

# Epidemiological Surveillance To Establish Thresholds For Influenza Among Children In Satellite Cities Of A metropolitan area of Tokyo, Japan

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## Research Article

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# Abstract

**Background:** Few reports have longitudinally investigated seasonal influenza epidemiological surveillance data of pediatric populations in the metropolitan areas of Japan. We aimed to provide descriptive characteristics of circulating influenza and to investigate the usefulness of setting thresholds for influenza in children (0–15 years old) in two satellite cities of a metropolitan area of Tokyo, Japan, for five consecutive seasons of the influenza epidemic.

**Methods:** The survey was conducted annually during the influenza season, from 2014 to 2018 (ending March 2019), at preschools (kindergartens and nursery schools), elementary schools, and junior high schools located in Toda and Warabi cities, Saitama prefecture. We investigated the epidemiological characteristics and established thresholds using the World Health Organization method.

**Results:** Of the 108,362 children (21,024 to 22,088 throughout five seasons) who received the questionnaire, 76,753 (70.8%; 14,652 to 15,808) responded. After exclusion of responses without basic information, 64,586 children were included in the analysis, of which 13,754 (21.3%) had tested positive for influenza. Influenza type A was generally dominant, whereas type B was responsible for a substantial share of all influenza cases (>40% in seasons 2015 and 2017, when type A circulated with low incidence). The weeks when the influenza epidemic peaked had no clear seasonal pattern among the surveyed years, i.e., the peaks appeared at week 51 (mid-December) or later, whereas the World Health Organization methods reported that the median period when a peak was observed was at 3 weeks (mid-January), regardless of school age group.

**Conclusions:** The present information obtained from the epidemiological survey regarding seasonal influenza in children would be useful for general practitioners, health policymakers, and planners who establish prevention and control methods against influenza.

## Background

The World Health Organization (WHO) estimated that annual epidemics cause 3 to 5 million influenza cases with severe illness worldwide [1]. The epidemiology of influenza changes markedly each year and from location to location [2]. In general, approximately 80% of influenza cases are caused by influenza type A, whereas influenza type B accounts for approximately 20% of the total global cases [3]. When considering the threat of influenza, school children are the primary vulnerable population, because they have the highest rates of influenza transmission and infection among infected populations [4]. In the Asia-Pacific region, influenza type B appeared to cause more illness in children between ages of 1 and 10 years than in other age groups [5]. Although surveillance data of influenza have been reported in various forms for populations across Japan [6–8], studies that investigated seasonal influenza among school children from the capital city of Japan, Tokyo, the most populous metropolitan area of the country, are scanty.

A variety of thresholds for the influenza epidemic has been proposed [9–12]. These include the WHO global standards for the collection, reporting, and analysis of seasonal influenza epidemiological surveillance data [9]. The WHO further recommends obtaining average epidemic curves and seasonal and alert thresholds as established tools to help control annual influenza epidemics [9]. Thresholds using the WHO methods are simple to implement and can be adapted easily for any influenza surveillance system with adequate historical data [13]. In some countries, the WHO method can be utilized to inform key decision makers in the areas of public health regarding influenza outbreak management [14–16]. Based on our recent surveillance, data of children (from preschool to junior high school age) during five consecutive influenza seasons in two satellite cities of the metropolitan area of Tokyo, Japan, we aimed to provide descriptive characteristics on circulating influenza and to investigate the usefulness of establishing thresholds for the influenza epidemic.

## Methods

### Study area

The study area comprised two cities, Toda and Warabi, which are located to the north of Tokyo, Japan. The study region was 23.3 km<sup>2</sup> (Toda: 18.2 km<sup>2</sup> and Warabi, 5.1 km<sup>2</sup>) and had a population of 208,410 (Toda: 136,150 and Warabi: 72,260), including a young population of 28,056 0- to 14-year-olds (Toda: 20,252 and Warabi: 7,804) in the 2015 census [17].

### Study procedure

Throughout five consecutive seasons, from 2014 to 2018 (ending March 2019), an annual survey was conducted of parents of children who were attending preschool (kindergarten or nursery school), elementary school, and junior high school in the Toda and Warabi regions. The questionnaire obtained parent responses about the following information regarding their children: school, sex, sibling, underlying disease, vaccination, and number of children with influenza by type. In clinical practice in Japan, the type of influenza (types A or B) is typically diagnosed by the children's local doctor or an emergency outpatient healthcare provider who administers an influenza antigen rapid test kit covered by the health insurance. The survey was conducted every June, and the responses pertained to the preceding season.

### Statistical analysis

We demonstrated the number of children, percentage of influenza cases by type, week of influenza epidemic peak by influenza type for each season; and seasonal, average, and alert thresholds of influenza. Data were also distributed by school group (preschool, 0–6 years old; elementary school, 7–12 years old; junior high school, 13–15 years old; in Japan, no repeat school year system has been applied for these school children). In the present analysis, we defined each influenza season as beginning in October of the start year and ending in March of the succeeding year; e.g., the 2014 season began in

October 2014 and ended in March 2015. The epidemic peak was defined for each influenza type as the week with the highest number of detected influenza cases.

According to the WHO protocol [9], we calculated the average and upper limit of 90% confidence interval curves and the seasonal, high, and alert thresholds based on the number of children with influenza each week throughout the five seasons. The average curves denote the peak weekly mean, and the 90% upper curve was for the upper limits of the 90% confidence intervals (CI) of the peak weekly mean [9, 13]. For these curves, the WHO protocol suggests utilizing the normal distribution to assign thresholds based on the mean and standard deviation of the aligned data for weekly counts [9]. The seasonal threshold was defined as the annual median amplitude of the number of children with influenza per week throughout the study period; therefore, half of the study weeks are necessarily above the seasonal threshold and these correspond to the seasonality in the influenza epidemic (e.g., from week 40 of 2014 to week 13 of 2015). The high threshold was defined as number of children with influenza higher than the average peak for each of the five seasons, i.e., the peak number of children with influenza of the average epidemic curves. Theoretically, we can expect that seasonal peaks can be over the high threshold in two or three of the five seasons. Finally, we defined the alert threshold as extraordinarily severe seasons, such as a pandemic [9, 13, 15] derived from the upper limits of the 90% CI of the high threshold defined as above. Data for the total number of children studied and for each school group from week 40 of 2014 to week 13 of 2019 were plotted against the calculated seasonal, high, and alert thresholds. We analyzed data using Stata version 16.0 (Stata Corp., College Station, TX, USA).

## Results

A total of 76,753 responses were collected using the survey conducted via post mail for 108,362 parents of children attending preschool, elementary school, or junior high school during the 2014 to 2018 seasons (the collection rate for the questionnaire was 70.8%). We excluded respondents who did not answer basic information ( $n = 4,445$ ) and had influenza vaccination before September 30 or incidence of influenza after April 1 for each season ( $n = 7,722$ ) [18]. The present analysis, therefore, consisted of 64,586 respondents (Fig. 1).

### **The prevalence of children with influenza and their distribution by influenza type**

The total number of children who were reported to have been infected with influenza was 13,754 (21.3% of the analyzed respondents; Table 1). With respect to the defined influenza season, the numbers in seasons 2014 to 2018 were 2,793 (influenza type A, 80.2%; influenza type B, 11.6%) in 2014; 2,594 (A, 45.7%; B, 43.7%) in 2015; 2,770 (A, 71.6%; B, 17.9%) in 2016; 3,070 (A, 28.7%; B, 45.9%) in 2017; and 2,527 (A, 84.3%; B, 6.6%) in 2018. Table 2 presents the relevant data for each school group. The proportion of type A influenza according to school group ranged from 70–85% in 2014, 2016, and 2019, and the proportion of type B influenza ranged from 38–55% in 2015 and 2017.

Table 1  
Number of children with influenza in 2014 to 2018 seasons

Season	Cases (%) / Total No. of Children	Type of Influenza (%)			Week of Epidemic Peaks		
		Type A	Type B	Unknown	All	Type A	Type B
2014	2,793 (20.0) / 13,961	80.2	11.6	8.2	51	51	51
2015	2,594 (21.6) / 12,020	45.7	43.7	10.6	6	5	9
2016	2,770 (22.0) / 12,616	71.6	17.9	10.5	51	51	12
2017	3,070 (24.0) / 12,783	28.7	45.9	25.4	3	3	5
2018	2,527 (19.1) / 13,206	84.3	6.6	9.1	3	3	3
Total	13,754 (21.3) / 64,586	61.2	25.7	13.1	N/A	N/A	N/A

We defined each influenza season as beginning in October of the start year and ending in March of the succeeding year; e.g., the 2014 season was from October 2014 to March 2015. The type of influenza was based on the questionnaire that usually reflected the results of the influenza antigen rapid test kit (details are described in the methods section)..

Table 2  
Number of children with influenza by school groups in 2014 to 2018 seasons

School Group	Cases (%) / Total  No. of Children	Type of Influenza (%)			Week of Epidemic Peaks		
		Type A	Type B	Unknown	All	Type A	Type B
Preschool							
2014	659 (17.3) / 3,809	79.2	11.1	9.7	2	2	7
2015	614 (18.5) / 3,321	48.4	41.0	10.6	5	5	7
2016	688 (20.5) / 3,348	70.8	17.3	11.9	3	5	12
2017	701 (20.2) / 3,472	37.8	42.9	19.3	5	2	5
2018	600 (18.1) / 3,310	85.3	7.0	7.7	2	2	3
Subtotal	3,262 (18.9) / 17,260	63.9	24.1	12.0	N/A	N/A	N/A
Elementary school							
2014	1,567 (21.6) / 7,269	80.6	11.5	7.9	51	51	51
2015	1,672 (25.9) / 6,445	45.9	42.6	11.5	6	6	9
2016	1,503 (22.1) / 6,793	71.1	19.0	9.8	3	51	12
2017	1,905 (28.0) / 6,807	28.7	49.0	22.3	3	51	5
2018	1,539 (20.1) / 7,652	83.6	6.4	10.0	3	3	3
Subtotal	8,186 (23.4) / 34,966	60.2	27.0	12.8	N/A	N/A	N/A
Junior high school							

School groups and age ranges are as follows: preschool, 0–6 years old; elementary school, 7–12 years old; junior high school, 13–15 years old.

		Type of Influenza (%)			Week of Epidemic Peaks		
		A	B	C	A	B	C
2014	567 (19.7) / 2,883	80.4	12.5	7.1	51	51	51
2015	308 (13.7) / 2,254	39.3	55.2	5.5	7	5	10
2016	579 (23.4) / 2,475	73.6	15.7	10.7	51	51	12
2017	464 (18.5) / 2,504	15.1	37.5	47.4	3	51	52
2018	388 (17.3) / 2,244	85.6	6.7	7.7	3	3	3
Subtotal	2,306 (18.7)/ 12,360	60.9	23.1	16.0	N/A	N/A	N/A
School groups and age ranges are as follows: preschool, 0–6 years old; elementary school, 7–12 years old; junior high school, 13–15 years old.							

### The week of the influenza epidemic peak by influenza type

As presented in Table 1, the epidemical peaks occurred earlier in 2014 and 2016 (week 51) than in 2015 (week 6), 2017 (week 3), and 2019 (week 3). The epidemical peaks of type B influenza occurred later than those of type A in 2015, 2016, and 2017. In school groups (Table 2), the epidemical peaks of preschool occurred later than those in other groups in 2014, 2016, and 2017.

### Curves and thresholds by the WHO methods

The thresholds from the WHO method are summarized in Table 3. Peak median number of children with influenza was similar to the corresponding peak mean number. The average epidemic curve determined by the weekly mean and the upper 90% CI threshold determined by the weekly upper 90% CI curve are presented in Figs. 2 and 3, respectively. The median week of the peak was observed at week 3 (mid-January; Table 3 and Figs. 2 and 3). The plotted curve of number of children with influenza crossed the seasonal threshold multiple times regardless of the five seasons. The start of the influenza season was between week 43 and week 1 (late October and early January), and the end of the influenza season was between week 8 and week 13 (late February and late March). The peak seasonal influenza activities in 2015, 2016, and 2017 did not reach high thresholds (Fig. 4). The peak seasonal influenza activity varied when children with influenza was stratified according to their school groups, as illustrated in Fig. 5. In none of the five seasons did the plotted curve of the influenza incidence cross the alert threshold (Fig. 4). The results were almost confirmatory when classified by school group, except for the junior high school group during the 2014 season, in which number of children with influenza was close to the alert threshold (Fig. 5).

Table 3  
Epidemic curve and seasonal high and alert thresholds of the influenza season

Variables	School Groups			
	Total	Preschool	Elementary School	Junior High School
Average and peak epidemic curve				
Median week of peak occurrence (week)	3	3	3	3
Peak median number of influenza cases	460	107	299	97
Peak mean number of influenza cases	468.2	103.2	279.4	98.4
Standard deviation	84.2	21.9	63.9	45.5
Upper 90% confidence intervals	606.7	139.2	384.5	173.2
Upper 95% confidence intervals	633.2	146.1	404.6	187.6
Three threshold levels				
Seasonal threshold	38	9	21	6
High threshold	468	103	279	98
Alert threshold	606	139	384	173
Definitions of the thresholds are described in the methods section. Values are the number of children with influenza per week unless otherwise stated. Peak median and mean numbers are calculated based on the average values of five seasons.				

## Discussion

We presented data on the circulation of influenza in children who were attending preschool, elementary school, or junior high school in Toda or Warabi, Japan, during five consecutive influenza seasons from 2014 to 2018. We also successfully established seasonal, high, and alert thresholds based on surveillance data from five consecutive seasons of influenza using the WHO method.

### Number of children with influenza and their distribution by influenza type

In Japan, the governmental agency (Ministry of Health, Labour, and Welfare) in collaboration with the National Institute of Infectious Diseases (NIID) provides a weekly influenza outbreak report [19]. This report is based on a school surveillance in which the absence of children and temporary closure of schools are recorded; therefore, the date of onset of influenza cannot be assessed. Nonetheless, the total number of temporary school closures peaked in 2017, which supports our findings that the greatest

number of influenza cases occurred in 2017. In junior high school children, our survey was different from the national report [19], i.e., the greatest prevalence of influenza cases were reported in 2016 (23.4%; Table 2). In our survey, influenza type B was responsible for a substantial share of all influenza cases, approximately > 40% in seasons where influenza type A circulated with low incidence in 2015 and 2017 (Table 1). The results of our survey are essentially similar to the outbreak trend summary of influenza for each season, as reported by NIID of Japan [19], whereas the prevalence of influenza type B among children in junior high school was approximately > 50% in 2015 (Table 2). Outbreaks differed by region, even within a single country, and surveillance in a local area of the present study was demanded.

### **Week of the influenza epidemic peak**

In the national report [19], each peak of temporary suspension of facilities occurred in weeks 4, 7, 4, 5, and 4 in the 2014, 2015, 2016, 2017, and 2018 seasons, respectively. The week of the influenza epidemic peak in our survey occurred consistently earlier than that in the national report, although the gross tendency was similar. Our survey was different from the national report [19], which was based on the dates of absence from school in children with influenza, and it is likely that the week with the highest number of detected influenza cases preceded the week of temporary school closures. Regional characteristics such as metropolitan area versus nationwide data [19] might affect the peak shift; however, relevant report has been lacking and we cannot say much about this difference.

The peaks of influenza type B occurred later than those of type A (Tables 1 and 2). The epidemic order is in accord with that observed in the northern hemisphere [20]. Understanding the geographical and temporal patterns of seasonal influenza could help strengthen influenza surveillance for the early detection of epidemics [21]. As Mosnier and his colleagues reported [22], timely data on the circulation of influenza collected within influenza surveillance systems is essential for optimizing influenza prevention and control strategies [21, 22].

### **Establishment and assessment of seasonal, high, and alert thresholds**

We used WHO method-based thresholds and epidemic curves to assess the influenza seasons from 2014 to 2019; these data represent the onset and end of the influenza season, as well as the severity of influenza. Epidemic peaks occurred at week 51 or later, in particular at  $\geq 2$  weeks among preschool children (Tables 1 and 2). We did not find any apparent seasonal pattern on the weekly fluctuations or on the week of influenza epidemic peaks. Meanwhile, the seasonal, high, and alert thresholds were explored without being affected by the diverse seasonal patterns. The NIID provides another warning outbreak system. When the number of influenza cases that occur at regional sentinel sites is more than 30 per week per site, the warning is issued to a responsible public health center [23]. We provided three threshold levels (seasonal, high, and alert thresholds) for children and each school group in Toda and Warabi based on the surveillance data that were captured in the same region. Our community-based survey in children can be used for pandemic influenza assessment by accounting for a potential increase, with high sensitivity. It should be noted that we should alter these threshold values according to region and country.

Previous studies have proposed that the analysis of surveillance data could provide information about seasonal thresholds and epidemic curves that might help healthcare personnel in clinical management [16]. Although there is room for debate on the definition of the period of influenza activity [24], future surveillance data would allow for an assessment of early warnings with a revision of the nominated threshold levels [9].

## Limitations

Although our approach can be crucial in guiding research in health plans for the prevention and control of influenza in a community, our study has several limitations. First, because the questionnaires were answered by parents of targeted children in preschool, elementary school, or junior high school, preschool-aged children who were not attending kindergarten or nursery school and children who were attending school out of town were excluded from the analysis. In the study area (Toda and Warabi), the total number of children who were aged 15 years or younger was 27,562, according to the 2015 census. Although approximately half of the respondents appropriately answered the questions in this metropolitan area survey, we cannot guarantee that the current findings accurately represent the epidemiology of children in the general population. External validity also requires further investigation. Second, we used a questionnaire in which we did not request detailed medical information, so the answers might not be accurate. However, we emphasize that the influenza antigen rapid test is widely available in Japan, and patients with a fever who visit an outpatient clinic are generally automatically checked using the test kit to detect influenza and its type. We are, thus, confident about the diagnosis of influenza, even though it is based on the questionnaire. Third, the survey was conducted in adherence with the anonymous principle, and we could not identify each respondent. Although the respondents overlapped among the five seasons, the overlapping degree varied; this might have caused bias in comparisons among the seasons. Finally, our survey was completed in March 2019, and it was not affected by COVID-19 and related confounding circumstances. No one knows whether the current estimates regarding the influenza epidemic will be applicable after the COVID-19 pandemic has subsided; this is the same issue for the epidemiology of most infectious diseases.

## Conclusions

The present study gives valuable insight into data on the circulation of influenza and the measurement of three threshold levels for children, which would support management approaches for annual influenza epidemics in the community. The vaccination timing should be redefined over time and adapted to each country as more local surveillance data become available [18]. Our findings based on influenza surveillance for children are useful for general practitioners, health policymakers, and disease control planners who are concerned with the prevention and control of influenza. More local surveillance data is expected to be utilized to review and improve the infectious disease prevention in each region.

## Declarations

## **Ethics approval and consent to participate**

Ethical approval for this study was obtained from the Institutional Review Board of Todachuo General Hospital (Number 0436). The data were anonymously collected. There was no additional disadvantage for subjects.

## **Consent for publication**

Not applicable

## **Availability of data and materials**

The datasets analyzed during the current study could be available from the corresponding author upon reasonable request.

## **Competing interests**

The authors have no competing interests.

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## **Authors' contributions**

AM, KA, and TO participated in the study design. AM performed statistical analysis and drafted the manuscript. All authors helped to collect data and draft the manuscript. KA and TO advised the statistical analysis. All authors read and approved the final manuscript.

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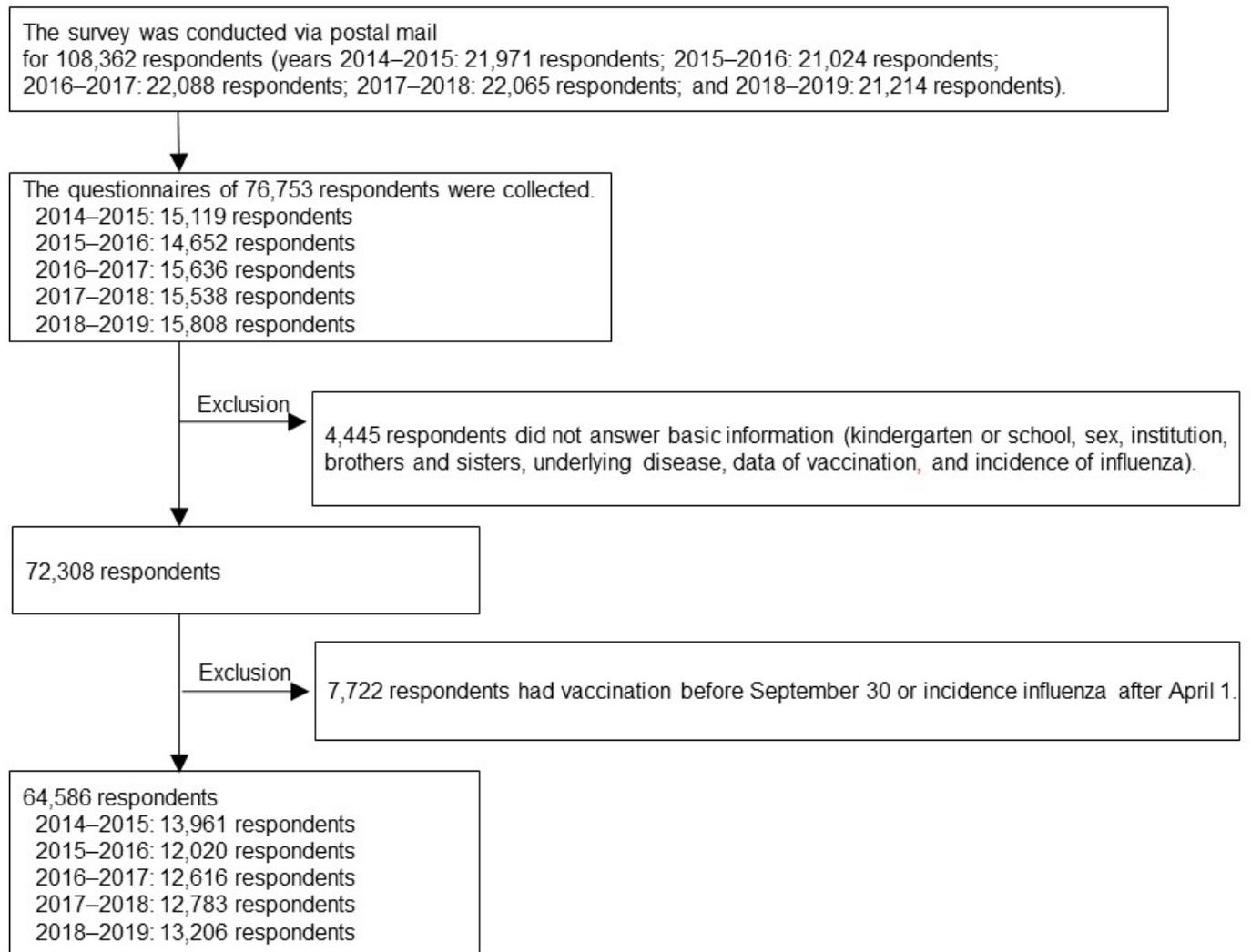
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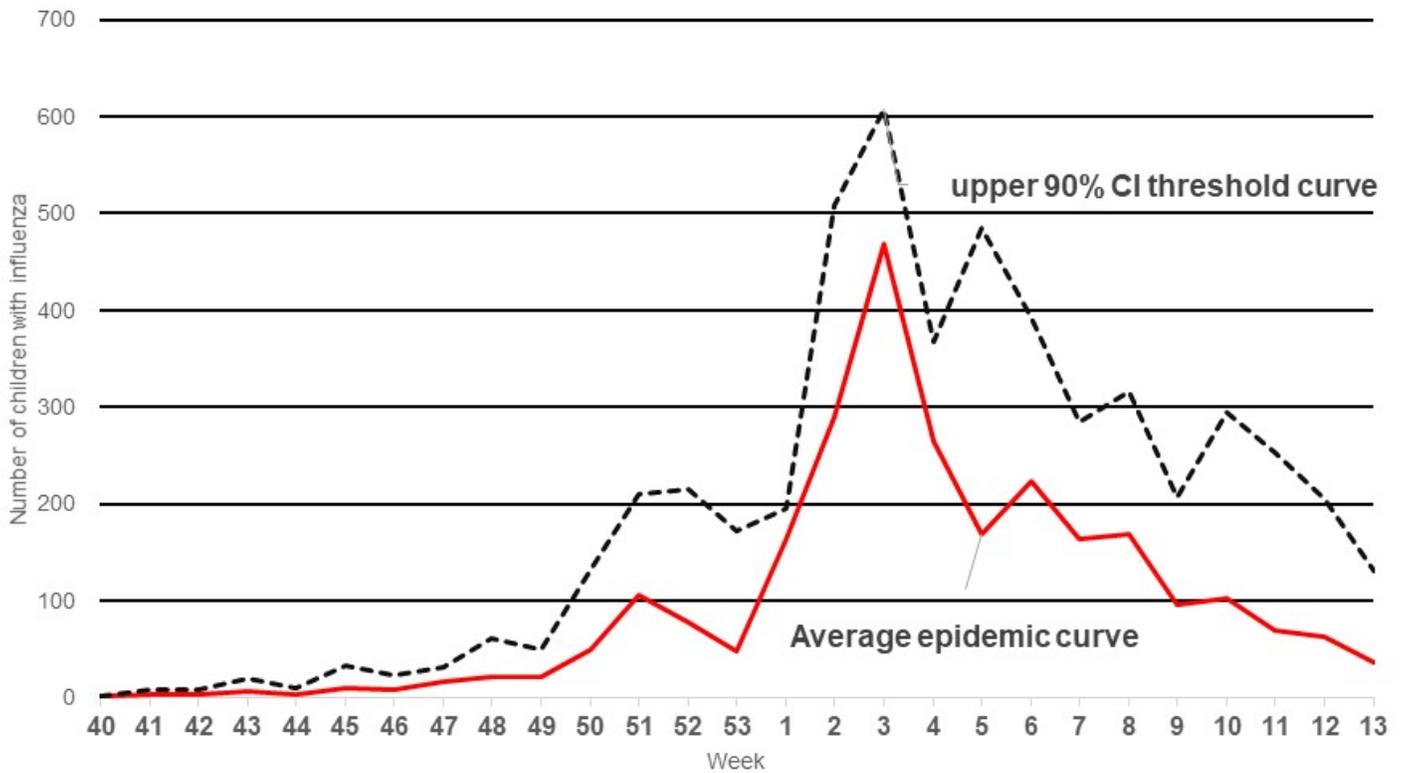
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## Figures



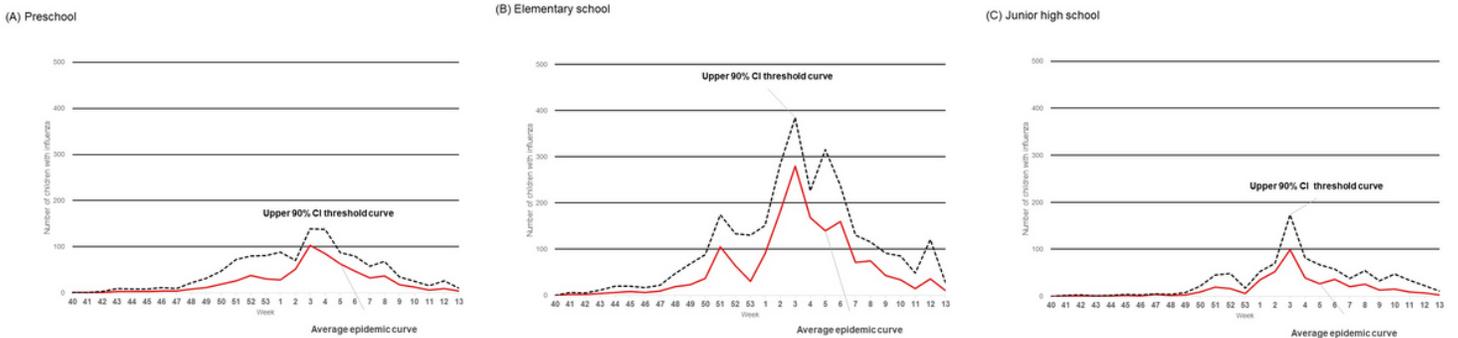
**Figure 1**

Selection of the study population



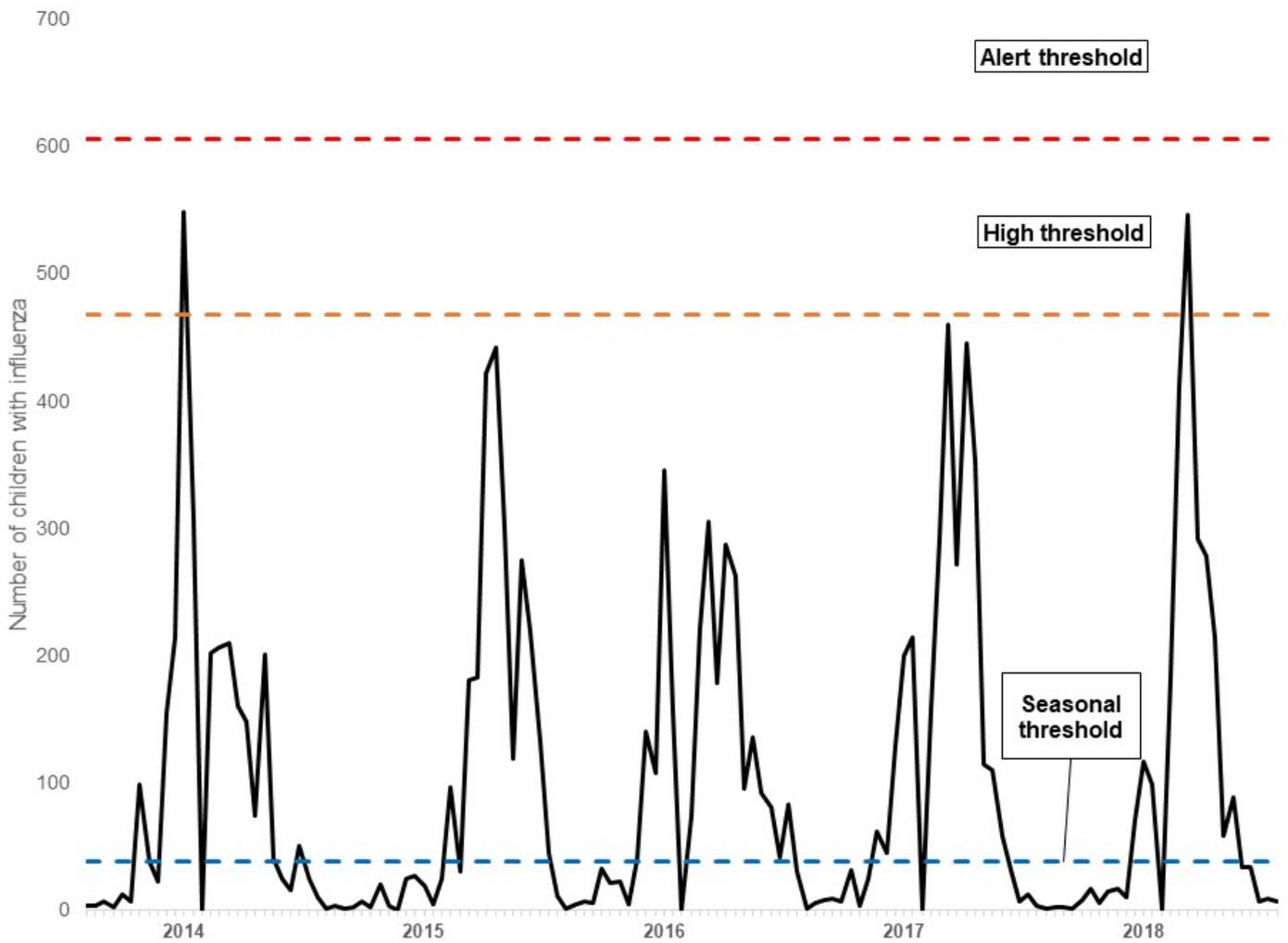
**Figure 2**

Average epidemic curve and upper 90% threshold curve Horizontal axis represents weeks of seasons, and curves are plotted based on mean values of five seasons. Average and upper 90% threshold curves are the mean and the upper 90% confidence interval, respectively of children with influenza each week.



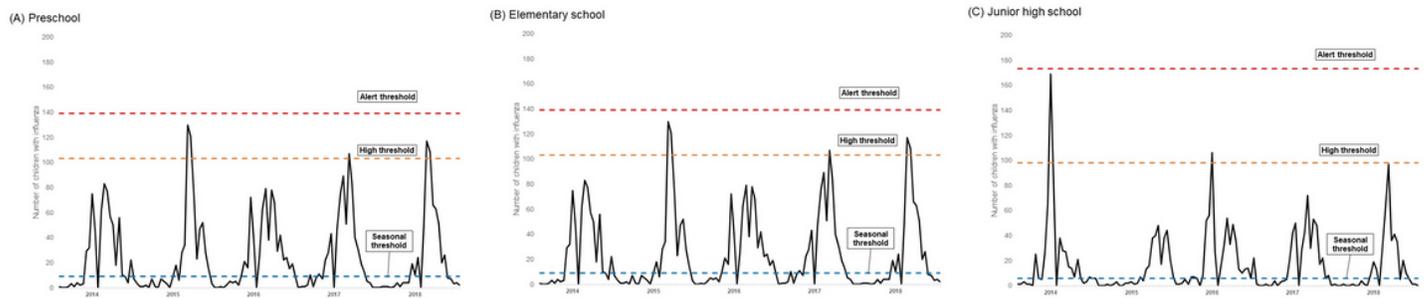
**Figure 3**

Average epidemic curve and upper 90% threshold curve in (A) preschool, (B) elementary, and (C) junior high school children Horizontal axis represents weeks of seasons, and curves are plotted based on mean values of five seasons. Average and upper 90% threshold curves are the mean and upper 90% confidence interval, respectively of children with influenza each week.



**Figure 4**

Surveillance data from 2014 to 2018 seasons plotted against calculated WHO thresholds



**Figure 5**

Surveillance data from 2014 to 2018 seasons plotted against calculated WHO thresholds categorized as (A) preschool, (B) elementary, and (C) junior high school children