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Research Article

Prevalence and Risk Factors Associated with Influenza Infections in Kampong Cham and Tbong Khmum Provinces, Cambodia

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ABSTRACT

Introduction

Influenza epidemics occur yearly worldwide, including in Cambodia. Two types of seasonal influenza cause significant human morbidity and mortality: influenza A [A (H1N1) pdm09 and A (H3N2)] and influenza B (B/Yamagata and B/Victoria). The overall prevalence of influenza in Cambodia was approximately 38.0% (2012–2015). We aimed to determine the prevalence of influenza infection from 2013–2017 and to assess the potential risk factors for human infection with influenza in the four villages of Kampong Cham and Tbong Khmum Provinces.

Methods

We used Stata V16 to analyze data from 3756 participants aged ≥ 06 months who were enrolled from 2013 to 2017 in a cohort study of acute febrile disease among villagers in Kampong Cham and Tbong Khmum provinces, Cambodia. Descriptive analysis was used to describe the prevalence and demographic characteristics of influenza infection. Multivariate logistic analysis was performed to determine the main risk factors associated with influenza infection.

Results

The participants' mean age was 14.0 years (SD = 0.3), and 38.9% were aged 0-5 years. Females accounted for 51.6%. A total of 27.7% were confirmed to be influenza positive, in which most participants were infected with influenza A viruses (53.6%) or influenza B (46.2%). The incidence of influenza infection peaked in the rainy season. Factors independently associated with influenza infection were age 6–12 years (AOR = 1.5, 95% CI: 1.12–2.02), age 13–19 years (AOR = 1.94, 95% CI: 1.30–2.90), primary education level 1–6 years (AOR = 1.53, 95% CI: 1.16–2.00), cough (AOR = 2.96, 95% CI: 2.34–3.75), runny nose (AOR = 1.87, 95% CI: 1.55–2.26) and chills (AOR = 2.03, 95% CI: 1.71–2.41).

Conclusion

The highest influenza incidence was observed for types A and B, which particularly emerged in the rainy season between June and October. Younger age group, primary education, cough, runny nose, and chills were the key predictors of influenza infection.

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Introduction

Influenza is an infectious disease caused by four types of influenza viruses: A, B, C and D. The regular types and subtypes of influenza A [A (H1N1) pdm09 and A (H3N2)] and influenza B (B/Yamagata and B/Victoria) viruses are responsible for seasonal flu outbreaks worldwide annually (1). It is associated with serious disease in individuals aged 65 years and older (2). The emergence of an influenza pandemic caused by a highly pathogenic avian influenza (HPAI) virus of the H5N1 subtype is a concern since people die after being infected with this type of virus (3). Influenza C viruses generally cause mild respiratory illness and are not thought to cause epidemics. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people (4). Globally, influenza contributes to morbidity and mortality, with an estimated economic burden of $87.1 billion. In 2015, the WHO estimated that the seasonal influenza-related illness burden affects 5-10% of the world's population per year, resulting in between 250,000 and 500,000 deaths (5). In developing countries, 99% of deaths from seasonal influenza are associated with lower respiratory tract infections among children under the age of 5 years (6).

Cambodia is an agricultural country with 45 million chickens and 11 million ducks (7) and a tropical climate where influenza is more variable in the rainy season from June to October despite circulation occurring year-round. This viral infection causes influenza-like illness (ILI) in approximately 30% - 40% of affected individuals every year (8). WHO-GISRS (WHO-Global Influenza Surveillance and Response System) laboratories examined 47,947 specimens, of which 1,900 were influenza virus-positive, with 1,674 (88.1%) listed as influenza A and 226 (11.9%) as influenza B (9). Another characterization of influenza viruses is responsible for acute respiratory illness from 2015-2016 revealed that they circulated year-round, peaking during the rainy season. Among the 10,105 specimens tested from 2007 to 2011 in Cambodia. Saha et al. reported that 1,574 (15.6%) specimens were positive for influenza (10). The most frequently reported viral strains were subtype influenza A (H3N2) (56.8%) and influenza B (34.1%) (10). A study in hospitalized children in Argentina showed that the incidence of influenza in children increased from winter to spring, with the peak incidence occurring in June (11). HPAI was first confirmed in poultry and humans in Thailand in 2004, with 83.0% of cases involving infected backyard chickens and ducks. More than 62 million birds were killed or culled, resulting in 17 human cases and 12 deaths (12). A case–control study in Nigeria revealed significant associations between infection with the HPAI H5N1 virus and the presence of visitors, the purchase of live poultry and poultry products, and farm workers living outside the premises (13). However, limited studies about this flu outbreak and its risk factors in Cambodia have been reported, particularly in rural provinces bordering neighboring countries where the flu could serve as a central supply delivery corridor for the trade and smuggling of live poultry and poultry products. Understanding this influenza epidemic is critically important for the development of key early detection strategies to control and prevent this disease effectively. This study aimed to determine the prevalence of influenza virus infection among rural provinces and its potential risk factors.

Methods

A. Data sources

This study was based on existing data from Acute Febrile Disease among Village Cohorts in Kampong Cham and Tbong Khmum Provinces, Cambodia, collected by the US Naval Medical Research Unit-2 (US NAMRU-2) in collaboration with the National Institute of Public Health (NIPH) from 2012–2019. The four surveillance sites located in Kampong Cham Province (Trapeang Chhuk and Roveang villages) and Tbong Khmum Province (Chong Angkrang and La Ork villages). This surveillance collected approximately 8,000 upper respiratory specimens from four villagers aged ≥ 6 months with confirmed fever or ILI who reported either an axillary temperature ≥ 37.5°C or tympanic temperature ≥ 38° C accompanied by one or more of the following respiratory symptoms: cough, sore throat, or shortness of breath. All persons identified with an illness of interest were asked to provide demographic and history information about the presence of illness. Then, upper respiratory specimens were collected for diagnostic testing. Fluorescence real-time reverse transcriptase polymerase chain reaction (real-time RT–PCR) assays were performed to identify the types or subtypes of influenza virus.

B. Study variables

The independent variables were socio-demographic characteristics (sex, age group, education level and occupation), seasonality, different levels of exposure to domestic animals and clinical symptoms of febrile and respiratory illness. The dependent variable was influenza virus infection, which was defined as positive or negative real-time RT–PCR results.

C. Data management and analysis

The original data were double entered into the MS access database (Microsoft Inc., Redmond, WA, USA) and imported to STATA V.16 (College

Station, Texas 77845 USA) for analysis. We restricted our analysis from June 2013- December 2019 with the total sample of 3756. Descriptive statistics, including frequency, percentage, mean, median, interquartile range (IQR) and standard deviation (SD), were used to describe the sociodemographic characteristics of the study participants.

Bivariate analysis with the chi-square test was used to determine the risk factors associated with influenza virus infection. The magnitude of association was calculated using the odds ratio (OR) with a 95% CI via univariate logistic regression. Then, a multivariate logistic regression analysis was performed to control for potential confounders and to assess the main effect of each risk factor with a p value ≤ 0.20 considered significant in the bivariate analysis. The final significance level was set at a p value ≤ 0.05.

Results

A. Sociodemographic characteristics, exposure to animals and clinical symptoms of influenza

Among the 3,756 participants, 40.65% were from La Ork, followed by Roveang (31.84%), Chong Angkrang (13.76%) and Trapeang Chhuk (13.74%). Most of them were female (51.57%). The mean age was approximately 14 years (SD = 0.28), with a range from 6 months to 73 years. Approximately 46.22% had a primary education, and close to two-thirds were unemployed (70.18%). Most of them were enrolled in the rainy season (May to October), at 62.22% (Table 1).

Moreover, 82.88% reported being exposed to dogs, followed by chickens (64.86%), cattle (51.01%), cats (45.37%), ducks (23.40%) and pigs (11.93%). The mean fever temperature was 38.13°C (SD = 0.61). Cough symptoms were the most common (80.72%), followed by headache (75.86%), runny nose (70.79%), sore throat (59.02%), chills (55.36%), shortness of breath (39.41%) and muscle ache (24.01%).

Table 1: Sociodemographic characteristics of the study participants, exposure to domestic animals and clinical symptoms of influenza

Variables	N = 3,756	
	Freq	%
Sociodemographic characteristics		
Village name		
La Ork	1,527	40.65
Roveang	1,196	31.84
Chong Angkrang	517	13.76
Trapeang Chhuk	516	13.74
Gender		
Female	1,937	51.57
Male	1,819	48.43
Age in years, mean (SD)	14 (0.28)	
Aged group in years		
0 – 5	1,461	**38.90**
6 – 12	1,129	**30.06**
13 – 19	353	9.40
20 – 45	485	12.91
≥ 46	328	8.73
Education levels		
No school	1,624	**43.24**
Primary school	1,736	**46.22**
Secondary school	245	6.52
≥ High school	151	4.02
Occupation		
Unemployed	2,636	70.18
Farmer	877	23.35
Student	170	4.53
Others*	73	1.94
Seasonality		
May-October	2,337	**62.22**
November-April	1,419	37.78
Exposure to domestic animals		
Dog	3,113	82.88
Chicken	2,436	64.86
Cattle	1,916	51.01
Cat	1,704	45.37
Duck	879	23.40
Pig	448	11.93
Clinical symptoms of influenza		
Mean temperature when enrolled (SD) in °C	38.13 (0.61)	
Cough	3,032	80.72
Runny nose	2,659	70.79
Headache (n = 3222)	2,444	75.86
Chills (n = 3737)	2,065	55.36
Sore throat (n = 3243)	1,914	59.02

(Continued)

(Continued)

Table 1: Continued

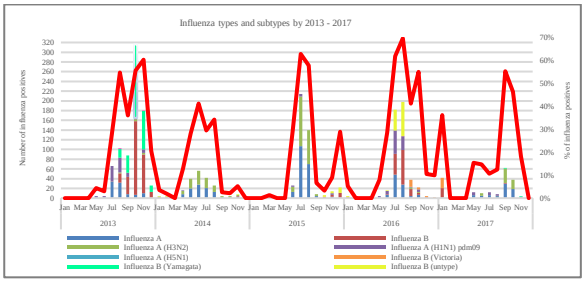
Variables	N = 3,756	
	Freq	%
Shortness of breath (n = 3712)	1,463	39.41
Muscle aches (n = 3245)	779	24.01

** Other: Government, construction, garment factory and restaurant*

B. Prevalence of influenza A and B infection from 2013–2017

Figure 1 illustrates the prevalence of influenza from 2013–2017. Of the 3,756 collected samples, 27.69% of participants were confirmed to be positive, in which influenza A virus was 53.65%, influenza B was 46.15% and coinfection with influenza A-B was (0.19%). The incidence of influenza infection peaked mainly in the rainy season between June and October. The percentage of influenza B/untyped was the highest (41.73%), influenza A/H3N2 subtypes was 33.94%, followed by influenza A/H1N1 pdm09 (19.52%) and influenza A/H5N1 (0.19%). Compared with the other subtypes, influenza B/Victoria (21 patients) was the most predominant subtype detected in January 2017.

Figure 1: Prevalence and trends of influenza A and B infection from 2013–2017



C. Factors associated with influenza virus infection

According to **Table 2**, seven covariates were ultimately found to be the main predictors of influenza infection after adjustment in the multivariate logistic regression model. These factors were age group 6-12 years (AOR = 1.50, 95% CI: 1.12 - 2.02) and age 13-19 years (AOR = 1.94, 95% CI: 1.30 - 2.90), primary education (AOR = 1.53, 95% CI: 1.16 - 2.00), clinical symptoms included a history of cough (AOR = 2.96, 95% CI: 2.34–3.75), a runny nose (AOR = 1.87, 95% CI: 1.55–2.26) and chills (AOR = 2.03, 95% CI: 1.71–2.41).

However, farmers with an AOR = 0.72 (95% CI: 0.55–0.94), and the dry season (November–April) were less vulnerable than those in the rainy season (AOR = 0.20, 95% CI: 0.16–0.24).

Table 2: Multivariate logistic regression analysis of factors associated with influenza virus infection

Risk factors	N = 3756		
	Adj. OR	95% CI	P value
Village			
Trapeang Chhuk	Ref.	-	-
La Ork	1.26	0.97 - 1.63	0.077
Roveang	1.01	078 - 1.30	0.905
Chong Angkrang	1.29	0.95 - 1.76	0.099
Aged group			
0 – 5	Ref.	-	-
6 – 12	1.50	1.12 - 2.02	**0.007**
13 – 19	1.94	1.30 - 2.90	**0.001**
20 – 45	1.48	0.99 - 2.20	0.05
≥ 46	1.46	0.99 - 2.17	0.055
Education levels			
No school	Ref.	-	-
Primary school (1 - 6)	1.53	1.16 - 2.00	**0.002**
Secondary school (7 - 9)	1.35	0.89 - 2.06	0.152
High school and above	1.15	0.71 - 1.86	0.551
Occupation			
Unemployed	Ref.	-	-
Farmer	0.72	0.55 - 0.94	**0.018**
Student	1.09	076 - 1.58	0.612
Others*	0.89	0.49 - 1.60	0.706
Seasonality			
May-October	Ref.	-	-
November-April	0.20	0.16 - 0.24	< **0.001**
Chicken exposure			
No	Ref.	-	-
Yes	1.07	0.89 - 1.28	0.422
Cough in the past 2 days			
No	Ref.	-	-
Yes	2.96	2.34 - 3.75	< **0.001**
Runny nose in the past 2 days			
No	Ref.	-	-
Yes	1.87	1.55 - 2.26	< **0.001**
Headache in the past 2 days			
No	Ref.	-	-
Yes	1.09	0.88 - 1.35	0.400
Chills in the past 24 hours			
No	Ref.	-	-
Yes	2.03	1.71 - 2.41	< **0.001**

(Continued)

Table 2: Continued

Risk factors	N = 3756		
	Adj. OR	**95% CI**	**P value**
Sore throat in the past 2 days			
No	Ref.	-	-
Yes	1.1	0.92 - 1.32	0.286
Shortness of breath in the past 24 hours			
No	Ref.	-	-
Yes	0.85	0.72 - 1.01	0.072
Muscle aches in the past 2 days			
No	Ref.	-	-
Yes	0.95	0.78 - 1.16	0.639

Discussion

Our findings highlight that influenza infection in Cambodia circulates annually, with an overall prevalence of 27.7%, mainly influenza A (53.6%) and influenza B (46.2%). Commonly, it spreads in the rainy season between June and October. The seven main predictors of influenza infection were younger age, lower education level, farmer status, rainy season, and three main clinical symptoms (coughing in the past 2 days, having a runny nose in the past 2 days and having a history of chills in the past 24 hours).

The overall high prevalence (27.7%) of influenza infection reported in the present study remains a public health concern in communities predominantly containing influenza A and B viruses, which are responsible for seasonal epidemics of clinical influenza with high incidence as reported in other studies (1, 14). There was almost equal distribution of influenza A viruses (H3N2, 33.94%, H1N1 pdm09, 19.52%) and influenza B (B-untyped), B-Victoria and B-Yamagata). In general, influenza infection was detected at all four sites, and there was no significant difference between the sites. Commonly, we found that the peak number of influenza cases was significantly high in the rainy season between June and October of the year, coinciding with increased enrollment of participants from May through October, possibly due to increased circulating influenza during this time. These influenza cases were similar to those in a recent report by Bonath Ka MV et al. (15).

The findings of this study revealed a significant association between influenza infection and age between 6 -12 years, and between 13-19 years. This result was comparable with the results of Chelsea R. Brown in 2015 (14). This may be related to a lack of sanitary attention among younger participants and the children who are probably overrepresented, which explains the low proportions of influenza infection in the older age range. Moreover, participants who were in primary school had 1.5 times more cases of influenza infection than those who reported not in primary school (16). This result is probably due to school exposure to contaminated materials and poor hygiene among school children. We also found a significant association between influenza infection and clinical symptoms. Among several reported clinical symptoms, only cough in the past 2 days, a runny nose in the past 2 days and chills in the past 24 hours were statistically significant. The clinical symptoms were evaluated by reporting from participants or their relative's respondents to the interviewer. Therefore, their responses might not be accurate data that caused information bias.

Limitations

This study had some limitations that need to be considered with caution. First, this research was conducted using existing data; therefore, the quality of the data and the information in the data were not under our control. There might be information bias from participants aged less than 18 years and their response to clinical symptoms. Second, the sample storage and transportation conditions were unknown, such as how many days the samples were transported from sites to Phnom Penh and how the storage conditions were in the site laboratory. Therefore, it may lead to a low viral load for testing, which may affect the test results. Third, all the information obtained from the respondents was structured into questionnaires and verbally face-to-face interviews; hence, information bias and recall bias may be present. Consequently, the significance of some variables associated with influenza infection may be underestimated. Despite these limitations, the five-year data from 2013–2017 provided us with a large dataset with a consistent trend in the prevalence of influenza infection that was reliable and consistent over the years. Moreover, the results of this study were consistent with international published literature (17-19).

Conclusion

The prevalence of influenza infection is relatively high in these rural provinces. The highest prevalence of seasonal influenza infection, especially types A and B, mainly occurred in the rainy season from May to October of the year. Our findings indicate that the main predictors of influenza included younger age group, education level, occupation, seasonal variation, and main clinical symptoms, including cough, runny nose, and chills. The findings could be useful for health care providers or health program planners to

establish vaccination plans and strategies to control disease spread that may cause severe respiratory illness. Preventive education should be improved and included in school programs, especially in primary school. Sanitary knowledge and hygiene should be provided to baby sitters who care for babies. Vaccination for preventing diseases should be encouraged for all people with main flu clinical symptoms, such as cough and runny nose, particularly children over six years old in the community and in the rainy season.

Ethics approval and consent

The original study was approved by the NAMRU-2 IRB and NECHR, Cambodia Ministry of Health. A field interview in each village obtained written informed consent and assent from all participants and parents or guardians for subjects less than 18 years of age who agreed to participate in the study. All samples were anonymized prior to laboratory testing. The current study proposal was approved by the NECHR on April 19, 2021 (Ref # 065). Additionally, the use of the data has been approved by the NAMRU-2 and NIPH.

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