



# Effectiveness of trivalent inactivated influenza vaccine among community-dwelling older adults in Thailand: A two-year prospective cohort study



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## ABSTRACT

**Background:** We conducted a two-year prospective cohort study to measure the effectiveness of trivalent inactivated influenza vaccine (IIV3) to prevent laboratory-confirmed influenza among community-dwelling Thai adults aged  $\geq 65$  years during 2015–16 and 2016–17 influenza seasons.

**Methods:** In 2015, we enrolled a cohort of 3220 participants. Trained health volunteers collected baseline data and followed participants for two years with weekly surveillance for new or worsened cough with self-collection of nasal swabs. Vaccine effectiveness (VE) was estimated as  $100\% \times (1 - \text{rate ratio of rRT-PCR -confirmed influenza})$  among vaccinated versus unvaccinated participants. Propensity score stratification was used to reduce differences between vaccinated and unvaccinated participants associated with access to and receipt of IIV3.

**Findings:** During 2015–16 and 2016–17, 1666 (52%) and 1498 (48%) participants received IIV3, respectively. The overall incidence of influenza during the two seasons was 14.3/1000 person-years among vaccinated participants and 20.2/1000 person-years among unvaccinated participants. VE was  $-4\%$  (95% confidence interval [CI],  $-83\%$ – $40\%$ ) during 2015–16 when there was poor antigenic match between the dominant circulating A/H3N2 viruses and the vaccine strain, and  $50\%$  (95% CI,  $12\%$ – $71\%$ ) during 2016–17 when circulating and vaccine strains were well-matched. Of all three influenza subtypes in both years, significant protection was observed only against Influenza A/H3N2 during 2016–17 (VE,  $49\%$ ; 95% CI,  $3\%$ – $73\%$ ).

**Interpretation:** During a season with well-matched circulating and vaccine strains, IIV3 was moderately effective against laboratory-confirmed influenza among older adults in Thailand.

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## 1. Introduction

Older adults are at increased risk for severe influenza and influenza-associated morbidity and mortality, and they are recom-

mended for annual seasonal influenza vaccination by the World Health Organization and many national governments [1,2]. However, the current evidence for influenza vaccine effectiveness (VE) among adults aged  $\geq 65$  years remains limited, particularly in tropical countries [3,4]. One recent systematic review reported the effectiveness of seasonal influenza vaccine against laboratory-confirmed influenza among older adults to be 0–42% in tropical countries, but the evidence was limited to only two studies, highlighting the paucity of data on influenza VE from tropical settings [4]. In settings where influenza vaccine is already

**Abbreviations:** IIV3, Trivalent inactivated influenza vaccine; VE, Vaccine effectiveness; ARI, Acute respiratory infection; SARI, Severe acute respiratory infection.

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recommended for specific populations, conducting placebo-controlled trials of influenza vaccine efficacy is not feasible, and influenza VE is largely measured using observational study designs such as cohort or test-negative studies [5]. Systematic reviews and meta-analyses of observational VE studies in the older adults population have concluded that the effectiveness of influenza vaccines is modest at best but that additional studies that better control for selection bias, unmeasured confounding, and confounding by indication are needed [4,6,7].

In Thailand, influenza transmission occurs year round with two annual peaks: a major peak in rainy season (June – August) and a minor peak in winter (October – February) [8]. Previous studies have documented that influenza is a major cause of morbidity and mortality in Thailand and results in substantial economic costs annually. A study conducted during 2005–2008 estimated an annual average of 36,400 influenza-associated hospitalizations and 300 deaths occurred, with significantly higher mortality rates in children and the elderly [9]. A subsequent study from 2018 estimated an influenza-associated infection rate of 258/100,000 population and mortality rate of 0.05/100,000 population using data from 77 Thai provinces [10]. In 2004, influenza was also estimated to cause US\$ 23.4–62.9 million in economic losses, with lost productivity accounting for 56% of all costs [11]. In response to the threat of influenza, Thailand targets high-risk groups for free annual vaccination with inactivated trivalent influenza vaccine (IIV3) and older adults aged  $\geq 65$  years have been recommended for influenza vaccination since 2008 [12]. However, IIV3 coverage among older Thai adults aged  $\geq 65$  years has remained low with estimates ranging between 14% and 15% [12], likely driven in part by low vaccine supply. A prior study also identified predictors of vaccination among older Thai adults including distance to the nearest vaccination center, high levels of a perception of benefits of influenza vaccination, and cues to action such as recommendations of healthcare workers [13].

Despite a long-standing recommendation for influenza vaccination of older adults  $\geq 65$  years in Thailand, few data are available on influenza VE in Thailand to assess the impact of the Thai influenza vaccination program. Three studies conducted among older Thai adults found influenza VE to be 47–56% [14–16] but these studies were limited to only hospitalized patients [14] or did not evaluate laboratory-confirmed influenza as an outcome [15,16]. Southeast Asia is often a place where some circulating strains of influenza like A(H3N2) tend to originate and spread [17], making VE data from Thailand particularly important, especially as Thailand is currently on the verge of scaling up its local IIV3 production [18]. We conducted a two-year prospective cohort study to measure VE against laboratory-confirmed influenza-associated acute respiratory infection (ARI) among community-dwelling adults aged  $\geq 65$  years, adjusting for factors that might affect propensity to receive vaccine among participants.

## 2. Materials and Methods

### 2.1. Setting

In 2008, Thailand's Advisory Committee on Immunization Practices began recommending influenza vaccination of persons aged  $\geq 65$  years and persons with chronic diseases; additional high-risk groups, including pregnant women and children 6 months through 2 years of age, were added in subsequent years [12]. The Southern Hemisphere influenza vaccine is allocated annually and provided free of charge to persons in recommended target groups through district and provincial hospitals. The Thai government purchases approximately 3.5 million doses of IIV3 each year for distribution, largely on a first-come, first-served basis [12,13].

The Thailand National Institute of Health (NIH) is the national reference laboratory and runs the national influenza sentinel surveillance system to monitor virus circulation and vaccine strain matching at 11 different sites throughout Thailand [8].

This study was conducted in Nakhon Phanom, a rural province located in the northeast of Thailand along the border with Laos. Prior to 2014, annual influenza vaccination coverage in adults aged  $\geq 65$  years was recorded at approximately 30% in Nakhon Phanom. The Nakhon Phanom Provincial Health Office selected four districts in 2014 for an enhanced influenza vaccine campaign run by the Ministry of Public Health during which community members aged  $\geq 65$  years were especially encouraged to become vaccinated [13]. Due to the feasibility of location and consent of district health directors, That Phanom and Plapak were two districts selected from the four pilot districts to be the sites for this subsequent VE study.

### 2.2. Study design and data collection

This was a prospective longitudinal cohort study conducted over two years from May 2015–May 2017. In May 2015, residents were selected for recruitment using a list of all residents  $\geq 65$  years obtained from an updated community registration after getting permission from the Department of Interior, just prior to sampling. A systematic random sample was used to ensure a proportionate distribution of residents across the study area and by age. Lists of residents were ordered alphabetically by their given name, according to district, sub-district, village, and 5-year age band, and then sampled using a random starting point and a fixed sampling interval calculated from the total number of residents and the desired sample size. Exclusion criteria included institutionalized persons, those who had not resided in the community for at least a year, inability to communicate with study staff, an inability or unwillingness to provide a nasal self-swab, presence of an acute medical condition, tumor in or near the nose, or a history of bleeding disorder. It was possible to enroll more than one adult from the same household.

The written informed consent process and enrollment questionnaire were conducted at participants' homes by trained health volunteers and study team members. The enrollment questionnaire collected data on socio-economic indicators, vulnerability status measured by the 13-item Vulnerable Elders Survey (VES-13) [19], co-morbidities, and household location coordinates to calculate the distance from home to the nearest health care center offering vaccination. At enrollment, participants were also provided with a nasal swab kit and trained to take a nasal self-swab and store it in viral transport media in their refrigerator after being shown a video of the process (available at <https://www.youtube.com/watch?v=yFnfH-xvOXw>). This process was validated previously [20].

Throughout the study period, participants were asked to take a nasal self-swab immediately upon experiencing an ARI or a severe ARI (SARI) and store the swab appropriately. Participants contacted their assigned health volunteer within 24 h of nasal self-swab collection to transport the swab to the district hospital. Health volunteers also conducted a brief interview with participants of their illness history. Health volunteers proactively contacted their assigned participants weekly to identify ARI/SARI events that may not have been reported. In the case of an unreported ARI/SARI event, participants who had not yet taken a nasal swab were asked to self-swab immediately. For any participants who did not have a phone, the assigned health volunteers made weekly household visits and collected nasal swabs from participants who reported an ARI in the past seven days.

Research nurses from each health center were responsible for the enrolled participants within their sub-district. In the event that

participants became ill and went to a sub-district health center or hospital for treatment of ARI/SARI, the research nurse at the location collected a nasopharyngeal swab from the participants, stored it in the refrigerator, conducted an interview with the patient on their illness history, and notified the study team.

### 2.3. Influenza vaccination

All persons aged  $\geq 65$  years in the two selected districts, along with other high-risk groups, were eligible for IIV3 through routine vaccine delivery strategies used by the Thailand MOPH in the 2015–16 and 2016–17 influenza seasons. Vaccination was provided at sub-district health centers and district hospital, along with mobile clinics during campaigns that occurred in May of each year. During 2015–16, the strain composition of the Southern Hemisphere vaccine was A/California/7/2009 (H1N1), A/Switzerland/9715293/2013 (H3N2), and B/Phuket/3073/2013; while during 2016–17, the composition was A/California/7/2009 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008.

The degree of matching between the circulating influenza virus strains and vaccine component strains was obtained from the national influenza surveillance system at the Thai NIH. Influenza vaccination status was verified by matching participants' 13-digit population identification codes to the National Vaccination Database. Participants were considered vaccinated if their 13-digit population identification code was registered in the National Vaccination Database for influenza vaccination during the year and any ARI developed within 14 days of vaccination was excluded.

### 2.4. Definitions

Since many influenza episodes may produce no or lower febrile responses in older adults [21], ARI was defined as new onset of cough or worsening of a chronic cough with or without self-reported fever; a similar case definition has been used to evaluate influenza vaccine effectiveness in the United States [22,23] and has been shown to have high sensitivity for influenza [24]. SARI was defined as an illness with measured axillary temperature  $\geq 38$  °C plus new onset of a cough, worsening of a chronic cough or difficulty in breathing, requiring hospitalization.

Participants with any chronic disease (respiratory, cardiovascular, or other) were considered to have a comorbidity (Supplemental Table 1). Vulnerability status was assessed using the VES, which collects information on participant's difficulty in performing routine daily tasks and is scored from 0 to 10, with higher scores indicating greater degrees of vulnerability [19]. Persons with VES scores  $\geq 3$  were defined as vulnerable or frail [25]. Wealth was defined by possession of household assets, which was analyzed using principal components analysis to generate a wealth index [26]. The study population was categorized according to their wealth in quintiles. Distance to healthcare center was defined as the straight-line distance between the geographic coordinates of participants' homes and the closest health facility where influenza vaccination was offered, and categorized in quartiles.

### 2.5. Storage and laboratory outcome

All self-collected nasal swabs were transported to refrigerators at sub-district health centers and kept between 2 and 8 °C before being frozen in liquid nitrogen tanks below  $-70$  °C. The frozen specimens were sent weekly to the Thai NIH in Nonthaburi for rRT-PCR analysis to specifically identify influenza virus type and subtype, including influenza A(H1N1), influenza A(H3N2), and influenza B. A specimen was considered to have tested positive for influenza virus if the rRT-PCR analysis yielded a cycle threshold value of  $< 37$  [27].

### 2.6. Sample size

The cohort sample size was calculated in OpenEpi ([www.OpenEpi.com](http://www.OpenEpi.com)) using the Fleiss Method with a correction factor to account for discrete data being approximated by a continuous distribution [28], assuming a 50% vaccination rate, 80% power, 5% type I error, and 6% attack rate of influenza-associated ARI per year. With an expected vaccine effectiveness of 40% based on our population's age and prior studies [14–16], the required sample size was estimated at 2724. Given a 15% loss to follow-up and assuming 10% refusal rate, a total of 3446 individuals, rounded to 3500, was required to assess overall VE; the sample size required for stratified analyses was not calculated.

### 2.7. Data analysis

For analytic purposes, influenza season was defined as June of each year through May of the following year (e.g. the 2015–16 season spanned June 2015–May 2016). Incidence per 1000 person-years of laboratory-confirmed, influenza-associated ARI and SARI were calculated for each season and by vaccination status as the total episodes of influenza-positive ARI and SARI cases divided by total person-time under observation. Weeks of intermittent loss to follow up (due to missed swab collection and missed surveillance contacts) were excluded from the person-time denominator. In 2015–16, 135 person-weeks were lost due to missed surveillance contacts (89 [0.11% of total weeks] missed weeks for the unvaccinated group and 46 [0.05% of total weeks] missed weeks for the vaccinated group). In 2016–17, 6 person-weeks were lost because of missed surveillance contacts (4 and 2 missed weeks for the unvaccinated and vaccinated groups, respectively).

To estimate influenza VE, a propensity score stratification approach was used to reduce differences between vaccinated and unvaccinated participants associated with their likelihood to access and receive influenza vaccination. Propensity score stratification using at least five strata has been shown to eliminate 90% of bias due to measured confounders in simulated analyses [29]. VE was estimated as  $100\% \times (1 - \text{rate ratio of laboratory-confirmed influenza virus infection in the vaccinated cohort compared to the unvaccinated cohort})$ . First, baseline demographic, socioeconomic and clinical characteristics of the vaccinated and unvaccinated cohort participants were compared in bivariate analysis using Fisher's exact chi-square or an exact probability test. Propensity scores were then constructed using a multivariable logistic regression model that included all pre-vaccination variables (age, sex, vulnerability status, comorbidity, educational status, smoking status, monthly household income, distance from home to nearest healthcare center, and wealth index) to estimate the probability of receiving influenza vaccination (Supplemental Table 2). We tested model fit using goodness of fit test (Pearson's chi square,  $p$ -value  $> 0.05$ ). Participants were then categorized by propensity scores into 10 equal strata to minimize residual confounding [30] and increase precision [31]. Poisson regression with log person-time at risk as an offset was used to calculate estimates of VE for each propensity score stratum; VE estimates were then pooled across propensity score strata. Multi-level mixed effect methodology was applied to the Poisson regression to account for propensity score clustering by cases.

All data analyses were conducted using STATA software version 14.2 (StataCorp LP, College Station, TX, USA).

## 3. Ethical considerations

Consent forms were translated into Thai and reviewed by a bilingual staff member. Written consent was obtained from all

participants prior to enrollment. The study was approved by the Ethical Review Committee, Department of Disease Control, Ministry of Public Health (Nonthaburi, Thailand); the US Centers for Disease Control and Prevention (Atlanta, Georgia) relied on this committee for ethical approval.

#### 4. Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### 5. Results

#### 5.1. Participant characteristics

In May 2015, 3500 persons aged  $\geq 65$  years were screened. Of 3287 persons who were eligible, 3220 (98%) were enrolled in the study. Of these, 3018 participants (94%) remained in the study at the end of the last week of follow-up (Fig. 1). The median age of the participants was 71 years (interquartile range [IQR] 68–75), 1324 (41%) were male, 524 (16%) had VES scores  $\geq 3$  indicating frailty, and 1265 (39%) had at least one underlying comorbid condition. Overall, 3049 (95%) participants had a monthly household income  $< 10,000$  baht (USD \$333), lower than the national median household income of 16,000 baht (USD \$533). Seventeen percent (533/3220) of participants were current smokers.

#### 5.2. Propensity to be vaccinated

In the 2015–16 season, 52% (1666/3220) of participants received influenza vaccine, and in the 2016–17 season, 48% (1498/3123) of participants received influenza vaccine (Table 1). During both years, vaccine recipients were less likely to be frail (VES score  $\geq 3$ ), less likely to be current smokers, and more likely to have a comorbidity at baseline, particularly hypertension, diabetes, and cancer (Table 1 and Supplemental Table 1). In 2015–16, being male, frail, earning higher than 20,000 THB a month, smoking, and having a cancer reduced the odds of vaccination (Odds Ratio [OR]  $< 1$ ) in a multivariable logistic regression (Supplemental Table 2). Similarly, in 2016–17, the propensity to get vaccinated reduced with frailty and having cancer or chronic liver disease (OR  $< 1$ ), but increased among those with at least primary school education, co-morbidity in general and diabetes (OR  $> 1$ ). These values were used to construct propensity score strata (Supplemental Table 2).

#### 5.3. ARI, SARI and influenza surveillance

In 2015–16, 1196 episodes (1178 ARI and 18 SARI) were reported by cohort participants, of which 1193 (99.7%) had swabs collected: 1099 nasal and 94 nasopharyngeal swabs. In 2016–17, 1169 episodes (1118 ARI and 51 SARI) were reported, with a swab collected during all episodes: 870 nasal and 299 nasopharyngeal swabs. The median time from symptom onset to nasal swab was 1 day (IQR 1–2) and from symptom onset to nasopharyngeal swab was 2 days (IQR 1–3) in both years. There was no difference between vaccinated and unvaccinated participants during either season in the proportion of episodes with swabs collected ( $p = 0.517$  in 2015–16 and  $p = 0.789$  in 2016–17; Fisher's exact test) and the median time from symptom onset to specimen collec-

tion (nasal swab:  $p = 0.516$  in 2015–16,  $p = 0.830$  in 2016–17; nasopharyngeal swab:  $p = 0.908$  in 2015–16,  $p = 0.657$  in 2016–17; Rank sum test).

In both years, there were two peaks of influenza transmission, with the highest peak occurring between September and October (Fig. 2) and a second smaller peak occurring between February and April. In 2015–16 and 2016–17, 49 (4%) and 56 (5%) of the episodes were laboratory-confirmed with influenza respectively. Influenza A(H3N2) was the most frequently detected influenza virus in both years (63.3% in 2015–16, and 76.8% in 2016–17), followed by A(H1N1) (22.4% in 2015–16 and 10.7% in 2016–17) and influenza B (14.3% in 2015–16 and 12.5% in 2016–17). Data from the Thai NIH showed differing levels of vaccine strain matching of the three influenza subtypes in the two years (Supplemental Fig. 1). While vaccine matching for the dominant A(H3N2) ranged from 0 to 78% in 2015–16, circulating A(H3N2) strains (100%) were antigenically similar to the vaccine (A/Hong Kong/4801/2014) in 2016–17.

#### 5.4. Influenza incidence

During 2015–16 and 2016–17, 49 of 3220 (1.5%) and 56 of 3123 (1.8%) participants, respectively, experienced at least one episode of laboratory-confirmed ARI/SARI. The incidence of laboratory-confirmed influenza-associated ARI/SARI among vaccinated participants was 15.7/1000 person-years (95% confidence interval [CI] 10.3–23.0) in 2015–16 and 12.7/1000 person-years (95% CI 7.6–20.0) in 2016–17; and among unvaccinated participants, it was 15.0/1000 person-years (95% CI 9.5–22.6) in 2015–16 and 25.3/1000 person-years (95% CI 18.0–34.7) in 2016–17. There were only two episodes of laboratory-confirmed SARI during the study period, both occurring in 2015–16. (Table 2).

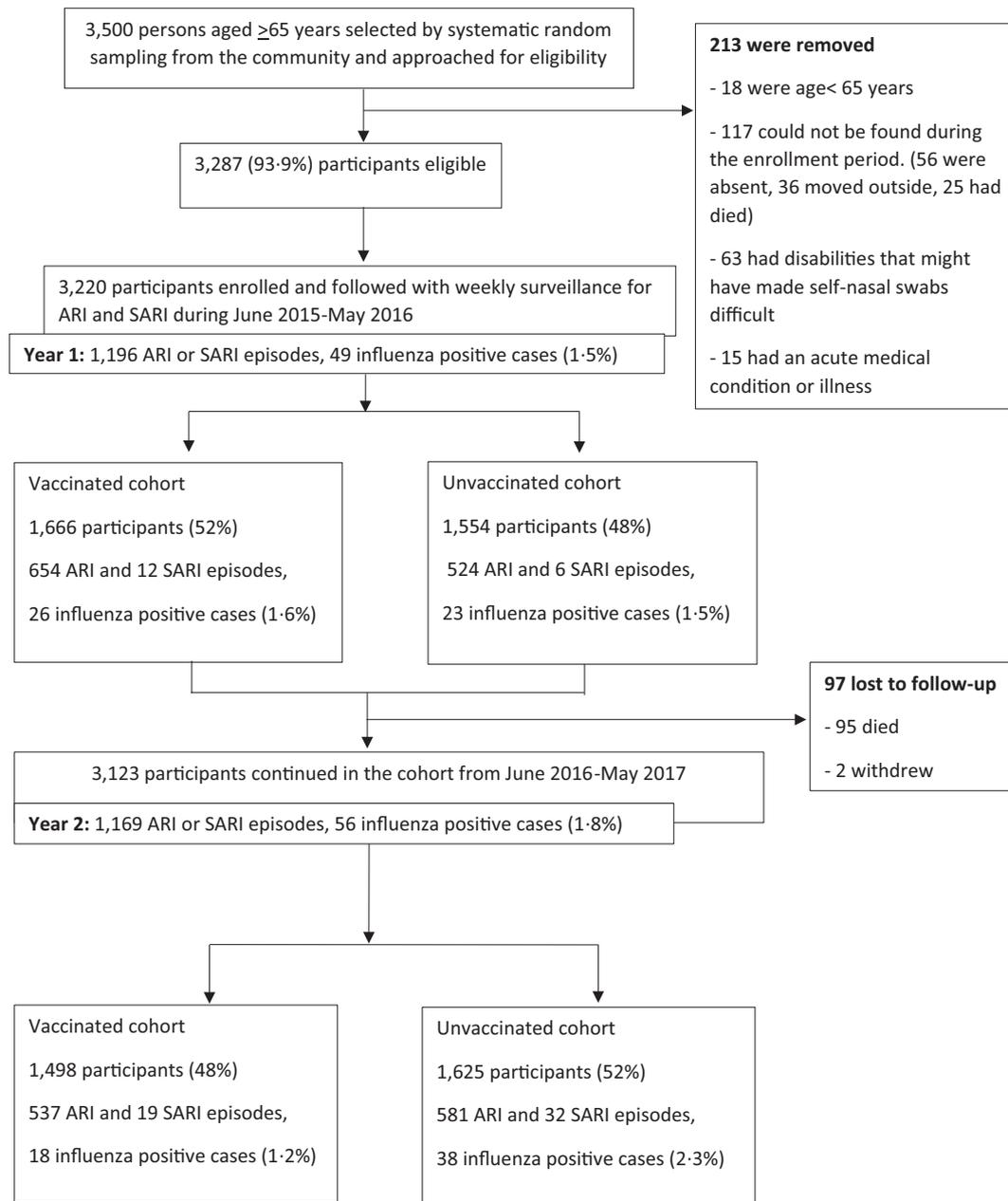
#### 5.5. Influenza vaccine effectiveness

After adjusting for propensity for vaccination, VE estimates against all lab-confirmed influenza cases for the 2015–16 and 2016–17 seasons were  $-4\%$  (95% CI,  $-83$ – $40\%$ ) and  $50\%$  (95% CI,  $12$ – $71\%$ ), respectively (Table 3). VE against the dominant influenza A(H3N2) was  $2\%$  (95% CI,  $-99$ – $51\%$ ) in 2015–16 and  $49\%$  (95% CI,  $3$ – $73\%$ ) in the 2016–17 season.

### 6. Discussion

Influenza vaccine was moderately effective (50%, 95% CI 12–71) against influenza-associated ARI during one season (2016–17) when the Southern Hemisphere vaccine strains were well matched with the predominant circulating strain in Thailand (i.e., influenza A(H3N2)). We measured a statistically significant VE despite relatively low influenza circulation in this population: overall 1.5% and 1.8% of cohort participants experienced an episode of laboratory-confirmed influenza during the two study seasons, respectively.

We used a novel definition of ARI, as the new onset of cough or worsening of cough, to maximize sensitivity. This definition of ARI has been used in the US to estimate VE [22,23] and been of utility in our pilot study [20]. By not including fever, the case definition was more sensitive and likely increased the chances of detecting respiratory episodes for self-collection of a nasal swab. Our case definition might have improved the case detection, particularly considering the low influenza rate, and decreased the chances of misclassification of outcome. However, it may be difficult to compare our results with other studies that use influenza-like illness (ILI) because these have fever in the case definition.



**Fig. 1.** Enrollment and follow-up of a community-based prospective cohort study in older adults aged  $\geq 65$  years Nakhon Phanom Province, Thailand, May 2015–May 2017.

Our overall VE estimate during the 2016–17 season when there was a good match between circulating and vaccine strains is similar to estimates from US of the same season (Adjusted VE 46%, 95% CI 4–70%) [23]. Our study was not powered to assess VE by influenza type or subtype. Nevertheless, we found higher VE (49%, 95% CI 3–73) against influenza A(H3N2) viruses than in the US, where VE against A(H3N2) was 44% (95% CI –3 to 69) [23] and pooled VE against A(H3N2) was 14% (95% CI –14 to 36) over five seasons with varying vaccine match [32]. Our VE results are also higher than the estimates from the A(H3N2) dominant 2016–17 season from Europe (Adjusted VE 17%, 95% CI 1–31%) [33] but similar to Canada (Adjusted VE 42%, 95% CI 18–59%) [34]. However, the estimates from Canada are not restricted to the older adults and include ILI cases with fever, limiting their comparison.

Our study was designed after identifying factors associated with influenza vaccine receipt among older adults in Nakhon Phanom Province to allow rigorous measurement and adjustment of poten-

tial confounders of influenza VE [13]. Because recent studies have identified frailty as a key predictor of both influenza vaccine receipt and influenza VE [35,36], we included the Vulnerable Elders Survey in our study to systematically assess vulnerability status using a validated tool. Similar to those studies, we found that frail older Thai adults were less likely to receive vaccines, indicating that future strategies to improve influenza vaccine uptake among persons aged  $\geq 65$  years in Thailand should focus on making the vaccine more accessible through outreach efforts such as mobile campaigns, and public health education that target these frail older adults. Since influenza vaccines are also recommended for people with chronic diseases in Thailand, we found that older adults were more likely to receive vaccination if they had an underlying medical condition. Therefore, these variables accounted for frailty bias and confounding by indication [37], along with other characteristics in the development of propensity scores to reduce the baseline differences between the two groups in the estimation of VE.

**Table 1**  
Baseline characteristics of older adults aged  $\geq 65$  years in a community-based prospective cohort study, Nakhon Phanom Province, Thailand, May 2015–May 2017, N = 3123.

Characteristics	2015–16 Season		2016–17 Season	
	(Jun 2015 to May 2016)		(Jun 2016 to May 2017)	
	Vaccinated n = 1666 n (%)	Unvaccinated n = 1554 n (%)	Vaccinated n = 1498 n (%)	Unvaccinated n = 1625 n (%)
<b>Age(years), median (IQR)</b>	71.4(68.6–76.4)	71.1(68.2–75.1) <sup>*</sup>	72.4(69.5–77.1)	72.0(69.4, 76.0) <sup>*</sup>
<b>Male</b>	614 (37)	710 (46) <sup>†</sup>	558 (37)	717 (44) <sup>†</sup>
<i>Vulnerability status<sup>a</sup></i>				
VES score < 3 (not vulnerable)	1466 (88)	1230 (79) <sup>*</sup>	1255 (84)	1315 (81) <sup>*</sup>
VES score $\geq 3$ (vulnerable)	200 (12)	324 (21)	243 (16)	310 (19)
<i>Co-morbidity</i>				
Yes	724 (43)	541 (35) <sup>†</sup>	793 (53)	618 (38) <sup>*</sup>
<i>Marital status</i>				
Married	909 (55)	823 (53)	804 (54)	880 (54)
Widowed	677 (41)	653 (42)	627 (42)	656 (40)
Divorced/Separated	33 (2)	40 (3)	32 (2)	40 (3)
Single	47 (3)	38 (2)	35 (2)	49 (3)
<i>Education</i>				
Never attended school	101 (6)	125 (8) <sup>*</sup>	84 (6)	135 (8) <sup>*</sup>
Primary school	1467 (88)	1311 (84)	1319 (88)	1382 (85)
Secondary school and over	98 (6)	118 (8)	95 (6)	108 (7)
<i>Household income<sup>b</sup></i>				
<5000 Baht	1023 (61)	927 (60)	886 (59)	992 (61)
5000–9999 Baht	570 (34)	529 (34)	532 (36)	544 (34)
10,000–19,999 Baht	62 (4)	71 (5)	62 (4)	69 (4)
$\geq 20,000$ Baht	11 (1)	27 (2)	18 (1)	20 (1)
<i>Wealth index<sup>c</sup></i>				
1 (Poorest)	313 (19)	331 (21)	272 (18)	353 (22) <sup>*</sup>
2	321 (19)	332 (21)	291 (19)	338 (21)
3	344 (20)	292 (19)	301 (20)	334 (20)
4	347 (21)	296 (19)	327 (22)	286 (18)
5 (Least poor)	341 (21)	303 (20)	307 (21)	314 (19)
<i>Smoking status</i>				
Never smoked	1159 (70)	965 (62) <sup>*</sup>	1043 (70)	1025 (63) <sup>†</sup>
Ever smoked but stopped $\geq 1$ month	283 (17)	280 (18)	256 (17)	285 (18)
Still smokes or ever smoked but stop < 1 month	224 (13)	309 (20)	199 (13)	315 (19)
<i>Distance from home to nearest health care facilities<sup>d</sup></i>				
1 (Nearest)	433 (26)	372 (24)	376 (25)	405 (25)
2	409 (25)	366 (25)	387 (26)	394 (24)
3	422 (25)	383 (25)	362 (24)	419 (26)
4 (Farthest)	402 (24)	403 (26)	373 (25)	407 (25)

<sup>\*</sup> Statistically different between vaccinated and unvaccinated participants (p-value < 0.05).

<sup>a</sup> VES: Vulnerable Elders Survey; VES score  $\geq 3$  indicates frailty, likely to be associated with increased mortality.

<sup>b</sup> Household monthly income categories correspond to data from the National Statistical Office.

<sup>c</sup> Wealth index constructed from principal components analysis. Median monthly income = 16,000 baht (537 US \$) (<https://www.vanderbilt.edu/lapop/insights/I0806en.pdf>).

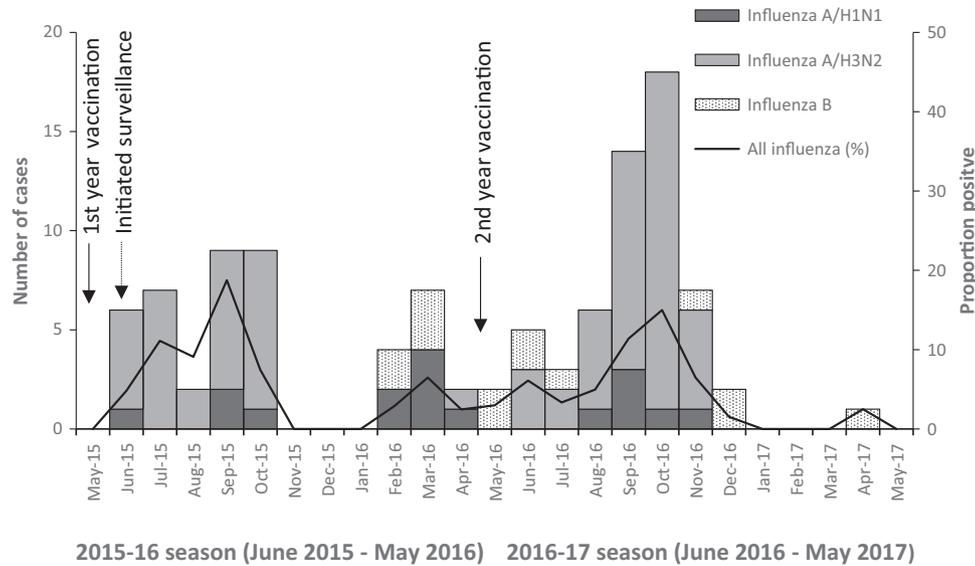
<sup>d</sup> Distance from home to the nearest health care facility categorized in quartiles.

However, our crude VE and adjusted VE estimates were almost identical, suggesting that the overall propensity to be vaccinated was not a confounder of the association between vaccination and prevention of flu ARI/SARI episodes in our study.

Some study limitations should be considered when interpreting our findings. First, our findings may not be generalizable to other Thai older populations. As there was intensive follow-up of all participants with frequent interactions with health volunteers, the study participants may have had a better health care experience as a result than other older population of Thailand. Nevertheless, data from our study can inform future meta-analyses to estimate influenza VE among older adults while providing important representation of populations in middle-income tropical countries. Second, although we used propensity score stratification to reduce bias due to measured confounders, there could have been some residual confounding from unmeasured factors such as differences in health literacy or illness reporting. However, we found no difference in the rate of swab collection between vaccinated and unvaccinated participants suggesting that illness reporting behaviors

were similar between the two groups, possibly due to the intense follow-up conducted as part of cohort participation. Third, we did not collect any data about other conditions that could be precipitated by influenza, such as cardiovascular morbidity, and our sample size was too small to be able to calculate VE for influenza-associated SARI.

Our study provides evidence of influenza VE in a middle-income tropical Asian country representative of a region that has been largely under-represented to date in global influenza VE studies. We show that seasonal influenza vaccines can provide moderate protection among community-dwelling older adults in Thailand, provided there is a good match between the circulating viruses and vaccine strains and document variation in influenza VE across two study seasons. We also demonstrate the feasibility of using self-swabbing and a prospective cohort design to assess VE among older adults. Future studies in other tropical countries can use a similar study design over multiple seasons to ensure at least one season with a good match, to assess the impact of influenza vaccination over time. In addition to contributing to the global evidence



**Fig. 2.** Influenza virus detection by type and subtype among older adults aged  $\geq 65$  years in a community-based prospective cohort study in Nakhon Phanom, Thailand, May 2015–May 2017.

**Table 2**  
Incidence of influenza-associated acute respiratory illness (ARI) and severe acute respiratory infection (SARI) by season among older adults aged  $\geq 65$  years in a community-based cohort study, Nakhon, Phanom Province, Thailand, May 2015 – May 2017.

	2015–16 Season			2016–17 Season		
	Vaccinated participants	Unvaccinated participants	Total	Vaccinated participants	Unvaccinated participants	Total
Person-week no.	85,851	79,212	165,063	73,653	77,946	151,599
Person-year no.	1650	1525	3175	1416	1498	2914
All causes	No. Rate <sup>a</sup> (95%CI)					
ARI or SARI	666 40.3 (38.0, 42.8)	530 34.8 (32.4, 37.3)	1196 37.7 (36.0, 39.4)	556 39.3 (36.7, 41.9)	613 40.9 (38.4, 43.5)	1169 40.1 (38.3, 41.9)
ARI	654 39.6 (37.3, 42.0)	524 34.4 (32.0, 36.9)	1178 37.1 (35.4, 38.8)	537 37.9 (35.4, 40.5)	581 38.8 (36.3, 41.3)	1118 38.4 (36.6, 40.2)
SARI	12 0.7 (0.4, 1.3)	6 0.4 (0.1, 0.9)	18 0.6 (0.3, 0.9)	19 1.3 (0.8, 2.1)	32 2.1 (1.5, 3.0)	51 1.8 (1.3, 2.3)
Lab. confirmed Influenza	No. Rate <sup>b</sup> (95%CI)					
ARI or SARI <sup>c</sup>						
All test positive	26 15.7 (10.3–23.0)	23 15.0 (9.5, 22.6)	49 15.4 (11.4, 20.4)	18 12.7 (7.6, 20.0)	38 25.3 (18.0, 34.7)	56 19.2 (14.5, 24.9)
A (H1N1)	7 4.2 (1.7, 8.7)	4 2.6 (0.7, 6.7)	11 3.5 (1.7, 6.2)	3 2.1 (0.4, 6.1)	3 2.0 (0.4, 5.8)	6 2.1 (0.8, 4.5)
A (H3N2)	16 9.7 (5.6, 15.7)	15 9.8 (5.5, 16.1)	31 9.8 (6.6, 13.8)	14 9.9 (5.4, 16.5)	29 19.3 (13.0, 27.7)	43 14.7 (10.7, 19.8)
B	3 1.8 (0.4, 5.3)	4 2.6 (0.7, 6.7)	7 2.2 (0.9, 4.5)	1 0.7 (0.02, 3.9)	6 4.0 (1.4, 8.7)	7 2.4 (1.0, 4.9)

ARI defined as a new onset of cough or worsening of chronic cough, with or without fever.

SARI defined as new onset of cough, worsening of chronic cough or difficulty breathing with a fever  $\geq 38.0$  °C that required hospitalization.

<sup>a</sup> Obtained by multiplying rates/100 person-weeks by 52 to calculate annualized rates/100 person-years.

<sup>b</sup> Obtained by multiplying rates/1000 person-weeks by 52 to calculate annualized rates/1000 person-years.

<sup>c</sup> There were only 2 episodes of laboratory confirmed SARIs in 2015–2016 season; 1 was occurred in vaccinated participant and another was occurred in unvaccinated participant both were influenza A (H1N1) and there had no laboratory confirmed SARI episode in 2016–2017 season.

**Table 3**  
Crude and adjusted influenza vaccine effectiveness (VE) among older adults aged  $\geq 65$  years in a community-based prospective cohort study, Nakhon Phanom Province, Thailand, May 2015 – May 2017.

	Crude VE		Adjusted	
	VE (95% CI)	P-value	VE <sup>*</sup> (95% CI)	P-value
<b>2015–16 season</b>				
All test positive	–4% (–91%, 43%)	0.885	–4% (–83%, 40%)	0.883
A(H3N2) <sup>a</sup>	2% (–114%, 54%)	0.963	2% (–99%, 51%)	0.965
<b>2016–17 season</b>				
All test positive	50% (10%, 73%)	0.014	50% (12%, 71%)	0.016
A (H3N2) <sup>a</sup>	49% (1%, 75%)	0.036	49% (3%, 73%)	0.039

<sup>\*</sup> Propensity score stratified Poisson regression analysis.

<sup>a</sup> Influenza A (H3N2) was dominant viral strain in both season.

base for influenza vaccination among older adults, data from this study will directly inform influenza vaccination policies in Thailand and other countries in the Southeast Asian region.

### Author contributions

Kriengkrai Prasert: Literature search, study design, data collection, data analysis, data interpretation, writing report, and final approval.

Jayanton Patumanond: Study design, data analysis, and final approval.

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### Declaration of interests

The authors declare that they have no personal or financial relationship that could lead to a conflict of interest.

### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2018.12.047>.

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