Clinical and laboratory predictors of influenza infection among individuals with influenza-like illness presenting to an urban Thai hospital over a five-year period.

Polymerase Chain Reaction

Reverse Transcriptase-Polymerase Chain Reaction

Research and Analysis Methods

Molecular Biology Techniques

Artificial Gene Amplification and Extension

Polymerase Chain Reaction

Reverse Transcriptase-Polymerase Chain Reaction

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Predictors of influenza infection among patients with influenza-like illness in Thailand

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Early diagnosis of influenza infection maximizes the effectiveness of antiviral medicines. Here, we assess the ability for clinical characteristics and rapid influenza tests to predict PCR-confirmed influenza infection in a sentinel, cross-sectional study for influenza-like illness (ILI) in Thailand. Participants meeting criteria for acute ILI (fever > 38°C and cough or sore throat) were recruited from inpatient and outpatient departments in Bangkok, Thailand, from 2009–2014. The primary endpoint for the study was the occurrence of virologically-confirmed influenza infection (based upon detection of

viral RNA by RT-PCR) among individuals presenting for care with ILI. Nasal and throat swabs were tested by rapid influenza test (QuickVue) and by RT-PCR. Vaccine effectiveness (VE) was calculated using the case test-negative method. Classification and Regression Tree (CART) analysis was used to predict influenza RT-PCR positivity based upon symptoms reported. We enrolled 4572 individuals with ILI; 32.7% had detectable influenza RNA by RT-PCR. Influenza cases were attributable to influenza B (38.6%), A(H1N1)pdm09 (35.1%), and A(H3N2) (26.3%) viruses. VE was highest against influenza A(H1N1)pdm09 virus and among adults. The most important symptoms for predicting influenza PCR-positivity among patients with ILI were cough, runny nose, chills, and body aches. The accuracy of the CART predictive model was 72.8%, with an NPV of 78.1% and a PPV of 59.7%. During epidemic periods, PPV improved to 68.5%. The PPV of the QuickVue assay relative to RT-PCR was 93.0% overall, with peak performance during epidemic periods and in the absence of oseltamivir treatment. Clinical criteria demonstrated poor predictive capability outside of epidemic periods while rapid tests were reasonably accurate and may provide an acceptable alternative to RT-PCR testing in resource-limited areas.

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Infection with influenza viruses poses a significant public health threat globally, with a disproportionate impact in the developing world [

As influenza vaccine programs build throughout Asia, important questions remain regarding regional epidemiology and vaccine effectiveness to inform local and global vaccination programs. In Thailand, influenza vaccination is recommended for health care workers, pregnant women, individuals with underlying comorbidities, young children, and the elderly. While vaccine coverage has been increasing, awareness of influenza vaccine recommendations and acceptance of vaccine administration remain a challenge in some target populations [

Neuraminidase inhibitors have been shown to decrease the duration of influenza-associated illness [

Multiple studies have sought to predict influenza from among influenza-like illness (ILI) cases based upon clinical data such as symptoms and exposure histories. Some clinical algorithms have demonstrated promising results and relatively high accuracy [

In this manuscript, we explore epidemiologic, demographic, and clinical factors associated with influenza infection, influenza vaccination, and vaccine effectiveness in a cohort of individuals presenting with ILI in Thailand over a five-year period. We present a predictive model to discern influenza from non-influenza ILI based upon clinical symptoms and explore factors related to performance characteristics of the QuickVue rapid influenza diagnostic test. We seek to improve the predictive capability for influenza infection in regions with limited laboratory capabilities and to therefore improve clinical management and clinical outcomes.

Materials and methods

The study was conducted at Phramongkutklao (PMK) hospital in Bangkok, Thailand. PMK is a 1200 bed hospital serving active and retired Royal Thai Army military personnel, their families, and other civilians. The majority of the patient population seen is civilian (60–70%). The hospital has inpatient and outpatient departments and sees both children and adults.

Study population and study methods

Sentinel surveillance for ILI was established as part of the Armed Forces Research Institute of Medical Sciences (AFRIMS) influenza surveillance program at PMK hospital, initiated in 2009. The surveillance period for this manuscript was August 2009 through August 2014. The study is cross-sectional in design, with no specimen or data collection occurring after the initial visit. Participants were enrolled from inpatient and outpatient departments with the following inclusion criteria: fever > 38°C accompanied by cough or sore throat, age > = 6 months, presentation to PMK within 3 days of fever onset for outpatients and within 5 days of fever for inpatients, and provision of consent or assent for participation. Exclusion criteria were the presence of any immunocompromising condition or suspected tuberculosis.

Enrolled subjects provided demographic information and exposure information (recent travel, sick contacts, smoking history) as well as clinical information (presence / absence of specific symptoms, receipt of any medications for the illness prior to enrollment, presence of select comorbidities). Additionally, subjects were asked to report whether and when they had received an influenza vaccine within the last 12 months. A nasal swab was obtained for rapid influenza testing (QuickVue), which was performed onsite. An additional set of nasal and throat swabs were obtained, although two throat

swabs were occasionally obtained from children per the parents' or child's wishes. Specimens were first tested for influenza A or B by reverse transcriptase polymerase chain reaction (RT-PCR); if positive for influenza A, they were further tested with primers specific for H1, H3 and H1 pandemic 2009 (pdm09). Primers and probes were designed by the US Centers for Disease Control and Prevention (CDC) [

The study was approved by the Institutional Review Boards of the Royal Thai Army in Bangkok, Thailand, PMK hospital, and the Walter Reed Army Institute of Research (WRAIR). Written informed consent was obtained from all subjects.

Bivariate analyses were conducted using χ

Classification and regression tree (CART) analysis was used to develop a predictive model of influenza PCR-positivity among ILI cases based upon symptoms reported. All symptom variables (

An initial training set was used to build the model, using data from the years 2009–2013. The model was subsequently applied to a test set of data from 2014. Measures of model performance were calculated by comparing the predicted outcome of RT-PCR (positive or negative for influenza) against the observed result. Performance measures for the QuickVue test were calculated using the RT-PCR result for influenza as the gold standard for comparison. All analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY) and R version 3.3.0 (R Core Team, Vienna, Austria).

A total of 4572 individuals were enrolled between August 2009 and August 2014, of which 1493 (32.7%) had detectable influenza RNA by RT-PCR (hereafter described as influenza "cases"). The majority of influenza cases were attributable to influenza B (38.6%), then influenza A(H1N1)pdm09 (35.1%), followed by influenza A(H3N2) (26.4%). All influenza A infections were attributable to influenza A(H1N1)pdm09 or influenza A(H3N2) in the cohort. There was one case of dual infection with influenza B and influenza A(H1N1)pdm09 detected by RT-PCR.

Comparison of influenza-positive and influenza-negative cases (

Influenza cases were significantly older than non-influenza ILI cases, with mean ages of 14.8 and 8.7 years, respectively ($p<0.01$ by t-test, data not shown). 46.5% of ILI cases occurred in children less than 4 years of age, however, only 15.5% of ILI cases in young children were influenza positive by RT-PCR versus 49.0% of individuals aged 15–59 years. Individuals with ILI and no comorbidities were more likely to test positive for influenza infection by RT-PCR (33.2%) than those with one or more comorbidity (27.4%). Outpatients with ILI were more likely to test positive for influenza infection than inpatients (33.6% versus 19.2%). Healthcare workers presenting with ILI were significantly less likely to be influenza-positive (38.2%), compared with homemakers (63.5%) and members of the military (53.6%). The proportion of ILI cases that were influenza positive by RT-PCR varied significantly by year, with maximum positivity in 2010 (42.8%) and minimum positivity in 2013 (18.4%).

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Predictors of influenza positivity among patients presenting with influenza-like illness, predictors of reported vaccination within the last 12 months, and vaccine efficacy.

Vaccination history and vaccine effectiveness (

21% (960 / 3612) of individuals with ILI reported a history of influenza vaccination in the last 12 months, with an associated overall vaccine effectiveness of 49.5% (95% confidence interval [CI] 40.0–57.1%). VE was highest for influenza A(H1N1)pdm09 (66.6%) and lowest for influenza A(H3N2) (36.2%). Young children were most likely to have been vaccinated within the last 12 months (27.0%) but VE was lowest in this age group at 24.5%. Individuals aged 15–59 years were least likely to report vaccination (9.8%) but VE was highest in this age group at 56.7%. 33.6% of those with any underlying comorbidity reported influenza vaccination, compared to 19.6% of those with none. Vaccination history varied by occupation, with healthcare workers the most likely to be vaccinated (22.4%) and office workers, university students, and members of the military the least. Notably, VE was very high in both healthcare workers (79.1%) and members of the military (85.1%). Likelihood of vaccination increased from 16.0% in 2009 to 32.0% in 2014. VE varied significantly by year, from a minimum of 17.9% in 2013 to a maximum of 59.1% in 2014.

Temporal trends in ILI cases

The seasonality of influenza cases roughly followed a biphasic pattern, with the largest peak often occurring between July and September and a smaller peak often occurring between January and March (

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Temporal distribution of ILI cases testing positive for influenza infection (RED) and negative for influenza infection (BLUE).

Solid circles indicate months identified as experiencing influenza outbreaks (defined as months wherein > = 25% of ILI specimens tested positive for influenza infection by RT-PCR).

A large increase in influenza cases in 2010 was largely attributable to influenza A(H1N1)pdm09 (

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Temporal distribution of subtypes, with southern hemisphere vaccine composition by year.

The percent of influenza A(H1N1)pdm09, influenza A(H3N2), and influenza B isolates matching the vaccine strain for each year is shown in parentheses [

Clinical predictors (

3.7% of influenza cases were hospitalized. Hospitalization was most common among young children with influenza infection (8.8%) and least common among those aged 15–59 years (0.9%). The rate of hospitalization among influenza cases varied significantly by year, from a minimum of 0.7% in 2012 to a maximum of 4.3% in 2014. 25.4% of inpatients with influenza infection received oseltamivir at some

point prior to enrollment versus 1.0% of outpatients. Oseltamivir administration prior to enrollment was most common in the youngest and oldest age groups. Individuals with underlying comorbidities were more likely to be hospitalized (8.9% versus 3.2%) compared to those without comorbidities. 22.4% of influenza cases reported having received antibiotics at some point prior to enrollment; reported rates of antibiotic administration were higher in individuals aged 0–4 years and greater than 60 years and for inpatients.

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Predictors of clinical severity and receipt of antimicrobial medications among those with PCR-confirmed influenza infection.

Among ILI cases, individuals who were influenza-positive were more likely to have had fever at enrollment and more likely to report cough, sore throat, chills, malaise, and generalized body aches (Supplemental table). They were less likely to have difficulty breathing, diarrhea, and lung findings on exam than non-influenza ILI cases. Individuals with influenza A(H3N2) infection were more likely to report fever, runny, nose, or malaise at enrollment and less likely to report cough.

CART analysis of symptoms predicting influenza RT-PCR positive and negativity

Age was the first cut-point identified by the recursive partitioning algorithm, with 84% of children less than 5 years of age with ILI testing negative by influenza RT-PCR (

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CART analysis to predict influenza RT-PCR positivity on the basis of clinical symptoms.

The overall accuracy of the model based upon the training set (data limited to years 2009–2013) was 72.8%. The specificity and negative predictive value (NPV) of the model were superior to the sensitivity and positive predictive value (PPV) for the model, at 82.9% and 78.4% versus 52.1% and 59.7%. When applied to the test set (data from 2014), the accuracy for correctly predicting influenza RT-PCR result based upon symptom data was similar (75.3%). Notably, PPV doubled when the algorithm was applied to epidemic periods (68.5% versus 31.9% for non-epidemic periods). Conversely, NPV was highest during non-epidemic periods (92.0% versus 71.4% for epidemic periods). The receiver operating characteristic (ROC) curves for the CART analysis overall, epidemic, and non-epidemic periods are shown in

10.1371/journal.pone.0193050.g004

Receiver operating characteristic (ROC) curves for (

Sensitivity and specificity of QuickVue (

The overall sensitivity of the QuickVue test was 77.0%, specificity was 97.2%, NPV 89.7%, and PPV 93.0%. The sensitivity of the QuickVue test was higher for influenza B than for influenza A viruses

(80.6% versus 73.4%); specificity was high for both at >98%. 16 specimens were positive for both influenza A and influenza B viruses by QuickVue testing; 11 (68.8%) of these subsequently tested negative by RT-PCR (data not shown). The performance of the QuickVue test was not notably different by inpatient versus outpatient status. The sensitivity of QuickVue was 62.9% if performed on the day of illness onset and peaked at 2 days post-onset of symptoms (79.8%). Sensitivity was lowest in those aged 15–59 years of age (72.8%) and highest at the extremes of age. Sensitivity was lower in those with a history of oseltamivir administration (65.5%) compared to those without a history of oseltamivir (77.2%). PPV was highest during epidemic periods (93.7%) compared to non-epidemic periods (87.7%). The ROC curves for QuickVue overall, epidemic, and non-epidemic periods are shown in

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QuickView test performance, as compared to RT-PCR (“gold standard”).

Lower limit of 95% confidence interval for each proportion is shown in parentheses.

Our clinical prediction algorithm to discern influenza from non-influenza ILI had moderate accuracy (73%) but poor PPV (59.7%). This is consistent with prior studies which indicated that it is more feasible to identify what is not influenza than what is influenza among patients with ILI [

Sensitivity of the QuickVue rapid test was >70% overall for both influenza A and B viruses, superior to prior studies reporting sensitivity in ambulatory populations of approximately 20–55% [

Early treatment with neuraminidase inhibitors is recommended in individuals hospitalized with influenza and individuals at high risk of progression to severe disease. Antiviral coverage was low in the study population, though notably this was a cross-sectional study and individuals may have received oseltamivir later in their treatment course. There was a relatively high rate of reported antimicrobial administration (22%), which did not differ significantly among individuals with PCR-confirmed influenza infection by the presence or absence of an infiltrate on chest X-ray, by lung findings on physical exam, or by the presence or absence of comorbidities that may predispose to severe disease (data not shown). The high rate of antibiotic use and low rate of oseltamivir administration prior to study enrollment in this population underscore the need for early and enhanced diagnosis of influenza influenza to facilitate patient triage and the appropriate targeting of antimicrobials.

Influenza vaccine coverage has been increasing in recent years in the study population but remains relatively low at 20–30%.

Citation

Anderson KB, Simasathien S, Watanaveeradej V, Weg AL, Ellison DW, Suwanpakdee D, Klungthong C, Phonpakobsin T, Kerdpanich P, Phiboonbanakit D, Gibbons RV, Fernandez S, Macareo LR, Yoon IK, Jarman RG. Clinical and laboratory predictors of influenza infection among individuals with influenza-like illness presenting to an urban Thai hospital over a five-year period.. PLoS One. 2018. DOI: 10.1371/journal.pone.0193050