A DESCRIPTION OF INFLUENZA-LIKE ILLNESS (ILI) SENTINEL SURVEILLANCE IN CAMBODIA, 2006-2008

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Abstract. Influenza-Like Illness (ILI) sentinel surveillance was initiated by the Communicable Disease Control Department (CDC), Ministry of Health, Cambodia and its partners to evaluate the epidemiology of influenza and identify the circulating strains. The surveillance started in late 2006 in four sentinel sites. The objectives of this study were 1) to document the incidence of ILI and confirmed influenza cases reported in the national surveillance system from 2006 to 2008, just after the system and the definition were revised, 2) to identify the strains of influenza virus, 3) to compare the major demographic and clinical characteristics between ILI patients having positive and negative tests for influenza virus. An ILI case was defined as having a fever of at least 38ºC (axillary), cough or sore throat. A total of 155,866 ILI cases were reported to the CDC from 4 sentinel sites in Cambodia from August 2006 to December 2008. Specimens were collected in 1.8%. Of these, 9.6% tested positive for influenza. Influenza was observed to occur mainly from August to December, with a clear seasonal peak in October, as shown in the data from 2008. A new case definition beginning in August 2008 resulted in a decrease in weekly ILI reported cases (from an average of 1,474 cases to 54 cases) and the proportion of positive tests for influenza increased (5.3% *vs* 29.3%). Influenza and ILI are seasonal in Cambodia. A higher body temperature was used to define ILI, which improved the influenza positivity rates.

Key words: Influenza-Like Illness (ILI), influenza, seasonality

INTRODUCTION

Influenza is estimated to result in three to five million cases of severe illness and approximately 250,000 to 500,000 deaths worldwide each year (PAHO, 2004a). Influenza viruses may spread rapidly around the world in annual seasonal epidemics. In temperate regions, seasonal influenza typically occurs every year in the late fall or winter. The epidemiology of seasonal influenza is less defined in tropical regions, especially in Southeast Asia (Shek and Lee, 2003). In 1952, the World Health Organization (WHO) established

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an international laboratory-surveillance network for influenza and in 2002 a global agenda on influenza surveillance and control was initiated (PAHO, 2004b).

Cambodia has had an ongoing outbreak of avian H5N1 influenza since 2005. The first human H5N1 infection was reported to the WHO on February 2, 2005. Up to the present, the Institut Pasteur – Cambodia (IPC) has confirmed 8 human H5N1 influenza cases from Kampot, Kampong Speu, Kampong Cham and Kandal Provinces (WHO, 2009). The outbreaks of avian influenza A (H5N1) among poultry and wild birds, and the concomitant risk to human health, has highlighted the need for surveillance systems capable of monitoring human influenza viruses in Cambodia.

In 2006, the Communicable Disease Control Department of the Cambodian Ministry of Health and its partners, the World Health Organization (WHO) and Pasteur Institute, Cambodia, launched a sentinel facility-based influenza like illness (ILI) sentinel surveillance system. The objectives of this study were 1) to document the incidence of Influenza-Like Illness (ILI) and confirmed influenza cases reported in the national surveillance system from 2006 to 2008, just after the system and the definition were revised; 2) to identify the strains of these influenza viruses; 3) to compare major demographic and clinical characteristics between ILI patients who test positive and negative for influenza virus.

MATREIALS AND METHODS

There are five sentinel surveillance sites in Cambodia: 1) the National Pediatric Hospital (NPH) in Phnom Penh, 2) Kampong Cham (the Pediatric ward of the provincial hospital and Boeung Kok Health Center), 3) Takeo (Provincial Hospital), 4) Battambang (the Outpatient Department of the Provincial Hospital and Svay Por Health Center), and 5) the Angkor Hospital for Children (AHC) in Siem Reap Province (Fig 1). The NPH, Kampong Cham Hospital and Takeo Hospital began surveillance on August 2, 2006 (Week 32). The Battambang site began 3 weeks later on August 23, 2006 (Week 35) and AHC began surveillance on October 15, 2008 (Week 43). All surveillance sites are public facilities, except for AHC, a hospital run by a non-profit organization. Each site had specially trained surveillance site managers. Hospital staff (both physicians and nurses) were asked to provide data for the system. The ILI surveillance weeks start on Wednesday and end on the following Tuesday.

From August 8, 2006 until August 5, 2008 a person was defined as having ILI when presenting with sudden onset fever (≥37.5ºC axillary), cough and/or sore throat in the absence of another diagnosis. The onset of fever was within 3 days of presentation and fever had to be present at the time of presentation. Due to low detection rates for influenza among patients with ILI (on average 5.8, 7.5 and 5.5% in 2006, 2007 and up to July 2008, respectively), the case definition of ILI was changed from a cut-off axillary temperature of 37.5ºC to ≥ 38.0ºC. We sampled ILI cases for the collection of respiratory specimens for diagnostic testing. Sampling of ILI cases for specimens collection varied by site depending on the ILI case load. Kampong Cham, Takeo and Battambang provided 5 specimens per week, whereas NPH and AHC provided 10 per week. Nasal swabs were collected on young children and nasopharyngeal swabs on older children and adults.

The respiratory specimens were stored at -80ºC until testing at IPC in

Table 1
ILI cases at sentinel sites, 2006-2008.

Years/Sites	NPH		Battambang		Kampong Cham		Takeo	
	No. cases	%	No. cases	%	No. cases	%	No. cases	%
2006	14,762	85.7	2,024	11.8	439	2.5	221	1.3
2007	68,771	84.9	5,876	7.3	6,340	7.8	1,477	1.8
2008	46,570	86.3	3,614	6.7	3,801	6.8	1,650	2.9

NPH, National pediatric Hospital

Table 2
ILI cases before and after the case definition for ILI was modified[a], 2006-2008.

	Aug 2006-Jul 2008	Aug 2008[a]-Dec 2008	Total
ILI cases	160,223	1,087	161,310
Age groups			
0-4 years	115,447 (72.1)	598 (55.0)	116,045 (72.4)
5-14 years	37.376 (23.3)	200 (18.4)	37,576 (23.5)
15-49 years	5,487 (3.4)	236 (21.7)	5,723 (3.6)
≥50 years	1,913 (1.2)	53 (4.9)	1,966 (1.2)
Gender			
Male	83,988 (52.4)	558 (51.3)	84,546 (52.4)
Female	76,235 (47.6)	529 (48.7)	76,764 (47.6)

[a] Case definition was modified August, 2008

Phnom Penh. Influenza A and B virus infections were detected using Multiplex Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) (Pujol-Bellau *et al*, 2005). Influenza RT-PCR positive specimens were inoculated onto Madin-Darby canine kidney (MDCK) cells as described previously (Kendal *et al*, 1982). Influenza A viruses were antigenically characterized by a hemagglutination inhibition (HAI) test using reagents provided by the WHO (WHO Collaborating Center, 2008). Sample of the identified strains (H1N1, H3N2, Influenza B) were sent to the WHO Collaboration Center in Melbourne, Australia for further genetic analysis.

Weekly reports of the number of ILI cases and number of ILI patients with influenza virus infection from each site were recorded. We subsequently compared influenza positive with influenza negative cases in regard to frequency of symptoms and demographics. The epidemiological and laboratory data were recorded using Microsoft Access and analyzed using Epi Info 3.1, Access Database 2003 and Stata 10.0 by time, place and person. We excluded AHC from the analysis as this sentinel site launched in August 2008.

RESULTS

There were a total of 155,866 ILI cases reported from the 4 sentinel sites from August 2006 to December 2008. The majority of reported cases each year were from NPH (Table 1). More than 95% of the ILI cases were aged less than 15 years old

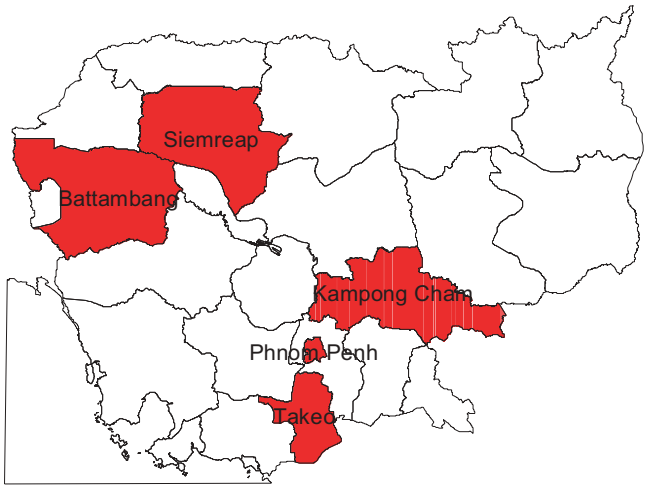

Fig 1–The provinces where ILI sentinel surveillance sites are located in Cambodia.

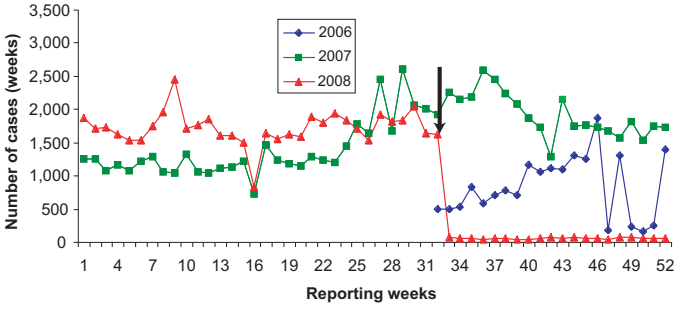

Fig 2A–The distribution of ILI cases by weeks, 2006-2008. The arrow indicates when the case definition was modified in August, 2008.

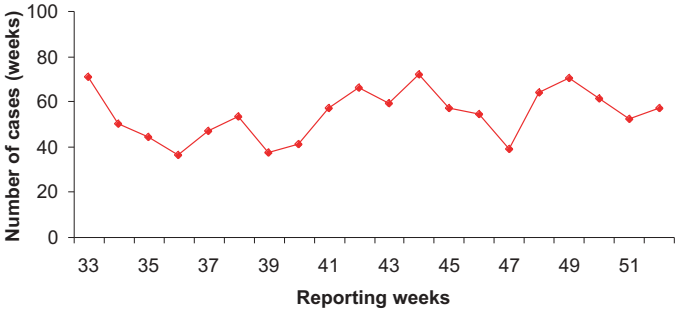

Fig 2B–The distribution of ILI cases by weeks after case definition was modified, August 2006-December 2008. Note that Fig 2A and 2B have different scales.

before the case definition changed (Table 2). After the case definition changed in August 2008, approximately 73% of the ILI cases were less than 15 years of age. There was no observed difference in the ILI cases by gender.

The number of ILI cases reported each week did not appear to change throughout the year (Fig 2A and 2B). The number of reported ILI cases declined sharply after August 2008, when the new case definition was implemented, to less than 26 cases a week from each site.

Among the ILI cases, 2,966 patients (1.8%) had respiratory specimens collected and analyzed at the Pasteur Institute. Among tested specimens, 9.5% were positive for influenza virus. The ILI patients from 5 to 14 years old were more likely to test positive for influenza viruses than the other age groups (12.1% *vs* 9.9%, 6.5% and 5.0% in 0-4, 15-49 and ≥50 year old age groups, respectively ($p<0.05$). After the new case definition was introduced in August 2008 the proportion of ILI cases which were positive for influenza increased (5.3% before the case definition was changed *vs* 29.3% after the case definition was changed). When comparing the proportion of positive ILI cases at the same time period during the year (week 33 to week 52), there

Table 3
Association between a positive influenza test and clinical manifestations.

	Temperature 37.5-38ºC			Temperature ≥ 38ºC		
	Flu (+)	Flu (-)	*p*-value	Flu (+)	Flu (-)	*p*-value
Cough	36/36 (100)	880/887 (96.1)	0.593	239/240 (12.6)	1,650/1,656 (99.6)	0.897
Sore throat	18/27 (66.7)	356/721 (49.4)	0.078	120/181 (66.3)	999/1,295 (77.1)	<0.05[a]
Body pain	11/26 (42.3)	252/710 (35.5)	0.476	44/162 (27.2)	610/1,194 (51.1)	<0.05[b]
Rhinorrhea	35/36 (97.2)	867/886 (97.9)	0.798	231/239 (99.6)	1,612/1,644 (98.1)	0.161

[a]Positive association; [b]Negative association; Flu, influenza

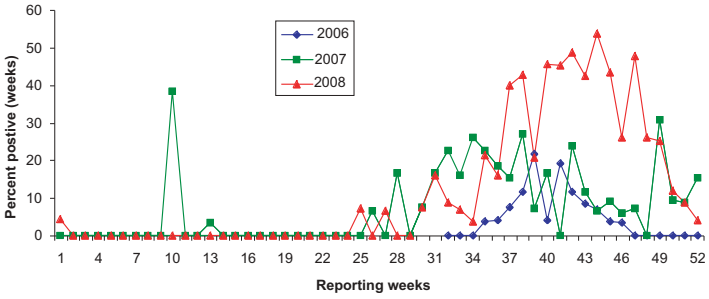

Fig 3– The proportion of ILI cases positive for influenza infection by week, 2006-2008.

was still a significant difference in the proportion of cases (5.4, 15.2 and 29.3% in 2006, 2007 and 2008, respectively). There were no observed differences in the proportion of ILI patients positive for influenza by gender either before or after the case definition changed (5.3% in males and 5.4% in females before the case definition was changed and 30.5% in males and 28.1% in females after the case definition was changed). The proportion of ILI cases positive for influenza increased per year (5.1% in 2006, 7.5% in 2007 and 15.9% in 2008).

In contrast to the reported ILI cases, we observed a clear seasonal peak in positive influenza cases (Fig 3). Each year most cases occurred between June and November, months corresponding to the rainy season in Cambodia (May to October). The median age of the influenza cases was 9 years old (range: 0.1-76 years old). Among people who tested positive for influenza, 37 (3.9%) had a temperature from 37.5ºC to 38ºC and 287 (14.3%) had a temperature greater than 38ºC.

We compared the frequency of cough, sore throat and other symptoms among patients who presented with a temperature 37.5-38ºC. and those >38ºC (Table 3). Cough was common among ILI patients with and without influenza infection, irrespective of temperature. Sore throat and myalgias were more common among ILI patients with influenza infection but only when the temperature was >38ºC.

Influenza A (H3N2), A (H1N1) and influenza B were found to be circulating in Cambodia (Fig 4). In 2006, we observed circulation of only H3N2 influenza viruses. In 2007, all three influenza types and subtypes were identified, with a predominance of influenza B viruses. In 2008, the H3N2 influenza viruses dominated. Interestingly, during 2008 the number of influ-

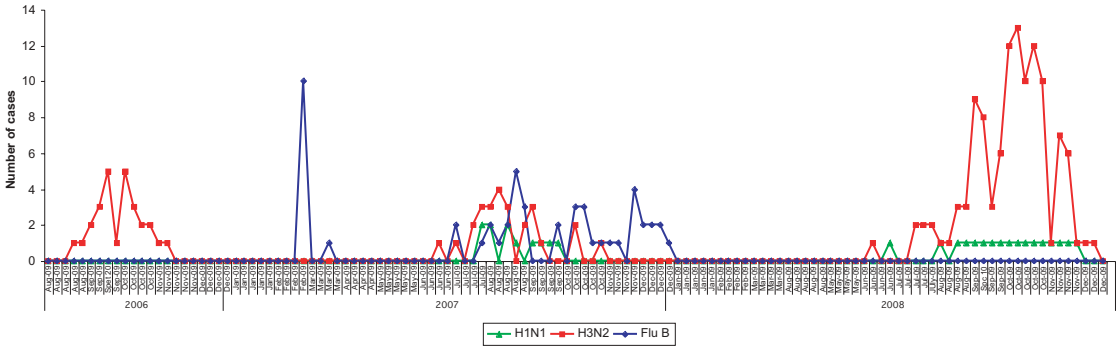

Fig 4–Weekly distribution of circulating influenza types and subtypes, 2006-2008.

enza positive ILI cases was approximately two times higher than the previous two years. In the same year, 2008, there was only one influenza B case detected.

DISCUSSION

The Cambodian ILI sentinel facility surveillance system demonstrated annual circulation among influenza viruses with a peak in influenza activity each year from June to November. By increasing the temperature requirements for the influenza case definition we improved the efficiency of our system. Fewer ILI cases were reported, fewer cases had respiratory specimens taken, fewer laboratory tests were performed, and a higher proportion of ILI cases were positive for influenza virus infection. The percent of ILI cases positive for influenza infection increased from 5.3% to 29.3%, although we only had partial year data after the case definition was modified, and it occurred during a time when influenza viruses had peak circulation in Cambodia.

Prior to August 2008, Cambodia did not enforce the WHO ILI surveillance requirement for fever. However, by modifying the case definition we improved our proportion of influenza positive ILI cases to values similar to those reported by other countries. In Indonesia the proportion of ILI patients that tested positive for influenza was 11.1% (Beckett *et al*, 2004) and in Thailand the proportions were 13.9% and 19.5% from outpatient ILI cases and inpatient pneumonia cases during 2006 and 2007, respectively (Waicharoen *et al*, 2008). Both countries used an ILI case definition that included a temperature ≥38ºC. Vietnam experienced a similar increase in the proportion of ILI cases positive for influenza when they increased the temperature requirement for ILI. In Vietnam during the period from 2001 to 2003 when the case definition included a temperature >37.8ºC, 2.5% of samples were collected and the annual positivity rate varied from 1.0 to 3.4%. In 2006-2007, when the definition changed (temperature ≥38ºC), similar to the Cambodian new case definition, the rate rose to 19% (Nguyen *et al*, 2007). In the future, we anticipate the Cambodia ILI surveillance will continue to perform at a level comparable to other countries using the WHO ILI definition.

Influenza viruses circulated annually in Cambodia and peaked during the months of June through November. This seasonality is similar to other reports from Southeast Asia. In Hong Kong, two peaks

in influenza activity are reported, one in winter (January-March) and another smaller peak in summer (July-August); the percentage of samples positive for influenza virus ranged from 2.0 to 43.4% (Li *et al*, 2006). In Thailand, 23% were influenza positive by RT-PCR (Simmerman *et al*, 2006). In Bangladesh, 16% of ILI cases were influenza positive (Brooks *et al*, 2007). Influenza A (H1/N1) viruses were detected throughout the 2006-2008 period. Influenza B was present in 2007 in March and accompanied H1N1. Few influenza H3N2 cases were observed. Similar findings were reported from other countries in the region (Beckett *et al*, 2004; Nguyen *et al*, 2007; Waicharoen *et al*, 2008).

ILI sentinel surveillance in Cambodia started in 2006 and has experienced gradual improvement due to many factors. First, all persons involved in the system are committed to the system and to implementing changes to improve the system. These changes were communicated through a regular refresher training workshop and follow-up visits by the central CDC and its partners. Inefficiencies in data collection and transporting specimens to the laboratory have improved over time. The new case definition improved the efficiency of the system, resulting in fewer reported ILI cases and a higher percentage of specimens positive for influenza; thus reducing the burden on the system in participating clinical centers and the laboratory. Overall, ILI surveillance has given a clearer epidemiological picture of influenza in Cambodia and will raise awareness of influenza among the public and health professionals.

In this study, we faced some limitations. The surveillance system has only collected data for 3 years. Additional years should provide more information about seasonality and circulating strains and to evaluate the effectiveness of the new case definition. The Cambodian Demographic Health Survey 2005 showed less than 30% of people seek care at public facilities (CDC, 2005). Thus, our surveillance may not be representative of the Cambodian population. Information from the reports, especially regarding laboratory results, was often incomplete, limiting our evaluation.

In summary, Cambodia has an annual increase in influenza infections that corresponds to the rainy season. Surveillance for ILI in Cambodia was improved by increasing the temperature requirement for the ILI definition. Monitoring of influenza viruses is crucial to track the emergence of new strains and for the development of vaccines. The seasonality of human influenza may be helpful to clinicians faced with a potential human H5N1 case. In the future Cambodia hopes to add surveillance for severe acute respiratory illness (SARI), in addition to ILI surveillance and estimate the influenza-related severity and mortality.

ACKNOWLEDGEMENTS

We thank Dr Alicia Fry, the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA for her help in writing this manuscript. We thank all the physicians and nurses who participated in ILI surveillance in Cambodia. We are indebted to Dr Nopporn, International Field Epidemiology Training Program, Ministry of Public Health, Bangkok, Thailand.

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