to August.

Another study by Kaul [16], showed a peak of Influenza activity from July to September. Tamerius et al*.,* [17] found in his study that humidity, temperature, and precipitation thresholds affect the transmission of influenza. Indian weather varies annually in context of amount of rainfall, humidity and temperature and these variations are plausible explanation for annual variation in timings and extent of influenza transmission.

Our study found peak activity of influenza B and H1N1 has wide variation. Influenza B peaked in later months of the Year (October and November) when H1N1 activity was at lowest. A yearly trend also demonstrates same as in 2016, It was the highest activity for B while the lowest for H1N1. The highest burden of influenza B was found among paediatric age category. An Australian study [18] has shown similar findings. Though in Indian context relation between H1N1 and type B influenza epidemiology need to explore further.

Wide variation in seasonal factors in India demands an extensive surveillance network. Local and sub-regional level insights into epidemiological trends of influenza will be helpful in formulating preventive strategies like timely vaccination.

6. CONCLUSION

Influenza shows enormous seasonal variation across geographical areas, as well as across years. This makes lab-based surveillance a critical need to timely detect and predict patterns. This study gives insight into patterns of influenza across age, gender, seasons, and regions/states, leveraging laboratories data. Our study shows a marked difference in seasonal patterns across north, south, and west India and this enforces need of region-wise evidence-based strategies. While higher positivity rate among children (3-5 years age group) suggest the need for timely vaccination among children, other age groups also show positive cases and therefore need proactive and comprehensive prevention measures.

5. LIMITATION

This is a lab-based study and information on the clinical-profile of patients is not available and it is not possible to ascertain symptoms and signs for which they were screened for influenza. As these diagnostic laboratories are situated in large and major or capital cities, it is possible that representation of populations living in peripheral areas might be inadequate. Sample size from Rajasthan was very small.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The confidentiality of subjects had been maintained by de-identifying personal information, and anonymised data had been used in-line with the EHR standards of India [10] defined by the Ministry of Health and Family Welfare (MOHFW). Ethical approval for the study had been taken from the Max Healthcare Ethics Committee (MHEC), New Delhi with reference number RS/MSSH/MHIL/SKT-1/MHEC/CD/18-17.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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