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Who Leads Influenza Epidemics?
Age-specific differences in the occurrence of seasonal and pandemic influenza A in Thailand (2003-2011)

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A.B.
Princeton University
2011

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Abstract

Background: Identifying the age group responsible for driving the spread of influenza epidemics could help inform mitigation strategies to combat seasonal and pandemic influenza. This study evaluated the hypothesis that older, rather than younger, children led seasonal influenza A epidemics in Thailand.

Methods: Using data from a surveillance system for acute lower respiratory tract illness in hospitalized patients and influenza-like illness in outpatients in Thailand, we describe influenza A seasonality in Sa Kaeo and Nakhon Phanom provinces. An epidemic was defined as any time period with more than 3 (Sa Kaeo) or 5 (Nakhon Phanom) cases for two out of 3 consecutive weeks. Survival analyses and log rank statistics were applied to test the hypothesis that 10-19 year olds lead influenza epidemics in Thailand when compared to all other age groups.

Results: Between 2003 and 2011, we identified 22 epidemics: 4 in outpatient data in Sa Kaeo, 8 in inpatient data in Sa Kaeo and 10 in inpatient data in Nakhon Phanom. Overall, log-rank differences between age groups were small during seasonal, pre-pandemic influenza. In outpatients, rank orderings indicated that 10-19 year olds led influenza A epidemics during pre-pandemic years (2003-2005), although this finding was not statistically significant ($p=0.07$). Similar findings were observed in hospitalized inpatients during pre-pandemic years (2005-2008): 10-19 year olds led epidemics in Sa Kaeo ($p=0.22$) and Nakhon Phanom ($p=0.07$). When the H1N1 pandemic strain was circulating (2009-2011), ages shifted to older individuals and orderings suggest that 30-64 year olds in Sa Kaeo ($p=0.05$) and 20-29 year olds in Nakhon Phanom ($p<0.0001$) led influenza epidemics. For pandemic years, there was a greater difference in the age groups that led influenza epidemics relative to young school-aged children.

Conclusions: In Thailand, there was little difference in the age group that led seasonal influenza A epidemics. In age-shifted pandemic years, older adults led the epidemics, suggesting that school closings may be less effective at limiting influenza transmission during outbreaks caused by a novel influenza virus. Given the small differences between age groups, vaccination remains the most important prevention approach in efforts to limit influenza A transmission at the community level.

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A review of influenza transmission dynamics in Thailand and current policies to mitigate influenza epidemics, with a focus on school closures as an effective way of preventing influenza outbreaks in Thailand

Introduction

Influenza viruses are an important contributor to the burden of respiratory disease worldwide (1-4). In temperate climates of Europe and North America, influenza peaks during winter months, resulting in large numbers of hospitalizations, deaths from influenza-associated illnesses in young children, the elderly, and those with underlying medical complications, as well as high economic losses due to work absenteeism (3-6). Although influenza dynamics differ in Thailand, a tropical middle-income country, recent studies have estimated that disease burden in Southeast Asia is analogous to that observed in the United States (7-9). An active, population-based surveillance system for respiratory illness, in conjunction with diagnostic laboratory testing, estimated an influenza disease burden 43 times greater than recorded by previous passive surveillance systems (10, 11).

The high burden of influenza-related illnesses in both elderly and young populations in Thailand highlights the importance of controlling the spread of influenza viruses. Successfully controlling influenza epidemics requires a deeper understanding of age-specific transmission dynamics in order to determine which age group serves as the backbone of local influenza spread. This chapter reviews influenza epidemiology and burden in Thailand and the measures used in-country to mitigate the spread of influenza viruses at the community and national level. Specifically, we review whether school closures as a social-distancing method has proved successful in Thailand and other countries in mitigating epidemic and/or pandemic influenza transmission.

Influenza transmission in Thailand

Thailand is a middle-income country with a total population of approximately 69 million and a gross national income per capita of US$ 8,190 (12, 13). Since 2000, Thailand has significantly increased its per capita total expenditure on health, resulting in a strong in-country health infrastructure. Beginning in 2002, the Thailand Ministry of Public Health and the U.S. Centers for Disease Control and Prevention (CDC) were able to use this health infrastructure to establish an active surveillance system for acute lower respiratory tract illness in two Thai provinces that evaluated individuals of all ages for influenza and other respiratory viruses (14). Data from this surveillance program have been used to describe seasonality, estimate age-specific incidence of influenza, and identify risk factors for influenza in Thailand.

Unlike seasonality in more temperate regions such as North America (15, 16), influenza seasonality in Thailand presents two peaks annually: a major peak during the rainy season (June-August) and a minor peak in winter (October-February) (14, 17). A review of sentinel surveillance for influenza-like illness and severe acute respiratory illness in 2010 found that influenza A dominated the rainy season peak, while influenza B viruses were in higher circulation during winter, minor seasonal peaks. Despite having a bi-modal seasonality, influenza viruses are detected yearly within Thai populations (17), resulting in high levels of morbidity and mortality in the population throughout the calendar year. One study projected annual incidences of 18-111/100,000 population among hospitalized inpatients and 1,420/100,000 population among outpatients (11). This study also estimated that between 2003 and 2004 influenza was estimated to have caused between US$ 23.4 and US$ 62.9 million in economic losses, the majority of which were directly linked to loss of productivity.

The high burden of influenza in Thailand merits the investigation and determination of which age groups are responsible for the local, communal transmission of influenza. Current age-specific estimates of influenza incidence suggest that the burden is highest in individuals <5 years and >50 years, which have an influenza incidence of 90.2% and 38.4%, respectively (14, 17). Although these estimates are helpful in determining which groups suffer high levels of morbidity and need to be prioritized during vaccination campaigns, they give little indication as to which age group serves as the backbone of influenza transmission at the local level.

Other studies on age-specific rates of viral shedding help us evaluate which groups may be responsible for shedding and thus spreading the highest viral loads (18, 19). A study assessing the effectiveness of prophylactic treatments on viral shedding approximated a ~40%-80% increased rate of shedding in children under 12 years compared to adults (18). In a study assessing influenza infection and disease in Tecumseh, Michigan, Monto and colleagues linked school activities with increased seasonal influenza transmission rates (19). Furthermore, studies evaluating household transmission dynamics suggest that school children may be responsible for bringing influenza viruses home to their families (20). Although these studies indicate schoolchildren as responsible for local influenza transmission, no studies exist on the age-specific timing of influenza incidence in Thailand. Understanding the age-specific transmission dynamics of influenza in Thailand would help inform intervention strategies to prevent large epidemics and control their spread.

Public health measures to mediate influenza transmission in Thailand

Since 2004, the Thailand Ministry of Public Health (MOPH) has provided free influenza vaccinations to 400,000 of its health care workers (11). This coverage later expanded to include individuals >65 years of age, pregnant women (third trimester), children 6-59 months old, persons with underlying clinical conditions, institutionalized individuals, and obese persons weighing >100kg (13, 21). Since 2000, Thailand has increased the number of influenza vaccine doses from 72,102 to exceeding 7 million doses (10,333 doses per 100,000 persons) in 2011 (13, 22).

Although efforts to increase vaccine distribution by the Thailand MOPH are notable, vaccine distribution figures suggest that vaccination coverage only reaches 10% of the population (13). Other measures recommended by the MOPH to alleviate influenza epidemics in Thailand include prophylactic treatment of sick individuals and social distancing methods such as avoiding large crowds or school closures (23). Next, we review several studies assessing the effectiveness of school closures on seasonal and pandemic influenza transmission in different countries and discuss whether school closures may work to mediate influenza epidemics in Thailand.

Understanding the effects of school closures

School closures are a non-pharmaceutical intervention often suggested for mitigating influenza epidemics and pandemics (24). For instance, in 2007 the U.S. Centers for Disease Control and Prevention recommended prompt school closures in the event of a newly emerging pandemic (25). Proponents of the mitigating effects of school closures argue that school age children have high contact rates, ~40% greater viral shedding than adults, while also tending to be more susceptible to influenza infection compared to other age groups (18). Closing schools would thus ostensibly slow down transmission. This would, in turn, reduce the total number of cases, allowing time for prompt vaccine production and distribution, and would reduce the incidence of cases at the peak of the epidemic. Therefore reducing influenza in children could lead to overall decreased transmission and illness in other age groups, as well as decreased epidemic impact.

School closures and seasonal influenza

School activities have been previously linked with increased influenza transmission rates, implying that holidays and school closings provide an opportunity to assess the effect of school terms on influenza transmission rates (19). Several studies have analyzed the mitigating effects of school closures during seasonal influenza epidemics. During the 2008 Hong Kong winter influenza season, several kindergartens and primary schools closed due to high proportions of influenza cases in children. After reviewing prospective surveillance data on influenza and influenza-like illness activity, Cowling and colleagues detected no substantial effect of school closure on community transmission of influenza, most likely because school closures were implemented after the epidemic peak, when cases were already waning (26). In a similar study, Heymann and colleagues compared influenza attack rates before and after school closures due to teacher strikes in Israel, finding a 22% reduction in physician visits and a 43% reduction in respiratory tract infection diagnoses and viral infections (27). In this particular example, the strike ended while the influenza epidemic was ongoing, and respiratory rates rebounded, suggesting that the strike may have had an impact on influenza rates.

In yet another study, Cauchemez and colleagues quantified the effect of school holidays in France on influenza transmission and found a 16-18% reduction in influenza-like illness incidence associated with the school winter-break periods (28). Another European study on the variation of contact rates also associated school holidays with a 13-40% reduction in the rate of secondary infections (R_t) in Belgium, Great Britain and the Netherlands (29). However when assessing the effect of school holidays on influenza transmission rates, one must also consider that during holiday seasons, other behaviors such as traveling, vacations or communal celebrations make contact patterns during holiday seasons much more distorted when compared to during school terms (24). For instance, if schools are closed for extended periods of time outside of holidays, contact between children may increase in other settings, such as within households and neighborhoods. Therefore although governments may rely on school closings to maintain influenza epidemics, they would need to ensure that children remain isolated outside of school in order for school closings to have a significant impact on the transmission.

School closures and pandemic influenza

School closures as a tool for attenuating tool influenza epidemics can be traced back to the 1918 influenza A (H1N1) pandemic when school closings and other social distancing measures were reported to have been effective in reducing transmission rates (30-32). In many U.S. cities, a combination of measures including closing churches, banning mass gatherings, mandated mask wearing, and case isolation were used along with school closures to prevent influenza transmission. Several studies evaluating 1918 pandemic data associated health benefits with early and prolonged implementation of interventions (30, 31). These studies estimated that combined interventions reduced total mortality by 10-30%, and peak mortality by 50% in some cities. Since school closures were done in combination with other measures, it is impossible to deduce the exact effect that closing schools had on transmission dynamics.

Similar to measures during the 1918 pandemic, during the 2003 severe acute respiratory syndrome (SARS) outbreak in Hong Kong, social distancing methods were mandated (33)—schools were closed, mass gatherings stopped, masks were worn in public, and many people stayed at home as frequently as possible. As with the 1918 pandemic in the United States, since school closures were used in combination with other methods, it is not possible to evaluate the independent effect of school closures on the pandemic. However in both the 1918 influenza and 2003 SARS pandemics, we can note that combinations of non-pharmaceutical methods proved effective in mediating pandemic influenza spread.

Since the recent H1N1 pandemic in 2009, several studies have modeled the effects of school closures on influenza pandemics. In a 2009 study specific to Thailand, Chieochansin and colleagues evaluated the effects of school closures during the start of the outbreak in Bangkok, Thailand (34). This study found that by late June to mid-July 2009, most patients infected by H1N1 were between 7 and 20 years old, whereas seasonal influenza was found among all age groups. After the Bangkok Metropolitan Administration mandated school closures in early July, the incidence of affected children (6-20 years) with H1N1 2009 infection declined, and subsequently increased among children below 6 years and adults 20-40 years. Despite the apparent health impacts of closing schools in Bangkok during the 2009 H1N1 pandemic, these patterns may not be comparable in non-metropolitan areas such as in rural Thailand. Other studies have also found significant benefits in closing schools during the 2009 pandemic. In a Hong Kong study, Wu and colleagues estimated that closing secondary schools due to summer holiday during the H1N1 2009 pandemic, was associated with a ~25% reduction in transmission across age groups (35). Conversely, this particular study also found little appreciable difference in transmission patterns across age groups when kindergartens and primary schools were closed.

Conclusions

For the reasons listed, ascertaining the health impacts of school closures during a seasonal or pandemic influenza outbreak remains a controversial topic. Studies vary in their conclusions of whether closing schools proves effective, and whether this effectiveness differs between seasonal and novel pandemic viral strains. There are several factors that need to be considered before the decision is made to mandate school closures in the event of an influenza outbreak. For instance, although this measure may prove effective, governments cannot keep schools closed for months (24). Several studies have suggested that economic losses associated with school closures can amount to US$ 2.7 million per 1000 population or 6% of the GDP in the U.S., making strategies involving school closures very costly to maintain (36). When considering that school closure interventions can be 14-21 times more costly than using vaccination or prophylactic treatments, a medium-income country such as Thailand may not be able to sustain school closures for the duration of an epidemic.

An additional problem of social distancing methods is that they are only effective for as long as they are strictly enforced. Once these efforts come to an end, transmission patterns may resume to levels present before the intervention. Furthermore, ethical concerns need to be addressed when closing schools. For instance, in his study on the ethics involved with mitigating influenza pandemics, Berkman discusses the potential for increased mortality in older individuals who may be involved in taking care of children when schools are closed (37).

A larger issue in determining whether school closures will be effective in containing pandemic influenza transmission is dependent on the specific dynamics of the virus, which can vary between pandemics and even within cultures and regions, and are thus difficult to determine *a priori*. For instance, the age-specific severity of a pandemic can vary between pandemic years (24). Therefore if transmission takes place largely among school-aged children, school closures may be critical in mitigating pandemic spread. However if attack rates are similar among children and adults, school closures will prove much less effective. Likewise, evidenced during the 1918 pandemic when individuals reduced personal contacts due to high mortality rates, human behavior is likely to change and is difficult to predict during a pandemic outbreak (31, 32). This limits our ability to determine whether school closures are important in limiting transmission, independent of other social distancing measures.

Finally, the study of holidays in France and the 1918 pandemic indicate that mitigation using school closures may lead to a reduction in the total number of cases, but it is more likely that they would have larger reductions in peak attack rates (24). This could help to delay pandemic burden, spread the burden over longer time periods and allow time for public health facilities to acquire vaccines.

Variances in the perceived and estimated benefit of school closures on mitigating influenza seasonal and/or pandemic outbreaks underscore the importance that decisions to close schools must be made using various data, including age-specific estimates of severity and local morbidity indicators. These findings in different countries prove difficult to extrapolate to a place such as Thailand, since so much of the effectiveness of school closures lies in their timely implementation. Most importantly, implementing this measure in a timely manner is highly dependent on a country's ability to quickly detect and subtype aberrant numbers of influenza cases. A country such as Thailand, with a strong public health and laboratory-diagnostic infrastructure and high health seeking behavior within the population, may be able to successfully implement school closures for seasonal influenza outbreaks. For pandemic influenza, however, school closures may prove to be less effective because viral severity and transmission dynamics may not be understood in time for implementation to have a significant impact on epidemic spread.

In order for school closures to become a viable solution for influenza epidemic control in Thailand, data are needed on the age-specific timing of influenza epidemics. Understanding the age-specific transmission dynamics of influenza in Thailand would help inform target groups for intervention strategies to prevent large epidemics.

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II

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Background: Identifying the age group responsible for driving the spread of influenza epidemics could help inform mitigation strategies to combat seasonal and pandemic influenza. This study evaluated the hypothesis that older, rather than younger, children led seasonal influenza A epidemics in Thailand.

Methods: Using data from a surveillance system for acute lower respiratory tract illness in hospitalized patients and influenza-like illness in outpatients in Thailand, we describe influenza A seasonality in Sa Kaeo and Nakhon Phanom provinces. An epidemic was defined as any time period with more than 3 (Sa Kaeo) or 5 (Nakhon Phanom) cases for two out of 3 consecutive weeks. Survival analyses and log rank statistics were applied to test the hypothesis that 10-19 year olds lead influenza epidemics in Thailand when compared to all other age groups.

Results: Between 2003 and 2011, we identified 22 epidemics: 4 in outpatient data in Sa Kaeo, 8 in inpatient data in Sa Kaeo and 10 in inpatient data in Nakhon Phanom. Overall, log-rank differences between age groups were small during seasonal, pre-pandemic influenza. In outpatients, rank orderings indicated that 10-19 year olds led influenza A epidemics during pre-pandemic years (2003-2005), although this finding was not statistically significant ($p=0.07$). Similar findings were observed in hospitalized inpatients during pre-pandemic years (2005-2008): 10-19 year olds led epidemics in Sa Kaeo ($p=0.22$) and Nakhon Phanom ($p=0.07$). When the H1N1 pandemic strain was circulating (2009-2011), ages shifted to older individuals and orderings suggest that 30-64 year olds in Sa Kaeo ($p=0.05$) and 20-29 year olds in Nakhon Phanom ($p<0.0001$) led influenza epidemics. For pandemic years, there was a greater difference in the age groups that led influenza epidemics relative to young school-aged children.

Conclusions: In Thailand, there was little difference in the age group that led seasonal influenza A epidemics. In age-shifted pandemic years, older adults led the epidemics, suggesting that school closings may be less effective at limiting influenza transmission during outbreaks caused by a novel influenza virus. Given the small differences between age groups, vaccination remains the most important prevention approach in efforts to limit influenza A transmission at the community level.

Introduction

Acute upper and lower respiratory infections cause a substantial burden of disease among adults and children worldwide (1). This burden is especially severe in children under five years of age in developing countries. The World Health Organization estimates that pneumonia alone is the leading cause of morbidity and mortality worldwide for children <5 years old, accounting for approximately 50% of visits by children to health facilities and an estimated over 2 million deaths annually, 15% of which are in children <5 years old (1-3).

Influenza viruses are an important contributor to the burden of respiratory disease. A study by Nair and colleagues estimated that in 2008, 90 million new cases of influenza occurred worldwide in children younger than 5 years (4). The study also estimated 28,000-111,500 deaths attributable to influenza-associated acute lower respiratory infection in children <5 years of age.

In Thailand, respiratory illness and influenza viruses in particular persist as large contributors to disease burden. In the mid-1980's, approximately 50% of all outpatient visits to hospitals among Thai children <5 years of age were due to respiratory illness (1). In 2010, estimates from sentinel surveillance for influenza-like illness in outpatients and severe acute respiratory illness among hospitalized patients in Thailand, found that 20% and 21%, respectively, had confirmed influenza infections; in both groups, 13% of infections were in children <5 years (5). Additionally, a recent study in 2012 estimated that a cumulative 9% of deaths in children <5 were solely attributable to pneumonia (6).

Identifying age groups that drive transmission might be important for facilitating targeted prevention strategies. Previous studies demonstrated that young school-aged children (5-9 years) were responsible for the spread of influenza within their communities due to their high clinical attack rates (7), social contact rates within the school environment (8), and significant role in the introduction of influenza infections into the household (9, 10). Other studies suggest that working-age adults may be responsible for the spread of influenza between communities (11). Using data from Canada collected over 10 seasons, Schanzer and colleagues reported that high school children and young adults (ages 10-19) were the most likely group to form the backbone of transmission for the next pandemic, due to the nature of their contact networks (12). This project aimed to identify if a certain age group was driving the spread of seasonal and pandemic influenza in Thailand.

Methods

Data Source

The data were collected between January 2003 and December 2011 from a population-based surveillance system for acute lower respiratory tract illness in hospitalized patients and influenza-like illness in outpatients in Sa Kaeo and Nakhon Phanom provinces of Thailand (*See Figure I*) (13). Participants for this analysis were drawn from the existing surveillance data. An Institutional Review Board at the US Centers for Disease Control and Prevention (CDC) and the Ethics Review Committee at the Thailand Ministry of Public Health approved this study. Approval by the Emory Institutional Review Board was not necessary for the purposes of this study—only secondary analyses were performed and the data contained no personally identifying information of study participants, who were referenced only by unique identifying numbers (*See Appendix A*).

Outpatient Data (2003-2005) (14): Persons of all ages presenting with influenza like illness (ILI) for care at five of eight hospital outpatient clinics in Sa Kaeo were consented and enrolled. Demographic information on each patient was recorded and nasopharyngeal swabs were taken and tested for influenza viruses using RT-PCR. We analyzed data from patients with laboratory-confirmed influenza A infection as defined by PCR positivity. Data were collected from 2003-2005.

Hospitalized Inpatient Data (2005-2011) (14, 15)**:** Persons of all ages admitted for acute lower respiratory tract illness at any of 20 hospitals in Sa Kaeo or Nakhon Phanom were consented and enrolled. Demographic information on each patient was recorded and a nasopharyngeal swab was taken and tested for influenza viruses by reverse transcription polymerase chain reaction (RT-PCR). We analyzed data from patients with laboratory-confirmed influenza A infection as defined by PCR positivity. Data were collected from 2003-2011, however analysis was only conducted on data collected from 2005-2011.

Defining Influenza Seasonal Epidemics

In Sa Kaeo, an epidemic peak was defined as >3 influenza A cases in 2 out of 3 consecutive weeks (*See Figure II*). In Nakhon Phanom, an epidemic peak was defined as >5 influenza A cases in 2 out of 3 consecutive weeks. Weeks were defined using the CDC epiweek definition (16). Different thresholds were used for defining epidemics due to the variation in magnitude of epidemics by province. The primary objective was to determine influenza occurrence at the beginning of each epidemic; therefore the beginning of each epidemic was defined as the lowest point (0 or 1 case) before the peak, and one week prior, while the end of an epidemic was defined as the lowest point (0 or 1 case) immediately after the peak. Using these criteria, instances do occur of one epidemic beginning before the previous epidemic has ended (i.e. overlapping epidemics).

Statistical analysis

Data sets were compiled of all individuals falling within the epidemic intervals as defined above. Since time between symptom onset and presentation at an outpatient clinic is usually shorter than presentation at hospital, we analyzed these data separately. Also, since age-specific population level immune characteristics likely differ during seasonal and pandemic influenza epidemics, we conducted separate analyses for the period before and after the 2009 influenza pandemic (pre June, 2009 and June 2009 on). Within subsets of pandemic period, the strata of Sa Kaeo and Nakhon Phanom inpatient epidemic periods were aggregated.

We calculated the time between each influenza A event (date of symptom onset for the outpatient data and date of hospital admission for the inpatient data) and the first corresponding influenza A event in each epidemic period. Due to the variable lengths of individual epidemic periods, we scaled each epidemic to a standard 100 days (~14 weeks), which served to preserve the rank ordering of individuals within an epidemic period while simultaneously allowing for a combined analysis across epidemic periods.

We used the life-table methods to evaluate differences in the time to event among the following age groups: <1, 1-4, 5-9, 10-19, 20-29, 30-64, >65 years. These age groups were set to mirror the Schanzer et *al.* methodology and, to put emphasis, biologically on the influenza dynamics in certain age groups that might be amenable to social distancing techniques. For each analytic subset, we initially evaluated Kaplan-Meier curves for each age category and Wilcoxon-Rank test statistics were used to evaluate whether the survivor function was the same among the different age groups.

In order to evaluate which age groups came before others and control for differences between epidemic periods, we used the "test" statement in SAS Proc LIFETEST with the age group categories using deviation from the means coding while stratifying (using the "strata" statement) by epidemic-period. The resulting log-rank statistics and p-values evaluate the failure time of each age category against all the other age groups combined. The log-rank statistics ranged between negative and positive numbers depending on the relative event times of each age category relative to the rest combined. We also conducted Cox proportional hazard models to evaluate statistically the hazard of the event in one age group (10 – 19 years) compared to each of the other age groups, stratified by epidemic period. Analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina) and all test results were interpreted at the α=0.05 significance level.

Results

For the purposes of this study, only log rank statistic results were reported. Please refer to *Appendix C* for a summary of Cox regression model results.

Influenza epidemics in outpatients:

Between 2003 and 2005, there were 1,941 outpatients with influenza-like illness and 303 (15.6%) tested positive for influenza A virus (*Table I*). Among persons who were positive for influenza A virus, 36% were aged 1-4 years, 28% were aged 5-9 years, 15% were aged 10-19 years, 3.1% were aged 20-29 years, 6.9% were aged 30-64 years and 1.2% were over 65 years (*Table I*). We identified four epidemics in outpatient data (average of two per year), which had a median duration of 8.5 epiweeks (range 8-27 epiweeks) (*See Figure III and Appendix B*).

Wilcoxon tests for equality across epidemics revealed no statistically significant differences in the timing of influenza A between age groups for outpatients (p=0.16) (*Table II*). Log rank test results suggested that outpatients 10-19 years old sought outpatient care first during influenza epidemics (p=0.04), followed by >65 year olds (p=0.07) (*Table III-A*).

Influenza epidemics in hospitalized inpatients:

Between 2005 and 2011, there were 26,452 hospitalized patients with acute lower respiratory tract illness and 2,073 (7.8%) were positive for influenza A virus (*Table I*). During pre-pandemic, seasonal influenza years (2005-2008), among individuals who tested positive for influenza A virus, 21.8% were aged 1-4 years, 9.8% were aged 5-9 years, 11.1% were aged 10-19 years, 5.5% were aged 20-29 years, 24.4% were aged 30-64 and 21.8% were aged over 65 years (*Table I*). The distribution was similar during pandemic influenza A years (2009-2011). We identified 8 epidemics for Sa Kaeo inpatient data (average of 1 per year), which had a median duration of 13.5 epiweeks (range 9-21 epiweeks), and 10 epidemics for Nakhon Phanom inpatient data (average of 1 per year), which had a median length of 16.5 epiweeks (range 11-28 epiweeks) (*See Figure IV and Appendix B*).

Combined seasonal, pre-pandemic influenza epidemics in hospitalized inpatients in Sa Kaeo and Nakhon Phanom provinces (2005-2008):

Wilcoxon tests for equality across combined inpatient epidemics detected statistically significant differences in the timing to influenza between age groups in seasonal, pre-pandemic influenza A epidemics (2005-2008) ($p=0.01$) (*Table II*). Log rank test statistics suggested that 10-19 year old inpatients were hospitalized first during seasonal, pre-pandemic influenza epidemics ($p=0.03$), followed closely by 5-9 year olds ($p=0.09$) (*Table III-A, Inpatients).*

Combined pandemic influenza A epidemics in hospitalized Inpatients (2009-2011):

During pandemic influenza years (2009-2011), Wilcoxon tests also detected statistically significant differences in the age-specific timing to influenza incidence in inpatient data ($p<0.01$) (*Table II*). For this time period, log rank statistics determined that 10-19 year olds were hospitalized first ($p=0.01$), followed closely by 20-29 year olds ($p<0.001$) (*Table III-A*). However when considering province-specific results, log rankings determined that 30-64 year olds ($p=0.05$) and 20-29 year olds ($p<0.0001$) led pandemic influenza seasons for Sa Kaeo and Nakhon Nakhon Phanom, respectively (*Table III-B*).

Discussion

Between 2003 and 2011, we identified 22 influenza epidemics: an average of two per year in outpatients and one per year in inpatients. After calculating log rank statistics and conducting survival analyses, we found some patterns in the age-specific timing of influenza A epidemics. For Sa Kaeo and Nakhon Phanom 10-19 year olds led seasonal, pre-pandemic influenza epidemics, followed closely by 5-9 year olds, in both outpatients and hospitalized inpatients, however the differences in timing between these age groups during seasonal, pre-pandemic influenza appear to be small. During pandemic influenza seasons, the age distribution of hospitalized inpatients shifted to include older individuals: 30-64 year olds in

Sa Kaeo, and 20-29 year olds in Nakhon Phanom led pandemic influenza A epidemics. For pandemic years, there appears to be a substantial difference in the age groups leading influenza epidemics, relative to the younger school age children.

Although we did not detect significant differences in the age-specific timing of incidence during seasonal, pre-pandemic years, our rank orderings are supportive of Schanzer and colleagues: older, rather than younger schoolchildren led seasonal influenza epidemics, thus forming the backbone of transmission at the community level (12). Although the samples may have been too small for log rank tests to detect statistical significances in the age-specific distributions for seasonal outpatient and inpatient data, log rank tests show a clear trend in the orderings of age groups. Alternatively, the differences may just be small in nature.

For pandemic years, the province-specific difference in findings may be attributable to different influenza transmission epidemiology between Sa Kaeo and Nakhon Phanom, rather than reflecting a true underlying difference in the shift of age groups during pandemic years. Additionally, the finding that the upward shift in age during pandemic years appears greater in Sa Kaeo than it does in Nakhon Phanom may be a function of sampling variability between the two provinces.

During pandemic years, young adults, compared to schoolchildren, may be more responsible for community-level influenza transmission due to their higher level of mobility throughout the community. Young adults continue to travel independently while sick schoolchildren will typically be kept at home by their parents, suggesting that young adults continue to have greater and broader access to the community despite potentially being ill (17).

Despite conclusions suggesting that on average, older schoolchildren and young adults, respectively, led seasonal and pandemic epidemics in Thailand, these findings do not necessarily imply that these age groups are most highly affected by influenza A. In fact, our findings are consistent with previous studies in Thailand and Southeast Asia highlighting that the highest burden of influenza A morbidity falls on the very young and elderly (18-20).

Our findings are in agreement with other studies such as the study by Glass and Glass, which found that high school students and young adults most likely drive local transmission of influenza epidemics due to the nature of their social contact networks (9). Our findings also suggest that younger school children (5-9 years) play a lesser role in driving seasonal influenza transmission at the community level. This is in contrast to findings from other studies assessing age-specific timing of influenza incidence, which found that young children play a significant role in the spread of seasonal influenza at the community level due to their high clinical attack rates (21), high social contact rates within the school environment (8, 22), and role in introducing and spreading influenza infections into the household (11, 23, 24).

The findings that schoolchildren may drive local influenza transmission has prompted targeted prevention measures such as school closures to mitigate the effects of influenza epidemics (25). In 2007, the U.S. Centers for Disease Control and Prevention provided pandemic mitigation guidelines that among other measures, also recommended prompt school closures in the event of a newly emerging pandemic (26). Proponents of school closures for influenza epidemics argue that schoolchildren spread transmission within their communities, therefore closing schools could help to either reduce the total number of cases in the course of an epidemic or the peak attack rates, allowing ample time for healthcare institutions to acquire the necessary prophylactic treatments and vaccines to prevent further spread of illness (26, 27). Modeling studies in particular suggest that when used in combination with other interventions, school closures would help to reduce substantial numbers of new influenza cases within an epidemic (28). Consequently, reducing influenza in children could lead to decreased transmission and illness in other age groups, as well as decreased epidemic impact.

Skeptics of school closures for influenza epidemics say that in order to be effective, health officials would need to mandate school closings before 1% of cases have been detected (25). This is hard to accomplish with influenza since symptoms are non-specific and a person can also be infectious prior to showing symptoms (29). Furthermore, some argue that by the time school closures are in effect, the epidemic would be waning, therefore casting doubts on the causal effect of school closures on the reduction of influenza cases (25).

Not all studies agree on the power of school closures as an effective prevention method, or on the role that age plays on the timing of influenza spread across a community (25, 30), yet closing schools continues to be a prevention method used by several countries, including Thailand. In a 2009 study specific to Thailand, Chieochansin and colleagues evaluated the effects of school closures during the start of the H1N1 pandemic outbreak in Bangkok, Thailand (31). This study found that by late June to mid-July 2009, most patients infected by H1N1 were 7-20 years old, whereas seasonal influenza was found among all age groups. After the Bangkok Metropolitan Administration mandated school closures in early July, the incidence of affected children (6-20 years) with H1N1 2009 infection declined, and subsequently increased among children below 6 years and adults 20-40 years.

Our results differ from the findings of Chieochansin and colleagues, suggesting that although methods such as school closures may be beneficial during seasonal epidemic waves, they may prove less potent at controlling transmission spread during pandemic influenza seasons. The differences between the findings may be explained by the population studied: Chieochansin and colleagues used urban data from metropolitan Bangkok whereas we used data from rural areas of Thailand (31). We hypothesize that as the age distribution of individuals leading epidemics shifts to an older age bracket during pandemic years, health policy makers may need to rely on other pharmaceutical and non-pharmaceutical methods to attenuate influenza spread. Ultimately, given the small differences in age groups in any given year, vaccination remains the most effective prevention approach in efforts to limit influenza A transmission at the community level.

Study Limitations

Our study had several limitations. Seasonality of influenza viruses in tropical Thailand made the process of defining epidemic periods very challenging, prompting us to rely on our data to define epidemic periods. In the absence of a clear 12-14 week influenza seasonality as found in temperate regions such as Canada or the United States (12), the methods used to define epidemics were highly data dependent. Furthermore, unlike Schanzer and colleagues, our method of standardizing influenza epidemics over a period of 14 weeks (~100 days) precluded us from calculating age-specific differences in terms of days (12).

Age-specific trends from our outpatient data supported our hypothesis that older school children lead influenza A epidemics, yet these findings were not statistically significant. This may be a consequence of limited sample size. Nevertheless, our outpatient data serve as an accurate portrayal of who becomes sick first, since individuals seen in outpatient care likely developed their symptoms more recently than those persons who are admitted. Furthermore, in our outpatient data we had information on the date of symptom onset, which gave us a better estimate of when an individual first acquired influenza.

In our inpatient data, we used hospital admission date as a proxy for date of illness onset. This could have biased our results by a function of age group if certain groups were more likely to seek medical care early compared to other age groups. Similarly, other factors affecting patient admittance (e.g., age of participant or severity of disease) could potentially confound the temporal relationship between influenza acquisition, development of symptoms and medical seeking behavior, thus restricting our interpretation of results derived from inpatient data. However the consistency in the log-ranking of age groups across outpatient and inpatient data suggests that the inpatient data may not be significantly affected by these potential biases.

Previous studies using community surveys on health seeking behavior indicate that community health seeking behavior in Thailand is high and consistent across Thai provinces (32). Yet perceived severity of disease can also influence health-seeking behavior and this relationship is further impacted by the age of sick individuals. For instance, a mother with a sick child (<5 years) might be more inclined to take her child to the hospital when compared to a mother who has a sick teenager (32). However if health-seeking behavior were purely a measure of the age of the patient, we would have a much higher distribution of infants (<1 year olds) in our data, which are typically the most vulnerable and fragile children when compared to other children <5 years. Additionally, mixed infections may alter the relationship between age, influenza, and admission. In a review of respiratory pathogens found in patients hospitalized for pneumonia in Thailand, Olsen and colleagues found that mixed infections of influenza and rhinovirus, adenovirus, or respiratory syncytial virus (RSV) were most commonly found in children <5 years (15). These findings are consistent in other countries (33). Mixed infections can often be more severe and are most common in young children, implying that individuals may be more likely to be hospitalized if they are infected with influenza and another viral or bacterial pathogen, rather than influenza alone (33).

Lastly, the number of patients recruited into the study represents only those individuals who consented to participate and gives no indication of the number of individuals who were approached about participation, yet refused. For instance, Olsen and colleagues demonstrated lower enrollment of children in a study estimating incidence of respiratory pathogens in hospitalized patients (15). This suggests that mothers with severely ill children may not consent to their child's participation in the study. Similarly, individuals who are hospitalized multiple times might be less inclined to continually agree to participate in the study. Despite these limitations, our findings still suggest a specific ordering in the age-specific occurrence of influenza A in outpatients and hospitalized inpatients.

Conclusions

In Thailand, there were small differences in the order that different age groups presented for care during seasonal influenza A epidemics. In age-shifted pandemic years, older adults led the epidemics, suggesting that school closings may be less effective at limiting influenza transmission during pandemic outbreaks. Given the small differences between age groups during seasonal epidemics and our inability to project transmission dynamics during a pandemic outbreak, vaccination remains the most important prevention approach in efforts to limit influenza A transmission at the community level.

Although this analysis found some associations between influenza epidemics and age-specific temporal trends, the role of older schoolchildren in influenza transmission and propagation in Thailand warrants further study. Additionally, this paper substantiates an association between influenza seasonality and age-specific temporal patterns of influenza incidence, yet further research is required to examine the extent to which this association serves as an important determinant in predicting seasonal and pandemic fluctuations in influenza.

Although this analysis suggests that younger children may not lead influenza epidemic waves, interventions targeting young children are still warranted due to the high burden of disease in this age bracket, and may still have a significant impact on the magnitude and severity of subsequent seasonal epidemics (21, 22). Finally, school closures, as an effective measure to mitigate waves of influenza epidemics, remains controversial (34). Influenza vaccination thus remains the best prevention strategy to control influenza A seasonal and pandemic outbreaks in Thailand.

List of Tables

Table I. Frequency of influenza A laboratory test results and distribution of age groups among influenza A positive outpatients and hospitalized inpatients seen for pneumonia-related illness in Sa Kaeo and Nakhon Phanom, Thailand (2003-2011)

	OUTPATIENTS (n=1,941)		INPATIENTS (n=26,452)	
	n	(%)	n	(%)
Influenza A Laboratory Test Results				
Positive	303	(15.6)	2,073	(7.8)
Negative	1,641	(84.4)	24,123	(91.2)
Not typed	-----		256	(1.0)
Age group distributions (Influenza A positive only)				
	Seasonal (2003-2005)		*Seasonal (2005-2008)*	
<1	311	(9.6)	116	(5.6)
1-4	1,164	(36.0)	452	(21.8)
5-9	899	(27.8)	203	(9.8)
10-19	497	(15.4)	230	(11.1)
20-29	99	(3.1)	114	(5.5)
30-64	224	(6.9)	505	(24.4)
>65	38	(1.2)	453	(21.9)
			Pandemic (2009-2011)	
<1	-----		39	(3.5)
1-4			207	(18.8)
5-9			113	(10.2)
10-19			147	(13.3)
20-29			91	(8.2)
30-64			299	(27.1)
>65			208	(18.8)

Table II. Wilcoxon test results for equality across epidemics, of age-specific timing of influenza A incidence for outpatients and hospitalized inpatients**

	OUTPATIENTS		INPATIENTS	
	Chi square	Pr	Chi square	Pr
Sa Kaeo & Nakhon Phanom			22.66	**<0.01***
Seasonal (2005-2008)	----		16.28	**0.01**
Pandemic (2009-2011)	----		19.87	**<0.01**
Sa Kaeo only	9.22	0.16	2.20	0.90
*Seasonal (2003-2008)***	----		6.25	0.40
Pandemic (2009-2011)	----		5.53	0.48
Nakhon Phanom only			29.42	**<.001***
Seasonal (2005-2008)	----		14.62	**0.02**
Pandemic (2009-2011)	----		39.07	**<.001***

* p<0.0001

** For seasonal influenza, Outpatient data spans from 2003-2005 and Inpatient data from 2005-2008

*** Bolded p-values are statistically significant at the α <0.05 level, indicating that epidemics are not equal in the age-specific timing of Influenza A incidence

Table III-A. Log rank survival analysis results assessing the combined age-specific timing to incidence of influenza A for outpatients and hospitalized inpatients in Sa Kaeo and Nakhon Phanom, Thailand (2003-2011)

	OUTPATIENTS*		**INPATIENTS**	
Age (years)	log rank test	Pr	log rank test	Pr
All detected influenza epidemics				
<1	-0.48	0.75	9.43	0.08
1-4	5.13	0.21	27.71	**<0.01**
5-9	2.31	0.58	-9.90	0.17
10-19	-7.89	0.07	-25.45	**<0.001**
20-29	1.17	0.48	-16.26	**<0.01**
30-64	1.95	0.43	-3.68	0.72
>65	-2.20	0.04	18.16	0.06
Seasonal influenza				
	(2003 - 2005)		*(2005 - 2008)*	
<1	-----		6.89	0.11
1-4			9.16	0.17
5-9			-7.78	0.09
10-19			-9.31	**0.03**
20-29			-0.62	0.81
30-64			-3.19	0.61
>65			4.85	0.47
Pandemic influenza (2009 - 2011)				
<1	-----		2.55	0.45
1-4			18.54	**0.01**
5-9			-2.12	0.71
10-19			-16.14	**0.01**
20-29			-15.64	**<0.001**
30-64			-0.49	0.95
>65			13.31	**0.05**

* Outpatient data collected from Sa Kaeo Province (2003-2005)

** Bolded p-values are statistically significant at the $\alpha < 0.05$ level, indicating that for log rank test results, the ranking of the age group is statistically significant when compared to other age groups, and across all designated epidemics.

Table III-B. Province specific log rank survival analysis results assessing the age-specific timing to incidence of influenza A for hospitalized inpatients in Sa Kaeo and Nakhon Phanom, Thailand (2005-2011)

	PROVINCE SPECIFIC*			
	Sa Kaeo		**Nakhon Phanom**	
Age (years)	log rank test	Pr	log rank test	Pr
All detected influenza epidemics				
<1	1.41	0.57	8.02	0.09
1-4	2.86	0.59	24.85	**<0.01**
5-9	1.86	0.64	-11.77	**0.05**
10-19	-3.94	0.25	-21.51	**<0.01**
20-29	-0.55	0.85	-15.71	**<0.001**
30-64	-8.10	0.12	4.43	0.62
>65	6.46	0.19	11.70	0.16
Seasonal influenza (2005 - 2008)				
<1	-0.10	0.96	6.98	0.07
1-4	3.00	0.32	6.17	0.30
5-9	-0.56	0.78	-7.22	0.08
10-19	-2.03	0.22	-7.28	0.07
20-29	-0.92	0.39	0.30	0.90
30-64	0.58	0.82	-3.77	0.50
>65	0.02	0.99	4.83	0.42
Pandemic influenza (2009 - 2011)				
<1	1.51	0.40	1.04	0.71
1-4	-0.14	0.98	18.68	**<0.001**
5-9	2.43	0.48	-4.55	0.31
10-19	-1.91	0.52	-14.23	**0.01**
20-29	0.37	0.89	-16.01	**<0.001****
30-64	-8.69	**0.05**	8.20	0.23
>65	6.43	0.10	6.87	0.23

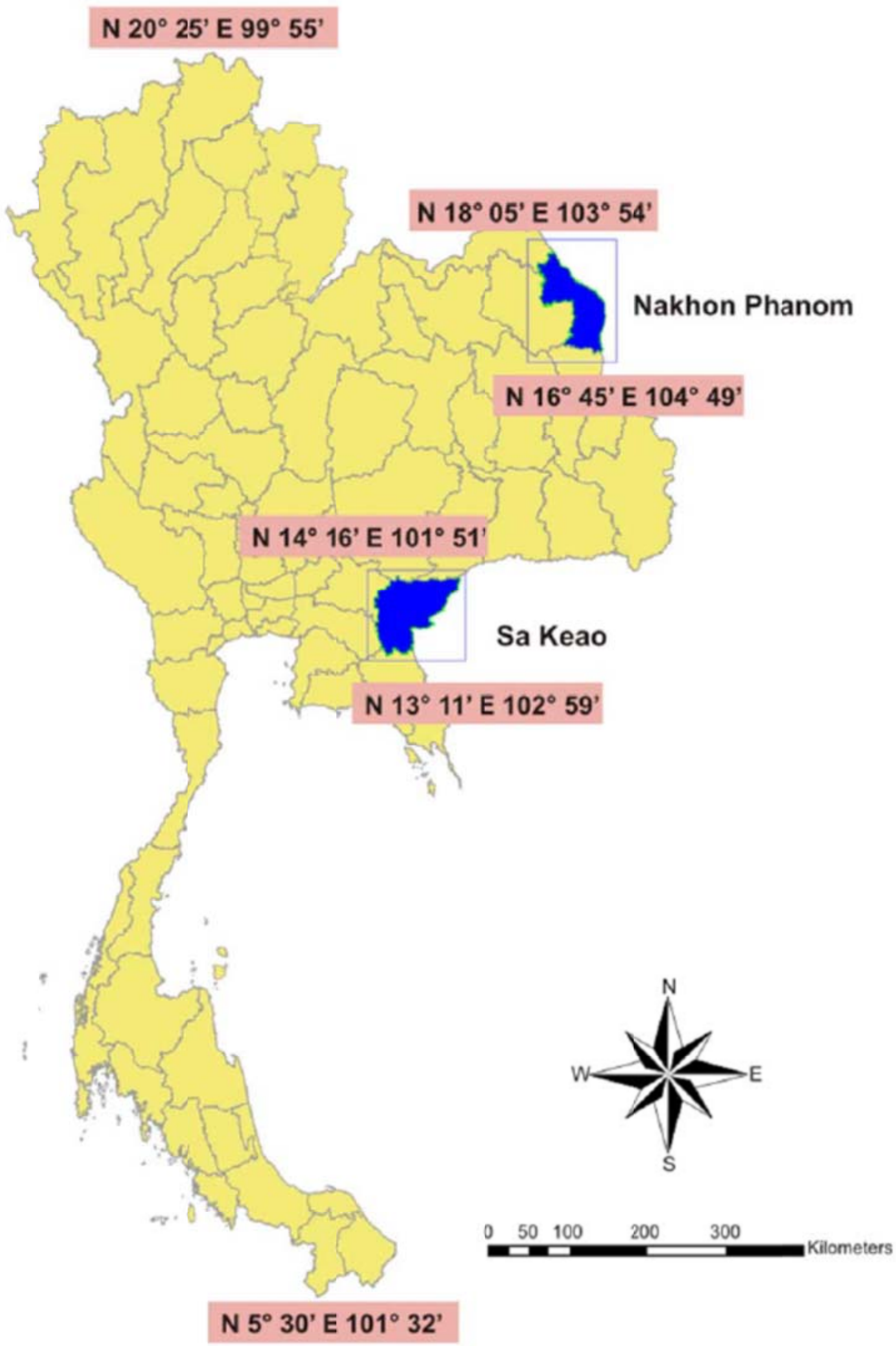
* Inpatient data only

** p<0.0001

*** Bolded p-values are statistically significant at the α <0.05 level, indicating that for log rank test results, the ranking of the age group is statistically significant when compared to other age groups, and across all designated epidemics.

List of Figures

Figure I. Locations of Sa Kaeo and Nakhon Phanom provinces in Thailand*



*(16) doi:10.1371/journal.pone.0007776.g001

Figure II. Defining influenza A epidemics in Thailand

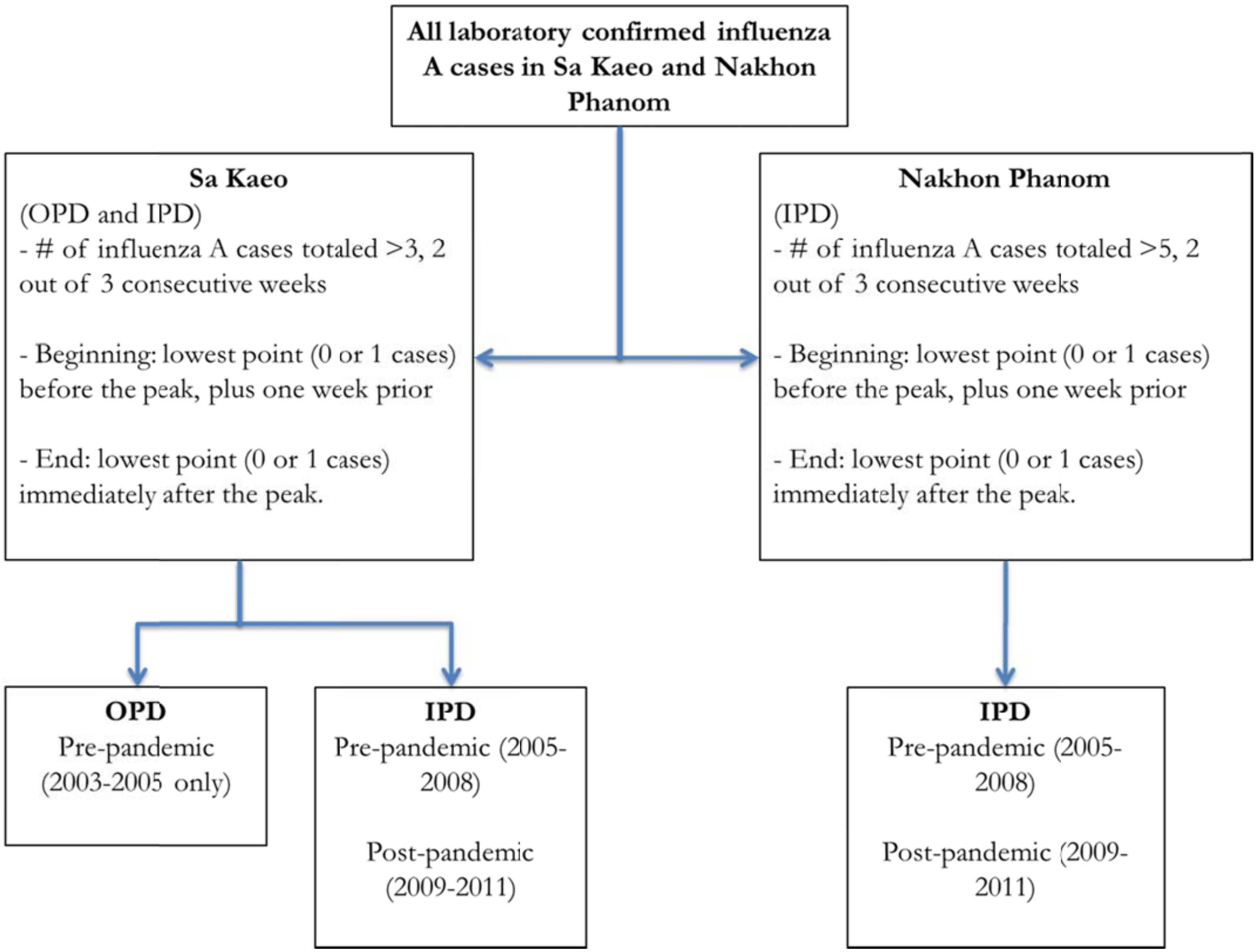


Figure III. Seasonality of influenza A positive outpatients in Sa Kaeo Province, Thailand (2003-2005)

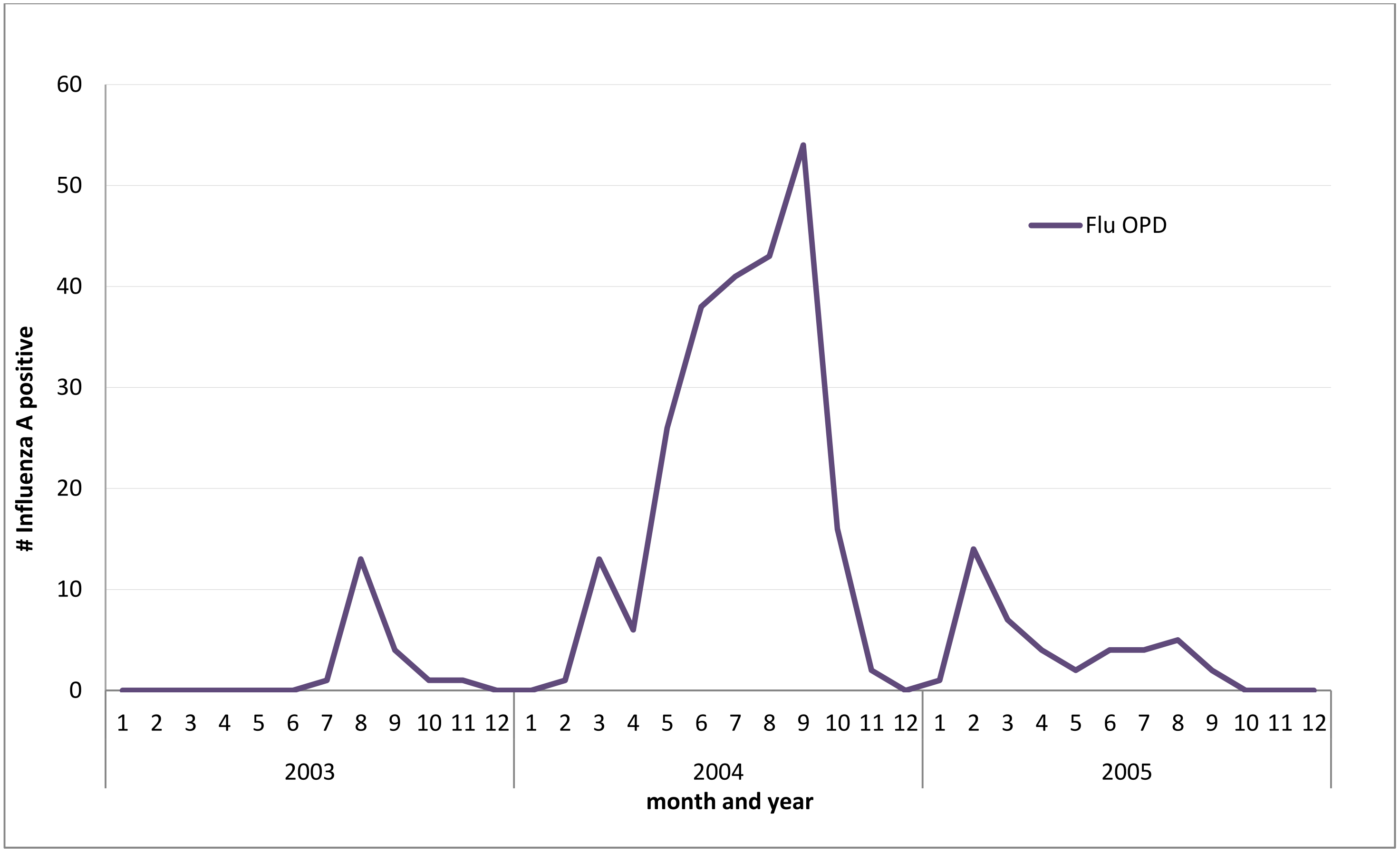
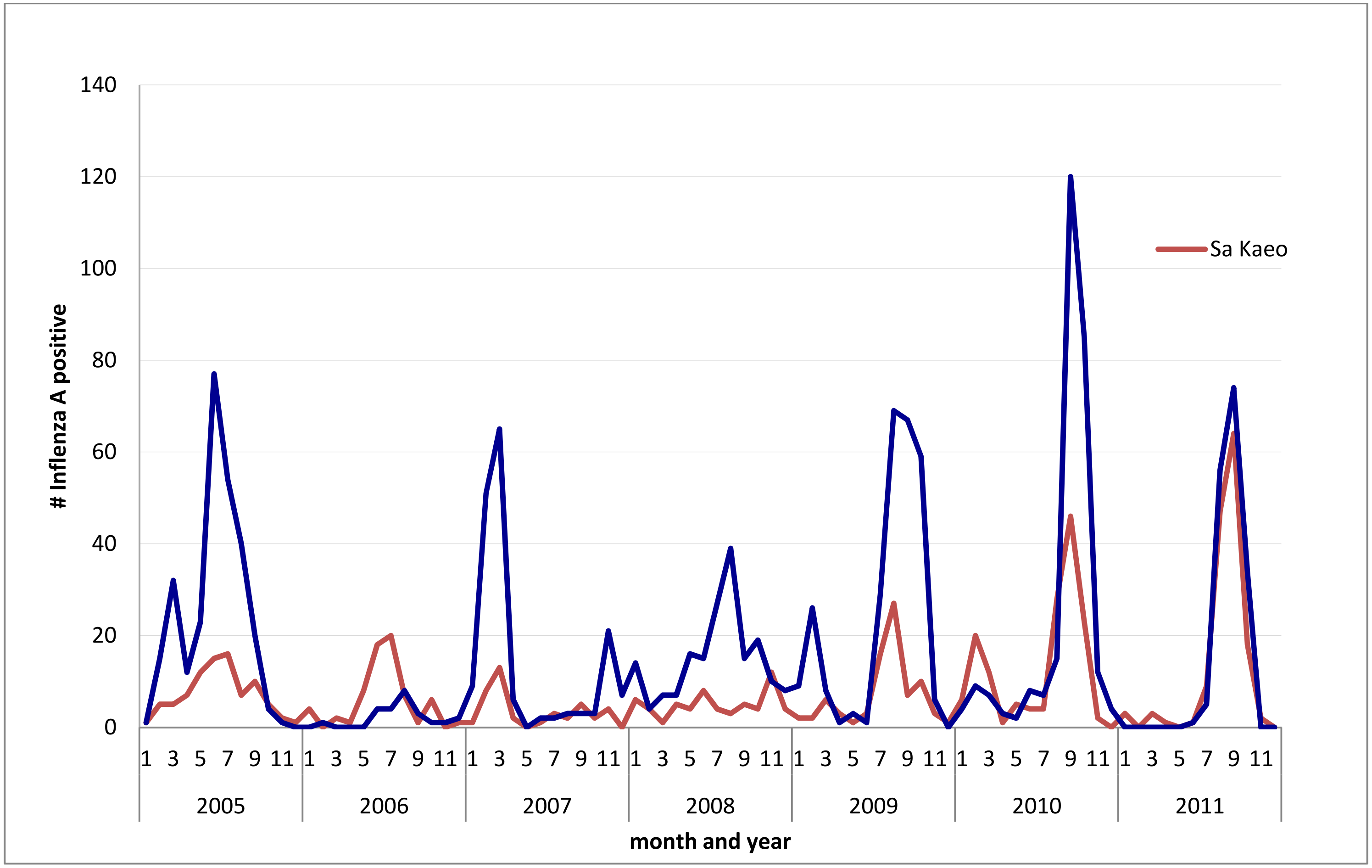


Figure IV. Seasonality of influenza A positive hospitalized inpatients in Sa Kaeo and Nakhon Phanom provinces, Thailand (2005-2011)



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III

Public health implications of the study

Summary of findings

Although our results indicate that school children most likely play a role in the spread of seasonal influenza in Thailand, we found very little differences in the age-specific timing of incidence between different school aged groups (5-9 and 10-19 year olds). However, when considering pandemic influenza epidemics in Thailand, the age distribution clearly shifted to older ages, calling into question whether social distancing methods such as school closures would have a significant effect in limiting influenza spread during a pandemic outbreak. Ascertaining the roles that different age groups play in influenza transmission dynamics will strongly dictate the acquisition and distribution of vaccinations and prophylactic treatments in Thailand, as well as have a strong impact on the methods that the Thai MOPH chooses to adopt in order to control influenza transmission.

Public health implications

Our results differ from prevailing ideas that younger school-aged children are responsible for spreading influenza. This has implications for the implementation of policies aimed to moderate the spread and transmission of influenza A, such as school closings. Consequently, it is prudent for the Thai influenza vaccination campaigns to continue to target risk groups as a primary means of prevention.

The US Advisory Committee on Immunization Practices (ACIP) currently recommends that influenza vaccinations be administered for all persons aged >6 months (1). Since 2008, vaccination campaigns in Thailand began in May of each year and targeted healthcare workers, people with underlying health conditions and older adults (>65 years) (2). In 2009, guidelines were expanded to include pregnant women, obese individuals, persons who are mentally disabled and children aged 6-24 months (3). Each year, the government has increased the amount of vaccine it purchases for the public and efforts are currently underway to increase local vaccine production (3). Despite efforts to augment vaccine distribution, influenza vaccine distribution only covers ~10% of the population in Thailand (3).

In the case of a pandemic outbreak, our results suggest that young adults should be included in target vaccine intervention groups, due to their potential role as drivers of pandemic influenza transmission at the community level. This may prove difficult in a country such as Thailand, which has limited resources and a low rate of influenza vaccinations. If relying heavily on influenza vaccination uptake in the case of a pandemic outbreak, Thailand must increase its vaccine purchasing or production, as well as devise plans to effectively disseminate vaccines to different parts of the country.

Ascertaining the roles that different age groups play in influenza transmission dynamics will strongly dictate the establishment of interventions to mitigate influenza spread.

Further studies are needed to deduce the local drivers of seasonal and pandemic influenza. Additionally, studies must also consider ways in which transmission dynamics may vary between different regions in Thailand. Province-specific variations in transmission dynamics may impact the effectiveness of strategies put in place to mitigate seasonal and/or pandemic influenza spread.

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IV

Appendices

APPENDIX A

Letter of invitation and Emory University Internal Review Board exemption

ศูนย์ความร่วมมือไทย — สหรัฐ ด้านสาธารณสุข (ศรทส)

Thailand MOPH – U.S. CDC Collaboration

การประสานงานระหว่างกระทรวงสาธารณสุข ประเทศไทย และศูนย์ควบคุมโรคแห่งชาติ ประเทศสหรัฐอเมริกา

A joint activity of the Thailand Ministry of Public Health & the U.S. Centers for Disease Control and Prevention

Rollins School of Public Health
Emory University
Atlanta, GA

February 25, 2012

RE: Letter of invitation for Ms. Neia Prata Menezes

To whom it may concern:

I would like to invite Ms. Menezes to work with the Influenza Program in Thailand from around mid-May to mid-August, 2012. The Influenza Program is part of an official collaboration between the Thailand Ministry of Public Health and the United States Centers for Disease Control and Prevention. I will provide direct supervision of Ms. Menezes. In addition, she will work closely with Thai nationals in our CDC office as well as staff at the Thailand Ministry of Public Health.

Ms. Menezes will explore temporal patterns of circulation of respiratory viruses, specifically influenza and RSV, by age group. These findings will be important to understand how these viruses move through the community and will have implications for targeting prevention and control strategies. She will do this analysis using 8 years of data from a population-based surveillance system for hospitalized respiratory disease in two provinces in Thailand. The project is already approved by the Institutional Review Board of CDC and the Ethical Review Committee of the Thailand Ministry of Public Health. As the project is an analysis of the data already collected, no additional human subject approval is needed.

Our office will provide Ms. Menezes with office space, assistance in finding local housing and translation services as needed.

We look forward to welcoming Ms. Menezes to our office. Please contact me if you have any questions.

Sincerely,

Sonja J. Olsen, PhD
Director, Influenza Program
Thailand MOPH – U.S. CDC Collaboration
Email: SOlsen@cdc.gov

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APPENDIX B

Influenza A epidemics in Sa Kaeo and Nakhon Phanom, Thailand (2003-2011)

Table I. Influenza A epidemics identified in outpatient* data (2003-2005)

Year	Epidemic months	Duration (epiweeks)	Magnitude (total flu positive)
Sa Kaeo			
2003	JUL-SEP	8	16
2004	FEB-APR	8	15
2004	APR-OCT	27	221
2005	JAN-MAR	9	22
Median length: 8.5 epiweeks (range 8-27 epiwks)			

* Outpatient data were collected from Sa Kaeo province only

Table II. Influenza A epidemics identified in inpatient data (2005-2011)

Year	Epidemic months	Duration (epiweeks)	Magnitude (total flu positive)
Sa Kaeo			
2005	APR-AUG	21	57
2006	MAY-AUG	13	53
2007	FEB-MAR	9	21
2008	NOV-DEC	9	16
2009	JUN-SEP	14	51
2010	JAN-MAR	11	37
2010	JUL-NOV	17	102
2011	JUL-NOV	18	140
Median length: 13.5 epiweeks (range 9-21 epiwks)			
Nakhon Phanom			
2005	FEB-MAY	14	63
2005	MAY-SEP	22	214
2007	JAN-APR	13	130
2007	NOV-DEC	11	28
2008	MAR-JUN	15	32
2008	JUN-DEC	28	127
2009	DEC-APR	17	51
2009	JUN-NOV	23	231
2010	JUL-DEC	19	235
2011	JUL-OCT	16	168
Median length: 16.5 epiweeks (range 11-28 epiwks)			

APPENDIX C

Tables depicting Cox proportional hazards model results

Table I. Log rank survival analysis and cox model regression results assessing the age-specific timing to incidence of influenza A for outpatients in Sa Kaeo, Thailand (2003-2005)

	OUTPATIENTS			
	Survival time		Cox model	
	log rank test	Pr	HR*	Pr
Age (years)				
<1	-0.48	0.75	0.71	0.37
1-4	5.13	0.21	0.76	0.10
5-9	2.31	0.58	0.82	0.21
10-19	-7.89	0.07	*ref*	
20-29	1.17	0.48	0.76	0.47
30-64	1.95	0.43	0.67	0.10
>65	-2.20	0.04	1.72	0.24

* HR, Hazard Ratio

APPENDIX C

Table II. Log rank survival analysis and Cox model regression results assessing the age-specific timing to incidence of influenza A for hospitalized inpatients in both Sa Kaeo and Nakhon Phanom, Thailand (2005-2011)

	INPATIENTS - BOTH PROVINCES			
	Survival time		Cox model	
Age (years)	log rank test	Pr	HR*	Pr
All detected influenza epidemics				
<1	9.43	0.08	0.66	**0.001**
1-4	27.71	**<0.01**	0.69	**<0.001**
5-9	-9.90	0.17	0.87	0.20
10-19	-25.45	**<0.001**	*ref*	
20-29	-16.26	**<0.01**	1.05	0.68
30-64	-3.68	0.72	0.80	**0.01**
>65	18.16	0.06	0.70	**<0.001****
Seasonal influenza (2005-2008)				
<1	6.89	0.11	0.63	**0.01**
1-4	9.16	0.17	0.69	**0.02**
5-9	-7.78	0.09	0.86	0.40
10-19	-9.31	**0.03**	*ref*	
20-29	-0.62	0.81	0.83	0.48
30-64	-3.19	0.61	0.76	0.09
>65	4.85	0.47	0.70	**0.02**
Pandemic influenza (2009 - 2011)				
<1	2.55	0.45	0.70	0.06
1-4	18.54	**0.01**	0.68	**<0.001**
5-9	-2.12	0.71	0.88	0.33
10-19	-16.14	**0.01**	*ref*	
20-29	-15.64	**<0.001**	1.14	0.39
30-64	-0.49	0.95	0.81	0.06
>65	13.31	**0.05**	0.70	**<0.01**

***** HR, Hazard Ratio

****** p<0.0001

******* Bolded p-values are statistically significant at the α <0.05 level, indicating that for Log Rank test results, the ranking of the age group is statistically significant when compared to other age groups, and across all designated epidemics. For Cox model results, bolded p-values indicate that the derived hazard of obtaining influenza A first (HR) for the age group is statistically significant when compared to the referent 10-19 age group.

APPENDIX C

Table III. Province specific log rank survival analysis and Cox model regression results assessing the age-specific timing to incidence of influenza A for hospitalized inpatients in Sa Kaeo and Nakhon Phanom, Thailand (2005-2011)

	PROVINCE SPECIFIC							
	Sa Kaeo				**Nakhon Phanom**			
	Survival time		Cox model		Survival time		Cox model	
Age (years)	log rank test	Pr	HR*	Pr	log rank test	Pr	HR*	Pr
All detected Influenza epidemics								
<1	1.41	0.57	0.80	0.42	8.02	0.09	0.62	**<0.01**
1-4	2.86	0.59	0.88	0.49	24.85	**<0.01**	0.63	**<.001****
5-9	1.86	0.64	0.69	0.69	-11.77	**0.05**	0.88	0.28
10-19	-3.94	0.25	*ref*		-21.51	**<0.01**	*ref*	
20-29	-0.55	0.85	1.01	0.97	-15.71	**<0.001**	1.09	0.54
30-64	-8.10	0.12	1.03	0.87	4.43	0.62	0.74	**<0.01**
>65	6.46	0.19	0.79	0.21	11.70	0.16	0.68	**<0.001**
Seasonal Influenza (2005-2008)								
<1	-0.10	0.96	0.72	0.48	6.98	0.07	0.61	**0.02**
1-4	3.00	0.32	0.61	0.19	6.17	0.30	0.71	**0.04**
5-9	-0.56	0.78	0.72	0.47	-7.22	0.08	0.88	0.54
10-19	-2.03	0.22	*ref*		-7.28	0.07	*ref*	
20-29	-0.92	0.39	1.54	0.53	0.30	0.90	0.77	0.37
30-64	0.58	0.82	0.60	0.21	-3.77	0.50	0.79	0.18
>65	0.02	0.99	0.69	0.32	4.83	0.42	0.70	**0.03**
Pandemic Influenza (2009 - 2011)								
<1	1.51	0.40	0.73	0.40	1.04	0.71	0.68	0.09
1-4	-0.14	0.98	0.97	0.90	18.68	**<0.001**	0.56	**<0.001****
5-9	2.43	0.48	0.95	0.84	-4.55	0.31	0.88	0.41
10-19	-1.91	0.52	*ref*		-14.23	**0.01**	*ref*	
20-29	0.37	0.89	1.02	0.94	-16.01	**<0.001****	1.26	0.18
30-64	-8.69	**0.05**	1.21	0.39	8.20	0.23	0.70	**0.01**
>65	6.43	0.10	0.79	0.30	6.87	0.23	0.67	**<0.01**

***** HR, Hazard Ratio

****** p<0.0001

******* Bolded p-values are statistically significant at the α <0.05 level, indicating that for Log Rank test results, the ranking of the age group is statistically significant when compared to other age groups, and across all designated epidemics. For Cox model results, bolded p-values indicate that the derived hazard ratio of leading influenza A epidemics (HR) for the age group is statistically significant when compared to the referent 10-19 age group.