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Field Epidemiology Training Program, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Tiwanond Road, Talad Kwan Subdistrict, Muang District, Nonthaburi 11000, Thailand

Tel: +662-5901734, Fax: +662-5918581, Email: osireditor@osirjournal.net

Website: <**http://www.osirjournal.net**>

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Field Epidemiology Training Program, Bureau of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625901734-5, Fax: +6625918581, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Editorial

Humans still Needed for Surveillance

Angela Song-En Huang, Chief Editor

For a number of years, Taiwan Field Epidemiology Training Program used a case study during its summer course to introduce the different surveillance methods used by the Taiwan Centers for Disease Control to understand the epidemiology of enterovirus infection, which may cause hand foot and mouth disease (HFMD) or herpangina, and may, at times, lead to severe neurologic, respiratory, or cardiovascular complications. The case study takes trainees through the history of enterovirus surveillance that included the use of sentinel physician surveillance, the establishment of real-time outbreak and disease surveillance (RODS), laboratory surveillance and reporting of enterovirus infection with severe complication to the National Notifiable Disease Surveillance System.

The sentinel physician surveillance was a network of more than 600 clinics and 71 hospitals. Participating physicians would report the number of HFMD/herpangina cases and the total number of patient visits during the previous week. A weekly phone call made by the surveillance team to the sentinel sites gathered the number from the entire country. Sentinel physician surveillance used much human resources, because, of the 704 clinic or hospitals that participated, only 98 entered the results using a web-based system; 442 faxed in their results and 164 relied on weekly phone calls. Information obtained through fax and phone calls were then manually entered.[1]

When RODS was introduced in 2006, it was slated as an eventual replacement for the sentinel physician surveillance. Originally developed by the University of Pittsburgh, RODS is a real-time electronic surveillance program that automatically collected and analyzed data from emergency department visits at participating hospitals, which upload patient information on a daily basis. After initial setup, RODS needed little manpower to gather information or produce outputs.

Time and manpower were saved when RODS replaced sentinel physician surveillance completely, and HFMD trend continued to be monitored. However, while RODS was good at providing disease trend, it was not able to give information on changes in circulating viruses or severity of diseases.

When the sentinel physician surveillance was abolished at the end of 2009, some physicians remained in the network to regularly provide clinical specimens from children with suspected HFMD or herpangina, as participants of the enterovirus infection laboratory surveillance. By providing clinical specimens for virus isolation, changes in circulating enterovirus could be monitored. Furthermore, cases of enterovirus infections which resulted in neurologic, respiratory, or cardiovascular complications should be reported to the National Notifiable Disease Surveillance System as cases of “enterovirus infection with severe complications”.

As we can see from an article in this issue, “Evaluation of Early Aberration Reporting System (EARS) for Dengue Outbreak Detection in Thailand”, this automated system had a very specific task, which was to detect early signals of upcoming outbreaks. Like RODS in Taiwan, EARS could not provide information on changing circulating virus type, often the reason for outbreaks, or disease severity.

To understand the “why” behind disease trends, additional information, which might only be gathered “non-electronically”, is needed. In “Malaria Situation and Expansion of Key Interventions for Malaria Elimination in Bago Region, Myanmar, 2007-2015”, through clinical specimen surveillance, changes in the proportion of *P. falciparum* malaria was detected, which might be associated with decreasing

malaria-associated deaths. In “Approaches to Prevent Influenza Transmission among New Conscripts in a Battalion during High Seasonality”, the first sign of outbreak was not detected through automated reporting. Information such as species of malaria parasite causing disease, or “five conscripts from a single unit in a battalion were sick” still needed human to human interaction to be detected, gathered, and reported.

In August 2017, nearly eight years after the sentinel physician surveillance was discontinued, a phone call-based surveillance system was re-established. This time, only about 120 physicians were recruited for unstructured information gathering on disease trends and possible rumors of outbreaks based on physician experience.[2] The network was also used to maintain working relationship between public health and healthcare professionals.

The use of automated systems is inevitable and often necessary as electronic technology becomes accessible to the remotest parts of our region. However, it is difficult to understand all aspects of a disease using just one surveillance system. Through different methods of surveillance, we can capture much more information in helping us to better monitor and control diseases. While more electronic surveillance systems are being incorporated, we need to also maintain systems which encourages human interaction to allow reporting of the unexpected.

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Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625901734-5, Fax: +6625918581, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Evaluation of Early Aberration Reporting System for Dengue Outbreak Detection in Thailand

Supharerk Thawillarp[1,*], Carlos Castillo-Salgado[2], Harold P. Lehmann[1]

1 Division of Health Sciences Informatics, Johns Hopkins University School of Medicine, United States

2 Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, United States

*Corresponding author, email address: sthawil1@jhmi.edu

Abstract

Thailand is one of the highest-burden countries for dengue infections in the South-East Asia Region of the World Health Organization. The 5-year median is normally used for outbreak detection; however, studies assessing the performance of this indicator against other detection methods are lacking. We, therefore, conducted a descriptive ecological study from a dataset comprised of patient visits to public hospitals for dengue treatment that were reported to the Ministry of Public Health. The aim was to evaluate the performance of an early aberration reporting system (EARS) in detecting dengue outbreaks, compared to using the 5-year median method. During 2003-2015, there were 1,014,201 patient visits and seven reported dengue outbreaks, with the largest occurring in 2013, and six seasonal peaks. The EARS was able to detect all seven dengue outbreaks and six seasonal peaks, including one outbreak that occurred in 2014 which was undetected by the 5-year median. However, EARS cannot provide information on trends, outbreak severity and issues noise signals. Our recommendation was to combine the EARS with the 5-year median method to reduce the number of false positive signals, or use the 5-year median method as a confirmatory tool.

Keywords: dengue, public health informatics, early disease detection, surveillance systems, disease notification, Thailand, EARS, 5-year median

Introduction

Dengue fever is a vector-borne disease caused by dengue virus. The virus is transmitted principally by *Aedes* mosquitoes, namely *A. aegypti* and *A. albopictus*, while both of which are commonly found in tropical regions. In 2012, dengue surpassed malaria as the most prominent vector-borne disease globally in terms of morbidity and cost of treatment.[1] The impact of dengue is the greatest in South-East Asia.[2] In 2015, 144,952 new dengue cases (223 per 100,000 population) were reported to the Ministry of Public Health (MOPH), including 147 deaths.[3] The burden of this disease in Thailand is one of the highest in the world.[4]

The World Health Organization formulated a dengue strategic plan in the South-East Asia Region, focusing on improving early detection and timely outbreak control efforts.[2] Most of the published papers focused on outbreak detection, yet only a few focused on detection of dengue outbreaks. Consequently, research on this topic was a high priority[5]. The MOPH currently uses the 5-year median as the threshold for outbreak detection. However, there were no studies assessing its performance against other detection methods.

The early aberration reporting system (EARS), developed by the US Centers for Disease Control and Prevention, was designed to detect early signals of upcoming outbreaks. The EARS has been used in several large public events such as the US Democratic National Convention in 2004, the Republican National Convention, the G8 Submit in Georgia 2004 and the 2004 Summer Olympics.[6] However, there are very few studies evaluating the implementation of EARS on vector-borne diseases, including early detection of dengue outbreaks[7,8].

This was the first study to examine the feasibility of implementing EARS and compare EARS against the current outbreak detection method (5-year median) in

Thailand. The objective was to compare the 5-year median method with the EARS for detecting dengue outbreaks in Thailand between 2003 and 2015.

Methods

Study Design

We conducted a descriptive ecological study based on secondary data obtained from the national (R506) surveillance system in the Bureau of Epidemiology, MOPH. The ecological unit was the weekly aggregation of dengue visits.

Study Population

The R506 national surveillance system captures health data from every public hospital in Thailand, which matches specific international classification of diseases (ICD)-10 codes and is compatible with disease prevention and epidemiological studies. The system is similar to the national electronic disease surveillance system of the United States Centers for Disease Control and Prevention. Data are submitted to provincial health offices on a weekly basis for validation and cleaning by local public health staff prior submission to the Bureau of Epidemiology. The target population was Thai patients using public hospitals with a diagnosis of any dengue condition.

Data Sources

A dataset of patients diagnosed with dengue (ICD-10 code A90 for dengue fever (DF), A91 for dengue hemorrhagic fever (DHF), and A99 for unspecified viral hemorrhagic fever) and visited a hospital during 2003 and 2015, which was created by the Bureau of Epidemiology. Approximately one million de-identified individual dengue records were obtained, containing data on individual visits for the following variables: gender, age, nationality, occupational status, location, hospital class, patient type, outcome, and time of diagnosis, visit and report.

Detection Methodologies

Five-year median

The 5-year median threshold was calculated from the weekly aggregated number of patient visits in the same week during the five years prior to the time point of interest. For example, the 5-year median for 52th week in 2015 was calculated from the number of patient visits in 52th weeks in 2014, 2013, 2012, 2011 and 2010.

An outbreak is signaled when the number of dengue patient visits for any particular week exceeds the 5-year median. This approach is recognized by the Department of Disease Control and it is currently implemented as the default outbreak detection threshold in Thailand. The highest case number of each year that does not surpass the threshold or threshold is not available will be considered as "seasonal peak".

EARS Algorithms

The EARS consists of three components called C1, C2 and C3. C1 implements a moving average based on the previous seven days while C2 implements a moving average based on 7-day period three days prior to the baseline measurement (in other words a 2-day lag). C3 is calculated using a modified 3-day cumulative sum of C2. An outbreak is signaled at time t when either of C1 or C2 exceeds three or when C3 exceeds two. The components are given by the following formulas[9,10].

$$C_1(t) = \frac{Y(t) - \bar{Y}_1(t)}{S_1(t)}$$

$$C_2(t) = \frac{Y(t) - \bar{Y}_3(t)}{S_3(t)}$$

$$C_3(t) = \sum_{i=t}^{t-2} \max[0, C_2(i) - 1]$$

In the formulas above, Y(t) is the observed frequency count in period t, while S_i are the moving averages and standard deviations in period t for component n as defined below.

$$\bar{Y}_1(t) = \frac{1}{7}\sum_{i=t-1}^{t-7} Y(i) \quad \text{and} \quad S_1^2 = \frac{1}{6}\sum_{i=t-1}^{t-7} [Y(i) - \bar{Y}_1(i)]^2$$

$$\bar{Y}_3(t) = \frac{1}{7}\sum_{i=t-3}^{t-9} Y(i) \quad \text{and} \quad S_3^2 = \frac{1}{6}\sum_{i=t-3}^{t-9} [Y(i) - \bar{Y}_1(i)]^2$$

Data Analysis

Descriptive statistics were presented using frequencies, percentages, medians and interquartile ranges. Visualization was used in this study to compare the detection of surveillance algorithms and thresholds. All data analyses were conducted in R version 3.3.2[11].

The 5-year median was used as the gold standard for calculation of the sensitivity and specificity of the EARS. As the purpose of the EARS is to signal an alert before an outbreak occurs, we modified the sensitivity calculation using the number of outbreaks detected by the 5-year median that were preceded by any component of the EARS divided by the total number of outbreaks.

Specificity was defined as the number of weeks with no outbreak, according to the 5-year median method, divided by the number of weeks with no alert signal from any EARS component.

Results

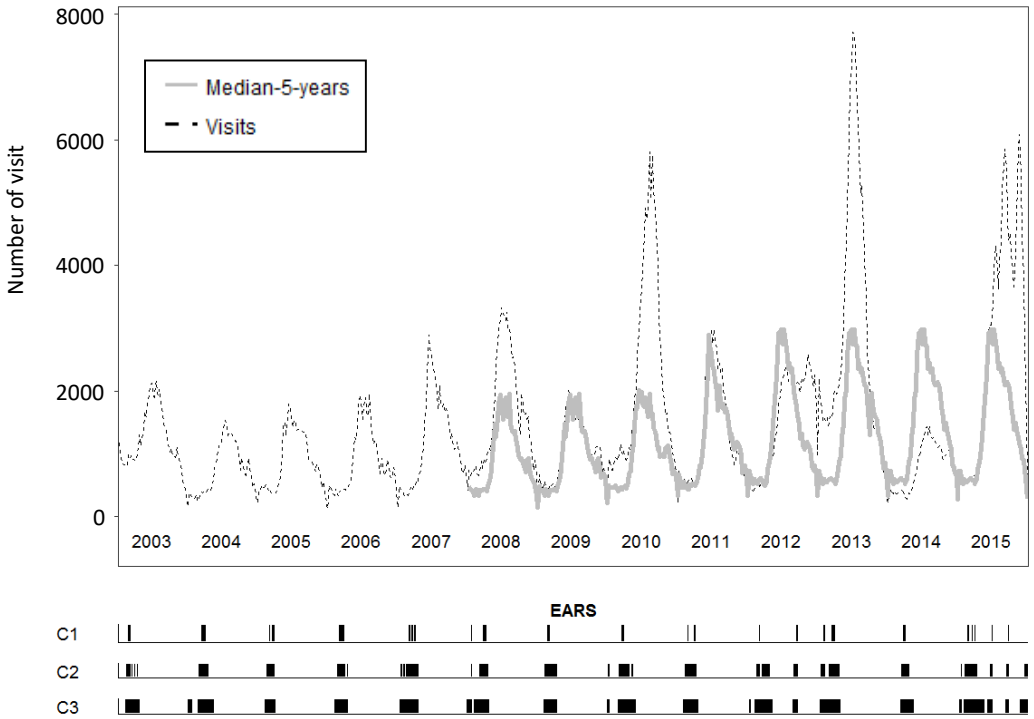
During 2003-2015, there were 1,014,201 patient visits to hospital with a diagnosis of either DF, DHF or dengue shock syndrome (DSS). During this time, there were 1,122 deaths recorded. There were 120 visits per 100,000 person-years. DF contributed the highest of the visits as 52.1% (528,291/1,014,201), followed by DHF as 46.2% (468,341/1,014,201) and DSS as 1.7% (17,569/1,014,201). Most patients were citizens of Thailand (97.9%) or Myanmar (1.3%). The median age was 15 years (Interquartile range 10-24 years), with a male to female ratio of 1.1:1. The age groups with the highest incidence were 5-12 years (28.6 per 100,000 person-years), followed by 13-18 years (25.3 per 100,000 person-years) and 26-45 years (18.8 per 100,000 person-year). Approximately half of the visits were by students (48.3%), followed by elementary workers (16.4%) and farmers (6.1%) (Table 1).

Five-year Median

There were seven dengue outbreaks and six seasonal peaks (2003-2007 and 2014) signaled in the study period based on the 5-year median. Most of the outbreaks exhibited a seasonal pattern with emergence (May) and subsidence (August), occurring at approximately the same period each year. The outbreak with the highest number of patient visits occurred in 2013 and the seasonal peak occurred in 2014 (Figure 1).

Table 1. Demographic characteristic of dengue patients who visited public hospitals under the Ministry of Public Health, Thailand, 2003-2015

Characteristic	Number of visit	Percent
Nationality (n=1,014,201)		
Thailand	99,2528	97.9
Myanmar	13,320	1.3
Others	8,353	0.8
Gender (n=1,000,914)		
Male	516,921	51.6
Female	483,993	48.4
Occupation (n=1,000,864)		
Student	489,746	48.9
Elementary service worker	164,430	16.4
Farmer	61,994	6.2
Unemployed	25,081	2.5
Merchant	16,386	1.6
Others	243,227	24.4
Age group (year) (n=1,000,706)		
0-4	50,196	5.0
5-12	283,197	28.3
13-18	266,846	26.7
19-25	153,129	15.3
26-45	182,211	18.2
46-60	47,558	4.7
>60	17,569	1.8



Solid black bars represent alert signals from C1, C2 and C3. As the 5-year median method requires five years of historical data, the threshold was available only after 2008 while the EARS needs only the previous 7-10 days, and was therefore readily available since 2003. EARS signals appear before every outbreak and disappear after visit numbers start to rise.

Figure 1. Comparison between algorithms of early aberration reporting system (EARS) and moving-5-year median of dengue infection, Thailand, 2003-2015

Table 2 Positive predictive value, sensitivity and specificity of early aberration reporting system (EARS) compared to the five-year median of dengue infection, Thailand, 2003-2015

Method	Total signal	Total number of week	Sensitivity[1] (n=7)	Specificity[2]
C1	23	291	100%	97.6% (122/125)
C2	80	291	100%	86.4% (108/125)
C3	122	291	100%	79.2% (99/125)

[1] As the purpose of the EARS is to provide an early warning, not an outbreak threshold, the sensitivity was calculated based on whether the signals appeared before the seven outbreaks defined by median-5-years.

[2] In contrary to the sensitivity, the specific was calculated using "week" unit. The nominator was the non-outbreak week without EARS signal and the denominator was the total non-outbreak week.

EARS

In 291 weeks during the study period, EARS C3 issued the highest number of signals at 122 while C2 issued 80 signals and C1 issued 23 signals. As the EARS detected every outbreak and seasonal peak by sending early warning signal, the sensitivity of all three EARS components was 100.0% (7/7 outbreaks). There were 125 weeks with no EARS signal. C1 had the highest specificity of 97.6% (122/125 weeks) while C3 had the lowest with a rate of 79.2% (99/125).

The three EARS components were able to detect every outbreak during 2008-2015, including the outbreak in 2014 which was a seasonal peak and did not classify as an outbreak by the 5-year median method. C3 often provided the first early signal, followed by C2 and C1. The durations of all three signals, from the first signal to the peak of the outbreak, were similar. When approaching the outbreak peak, all three EARS algorithms signaled an outbreak in the period, leading up to the peak with C3 often providing the first signal. However, after the peak, the signals disappeared altogether. From figure 1 and table 2, C3 issued more signals than C2 while C2 issued more signals than C1. C3 often overlapped with C2 while C2 overlapped with C1. In other words, C1 seemed to retain the EARS early warning capacity while issuing the lowest number of signals. All three EARS components were able to signal a seasonal peak during 2003-2007 while the 5-year median threshold was not available due to lack of historical data.

Discussion

Dengue outbreaks occur every year in Thailand, and thus, detection methods that can provide information on the timing and severity of any impending outbreak is important. This was the first national study to evaluate the EARS for dengue outbreak detection in Thailand.

The 5-year median threshold method has been used in Thailand for several years for detecting dengue outbreaks. It is easy to comprehend and calculate, and based on our results, could detect all, except one with the seasonal peak in 2014. However, at the beginning of each dengue outbreak, the number of patient visits will increase rapidly and the current 5-year median detection method cannot detect any outbreak early enough to allow preparation for control measures to be implemented. In effect, it can only be used as a confirmatory indicator, not as early warning system for an impending outbreak. Although emergence of a dengue outbreak can be anticipated during the rainy season, having an early warning system is very important for public health as it allows more time to prepare for the upcoming outbreaks or unanticipated second peaks in MOPH.

The EARS, while able to signal all the outbreaks beforehand, was able to detect the upcoming second peak during 2012, 2013 and 2015 outbreaks as well. Normally, the EARS stopped issuing signals after a peak, except during the outbreaks in 2012, 2013 and 2015, and continued to issue signals after the peak. These alerts were followed by a second peak. This finding was consistent with a recent study in China which found that the EARS was able to provide an early signal predicting an upcoming outbreak as well as its peak[12].

EARS also successfully detected every seasonal peak during 2003-2007. These outbreaks could not be confirmed by the 5-year median method since the method requires five years of historical data for the threshold calculation. EARS proved to retain warning performance even without historical data. Implementation of EARS, therefore, might prove to be of great benefit as a signal for upcoming dengue outbreaks and seasonal peaks, encouraging the Thai MOPH to initiate timelier dengue control measures.

However, there are some drawbacks of the EARS. Firstly, it does not provide any information on the severity of an outbreak. Secondly, many alerts are signaled before an outbreak actually occurs, a situation which can make interpretation difficult.

Recommendations

Even though the EARS provides potentially invaluable information, it can cause confusion among decision makers whether they should take actions since there could be also noise signals. Many of the EARS algorithms on influenza and influenza-like illnesses exist challenges[13]. This can result in putting more burden on local health workers as MOPH depends on them to validate and respond to noise signals[14]. We recommended that the EARS should be used for early warning purpose in combination with the 5-year median method as a confirmatory indicator in MOPH.

This study was conducted using weekly dengue information from Thailand, a tropical country in South-East Asia. Application of the EARS to other countries should take into consideration of differences in the data reporting systems, dengue outbreak characteristics and available public health infrastructures. We would like to encourage other public health authorities and researchers from tropical countries to review and evaluate these innovative early detection methods to continuously improve their public health surveillance and control programs.

Limitations

Our data sources were collected merely from the public hospitals. Private hospitals and clinics in Thailand are not required to submit health data to MOPH. However, as the capacity of private hospitals in Thailand is much lower than that of the public hospitals, they would have contributed a small proportion of the cases.

The number of dengue patient visits was used, not the number of illness episodes, as the numerator for calculating the incidence rate due to lack of computational resources. However, the data were validated and deduplicated from local and regional health offices. Thus, the use of patient visits should be acceptable for estimation of incidence rates.

Conclusion

In summary, implementing the EARS is valuable in detecting dengue outbreaks. However, there is no one-fit-all solution for early outbreak detection of dengue. The 5-year median method is simple to calculate and widely used, yet it does not provide an early warning mechanism and therefore, can only serve as a confirmatory indicator. The EARS algorithms were able to detect every outbreak during 2008-2015, including the seasonal peak in 2014. However, the EARS does not provide information on trends and outbreak severity and issues noise signal. To reduce the number of noises, we suggested MOPH to rely mainly on C1 as we did not observe any information gained in adding C2 or C3, or any combination, to C1. Another possible approach was to combine C1 with the 5-year median method to reduce the number of false signals or use the 5-year median method as a severity and confirmatory indicator only. As this study was specific for climate and the reporting system in Thailand, implementing our recommendations in other countries might need to consider the specific contexts of local public health surveillance systems and epidemiological risk factors of dengue outbreaks in the areas. However, there are several other early detection methods available and other countries are encouraged to explore the specific dengue data and epidemiological situations in order to improve the public health surveillance systems.

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Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625901734-5, Fax: +6625918581, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Situation of Malaria and Expansion of Key Interventions for Malaria Elimination in Bago Region, Myanmar, 2007-2015

Wint Phyo Than[1,3,*], Krongthong Thimasarn[2], Than Naing Soe[1], Aung Thi[1]

1 National Malaria Control Program, Public Health Department, Ministry of Health and Sports, Myanmar

2 Department of Disease Control, Ministry of Public Health, Thailand

3 International Field Epidemiology Training Program, Bureau of Epidemiology, Ministry of Public Health, Thailand

*Corresponding author, email address: wintphyothan@gmail.com

Abstract

Analysis of malaria trends is important for planning of malaria elimination. Therefore, we reviewed the malaria monthly reports and key interventions for malaria elimination in Bago Region of Myanmar between 2007 and 2015. Secondary data analysis revealed the trends in malaria morbidity, mortality, malaria positive rate (MPR), malaria species, annual parasite incidence (API) and annual blood examination rate (ABER). Key interventions included distribution of insecticide-treated net (ITN), long lasting insecticidal net (LLIN) and case detection. Over the 8-year period, malaria morbidity and mortality rates markedly reduced from 8 to 0.3 per 1,000 population and 1.4 to 0.1 per 100,000 population respectively. During 2010-2015, API and MPR correspondingly reduced. Together with the concomitant increase in ABER and townships with API lower than one per 1,000 population, confirmed cases of *P. falciparum* malaria markedly decreased from 91.1% in 2007 to 55.4% in 2015. Meanwhile, the ITN/LLIN scaling-up activities resulted in an increase in population coverage from 23.5% in 2011 to 69.3% in 2015. Data from the public sector showed declining trends in malaria morbidity and mortality and low API, increasing the chance of malaria elimination. Still, there is a possibility of residual malaria that may trigger a resurgence, and thus, it is worthwhile to promote surveillance systems, especially in private sector health care establishments.

Keywords: malaria situation, annual blood examination rate, annual parasite incidence, Myanmar

Introduction

Globally, there was 18% decline in malaria cases from 262 million in 2000 to 214 million in 2015 and 48% decline in malaria deaths from 839,000 in 2000 to 438,000 in 2015. Several countries in South-East Asia are now moving towards malaria elimination.[1] In Myanmar, the incidence of reported malaria decreased by 82% from 622,373 in 2005 to 112,776 in 2015 and deaths from malaria decreased by 98% from 1,707 in 2005 to 37 in 2015.[2] Furthermore, there was an accelerated decrease of 40% in the number of malaria cases in the public sector from 2015 to 2016.[2-3] The proportions of *Plasmodium falciparum* (Pf), *P. vivax* (Pv) and mixed infections in 2015 were 65.4%, 31.8% and 2.8% respectively.[2] The main source of data capture is from the regular reporting system in the public health facilities. The main vectors reported from all states and regions of Myanmar are *Anopheles minimus* and *An. dirus*.[3] The national malaria control programme (NMCP) aims to achieve malaria elimination in 2030 in line with the elimination strategy in the Greater Mekong Subregion.[4]

There are total 28 townships with a population of 4.9 million in Bago Region, Myanmar. Due to relatively low malaria incidence report, the region has been targeted by NMCP for malaria elimination in 2020.[3] In Bago Region, there were two malaria implementing partners during 2007: Japan International Cooperation Agency (JICA) and United Nations International Children's Emergency Fund. In 2015, there were seven partnerships tackling malaria, including JICA, University of Research Co., American Refugee Committee, Population Service International, Burnet Institute Myanmar, Myanmar Medical

Association and Myanmar Health Assistant Association. In 2007, there were 859 health facilities, 1,071 basic health staff and no village health volunteers. However, in 2015, the workforce capacity increased to 1,450 health facilities, 2,529 basic health staff and 1,525 village health volunteers.[4]

Alongside capacity building of basic health staff and village health volunteers, key interventions implemented for malaria elimination include early case detection and effective treatment, distribution of insecticide-treated nets (ITN) and long lasting insecticidal nets (LLIN) to communities, active case finding, and screening point activities. Indoor residual spraying was highly selective and implemented only in a few townships. Bago Region is well known as a model for good collaboration of implementing partners and existing JICA-initiated pilot studies. Hence, it was selected purposively to explore the malaria situation and the expansion of key interventions for malaria elimination during 2007-2015. Furthermore, malaria trend analysis is important in the planning and tracking the progress of malaria elimination in endemic settings. Therefore, the objectives of this study were to assess the malaria situation in Bago Region during 2007-2015 in terms of morbidity and mortality and assess the effectiveness of expanding key interventions for malaria in relation to coverage and population targeting, implementation of case detection, and scaling-up of ITN and LLIN distribution.

Methods

We conducted a cross-sectional study of malaria cases in Bago Region of Myanmar (Figure 1) during 2007-2015 using the secondary data analysis method.

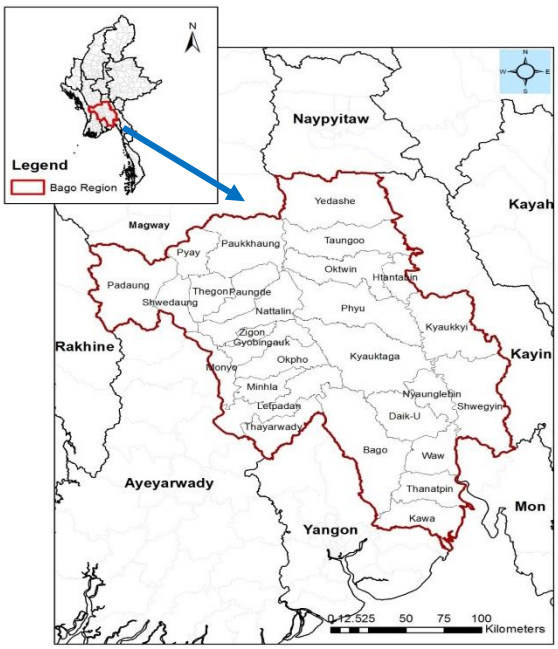

Figure 1. Map of Bago Region, Myanmar

Probable malaria cases were used during 2006-2010 since the monovalent rapid diagnosis test (RDT) used during that period could detect only Pf. Thus, RDT-negative patients with fever and travel history were presumed to have species other than Pf and were treated with chloroquine[2].

Confirmed malaria cases referred to cases confirmed either by microscopy or RDT, regardless of clinical signs and symptoms or travel history. In 2011, NMCP switched to using combination RDT which can differentiate Pf and Pv, and thus, used the term "confirmed malaria".

Annual blood examination rate (ABER) is the number of parasitological tests carried out per 100 mid-year population. Annual parasite incidence (API) is the number of confirmed malaria cases per 1,000 mid-year population at risk. Malaria positivity rate (MPR) is the percentage of positive tests among all tests taken and examined. Malaria morbidity rate is the number of confirmed and probable malaria cases during the reporting period divided by mid-year total population and multiplied by 1000. Malaria mortality rate is the number of malaria deaths during the reporting period divided by total mid-year population and multiplied by 100,000. Case fatality rate (CFR) is the number of malaria deaths divided by the number of malaria in-patients multiplied by 100.[5,6]

Population at risk refers to the population living in a geographical area where locally acquired malaria cases were reported in the past three years.[7]

Net coverage is the percentage of households owning at least one ITN or LLIN. Net utilization is the percentage of the population that slept in a treated mosquito net during the previous night prior to the survey.

Data Source and Data Analysis

Data were collected from township-wise monthly reports and regional annual reports. The number of in-patient malaria cases and deaths and out-patient malaria cases were extracted from township hospital reports and monthly carbonless registers of both basic health staff and village health volunteers.[8-9] Data were validated using EpiData Entry software (version 3.1, EpiData Association, Odense, Denmark).

The LLIN coverage was obtained from the periodic net surveys. The study was carried out in eight randomly selected townships in Bago Region and eight randomly selected villages from each township.

Data of monthly malaria reports from all 28 townships and Bago Region in 2007-2015 were analyzed for frequencies, proportions and rates.

Results

In Bago Region, the number of reported malaria cases was 37,170 (morbidity rate 8/1,000) in 2007 and 1,342 confirmed cases (morbidity rate 0.3/1,000) in 2015, resulting in reduction of morbidity rate by 96.3% over eight years. Malaria cases accounted for 4.3% (34,872/810,977) of all out-patients in 2007 and 0.1% (877/1,291,052) in 2015. The overall patient attendance for malaria treatment significantly increased by 53.0% for out-patients and 62.4% for in-patients during 2007-2015.

Regarding to malaria fatalities, there were 85 deaths (mortality rate 1.4/100,000) in 2007 and four deaths (mortality rate 0.1/100,000) in 2015. Thus, malaria mortality rates were reduced by 95.5% over eight years. The CFR reduced from 2.0% (85/4,298) in 2007 to 0.9% in 2015. However, there was a slight increase in CFR from 0.4% (8/1,940) in 2013 to 0.9% (4/465) in 2015. For admitted patients, malaria deaths accounted for 3.9% (4,298/110,205) of all patients in 2007 and 0.2% (465/207,622) in 2015. Total malaria deaths accounted for 5.9% of total deaths in hospital during 2007 and reduced to 0.2% during 2015 (Figure 2).

Concerning the case detection method, a programmatic shift was apparent in blood examination by microscopy to RDT being introduced in 2007. The number of RDT examinations increased from 46,228 in 2007 to 61,307 in 2012, then decreased to 40,729 in 2015. The number of RDT examinations increased by 25% between 2007 and 2015. However, during 2013-2015, there was a slight reduction in the number of malaria cases and RDT examination. For instance, RDT usage decreased by 27% during 2012-2013 and 9% in 2013-2015 (Figure 3).

ABER changed from 2.6% in 2007 to 7.1% in 2015, based on population at risk and API correspondingly reduced from 10.4 to 2.0 per 1,000 population (Figure 4). There were seven townships with an API lower than 1 per 1,000 population in 2010 and this increased to 14 townships in 2015. The malaria positivity rate was reduced by 92.1% during the same period, from 35.0% in 2007 to 2.8% in 2015.

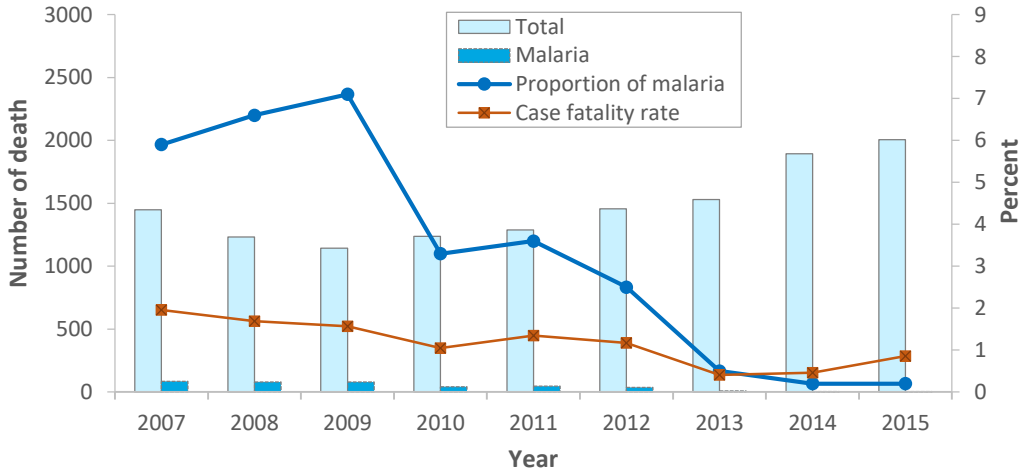

Figure 2. Malaria death among total deaths annually reported in Bago Region, Myanmar, 2007-2015

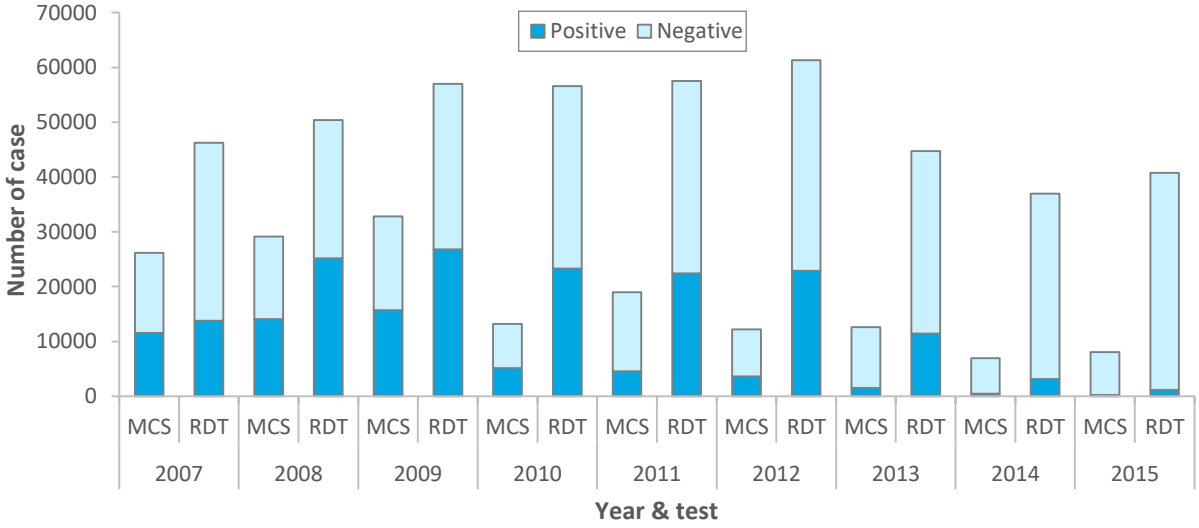

Figure 3. Results of blood examination by microscopy (MCS) and rapid diagnostic test (RDT) annually reported in Bago Region, Myanmar, 2007-2015

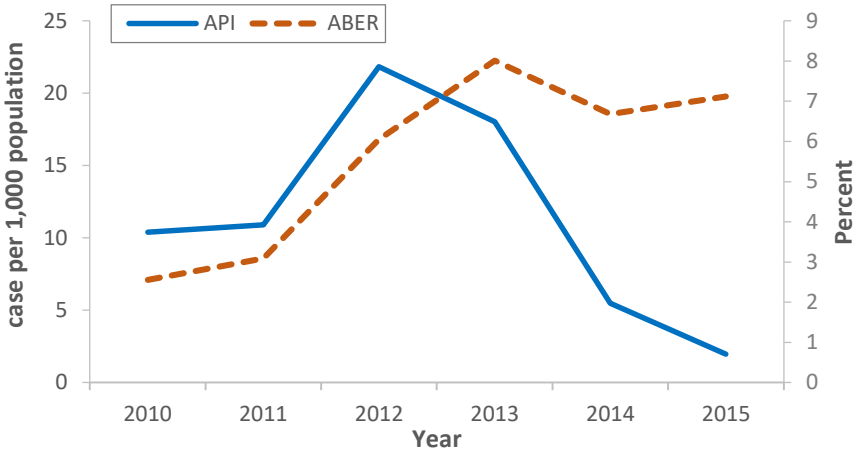

Figure 4. Annual parasite incidence (API) and annual blood examination rate (ABER) based on population at risk annually reported in Bago Region, Myanmar, 2010-2015

The proportion of Pf decreased from 91.1% in 2007 to 55.4% in 2015. Although the difference in proportion between Pf and Pv cases was wide (91.1% and 8.6%) in 2007, it was significantly narrow (55.4% and 40.2%) in 2015 (Figure 5).

At the same time, the number of LLINs distributed gradually increased and replaced ITNs. The coverage mosquito net distribution increased from 23.5% in the first year of the survey during 2011 to 69.3% in 2014 (Table 1).

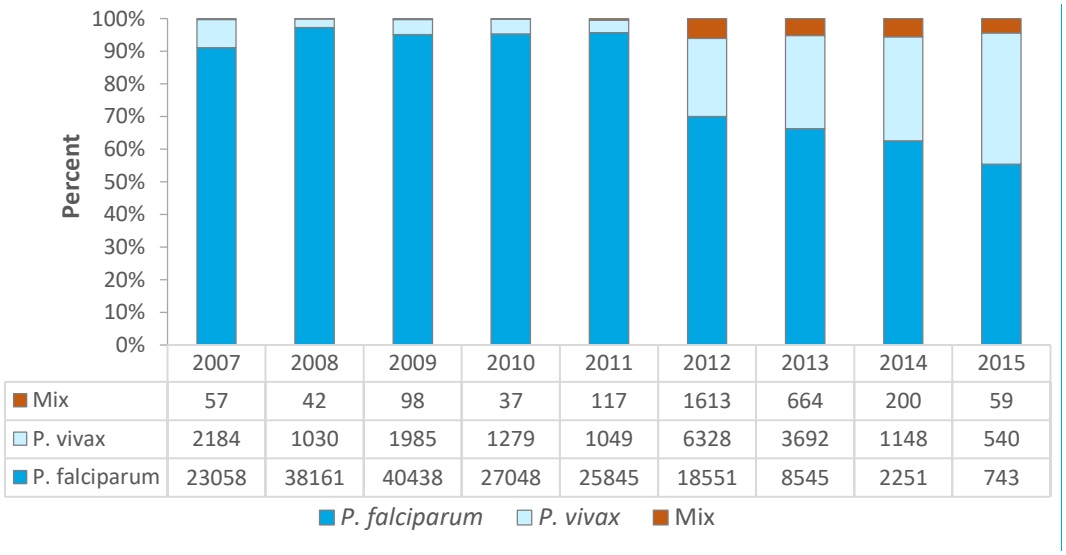

Figure 5. Distribution of malaria species annually reported in Bago Region, Myanmar, 2007-2015

Table 1. Number of insecticide-treated net (ITN) and long lasting insecticidal net (LLIN) distributed in Bago Region, Myanmar, 2007-2015[4]

Year	ITN		LLIN		Population Coverage of ITN/LLIN (Percent)
	Number of township	Number of ITN	Number of township	Number of LLIN	
2007	0	0	2	13,487	N/A
2008	4	5,413	0	0	N/A
2009	5	14,467	9	37,106	N/A
2010	4	21,500	4	43,880	N/A
2011	5	65,254	1	2,556	23.5
2012	18	238,829	8	119,310	73.2
2013	14	68,812	16	20,980	56.9
2014	0	0	0	16,044	69.3
2015	0	0	15	206,902	N/A

N/A = data not available

Discussion

Malaria morbidity and mortality rates reduced during 2007-2015 in light of expanding key program interventions in Bago Region. The CFR reduced during 2007-2013, yet slightly increased in 2014-2015 possibly due to reporting variability. This might also be due to lack of awareness in malaria and its complications leading to late arrival at the hospitals, reduction of herd immunity in the community, or competency gaps of hospital staff in managing severe malaria patients. As the number of people with malaria who visited health facilities decreased, basic health staff at the peripheral level had less awareness and reduced skills in malaria diagnosis and treatment. This might cause delayed treatment, severe complicated malaria and even death. This issue is important for malaria elimination and needed to be explored further.

However, as government health facilities are the main sources for detection of confirmed cases by standard procedures and malaria treatment according to the national treatment guidelines, the reduction in malaria proportion in these facilities might reflect a massive decline in malaria incidence.

The equal proportion of Pf and Pv cases might be due to the switch from monovalent to bivalent RDT from 2011 onwards and the change in operational definition[2] as recommended by NMCP[3]. However, the gradual reduction in proportion of Pf, especially during 2012-2015, matches well with the reduction in trends of malaria incidence due to Pf[5]. As Pf causes severe complicated malaria and deaths, reduction in proportion of Pf malaria cases is a good sign for Pf elimination. We compared this information with the data from Rakhine State where malaria transmission was more active and found that the proportion of Pf (82.1%) was much higher than that of Pv (14.2%)[10] in 2014. However, introducing ultra-sensitive RDTs in areas targeting malaria elimination could facilitate accurate detection and treatment[11-13].

The frequency of microscopic examination reduced since 2009 due to lower availability of microscopic facilities (laboratory technicians, microscopes, electricity at hospital level), and easily available and more user-friendly RDT test-kits as also noted by other studies from Asia and Africa[12-14]. The ability to perform microscopy depends on training, practice, skills maintenance, slide preparation techniques, workload, condition of microscope and quality of essential laboratory supplies. Reputed experts, even in developed countries, are scarce.[14-17] Revitalization of microscopy is essential as it is the gold standard for drug efficacy studies and for malaria elimination.[7]

Using population at risk as denominator, there was an increasing coverage of case detection (ABER). This clearly indicated better targeting of population at risk in low malaria endemic settings. This explained why the number of blood examinations increased among malaria-risk populations, yet decreased among the general population, indicating better program performance in case detection. The total malaria positivity rate in 2015 was 2.8% in Bago Region and 6.9% nationwide.[3] Improved active case detection methods, in addition to passive case detection methods, are indispensable, especially in hard-to-reach areas of artemisinin resistant containment as proven by one recent study from Myanmar in 2017[18].

Another study from Myanmar pointed out the necessity to strengthen health information and monitoring systems to avoid missing information[19]. Furthermore, a scaling-up of ITN and LLIN distribution in Bago Region during the study period indicated higher population coverage and utilization, not only ensuring a reduction in malaria transmission, but also usage of ITN and LLIN could thwart the spread of malaria resistant parasite strains noted by one recent study in Myanmar[20]. This would have an impact on malaria incidence reduction.

Limitations

All malaria cases analyzed were from public health facilities, exclusive of those from clinics run by implementing partners and private organizations. Data validity was relatively weak as the suspected and probable case definitions for malaria before and after 2011 differed.

Patient duplication might have occurred in program records as out-patients without any relief at health facilities from the periphery were referred to hospitals from the public sector and were registered as in-patients without any record link. However, malaria deaths might have been under-reported as the major source of death reports were from public hospitals, not private hospitals or communities.

Conclusion

The data from the public sector revealed declining trends of malaria morbidity, mortality and low API in Bago Region during 2007-2015, increasing the chance of malaria elimination in the near future. The decline might be linked to improved program efforts in terms of better targeting of populations at risk of malaria, an increase in the number of malaria testing and treatment according to program guidelines, and the expansion of ITN/LLIN programs to reduce malaria transmission.

Recommendations

As there was still a possibility of residual malaria that might stimulate resurgence, it was important to promote surveillance, especially in private health care establishments in Bago Region as well as in other endemic regions of Myanmar in order to gain a complete picture of the situation. The NMCP should advocate for a higher level of commitment to categorize malaria as a notifiable disease to increase reporting, case yield and better estimates, especially from private and non-health sectors. More in-depth studies on the epidemiology of malaria and the association of the two key interventions and their impact on malaria trends are needed for better planning and evaluation in order to reach the elimination target.

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Suggested Citation

Situation of malaria and expansion of key interventions for malaria elimination in Bago Region, Myanmar, 2007-2015. OSIR. 2018 Dec;11(4):7-13.

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Field Epidemiology Training Program, Bureau of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625901734-5, Fax: +6625918581, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Approaches to Prevent Influenza Transmission among New Conscripts in a Battalion during High Seasonality

Thanachol Wonghirundecha[1,*], Worrayot Darasawang[1], Tanaporn Tankasikit[2], Thanaluck Sukprasan[3], Pornpimol Baramee[3], Pantasak Boonrat[4], Pantila Taweewigyakarn[1], Panithee Thammawijaya[1]

1 Field Epidemiology Training Program, Bureau of Epidemiology, Ministry of Public Health, Thailand

2 Wing 41 Military Hospital, Chiang Mai Province, Ministry of Public Health, Thailand

3 Office of Disease Prevention and Control Region 1, Chiang Mai, Ministry of Public Health, Thailand

4 Chiang Mai Public Health Office, Ministry of Public Health, Thailand

*Corresponding author, email address: w.thanachol@gmail.com

Abstract

On 1 Aug 2017, the Bureau of Epidemiology was notified that five conscripts from a single battalion unit in Chiang Mai Province presented with influenza-like illness (ILI) in two days. A joint investigation was performed to confirm the outbreak, describe the epidemiological characteristics, and identify the source of infection and risk factors. Active case finding was conducted, and either nasopharyngeal or throat swab from 11 patients were collected. Environment and activities in the unit were studied, and a retrospective cohort study was conducted. An influenza outbreak occurred in the new conscript unit during 17 Jul to 20 Aug 2017, with 40.6% attack rate. Major symptoms were fever (100%), cough (83.8%) and runny nose (75.0%). Out of 86 clinically diagnosed cases, 11 were laboratory confirmed. None developed pneumonia. Influenza A(H3N2) was identified in all 11 specimens tested by reverse transcription polymerase chain reaction. Basic reproductive number (R_0) among conscripts in the affected unit was 1.3 (95% CI = 1.24-1.38). Close contact with an ILI case was a significant risk factor for influenza infection (adjusted odds ratio = 3.56, 95% CI = 1.68-7.45). A strict protocol for daily screening and early isolation during the epidemic season could prevent influenza outbreaks in a military setting.

Keywords: influenza, outbreak, military, conscript

Introduction

Influenza A viruses belong to the *Orthomyxoviridae* family which comprises of seven genera: A, B, C and D, *Thogotovirus*, *Isavirus* and *Quaranfilvirus*. Currently, 18 hemagglutinin (HA) and 11 neuraminidase (NA) subtypes are identified for influenza A viruses. The common subtypes circulating among humans are A(H1N1) and A(H3N2).[1] The genetic reassortment influenza A(H1N1) virus emerged in 2009, which provoked the influenza pandemic on 11 Jun 2009.[2]

The influenza viruses can be transmitted from person-to-person mainly via respiratory droplets, direct contact and small aerosol particles. The average incubation period is two days (range 1-4 days[1], mean 1.4 days[3]). Some can transmit the virus as early as one day before the onset.[4] Most of the infected people develop fever with myalgia and upper respiratory symptoms such as cough. Only 1-2% progressed to severe pneumonia whereas 18-30% could be asymptomatic.[5,6]

Influenza infection exhibits an annual global attack rate of 5-10% in adults and 20-30% in children.[7] In Thailand, a national study from 2006 to 2011 revealed the average influenza-associated mortality rate as 4.3 per 100,000 population in non-pandemic years, and 2.4 per 100,000 population in 2009.[8]

On 1 Aug 2017, the Bureau of Epidemiology (BOE) received a notification from Chiang Mai provincial

health office that five conscripts from a single unit in a battalion were seeking treatment for influenza-like illness (ILI) at a military hospital on 30-31 Jul 2017. The staff from BOE, Office of Disease Prevention and Control 1, provincial heath office and the military hospital jointly conducted an investigation on 2-4 Aug 2017 to confirm the diagnosis and outbreak, describe the epidemiological characteristics, identify the origin and risk factors, and recommend control measures.

Methods

Influenza Situation in Chiang Mai Province

To identify the influenza outbreaks in Chiang Mai Province, information from the event-based surveillance system in BOE reported from 1 Jan to 1 Aug 2017 were reviewed.

Descriptive Epidemiology

Active case finding was conducted among soldiers in Battalion X from 2 to 4 Aug 2017 using three methods. The out-patient and in-patient medical records of soldiers from the battalion who visited the military hospital from 17 Jul till 4 Aug 2017 were reviewed using the international classification of diseases (ICD)-10 codes (J11.1, J00-06, J09-18, J20-22). Subsequently, commanders in the battalion announced and sought for soldiers with ILI symptoms during the same period. Meanwhile, the soldiers in the affected unit were investigated as well. Information was gathered using a self-administered semi-structured questionnaire.

A clinically diagnosed case of influenza infection was a soldier in Battalion X presented with fever (subjective or body temperature more than 37.8°C) with at least one of the symptoms: cough, sore throat, runny nose, headache, or myalgia between 17 Jul and 4 Aug 2017. A laboratory confirmed case was a clinically diagnosed case tested to have influenza virus in nasopharyngeal or throat swab by rapid test or reverse transcription polymerase chain reaction (RT-PCR).

Descriptive findings were presented in percent, median and interquartile range. Moreover, the basic reproductive number (R_0) was calculated using attack rates in R_0 package of R-program[9] during the exponential curve from 26 Jul to 1 Aug 2017.

In the simple SIR model, relation between R_0 and attack rate is in the form:

$R_0 = -\ln((1-AR)/S_0) / (AR -(1-S_0))$

where AR is the attack rate during the period from the first case to the epidemic peak and S_0 is the initial proportion of the population considered susceptible. The variance of R_0 was estimated using the delta method and the correction for incomplete susceptibility was based on the SIR model equations. Confidence interval (CI) was computed for the attack rates, considering the population size (CI(AR) = AR +/- 1.96*sqrt(AR*(1-AR)/n)), and thus, CI for the reproductive number was computed with this extreme values.[10]

Laboratory Testing

Clinical specimens were collected from 11 patients who had the onset date within four days. All 11 specimens were tested by both rapid test and RT-PCR. The rapid test kit was the immunochromatographic assay that can detect three subtypes of influenza: A, B, and/or H1N1.[11,12]

Regarding to RT-PCR testing, nine were sent to the Chiang Mai Laboratory Center for Epidemiology at Sansai Hospital and two specimens were tested at the Regional Medical Science Center for region 1.

Analytic Studies

A retrospective cohort study was conducted to identify the potential risk factors of influenza infection among the conscripts in the affected unit. The cohort was the conscripts who was in the affected unit during 17 Jul to 4 Aug 2017. The case definition was the same as in the descriptive study. ILI cases for contact history referred to persons with coughing, sneezing or fever within one week. Risk ratio and 95% confidence interval (CI) were calculated to determine strength of association. The potential risk factors to include in the analytic study were identified by reviewing the previous studies. Multiple logistic regression was employed to control possible confounders observed from the descriptive study, regardless of the univariate p-value.

Environmental Investigations

An environmental study was performed to assess the potential risk factors related to dormitories, canteen, water supply, garden and activities in the battalion. The infection prevention and control practice in the military hospital were observed as well.

Results

Influenza Situation in Chiang Mai Province

Chiang Mai is the second largest province in Thailand and situated at the northern part. Reviewing the national event-based surveillance data revealed six influenza outbreaks in institutional settings such as schools, battalions and prisons in Chiang Mai Province from 1 Jan to 1 Aug 2017. The attack rates ranged from 2.5% to 37.8%. The incidence of influenza in Chiang Mai during 2017 tended to be higher in monsoon and winter. Causative agents were two predominant subtypes of influenza: A(H3N2) and B. The median of

interval between disease onset and notification to BOE was seven days.

Descriptive Epidemiology

The event occurred at the new conscript unit of Battalion X located in Muang District, Chiang Mai Province, Thailand. There were total 213 conscripts, 13 trainers and nine commanders in the unit while all were male. The conscripts were divided into nine groups related to sleeping patterns and parade drill arrangements (Table 1).

Screening and interview coverage was 90.2% (212/235), which included 193 conscripts, 12 trainers and seven commanders. Of which, 86 clinically diagnosed cases of influenza were recorded, with the attack rate of 40.6%, while all of them were conscripts in the new conscript unit. Although 10.4% (9/86) were hospitalized, none developed pneumonia or died in this event.

The median age of the cases was 21 years old (range 20-25 years). In addition to fever in all cases, clinical manifestations were cough (83.8%), runny nose (75.0%), headache (66.3%), myalgia (53.8%), sore throat (46.3%) and dyspnea (23.8%).

The attack rate among conscripts who stayed in dormitory 1 was 43.3% (42/97) and that of dormitory 2 was 48.2% (40/83). There were 11 conscripts who did not stayed in the dormitories and four (36.4%) out of them became ill as well (Table 1).

The first case of this outbreak was a 21-year-old conscript and had not been vaccinated for influenza. He had fever, runny nose, myalgia, headache and conjunctivitis on 20 Jul 2017 and self-medicated. Nonetheless, he did not take oseltamivir. He had not been out of the camp or contacted with any ILI case within seven days before developing the symptoms. He sometimes shared drinking glasses with others.

The first case belonged to group 11 in dormitory 1 and subsequently, two conscripts in dormitory 1 developed the symptoms in two following days. The conscripts in dormitory 2 started to have the symptoms on 4th day after the first case's onset. The number of clinically diagnosed case climbed with the same magnitude in both dormitories since 27 Jul 2017, and the peak with 56 cases appeared on 1 Aug 2017 when the notification was delivered to Chiang Mai provincial health office (Figure 1).

Out of three (3.5%) conscripts reported to have influenza vaccination before the onset of illness, there was one (33.3%) clinically diagnosed case of influenza infection.

Table 1. Attack rate of influenza A(H3N2) infection among conscripts by residence in Battalion X, Chiang Mai Province, Thailand, 2017

Residence	Group Number	Total conscript	Screened	Clinically diagnosed case	Attack rate (%)
Dormitory 1	11, 12, 13, 31, half of 32	101	97	42	43.3
Dormitory 2	21, 22, 23, half of 32, 33	89	83	40	48.2
Others (convenient store, pavilion)	-	20	11	4	36.4

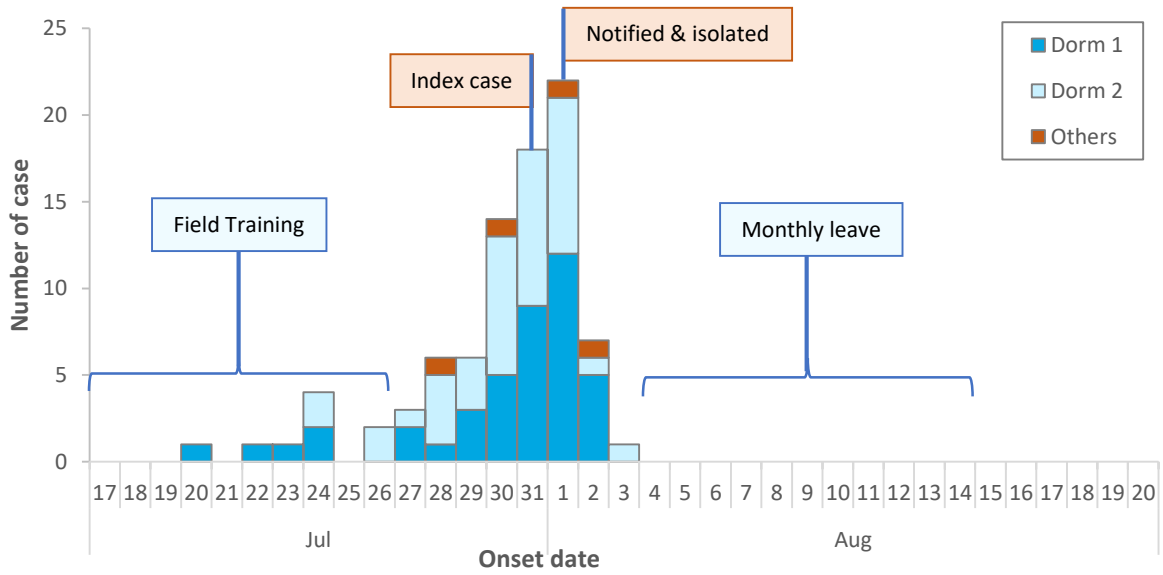

Figure 1. Clinically diagnosed and laboratory confirmed cases of influenza A(H3N2) infection among conscripts in Battalion X, Chiang Mai Province, Thailand, 12 Jul-20 Aug 2017 (n=86)

Laboratory Testing

Out of 11 nasopharyngeal and throat swabs collected, five of them were tested positive for influenza A virus by the rapid test and all 11 specimens were confirmed to have influenza A(H3N2) by RT-PCR. Regarding to 11 laboratory confirmed cases, their residency status showed seven (63.6%) in dormitory 1, two (18.2%) in dormitory 2 and two (18.2%) assigned in other places such as the convenient store and pavilion.

Analytic Studies

Nine reviewed risk factors were included in the retrospective cohort study, and exposed and non-exposed groups were compared for each factor. The univariate analysis showed three factors with high risk ratios for influenza infection, yet only one factor was significantly associated. The conscripts who had close contact with an ILI case were 2.19 times more likely to have influenza infection compared to the others (95% CI = 1.60-2.99) (Table 2).

To control the potential confounding factors, multiple logistic regression was employed and three potential risk factors were included. The conscripts who had close contact with an ILI case had adjusted odds 3.56 times (95% CI = 1.68-7.45) compared to the others (Table 3). R_0 among conscripts in the new conscript unit was 1.3 (95% CI=1.24 -1.38).

Environmental Investigations

During the environmental survey, two dormitories of the new conscript unit were located between the canteen and an open-air hall. The distance between conscripts' beds within the same group was 0.3 meter while that of each group was one meter. Trainers' beds were on the either end of the room, which were three meters apart from the conscripts' (Figures 2 and 3).

Table 2. Behavioral risk and risk ratio of influenza A(H3N2) infection among soldiers in Battalion X, Chiang Mai Province, Thailand, 2017

Exposure factor	Expose			Non-expose			Risk ratio	95% CI
	Total	case	Attack rate (%)	Total	case	Attack rate (%)		
Contact								
Contacted with ILI case (n=176)	64	45	70.3	112	36	32.1	2.19	1.60-2.99
Slept with leaning head against case (n=146)	7	5	71.4	139	62	44.6	1.60	0.97-2.65
Slept beside case (n=146)	24	9	37.5	122	58	47.5	0.79	0.46-1.37
Exercised near case (n=146)	58	27	46.6	88	40	45.5	1.02	0.71-1.47
Lined up beside case (n=146)	65	26	40.0	85	41	48.2	0.88	0.61-1.27
Dining								
Always or sometimes shared drinking glass (n=185)	156	68	43.6	29	14	48.3	0.90	0.60-1.40
Shared table with case (n=146)	56	24	42.9	90	43	47.8	0.90	0.62-1.30
Personal hygiene								
Always washed hand (n=185)	25	9	36.0	160	73	45.6	0.79	0.46-1.37
Flu history								
History of flu within last 12 months (n=158)	3	1	33.3	155	69	44.5	0.75	0.15-3.75

Table 3. Multiple logistic regression of behavioral risk factors and adjusted odds ratio in influenza A(H3N2) outbreak among soldiers from Battalion X, Chiang Mai Province, Thailand, 2017 (n=136)

Exposure factor	Adjusted odds ratio	95% CI
Close contact with influenza-like illness case (Y/N)	3.56	1.68-7.45
Slept with leaning head against case (Y/N)	2.77	0.47-16.28
Exercised near case (Y/N)	0.77	0.36-1.64

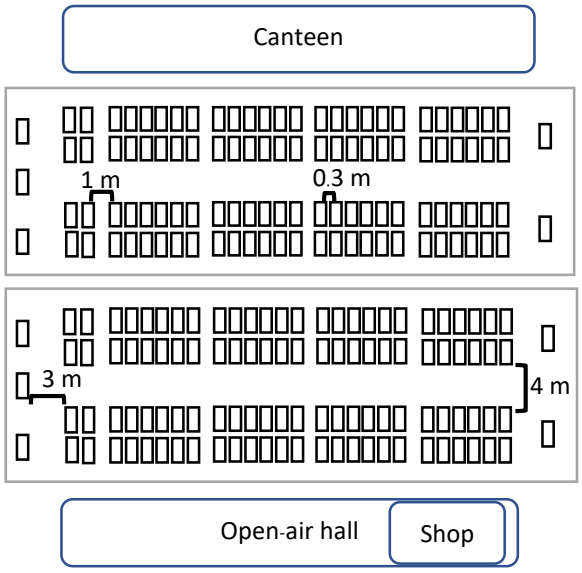

Figure 2. Crowded bed arrangement in the dormitory of the new conscript unit in Battalion X, Chiang Mai Province, Thailand, 2017

Figure 3. Dormitory in Battalion X, Chiang Mai Province, Thailand, 2017

Prior to meals, the conscripts had only a short time to wash their hands in a bucket before going inside the canteen. No wash-basin or soap was available in the camp. Although there were a drinking water container, some did not bring along with them and thus, shared the drinking glasses with others. The dining tables were 80 centimeters in width. Before having meals, they have to sit and sound off about 2-3 minutes at the dining tables.

Field training was the military practice took place on 10-26 Jul 2017. All conscripts were re-arranged into new seven groups according to the types of training activities. They stayed closely during the break times.

Screening and Response

During the recruitment process, no vaccination was provided to new conscripts in the battalion. In addition, there was no routine screening procedure for respiratory infections during the period of high influenza transmission. When a conscript got sick, he informed the responsible trainers who in turn asked for permission from the commander to seek treatment at the military hospital which located about five kilometers away. Occasionally, the permit was not granted due to compulsory activities such as the field training during 10-26 Jul 2017.

There was no designated isolation room for sick conscripts in the battalion or at the hospital. During this event, the hospital prepared two rooms, with about 9 m2, to isolate 4-5 ILI cases in each room, which was not sufficient for this outbreak. The event took 12 days from identification of the primary case (20 Jul 2017) to notification to the relevant sectors (1 Aug 2017).

Actions Taken

Health education on influenza transmission and preventive measures was provided to the soldiers in the affected unit. Extensive cleaning up in all units and daily cleaning of frequently hand-touched materials were performed to prevent fomite transmission. Beds in dormitories, activities and dining tables were set separately for sick conscripts. In the dormitories, all beds were rearranged by putting feet against each other instead of head-to-head.

There was a period of 10-day leave in the battalion on 4-14 August 2017. As the infectious period of influenza is 5-7 days from the onset date,[1] we suggested the camp not to allow those with ILI symptoms within five days to take leave. Nonetheless, challenges existed to follow the suggestion and since the sick conscripts could spread the infection to their family members, face masks and health education on influenza transmission were provided to them, emphasizing on frequent handwashing and practice of social distancing.

Discussion

An outbreak of influenza A(H3N2) in a military setting was confirmed among new conscripts in Battalion X, with 11 cases confirmed out of 86 clinically diagnosed cases during the period from 17 Jul to 4 Aug 2017. All the affected persons were conscripts. The possible risk factor of transmission identified in this outbreak was having close contact with a soldier with ILI symptoms.

The outbreak occurred in the second half of July, which followed the seasonal trend of the event-based influenza surveillance data in Chiang Mai during 2017. This was compatible with the seasonality trends in the influenza sentinel and ILI surveillance systems.[13]

The attack rate in this event was higher than previous outbreaks reported from other institutional settings in

Chiang Mai to the event-based surveillance system during 2017. However, it was similar to 44% of a military setting in Surat Thani Province during 2014[14] as well as 28-50% from other military bases in the country[15-16].

The attack rates among conscripts resided in dormitories were found to be high. However, trainers stayed in the dormitories and commanders did not become ill as they did not share the activities with sick conscripts. In contrast, conscripts who did not stay in the dormitories were also infected, which could be due to close contact during the activities, the field training, vowing and sounding off before having meals, or via fomites[17] such as door knobs and water jars. Close contact with an ILI case was the only significant risk factor in this study, which matched with the results from other prior studies[14,18].

Despite the battalion was populated with high number of conscripts, the R_0 resulted in this study was similar to the findings from other seasonal influenza outbreaks[14,19], implying that soldiers are ordinarily in better health condition and might prevent the extensive spread in this outbreak.

Influenza was one of the public health concerns in the military settings nationwide in Thailand[20] as well as in other military bases[21]. Previous investigations in Thailand recommended not to contact with cases, share drinking glasses or sleep nearby the cases.[14-17] However, those recommendations could not be followed due to the compulsory activities in the battalion.

Only about 3.5% of conscripts were found to have been vaccinated for influenza infection. In Thailand, the influenza vaccine under the national vaccination program is administered to merely high risk groups[22]. In addition, as no immunization program was provided in the battalion camp during the recruitment process, the majority of screened soldiers were assumed to be susceptible hosts. Thus, in addition to the routine recommendations on behavior and infrastructure setting, influenza vaccination should be considered to prevent influenza outbreak among new conscripts in parallel with other control measures. Evidences existed that implementation of influenza vaccination effectively can prevent morbidity among military population.[23] Influenza vaccine effectiveness in the previous studies were reported to be 30-70% in military settings.[24,25]

The routine screening was not performed for respiratory infections. Moreover, the sick conscripts were not granted for exemption of compulsory activities due to the military rules. Passive surveillance for influenza is crucial for not merely as a regular operation, it can convert into active surveillance to reduce the influenza spread in military settings.[26]

There was no isolation room in the camp and only two rooms were used to isolate ILI cases in the military hospital. This might affect the isolation measures, especially when a recovering patient was discharged from the hospital and sent back to the camp. Isolation is one of the effective methods to reduce influenza spread by preventing direct contact and airborne transmission.[27]

Furthermore, the index case was detected on the day of the epidemic peak. The compulsory activities in the military schedule such as field training might prevent sick soldiers to seek medical treatment, thereby causing delayed detection of outbreak by staff in the military hospital. In addition, asymptomatic or mild case might not be detected and this could hinder the identification of infection source in this outbreak, corresponding to the findings from other influenza outbreaks[14,28].

Limitations

The clinical specimens were tested by RT-PCR at two centers in order to compare the laboratory results. However, limited number of specimens were able to send to the Regional Medical Science Center due to high cost, about 90 USD for one specimen.

Evidences of prior vaccination was not be able to obtain due to unavailable vaccination records. In addition, some soldiers who had mild symptoms or recovered before the investigation were unlikely to disclose their illnesses so that they could take leave for 10 days. This could cause an information bias and affect the true magnitude of the outbreak.

Recommendations

The influenza vaccine should be administered to the new conscripts during the recruitment process, which could be supported by further studies on cost-effectiveness of vaccine and antiviral drug in institutional settings and other areas with high population density.

Instructions on daily ILI screening should be integrated into the routine training guideline in military medical departments during the epidemic seasons, especially rainy and winter seasons. In addition, as the guideline for heat stroke prevention by screening body temperature is available in the military settings of Thailand,[29] it could be adapted for fever screening during influenza epidemic season for early detection of influenza infection.

The isolation room should be planned in advanced and set up before the epidemic season in the battalion in order to promptly isolate the affected persons as well as managing the lodging space, dining tables and compulsory activities[30]. Handwashing basins with soap were suggested to set up in front of the canteen.

Communication channel between military camps and hospitals should be strengthened to avoid delayed notification and implement effective control measures. A strict protocol for influenza protection should be cooperated by hospital staff along with military staff. We also recommended the hospital staff to continue ILI screening from 2 to 4 Aug 2017 and until one week after the sick conscripts returned to the camp.

Acknowledgement

This outbreak was conducted under the activity of the International Field Epidemiology Training Program, Thailand, with tremendous support from public health authorities in relevant offices. The appreciation also goes towards the commanders, trainers and conscripts from the new conscript unit in Battalion X for responding to interview and providing the clinical samples.

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Grammar of Science: Gee Whiz… It's GEE!

Jaranit Kaewkungwal*

Mahidol University, Thailand

* Corresponding author, email address: jaranit.kae@mahidol.ac.th

"I have one to many children in a house!" A public health officer looks so worried.

"What is the problem with that?"

"I did home visits in a community, to the household with a tuberculosis (TB) case; and I want to know whether the TB case will be the source of disease transmission to the children under five years old within his/her house or not. But each house has different number of children: some houses only one child, others vary 2-5 children. I even find a house with 10 children. I performed tuberculin skin test in all children – and some of them are positive while other negative, though they are living in the same house. If the children in a house are called household contacts and the TB patient is called an index case – then, how can I estimate the risk of acquiring infection from the index case among the household contacts?"

"This is called 'clustered data' structure. There are many ways to analyze clustered data. One of the popular statistical methods that can handle this type of data is 'Generalized Estimation Equation', so-called GEE. This clustered data cannot be analyzed by standard statistical models like linear regression, logistic regression, etc. The main reason is that the outcomes measured from each individual are considered "not independent", but potentially "correlated", among the individuals (household contacts) who share the same exposures (index case and other household characteristics). Let's take a look in more detail."

What kinds of data can be used in GEE model?

GEE is a statistical method that can be applied for "clustered data" and "repeated measures data".[1-4] When we talk about these two types of data structure, they are the "multivariate" datasets, meaning that there are more than one outcome observations (Y's) per case/unit, which is different from the "univariate" datasets with only one outcome observation (Y) per case/unit (Figure 1). Repeated measures data structure refers to the sets of data when we have repeated observations of an outcome variable measured from each individual (case) over time on multiple visits (Y's of an individual at different times: Yt1,Yt2,Yt3). Clustered data structure refers to the sets of data when outcome observation of different individuals (Y's) are grouped (or nested) within a certain unit (subgroup/cluster). The study may have either one exposure variable (X) or more than one exposure variables (Xs). The statistical method with >1 Xs is called "multi-variables" analysis.

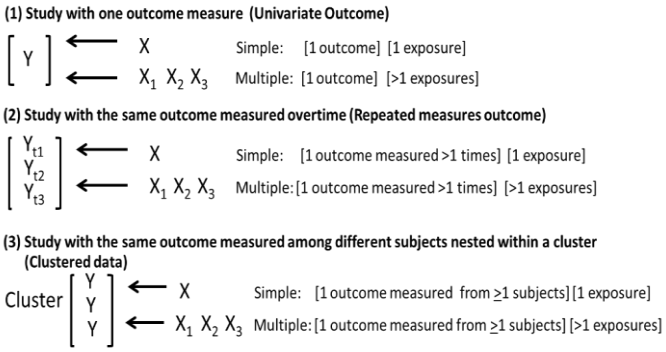

Figure 1. Univariate vs. multivariate data structure

Repeated data structure is shown as an example in figure 2 (a). In the study to determine the association between vitamin A deficiency and respiratory infection in school children, the researchers collected data on respiratory infection from each student at three time points (Months 0, 6, 12). Clustered data structure is shown in figure 2 (b) for the study of the public health officer in which he collected data on TB infection among all household contacts within each house. In fact we can say that, in repeated measures, study outcome data are clustered (repeated) within an individual; and in clustered or nested study, outcome data of individuals are clustered within a certain unit. These are the examples of only one level of clustering. It is also possible to have a multilevel data structure, in which we have multiple levels of grouping units, for example: children are clustered

(1) Example of "longitudinal data" or "repeated measures" (1-level)

	id	month	infc	vita	gender
1.	1	0	0	0	1
2.	1	6	0	0	1
3.	1	12	0	0	1
4.	2	0	0	1	0
5.	2	6	0	1	0
6.	2	12	0	1	0
7.	3	0	1	0	1
8.	3	6	1	0	1
9.	3	12	0	0	1

Level - Child (id)
Analysis Unit – Visits (month: 0, 6,12)
Outcome - Infection (infc: 0,1)
Exposures/Covariates-
- ✓ Vitamin A deficiency
- ✓ Sex

(2) Example of "clustered data" (1-level)

	hh_id	child_id	tb_child	childage	tb_case	hrscont
1.	1	101	pos	2	mother	17 - 24
2.	2	201	neg	8	other	1 - 8
3.	2	202	neg	2	other	1 - 8
4.	2	203	neg	3	other	1 - 8
5.	2	204	neg	6	other	1 - 8
6.	2	205	neg	2	other	1 - 8
7.	2	206	neg	6	other	1 - 8
8.	2	207	neg	11	other	1 - 8
9.	3	301	pos	14	mother	9 - 16
10.	3	302	pos	14	mother	9 - 16
11.	3	303	pos	10	mother	9 - 16
12.	4	401	neg	3	grandpar	9 - 16
13.	4	402	pos	8	grandpar	9 - 16
14.	5	501	neg	3	father	9 - 16
15.	6	502	pos	4	mother	9 - 16

Level - Household (hh_id)
Analysis Unit – Child (child_id)
Outcome - TB infection (tb_child: neg, pos)
Exposures/Covariates-
- ✓ Child age
- ✓ Index case relationship (mother, father, grandparent, other)
- ✓ Number of hours spent between Index cases and Child

Figure 2. Examples of repeated measures datasets and clustered datasets

within a classroom (level 1), and classrooms are clustered in a school (level 2), and so on.

What is GEE?

GEE was proposed by Liang K-Y and Zeger SL in 1986[5]. GEE is a generalized model unifying in a single method. The model of GEE can be transformed into three classic generalized linear models (GLM): linear, logistic and poisson depending on the type of the outcome (Y) variable.[1,2,6]

- Linear regression (continuous outcome)
  - Distribution of Y: ~ Normal; mean of Y is μ, average of the outcome
  - Transformation of Y: none (identity link)
  - Equation $\mu = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k$
- Logistic regression (binary outcome)
  - Distribution of Y:~ Bernoulli; mean of Y is p, probability of having outcome
  - Transformation of Y: logit link
  - Equation: $logit(p) = log\ (Odds) = log\ (p/1-p) = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k$
- Poisson regression (incidence or count outcome)
  - Distribution of Y ~ Poisson, mean of Y is λ, rate per time unit, or mean count per unit, of the outcome events
  - Transformation of Y: *log link*
  - Equation: $log(\lambda) = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k$

The three classic GLM models are based univariate data. In GLM, an outcome variable (Y) is measured for each individual, and thus, the Y's for all individuals in the study are considered "independent". In contrast, GEE models are based on multivariate data where outcome variables are potentially "correlated" because Y's are measured within the same individual (for repeated measures) or among different individuals within the same exposure variable(s) (for clustered data). GEE thus simply extends such GLM models by taking into account the correlated Ys within a case (of repeated measure) or a grouping unit (cluster). If the researchers did not take into account the correlation among Ys, the estimated regression coefficients (βs) will be less efficient (i.e., widely scattering around the parameters or true population values estimated)[7].

How does GEE model fit the data?

In fitting the extended regression model, GEE uses quasi-likelihood estimation method to estimate the expected (predicted) value of the outcome, [E(Y)], via the consistent estimates of regression coefficients, β of Xs - $[g(\beta_i X_i)]$, and its variance-covariance (correlations) among Ys.[5,8]

$E(Y) = g(\beta_i X_i)$, $Var(Y) = Corr(Y_{ij}, Y_{ik})$ for subject i^{th} and j-k^{th} times/units

Liang and Zeger (1986) proposed GEE under the asymptotic theory in which they utilize outcome values across study subjects to estimate a "working correlation" matrix, assuming that such correlations are explicitly accounted for the time dependence or the clustering effect, and to achieve greater asymptotic efficiency[5]. To explain asymptotic theory

in layman terms, it means "a large sample theory" which is typically used when estimating any parameters or statistical tests based on the assumption that the sample size would grow indefinitely ($n \rightarrow \infty$)[9]. That means GEE fits better when the sample size is getting larger.

GEE is considered as a semi-parametric model as it estimates parameters (β coefficients) in the equation without full specification of the joint distribution of the outcome observations overtime or within clusters. The model derives from the specification of the likelihood for the (univariate) marginal distributions of the outcome variables (Ys) and then incorporates the "working correlation" matrix into the model.[4] In other words, there are three steps in modeling GEE. The three steps are: (1) a naive regression analysis is carried out, assuming the outcome observations within the individual/cluster are independent; (2) the residuals (observed - predicted) are then calculated from the naive model, and used to estimate the working correlation matrix; and (3) the regression coefficients are subsequently refitted using iterative process by treating the within-subject correlation as a nuisance (covariate) variable.[10]

The "working correlation" matrix is based on an important assumption that the outcome observations (Ys) measured over time or within individual/unit are correlated or clustered. That means observations (Y at time 1, 2, 3, ... of each individual; or Y of individuals within each unit) are not independent[3]. There are typically four types of correlation structures that we have to assume prior to fitting the model. Figure 3 presents structure and assumption of each type of correlation matrix[3,6,7].

In analyzing the clustered data, we will typically have an outcome response measured from each study subject within a cluster/unit, and thus, there is usually no problem with missing outcome data. But in the repeated measures situation, there are always study subjects who missed some visits and thus, outcome data are missing.

In analyzing the repeated measures data with missing outcome values at different visits, GEE uses the pairwise method (i.e., "all available pairs"); all non-missing pairs of data are used in estimating the working correlations. That means we do not lose the study subjects that had missing outcome data at certain visit(s)[10]. There is no need to perform imputation for the missing data. However, GEE with robust and optimal option was developed to handle missing data that are either missing at random (MAR) or missing not at random (MNAR)[1].

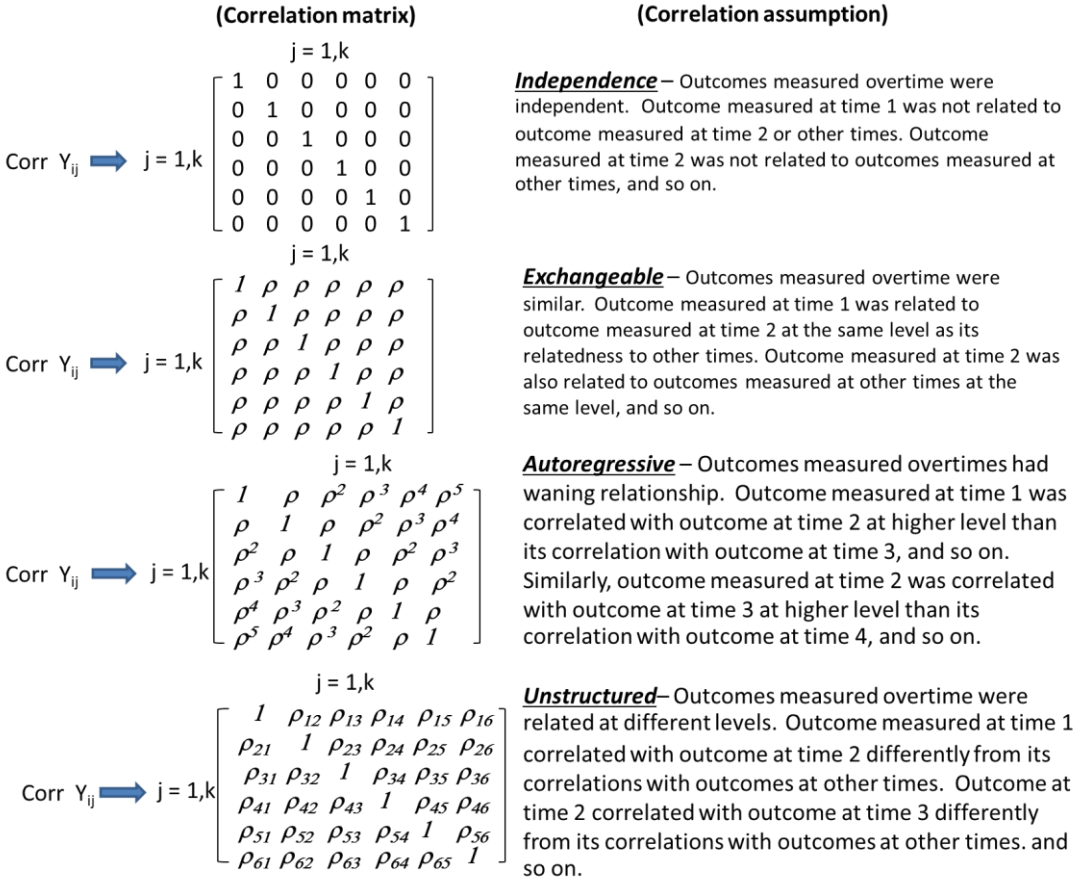

Figure 3. "Working correlation" matrix

Case study of GEE

For the case scenario of the public health officer, the GEE model to be fitted is for the clustered categorical outcome (not having or having TB infection). We now consider to fit the logistic regression model with binary outcome data (Y=0,1). Note that, similar to all regression models, the exposures (X's) can be categorical or continuous data. In this study, the exposures are child's age, types of TB index case (father, mother, grandparent, other) and duration of contact/exposure (1-8, 9-16, 17-24 hours per day). As shown in figure 4, the GEE model to be fitted is the extended logistic regression with correlated and clustered data (children residing in each household). While the working correlation matrix for a repeated measures study can be specified as one of the four structures, the appropriate working correlation matrix to be used for clustered data study is only exchangeable.

Based on the analysis of the data collected by the public health officer, the results are shown in figure 5. The goal of GEE is to make inferences about the population parameter(s) when accounting for the within-subject correlation. As GEE is the extended regression model, the interpretation of the model follows the regular regression model such that that for every one-unit increase in a covariate (X) across the population, how much the outcome response (Y) would change[7]. We can say that the odds that a child got infected with TB increases significantly by 2.3 and 4.9 times if the TB-case is the child's father and mother respectively, when compared to the odds of the reference group (TB case whose relationship with the child in "other" category). Compared children whose ages are different by one year, the odds seems to increase by 1.4 times, but is not statistically significant different. Notice the differences of the two logistic regression models, GEE (Figure 5) vs. GLM (Figure 6), the estimates of odds ratios and p-values are different.

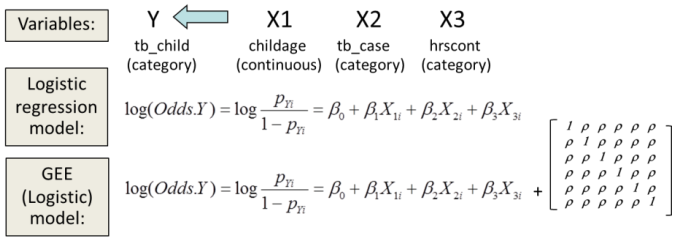

Figure 4. GEE (extended logistic regression) model

```
. xtgee tb_child childage ib4.tb_case i.hrscont,i(hh_id) fam(bin) eform
```

tb_child	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
childage	1.401464	.2483005	1.91	0.057	.9903136	1.983313
tb_case						
father	2.393673	.8601755	2.43	0.015	1.183538	4.841137
mother	4.987524	2.306963	3.47	0.001	2.014487	12.34825
grandparent	1.502095	.9032813	0.68	0.499	.4621991	4.881637
hrscont						
9 - 16	1.529526	.4869222	1.33	0.182	.8195552	2.854536
17 - 24	2.5544	1.900136	1.26	0.207	.5944391	10.97666
_cons	.2563081	.1105602	-3.16	0.002	.1100503	.5969443

```
Estimated within-hh_id correlation matrix R:

        c1      c2      c3      c4      c5      c6      c7
r1   1.0000
r2   0.4658  1.0000
r3   0.4658  0.4658  1.0000
r4   0.4658  0.4658  0.4658  1.0000
r5   0.4658  0.4658  0.4658  0.4658  1.0000
r6   0.4658  0.4658  0.4658  0.4658  0.4658  1.0000
r7   0.4658  0.4658  0.4658  0.4658  0.4658  0.4658  1.0000
```

Figure 5. Analysis of the case scenario with generalized estimation equation (GEE)

```
. logistic tb_child childage ib4.tb_case i.hrscont
```

tb_child	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
childage	1.383615	.2591553	1.73	0.083	.9584795	1.997321
tb_case						
father	2.144275	.6850383	2.39	0.017	1.146422	4.010666
mother	4.541624	1.918767	3.58	0.000	1.984228	10.39515
grandparent	1.450702	.7609011	0.71	0.478	.5189414	4.055441
hrscont						
9 - 16	1.811087	.537264	2.00	0.045	1.012577	3.239296
17 - 24	3.15085	2.418971	1.49	0.135	.6997506	14.18771
_cons	.24001	.0984541	-3.48	0.001	.1074136	.5362896

Figure 6. Analysis of the case scenario with binary logistic regression (GLM)

The GLM model considers the outcome of each record (household contact case) are independent while the GEE model takes into consideration that the outcomes of household contacts within the same house are correlated. In fact, if GEE model is fitted with working correlation matrix specified as "independent", we will get the same results as shown in GLM model.

How good is GEE?

In fact, another popular method that can be used to analyze repeated measures or clustered data is the "Multilevel Mixed Model" which handles within-subject variation in the regression model with random intercepts/slopes for each individual rather than using the "working correlation" matrix[11]. (We may talk about the Mixed model at other time.) Note that GEE provides the result as a generic equation applied to all in the population of the study, that is why it is called "marginal population average" model; but the Mixed model will provide the result as equations that are subject-specific[2,10,12]. Basically GEE generates the fix effect only. But when the question is to find out the variation of the effect between clusters AND within the clusters, then random effect model like the Mixed effect model could be used. The use of working correlation (or variance-covariance) matrix as a nuisance parameter in the equation has made fitting GEE model easier than Mixed model[1]. Both methods can handle missing data, time-varying covariates (exposures changed overtime or across individuals), irregularly-timed (timing of visits varied across individuals in repeated measures). GEE typically provides consistent estimates even if incorrect correlation structure is specified; but the Mixed model has assumption that the researchers should correctly specified the correlation structure, which is sometimes difficult in practice. GEE is not very strict with the distributional assumptions, but Mixed model requires normality assumptions.[10,12]

GEE is limited that it can handle only one level of correlation or cluster. In the example showed in figure 2, the observations are nested at one level (times/visits within each student, or children within household). However, the Mixed model can handle data nested within more than one level of clusters[10]. For example, malaria patients nested within villages, and villages nested within sub-district, and sub-district nested within district. If the researchers considered different layers of clustering, they need to use the Mixed model.

"Gee Whiz…. It is GEE to handle my clustered data…", the public health officer exclaims.

Suggested Citation

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