Journal of Public Health and Development
Vol.19 No.2 May-August 2021

ORIGINAL ARTICLE

Seasonal influenza vaccine effectiveness among individuals with COPD in Thailand: a retrospective national cohort study of 2011-2013 influenza seasons

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Received: 6 October 2020
Revised: 12 November 2020
Accepted: 13 November 2020
Available online: May 2021

ABSTRACT

The effectiveness of trivalent inactivated influenza vaccine against respiratory illness outpatient visits and hospitalizations among patients with chronic obstructive pulmonary disease (COPD) is less established in Thailand. Using the Thailand National Health Security Office's database, we assembled a retrospective cohort of Thai adults aged ≥18 years with COPD before each of the 2011 to 2013 influenza seasons. We used ICD-10 codes (J40, J41, and J44.1) to identify participants from all public COPD clinics in Thailand, and abstracted data on COPD history, hospital visits and admissions, and influenza vaccination status. Influenza vaccine effectiveness (VE) was estimated by comparing ICD-10 coded discharge diagnosis for influenza and pneumonia (J9-J18) and COPD exacerbations (J44.1) in each season between vaccinated and unvaccinated COPD patients using Poisson regression analysis. Propensity scores were used to match vaccinated with unvaccinated patients with COPD by age, sex, smoking status, severity of COPD, and numbers of COPD exacerbations and hospitalizations in the previous year. Overall, 117,894 patients with COPD were included in the cohort; the median age was 70 years (inter-quartile range 61-77) and 90,161 (77%) were male. Influenza vaccination coverage was 35% in 2011 and 41% in 2012 and 2013. The predominant circulating strain in 2011 and 2013 was A(H3N2), well-matched by the vaccine strain. In 2012, the predominant circulating strain was influenza B, but the vaccine strain had a poor antigenic match. Overall, the pooled VE for three years against ICD-coded influenza, pneumonia, and COPD exacerbations were estimated at 20% (95%

confidence interval [CI], 6%-34%), 35% (95% CI, 34%-36%), and 38.8% (95% CI, 38.3%-39.3%), respectively. Overall, influenza vaccination was associated with a modest protection among people with COPD against ICD-10 coded influenza, pneumonia, and COPD exacerbations. However, despite propensity score matching, our results may have been affected by residual confounding and some measurement bias.

Key words: seasonal influenza vaccine, vaccine effectiveness, COPD, retrospective cohort study, Thailand

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory illness characterized by chronic airflow obstruction that is not fully reversible. Globally, more than 250 million people were estimated to have COPD in 2016,[1] and 3.2 million people died from COPD in 2015 (5% of all global deaths in 2015);[2] with an estimated 90% of all COPD cases occurring in low and middle-income countries.[3] COPD exacerbations, involving acute worsening of airway function in the context of a chronic condition, are associated with most COPD morbidity and mortality, and viral infections are estimated to trigger one-third of such COPD exacerbations.[4] Individuals with COPD are at increased risk for influenza-like illness (ILI) during influenza outbreaks, and influenza virus infections are associated with 5-22% of exacerbations.[5-8] Influenza vaccination among patients with COPD may reduce the risk of all-cause mortality by 41-70%,[9] as well as influenza-associated acute respiratory illnesses by 76%.[10] A recent Cochrane review has suggested that influenza vaccination reduces exacerbations and ILIs by 60% and 80%, respectively, among individuals with COPD.[4] However, randomized controlled trials (RCT) in the review were limited in number and more than a decade old.

In Thailand, COPD is the sixth leading cause of death.[11] In 2008, Thailand's Expanded Program on Immunization began providing influenza vaccines free of cost to individuals with a chronic disease including patients with COPD in public healthcare facilities and seasonal influenza vaccine coverage among all individuals with a chronic disease was 14% in 2012.[12] However, limited data is available on influenza vaccine effectiveness (VE) among patients with COPD in Thailand, with only one VE study conducted among hospitalized patients with COPD nearly 20 years ago,[10] and another RCT comparing the immunogenicity of intradermal and intramuscular trivalent influenza vaccines.[13]

Individuals with a chronic disease are prioritized for seasonal influenza vaccination in Thailand and the Ministry of Public Health (MOPH) has recently determined patients with COPD to be the highest priority within this population. While RCT is the gold standard, it is ethically challenging to conduct an RCT among high-risk groups who have already been recommended for influenza vaccination.[14] Therefore, we used a retrospective cohort design utilizing a national administrative database to estimate influenza vaccine effectiveness (VE) against respiratory-related illnesses among patients with COPD in Thailand during the 2011-2013 influenza seasons.

MATERIALS AND METHODS

Administrative databases

NHSO inpatient/outpatient data

The National Health Security Office (NHSO) was established in 2002 to operate the Thai universal healthcare coverage system, available at no cost to approximately 50 of the 67 million Thai population. The remainder are covered under schemes for government workers or social security. Electronic medical records are part of the NHSO system to ensure accountability and transparency, as well as to track diagnoses for billing purposes. Every eligible Thai citizen is given a 13-digit unique identification number which is used to access health care and to organize medical records. Every patient encounter with the universal health care scheme is recorded, and the 10th Revision of the International Classification of Diseases (ICD-10) codes are used to record the physician or discharge diagnoses. In this study, we included only the patients cared for at public healthcare facilities.

Vaccine database

The NHSO also keeps a separate registry to record the receipt of annual seasonal influenza vaccines by recommended high-risk groups in public health settings in Thailand for reimbursement purposes. Each vaccination event is recorded at a public hospital in an electronic health record in which the hospital staff enters the vaccine recipient's 13-digit unique identification number, date of birth, date of vaccination, province, risk group category, and the type of health insurance.

Study design

We used a retrospective cohort design to compare the incidence of influenza, pneumonia, and COPD exacerbations among vaccinated and unvaccinated patients with COPD during the 2011-2013 influenza seasons. The cohort was composed of all adults aged 18 years and older who were diagnosed with COPD before each influenza season from 1 June 2011 to 31 May 2014. Administrative data from the NHSO databases were used to determine episodes of influenza, pneumonia, COPD exacerbations, as well as seasonal influenza vaccination status. We also used a pre-test, post-test design to compare the rate of exacerbations in the two weeks before and after vaccination among the vaccinated patients with COPD to determine the adverse effect of vaccination.

Cohort participants

Patients with COPD refer to adult patients with a diagnosis of COPD by a physician. ICD-10 primary and secondary discharge codes were used to determine the COPD diagnosis. ICD-10 codes for COPD included J40, J44.0, and J44.1. The NHSO database supports two diagnostic fields and both were used to determine COPD status. Forced expiratory volume in 1 second (FEV1) values, which are measured by spirometry, is a standardized method of determining COPD severity; however, this information is not routinely collected in Thailand. As a result, other available tools were used to measure severity, as recommended by the WHO Global Initiative for Chronic Obstructive Lung Disease.[15] For our study, COPD cases were classified into four categories of severity at the beginning of each influenza period based on a combination of medications prescribed, the Medical Research Council (MRC) dyspnea scale,[16] the COPD assessment test (CAT),[17] the number of exacerbations in the past year, and chronic symptoms. The categories ranged from the least severe form of COPD (Class A) with low-risk symptoms, using short-acting bronchodilators, or MRC scale ≤1, CAT score <10, and ≤1 COPD exacerbation in

the previous year to the most severe form (Class D) in which the patients presented more high-risk symptoms, were using long-acting bronchodilators, had MRC score ≥2, CAT score ≥10, and ≥2 exacerbations in the previous year. Patients with high-risk conditions such as respiratory failure or right heart failure were considered as severe regardless of the type of bronchodilator used and/or MRC score (Supplementary Table 1). Conflicts between these different measures were resolved by using the higher severity classification.

Separate cohorts were formed for each of the three influenza seasons to account for differences in vaccine composition, circulating viruses, and the level of transmission. We identified all adults (aged 18 years and older) diagnosed with COPD prior to June 1 of each year (2011-2013) who registered with the COPD clinic at any public hospital. Presence of other chronic conditions was also abstracted from the NHSO database. We excluded individuals who had a history of lung fibrosis, lung cancer, lung surgery or sarcoidosis, and those who were immuno-compromised or taking any immunosuppressive drugs. Patient files with missing data in any of the key covariates likely to be associated with vaccination, or those who had missing information needed to determine COPD severity were discarded (Figure 1).

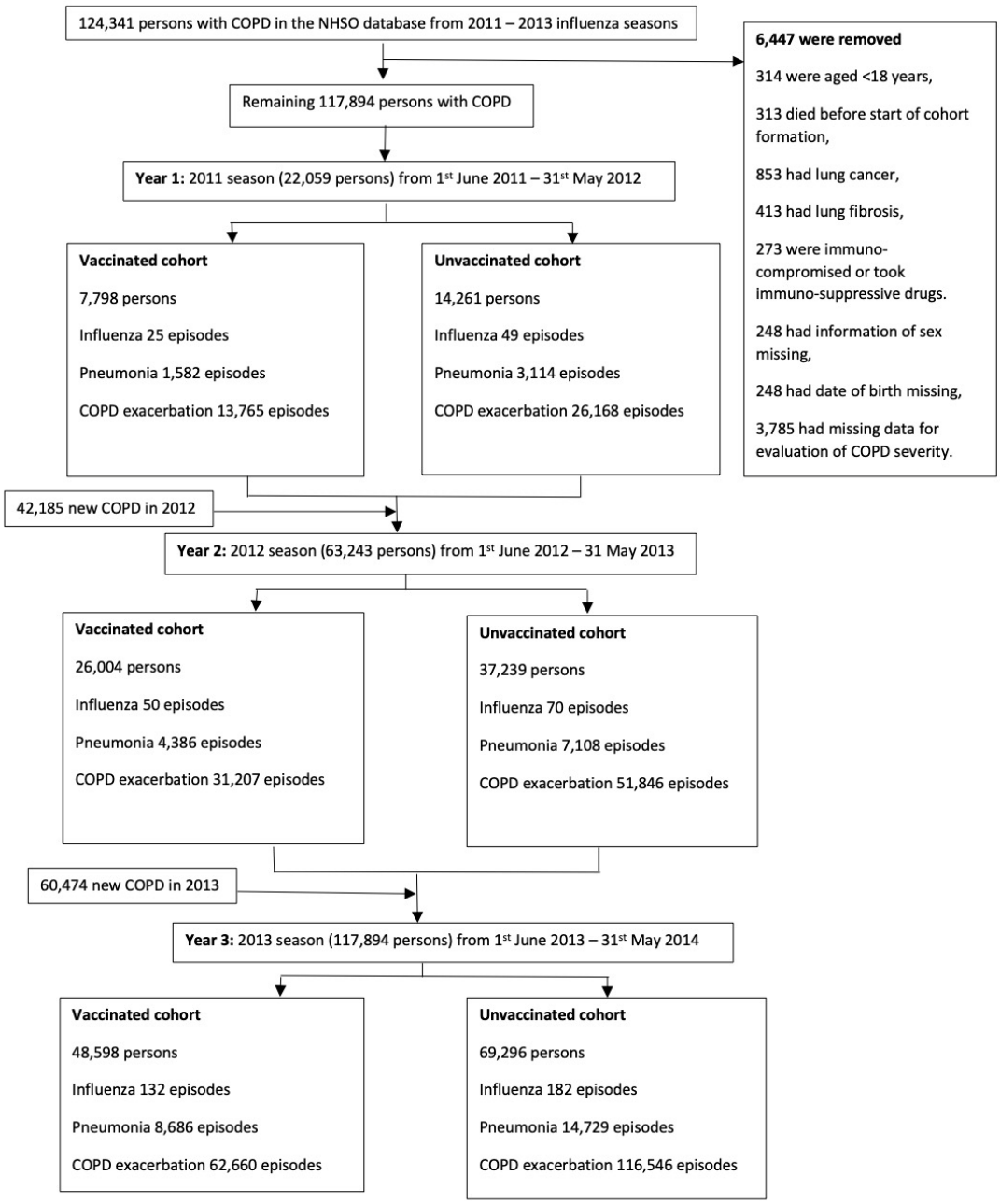


Figure 1 Flowchart of study participants based on a national administrative database, 1st June 2011 – 31st May 2014

Exposure assessment

The primary exposure of interest was seasonal trivalent influenza vaccination with Southern Hemisphere influenza vaccines used in Thailand. In Thailand, the transmission of influenza persists throughout the year with two typical peaks. Often, the peak of the infections occurs during the rainy season (June – August) and another peak in October – February.[18] For the purposes of this investigation, the annual calendar for VE analyses began on 1st June of one year to 31st May of the next year. Eligible patients for each year were

linked to the vaccination database using the 13 digit identification number. In each of the three study seasons, vaccinated cohorts received a single 0.5 ml intramuscular injection of trivalent inactivated subunit influenza vaccine Influvac® (Abbott Biologicals B.V., The Netherlands). The date of vaccine receipt for individuals with COPD was identified from the NHSO vaccine registry using the 13 digit national identification number. Individuals were considered vaccinated 15 days after receipt of vaccination and were considered to remain vaccinated until the start of the next year, or until vaccinated again. Time from receipt of vaccination was calculated and used to estimate the period of immunity. The beginning point of person-time of observation for unvaccinated patients was the date of registration at a COPD clinic or 1st June of each year. All patients were classified according to COPD severity (four categories) and vaccination status (two categories). Individual patients could appear in any or all of the cohorts and could change in severity or vaccination status for different season cohorts.

Clinical outcomes

Outpatient visits and inpatient admissions for influenza and all-cause pneumonia were identified from ICD 10 codes J09-J18 in either of the two diagnostic fields, and all-cause COPD exacerbations were identified from ICD 10 code J44.1 in either of the two diagnostic fields. Exacerbations occurring within 15 days of vaccination were classified as acute/early exacerbation.

Vaccine strain matching

Southern hemisphere influenza vaccines used in Thailand in the 2011 influenza season contained the following strains: A/California/7/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus.[19] The 2012 influenza seasonal vaccine contained A/California/7/2009 (H1N1)pdm09-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus.[20] The 2013 influenza seasonal vaccine contained A/California/7/2009 (H1N1)pdm09-like virus, A/Victoria/361/2011 (H3N2)-like virus, and B/Wisconsin/1/2010-like virus.[21] The prevalence of circulating strains and their matching with the vaccine component strains in the study years were obtained from the Thai National Institute of Health (NIH), which is also the WHO National Influenza Center. The Thai NIH has been conducting national influenza sentinel surveillance in Thailand since 2004.[18]

Sample size

We examined a range of protective effectiveness estimates from 20-50% over one year of follow-up, assuming equal numbers of vaccinated and unvaccinated individuals with 80% power, a type I error of 5%, and a two-sided test. Assuming a VE of 40% or higher, a conservative incidence of pneumonia among patients with COPD of 50 cases per 1000 population per year, and a background rate of COPD exacerbations of a minimum of 16% per year, a sample size of 2,636 was needed for a pneumonia outcome. To stratify the analysis by the severity of COPD into four categories, we multiplied the sample size by four for a total of 10,544 participants, comprising of 5,272 of vaccinated and unvaccinated patients with COPD. For the outcome of COPD exacerbations, 3,296 individuals were needed: 1,648 vaccinated and 1,648 unvaccinated.

Data analysis

Categorical variables were summarized using frequencies and percentages and continuous variables using the mean ± standard deviation (SD). Student's t-test was used to assess the differences in continuous variables between

vaccinated and unvaccinated groups, and exact probability test was used to assess proportions. Recognizing that the association between vaccination and disease outcomes is likely to be biased by characteristics of those vaccinated, we used propensity score matching with 10 strata to balance the covariates between the vaccinated and unvaccinated groups. Sub-classification on the propensity score of at least five strata has been shown to balance up to 90% of all covariates in simulated analyses.[22] Propensity scores were constructed by a logistic regression using age, sex, co-morbidity, smoking status, severity of COPD, and number of COPD exacerbations and hospitalizations in the previous year as covariates. Incidence per 1000 person-years of clinical outcomes was calculated for each season, and by vaccination status as the total episodes of outcomes divided by total person-time under observation.

VE was expressed as a percentage and represents a reduction in risk provided by the vaccine for a given outcome. VE was estimated as (1-RR)*100, where RR is the ratio of the rates of clinical outcomes for the vaccinated divided by the unvaccinated. Propensity score matched Poisson regression analyses were used to compare the counts of ICD-10 coded discharge diagnoses for influenza and pneumonia (J9-J18) and COPD exacerbations (J44.1) in each season between vaccinated and unvaccinated patients with COPD. The ability of the model to control for confounding was tested by comparing VE estimates in the periods of differing influenza activity for which we categorized weekly influenza activity as low (<15%) and high (≥15%) for each of the three seasons. To assess possible adverse effects of vaccination, the difference in the rate of exacerbations during the two weeks before and after vaccination among the vaccinated patients with COPD was evaluated using a generalized linear model. All data analyses were conducted using STATA Software Version 14.2 (StataCorp LP, College Station, TX, USA).

Ethics approval and consent to participate

As these administrative data were already collected, and no data were provided to study investigators containing personal identifiers, no consent was sought from individuals whose records were obtained. The study was approved by the Ethics Review Committee, Department of Disease Control, Ministry of Public Health (Nonthaburi, Thailand).

RESULTS

Sample attrition

The sample attrition data and flow-diagram are shown in Figure 1. The initial data extraction process selected 124,341 patients with a diagnosis of COPD during 2011-2013 from the NHSO database. After removing those not meeting the inclusion criteria (aged less than 18 years, had lung diseases, died, immune-compromised, or had missing data of key covariates), 117,894 individuals remained at the start of the 2013 season. In 2011, there were 22,059 COPD patients, of which 1,001 died. In the 2012 season, 42,185 new patients with COPD were added and 5,823 died. In the 2013 season, 60,474 new patients with COPD patients were added, of which 8,756 died during the 2013 season.

Cohort characteristics

Of a total of 124,718 individuals with COPD included in the cohort, 96,550 (77.4%) were male, the median age was 70 years (inter-quartile range[IQR]: 61-77). Similarly, of 3,646 individuals with COPD patients who were excluded from the cohort due to missing data, 2,860 (78.4%) were male and the median age was 69 years (IQR: 61-77). Influenza vaccination rates

were 35.3% in 2011 (7,798/22,059), 41.1% in 2012 (26,004/63,243), and 41.2% in 2013 (48,598/117,894). While no significant difference was found between vaccinated and unvaccinated cohorts in the presence of co-morbidities, vaccinated participants were more likely to be older, female, have quit smoking, and to have more COPD exacerbations and hospital visits in the prior year than their unvaccinated counterparts (Table 1). The baseline characteristics of both groups were matched according to their propensity to receive influenza vaccine using propensity scores (Supplementary Table 2).

Table 1 Baseline characteristics of study participants based on a national administrative data, 1st June 2011 – 31st May 2014[a]

	2011 influenza season		2012 influenza season		2013 influenza season	
Characteristics	**vaccinated (n=7,798) n (%)**	**unvaccinated (n=14,261) n (%)**	**vaccinated (n=26,004) n (%)**	**unvaccinated (n=37,239) n (%)**	**vaccinated (n=48,598) n (%)**	**unvaccinated (n=69,296) n (%)**
Age (years)						
Mean ± SD	69 (11)	68 (12)*	69 (10)	68 (12)*	69 (10)	68 (12)*
Sex (male)	6,071 (78)	11,228 (78)	19,605 (75.4)	28,986 (77.8)*	36,581 (75.2)	54,480 (78.6)*
Co-morbidity						
Yes	15 (0.2)	24 (0.2)	71 (0.3)	91 (0.2)	126 (0.26)	177 (0.26)
Smoking status						
Never smoked	1,664 (21.3)	3,082 (21.6)*	5,672 (21.8)	8468 (22.7)*	10,781 (22.2)	15,419 (22.2)*
Quit smoking	5,658 (72.6)	9,826 (68.9)	18,670 (71.8)	25501 (68.5)	35,057 (72.1)	48,135 (69.5)
Current smoker	476 (6.1)	1,353 (9.5)	1662 (7.4)	3270 (8.8)	2,760 (5.7)	5,742 (8.3)
COPD severity						
Class A	4,519 (57.9)	8,270 (58.0)	14,463 (55.6)	21079 (56.6)*	27,314 (56.2)	40,198 (58.0)*
Class B	1,336 (17.1)	2,377 (16.7)	4,974 (19.1)	7440 (20.0)	12,374 (25.5)	18,845 (27.2)
Class C	1,390 (17.8)	2,635 (18.4)	4,193 (16.1)	5578 (15.0)	5,207 (10.7)	5,805 (8.4)
Class D	553 (7.1)	979 (6.9)	2,374 (9.2)	3142 (8.4)	3,703 (7.6)	4,448 (6.4)
Number of exacerbations in the prior year						
Mean ± SD	2.1 (4)	1.8 (4)*	1.2 (3)	1.0 (3)*	1.0 (3)	0.8 (3)*
Number of hospital visits in the prior year						
Mean ± SD	9 (8)	8 (7)*	5 (6)	4 (5)*	7 (7)	5 (6)*

Abbreviations: SD, Standard deviation; COPD, Chronic obstructive pulmonary disease.
[a]Influenza season in Thailand is considered as the one year period from 1st June of one year to 31st May of next year.
**Statistically different between vaccinated and unvaccinated cohorts in the same influenza season (p-value < 0.05).*

Vaccine strain matching

According to the Thai NIH, influenza A(H3N2) was the predominant circulating strain in 2011 and 2013, and influenza B in 2012 (Supplementary Table 3). The vaccine match for influenza A(H3N2) in 2011, 2012, and 2013 was 86.36%, 0%, and 100%, respectively. Similarly, the vaccine match for influenza B in the same periods was 83.7%, 26.3%, and 15.4%, respectively; while 100% vaccine match

was observed for influenza A(H1N1) in all three years (Supplementary Table 4).

Outcome incidence

Of the three study seasons, the highest incidence of all study outcomes was observed during the 2011 season in which the incidence rate of ICD-10 coded influenza was 3.8/1000 person-years among vaccinated and 8.0/1000 person-years among unvaccinated; pneumonia incidence was 239/1000 person-years among vaccinated and 517/1000 person-years among unvaccinated; and the rate of exacerbation of COPD was 2,082/1000 person-years among vaccinated and 4,347/1000 person-years among unvaccinated group (Table 2). Among the vaccinated and unvaccinated cohorts, the incidence rates of ICD-10 coded influenza, pneumonia, and exacerbations of COPD in 2012 were 2.4/1000 and 2.6/1000; 208/1000 and 264/1000; and 1483/1000 and 1924/1000 person-years, respectively. In 2013, the incidence rates of the same were 3.3/1000 and 3.2/1000; 216/1000 and 256/1000; and 1559/1000 and 2027/1000 person-years, respectively (Table 2).

Table 2 Incidence per 1,000 person-years of influenza, pneumonia, and COPD exacerbation among persons with COPD by season

	2011 influenza season[a]		2012 influenza season[a]		2013 influenza season[a]	
Outcomes[b]	**Vaccinated**	**Unvaccinated**	**Vaccinated**	**Unvaccinated**	**Vaccinated**	**Unvaccinated**
Person-weeks, no.	343,616	312,988	1,094,028	1,401,192	2,094,248	2,988,596
Person-years, no.	6,608	6,019	21,039	26,946	40,274	57,473
Influenza						
Episodes	25	48	50	70	132	182
Rate*,	3.8	8.0	2.4	2.6	3.3	3.2
(95% CI)	(2.4 – 5.6)	(5.9 – 10.6)	(1.8 – 3.1)	(2.0 – 3.3)	(2.7 - 3.9)	(2.7 - 3.7)
Pneumonia						
Episodes	1,582	3,114	4,386	7,108	8,686	14,729
Rate*,	239	517	208	264	216	256
(95% CI)	(229 – 250)	(505 – 530)	(203 – 214)	(259 – 269)	(212 – 220)	(253 – 260)
COPD exacerbation	13,765	26,168	31,207	51,846	62,660	116,546
Episodes	2,082	4,347	1,483	1,924	1,559	2,027
Rate*,	(2,049 – 2,118)	(4,295 –4,400)	(1,467 –1500)	(1,908 – 1,941)	(1,544 –1568)	(2,016 – 2039)
(95% CI)						

Abbreviations: COPD, Chronic obstructive pulmonary disease; No., Number; CI, Confidence interval.

[a]Influenza season in Thailand is considered as the one year period from 1st June of one year to 31st May of next year.

[b]Outcomes are medically-attended inpatient and outpatient cases with ICD-10 discharge diagnosis

**Obtained by multiplying rates/1,000 person-week by 52 to calculate annualized rates/1,000 person-years.*

Influenza vaccine effectiveness

Overall, the pooled crude VE of three years against ICD-10 coded influenza, pneumonia, and COPD exacerbation was estimated at 8% (95% CI, -10%-23%), 22% (95% CI, 20%-33%), and 26.3% (95% CI, 25.8%-26.9%), respectively. After adjusting for the propensity to be vaccinated, the pooled VE increased to 20% (95% CI, 6%-34%) against ICD-10 coded influenza, 35% (95% CI; 34%-36%) against pneumonia, and 38.8% (95% CI,

38.3%-39.3%) against COPD exacerbations (Table 3). Stratified by season, the adjusted VE against ICD-10 coded influenza was 59% (95% CI 31%-76%) in 2011, 27% (95% CI -5%-50%) in 2012, and 10% (95% CI -14%-29%) in 2013. Adjusted VE against pneumonia in 2011, 2012, and 2013 was 58% (95% CI 55% - 60%), 34% (95% CI 33% - 37%), and 32% (95% CI 31% - 34%), respectively; while the adjusted VE against COPD exacerbations in the same periods was 54% (95% CI, 53%-55%), 37% (95% CI 34%-38%), and 38.7% (95% CI 38.0%-39.3%), respectively (Table 4).

Table 3 Overall crude and adjusted influenza vaccine effectiveness among study participants

Outcomes[a]	Crude RR (95% CI)	Crude VE (%) (95% CI)	p-value	Adjusted RR* (95% CI)	Adjusted VE (%) (95% CI)	p-value
Influenza	0.92 (0.77, 1.10)	8 (-10, 23)	0.348	0.80 (0.66, 0.94)	20 (6, 34)	0.017
Pneumonia	0.78 (0.77, 0.80)	22 (20, 33)	<0.001	0.65 (0.64,0.66)	35 (34, 36)	<0.001
COPD exacerbation	0.737 (0.731, 0.742)	26.3 (25.8, 26.9)	<0.001	0.612 (0.607,0.617)	38.8 (38.3, 39.3)	<0.001

Abbreviations: RR, Rate ratio; VE, Vaccine effectiveness; COPD, Chronic obstructive pulmonary disease; CI, Confidence interval.
[a] Outcomes are medically-attended inpatient and outpatient cases with ICD-10 discharge diagnosis
**Propensity score matched Poisson regression analysis; propensity scores were developed by a multivariate logistic regression using age, sex, co-morbidity, COPD severity, smoking status, number of exacerbations in prior year, and number of hospital visits in prior year.*

Table 4 Adjusted influenza vaccine effectiveness among study participants in each influenza season

Influenza season[a]	Adjusted VE[b] with 95% CI against		
	Influenza	Pneumonia	COPD Exacerbation
2011	59% (31% - 76%)*	58% (55% - 60%)*	54% (53% - 55%)*
2012	27% (-5% - 50%)	34% (32% - 37%)*	37% (34% - 38%)*
2013	10% (-14% - 29%)	32% (31% - 34%)*	38.7% (38.0% - 39.3%)*

Abbreviations: VE, Vaccine effectiveness; COPD, Chronic obstructive pulmonary disease; CI, Confidence interval.
[a]Influenza season in Thailand is considered as the one year period from 1st June of one year to 31st May of next year.
[b]propensity score matched Poisson regression analysis.
**Statistically significant at p<0.05*

VE against all three outcomes was higher in the high influenza activity period than that in the low period in the 2013 season. In the 2011 and 2012 seasons, VE was non-significant against ICD-10 coded influenza in both high and low periods, while the VE against pneumonia and COPD exacerbations remained significant in both high and low activity periods with higher VE during low influenza activity periods (Table 5).

Table 5 Influenza vaccine effectiveness against three outcomes, stratified by yearly influenza activity

	Influenza		Pneumonia		COPD exacerbation	
Subgroup analysis Stratified by	**VE (%) [a] (95% CI)**	**p-value**	**VE (%) [a] (95% CI)**	**p-value**	**VE (%) [a] (95%CI)**	**p-value**
2011 Influenza activity						
Less than 15%	50% (-124, 89)	0.365	54% (44, 60)	<0.001	71% 70, 72)	<0.001
15% and over	35% (-83, 77)	0.418	47% (38, 54)	<0.001	32% (30, 34)	<0.001
2012 Influenza activity						
Less than 15%	18% (-306, 83)	0.807	34% (25, 41)	<0.001	61% (59, 62)	<0.001
15% and over	33% (-29, 65)	0.228	21% (15, 27)	<0.001	32% (30, 34)	<0.001
2013 Influenza activity						
Less than 15%	8% (-86, 55)	0.814	21% (14, 27)	<0.001	28% (27, 29)	<0.001
15% and over	39% (11, 59)	0.011	35% (31, 38)	<0.001	32% (30, 34)	<0.001

Abbreviations: VE, Vaccine effectiveness; COPD, Chronic obstructive pulmonary disease; CI, Confidence interval.
[a] propensity score matched Poisson regression analysis.

Adverse effect of influenza vaccination

The incidence rate of COPD exacerbations was 4% higher during 15 days post influenza vaccination than during the 15 days pre-vaccination, but this excess risk was not statistically significant (incidence rate ratio 1.04, 95% CI 0.99 – 1.10; p-value=0.113) (Table 6).

Table 6 Analysis of exacerbation of COPD between 15 days pre and post vaccination in 2011-2013 influenza seasons (adverse effect of influenza vaccination)

COPD exacerbation	**15 days prior vaccination**	**15 days post vaccination**	**Rate Ratio* (95% CI)**	**p-value**
	(n= 82,400)	**(n = 82,400)**		
Person-weeks, no.	164,800	164,800		
Number of episodes	2,572	2,687	1.04 (0.99 -1.10)	0.113
Incidence rate /1000 person-weeks	15.6	16.3		

Abbreviations: VE, Vaccine effectiveness; COPD, Chronic obstructive pulmonary disease; CI, Confidence interval
**Adjusted for age, gender, co-morbidity, COPD severity, number of exacerbations in prior year, smoking status, number of hospital visits in prior year, and cohort year by generalized linear model*

DISCUSSION

In this study, we evaluated the effectiveness of seasonal influenza vaccine against three ICD-10 coded clinical outcomes: influenza, pneumonia, and exacerbation among patients with COPD attending public hospitals in 2011 – 2013 influenza seasons and found that influenza vaccination reduced the rates of all outcomes. Our results also showed no significant increase in the risk of immediate COPD exacerbation following the receipt of influenza vaccine. Although the influenza vaccination coverage observed in our study was higher than that in other high-risk groups,[12] it remained sub-optimal, and patients with COPD should be further encouraged for annual influenza vaccination and reassured about its safety.

Our pooled VE estimate of 20% against influenza is lower than those recorded among individuals with COPD in previous studies in Thailand and elsewhere.[10,23] However, our retrospective study design and use of medium specificity outcome of ICD-10 coded influenza discharge diagnosis may limit a true comparison with those studies. For instance, a VE of 76% was observed during the 1997-98 season in the prior Thai study which was an RCT with a highly specific outcome of serologically-confirmed influenza and measured efficacy after two doses of the vaccine in the same season among patients with COPD who had never received any influenza vaccines before.[10] Similarly, 38% VE was observed during 2011-2014 seasons in Canada in a prospective cohort study that also assessed VE against hospitalizations associated with laboratory-confirmed influenza infection.[23] Additionally, both of these studies revealed high levels of vaccine match with the circulating influenza strains,[10,23] while the vaccine match in our study varied by season and may have contributed to our lower pooled VE against influenza. We found significant protection against ICD-coded influenza episodes requiring hospital visits/admissions in the 2011 season in which the vaccine strain match for all three influenza strains ranged from 84 to 100%, whereas the lower bound of the vaccine match decreased to 0% in 2012 and 15% in 2013 season, and VE was not significant in both 2012 and 2013 seasons. Notably, the vaccine was well matched against the most predominant strain i.e. A(H3N2) in the 2013 season.

Interestingly, protection against pneumonia and COPD exacerbation was observed even during the vaccine mismatched seasons. This is a promising finding as much of the morbidity and mortality associated with COPD is due to COPD exacerbations.[24,25] Our findings are similar to a systematic review in low and middle-income countries reporting significantly reduced hospitalizations and acute exacerbations among vaccinated patients with COPD when compared with those unvaccinated.[26] In the Cochrane analysis, inactivated influenza vaccines were found to reduce the total number of exacerbations per vaccinated participant compared with those who received placebo (mean difference: -0.37, 95% CI -0.64 to -0.11; p=0.006).[4] While our finding of the protective effect of influenza vaccine against outpatients visits and hospitalizations due to COPD exacerbation is in alignment with the previous Thai study reporting fewer hospitalizations due to exacerbation and decreased number of acute exacerbation in the vaccinated group,[10] our VE estimate is much lower compared with the adjusted VE of 90.8% (95% CI 83.5%-94.8%) against hospitalization due to COPD exacerbation reported in a retrospective cohort study from Spain in the 2011-12 season.[27]

Observational studies play an important role in measuring influenza VE,

especially when conducting an RCT is unethical after the vaccine has been licensed and widely recommended.[14,28] A related systemic literature review suggested that additional large and well-designed observational studies are required to understand the impact of disease severity and patient characteristics on the response to influenza vaccination among COPD patients.[28] Addressing the knowledge gap, our retrospective cohort design was a cost-effective and time-efficient way to estimate influenza VE in a nationally representative sample of individuals with COPD in Thailand. The strengths of our study lie in using a large national electronic database and propensity score matching to reduce baseline differences between the vaccinated and unvaccinated groups. We also demonstrated that influenza vaccination is safe and does not result in an increase in immediate COPD exacerbation following the vaccination.

However, there are several limitations in our study. First, ICD-10 codes were used as clinical endpoints without laboratory confirmation for influenza, which lowers the specificity of the outcome. ICD-10 diagnosis based on ILI can also be related to other respiratory viruses, not just influenza alone, especially in absence of laboratory results.[29] The assignment of the ICD-10 codes itself can be influenced by reimbursement patterns and local practices, institutions, or subject to error,[30-31] and therefore needs to be validated because inaccurate diagnosis can compromise the measurement of influenza and the impact of vaccination. Until recently, influenza was not considered as a disease causing significant illness in Thailand and this may have affected our data as the number of influenza discharge diagnoses in our study is comparatively lower than the other two outcomes. Second, we tested our model's ability to control for confounding by comparing VE estimates in differing periods of influenza activity during the season. If confounding bias had been controlled, there should have been a positive VE during the high influenza activity period and no effect during the low period. However, influenza circulates year-round in Thailand,[18] so a small effect of influenza vaccine during the low influenza activity period was expected. Our results on VE estimates in differing influenza activity periods suggest that despite propensity score matching, there may be some residual confounding bias. Additionally, the lack of significant VE against influenza in the 2013 season when the vaccine was well-matched with the predominant strain and presence of significant VE against low specificity outcomes such as pneumonia and COPD exacerbation in absence of VE against medium specificity ICD 10 coded influenza also point towards residual confounding.[32] This may be in part due to our retrospective design and lack of available data on unmeasured confounders (such as frailty, body mass index, history of dyspnea, pneumonia vaccination, education level, and occupation) in the model. For instance, as the median age of the cohort was 70 years with an IQR of 61-77, most participants in our study were older adults whose vaccination uptake and healthcare seeking can be affected by frailty and bias the VE estimates if not accounted for.[33] Newer test-negative case control designs in which patients enrolled in outpatient clinics or hospitals based on a clinical case definition of ILI are tested for influenza virus and VE is estimated from the odds of vaccination among patients testing positive for influenza versus those testing negative, may be more efficient in minimizing selection bias by healthcare seeking behavior.[34] Finally, there could be a misclassification of COPD severity due to lack of forced expiratory volume in one second (FEV1) measurement in the general

practice at COPD clinics in public hospitals.

CONCLUSIONS

Overall, influenza vaccination was associated with a modest protection among people with COPD against ICD-10 coded influenza, pneumonia, and COPD exacerbations in Thailand during 2011-2013 influenza seasons. While our results may have been affected by residual confounding and some measurement bias, influenza vaccination should be further encouraged in this population. Despite propensity score matching, retrospective cohort design using administrative data can have inherent limitations in monitoring the severity of influenza seasons and effectiveness of influenza vaccine if all known confounders and biases cannot be addressed. Future research should consider residual confounding in retrospective study design and may benefit from using a prospective cohort design or a test-negative case control study.

ACKNOWLEDGMENTS

We are grateful to the NHSO who provided the administrative databases for our analyses and Dr. Charung Muangchana, the former director of the National Vaccine Institute (public organization), Thailand who supported the study on administrative issues. We also thank Kanlaya Sornwong for her assistance in cleaning the data.

AVAILABILITY OF DATA AND MATERIAL

The data for this analysis, available from the NHSO, was acquired by the investigators after an official request letter (no. O5900017) and the analysis was conducted in agreement with the NHSO.

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Supplementary Table 1. COPD severity classification

Class	Characteristics	Bronchodilator	MRC Scale Score	CAT	Exacerbations in the previous year	Chronic Symptoms
A	Low risk, less symptoms	Short Action	0-1	<10	≤1	N/A
B	Low risk, more symptoms	Long Action	≥2	≥10	≤1	N/A
C	High risk, less symptoms	Long Action	0-1	<10	≥2	Respiratory Failure; Right Heart Failure*
D	High risk, more symptoms	Long Action	≥2	≥10	≥2	Respiratory Failure; Right Heart Failure*

Abbreviations: COPD, Chronic obstructive pulmonary disease; MRC, Medical Research Council; CAT: COPD assessment test
** COPD patients with respiratory failure or right heart failure are classified as severe, regardless of the bronchodilator used and/or MRC score*

Supplement Table 2. Baseline characteristics of study participants after propensity score matching

	2011 season [a]		2012 season [a]		2013 season [a]	
Characteristics	**vaccinated n=(7,796) n (%)**	**unvaccinated n=(7,796) n (%)**	**vaccinated n=(25,895) n (%)**	**unvaccinated n=(25,895) n (%)**	**vaccinated n=(47,918) n (%)**	**unvaccinated n=(47,918) n (%)**
Age (years)						
Mean ± SD	69 (10)	69 (11)	69 (11)	69 (12)*	70 (10)	70 (11)
< 65 year	2,392 (31)	2,456 (31)	8,012 (31)	7,829 (30)	13,999 (29)	13,843 (29)
≥ 65 year	5,404 (69)	5,340 (69)	17,883 (69)	18,066 (70)	33,919 (71)	34,075 (71)
Sex (male)	6,069 (78)	6,077 (78)	19,548 (75)	19,471 (75)	36,219 (76)	36,113 (75)
Co-morbidity						
Yes	15 (0.19)	11 (0.14)	71 (0.27)	77 (0.30)	124 (0.26)	132 (0.28)
Smoking status						
Never smoked	1,664 (21)	1,649 (21)	5,658 (22)	5,827 (23)	10,753 (22.2)	10,841 (22.4)
Quit smoking	5,657 (73)	5,657 (73)	18,577 (72)	18,399 (71)	34,929 (72.1)	34,973 (72.2)
Current smoker	475 (6)	490 (6)	1,660 (6)	1,669 (6)	2,759 (5.7)	2,627 (5.4)
CAT score						
< 10	7,172 (92)	7,160 (92)	22,229 (86)	22,223 (86)	36,614 (76)	36,560 (76)
≥ 10	624 (8)	636 (8)	3,666 (14)	3,672 (14)	11,304 (24)	11,358 (24)
Dyspnea severity						
mild	6,321 (81)	6,342 (81)	20,985 (81)	20,931 (81)	39,125 (82)	39,132 (82)
moderate	1,362 (17)	1,337 (17)	4,629 (18)	4,698 (18)	8,368 (17)	8,358 (17)
severe	113 (2)	117 (2)	281 (1)	266 (1)	425 (1)	428 (1)
Number of exacerbations in the prior year						
Mean ± SD	2.1 (4)	2.0 (4)	1.2 (3)	1.1 (3)*	1.0 (3)	0.9 (3)*
Number of hospital visits in the prior year						
Mean ± SD	9 (8)	8 (8)*	6 (6)	5 (6)*	7 (7)	6 (8)*
Respiratory failure	528 (7)	532 (7)	1,858 (7)	1,784 (7)	1,880 (4)	1,850 (4)
Right heart failure	393 (5)	406 (5)	1,050 (4)	1,001 (4)	1,598 (3)	1,569 (3)

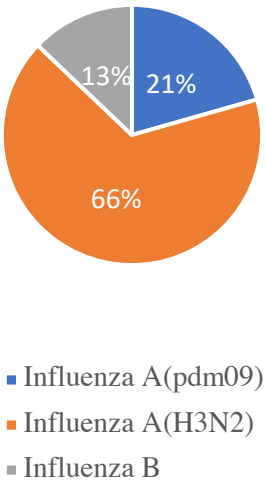
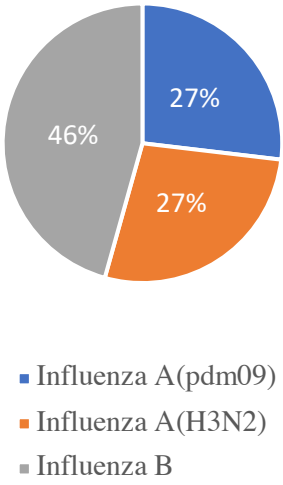
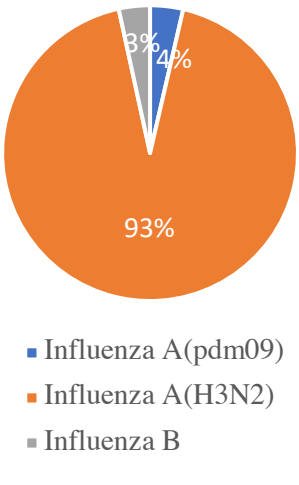
Abbreviations: SD, Standard deviation; COPD, Chronic obstructive pulmonary disease; CAT score, COPD Assessment Test)

[a] Influenza season in Thailand is considered as the one year period from 1st June of one year to 31st May of next year.

[b] Dyspnea severity; mild = MRC (Medical Research Council) score 0 – 1, moderate = MRC score 2 – 3, severe = MRC score 4.

**Statistically significant difference between vaccinated and unvaccinated cohorts in the same influenza season (p-value <0.05).*

Supplemental Table 3. Vaccine strain composition of southern hemisphere influenza vaccines and percentage of circulation strain in the study years

Vaccine strain composition	2011	2012	2013
A(H1N1)	A/California/7/2009 (H1N1) pdm09-like virus	A/California/7/2009 (H1N1) pdm09-like virus	A/California/7/2009 (H1N1) pdm09-like virus
A(H3N2)	A/Perth/16/2009 (H3N2)-like virus	A/Perth/16/2009 (H3N2)-like virus	A/Victoria/361/2011 (H3N2)-like virus
B	B/Brisbane/60/2008-like virus	B/Brisbane/60/2008-like virus	B/Wisconsin/1/2010-like virus
Percentage of circulating strain			

Supplemental Table 4. Percentage of circulating strain in each sub-type and degree of matching with southern hemisphere influenza vaccines in the study years

Circulating strains	**2011**	**2012**	**2013**
A(H1)	A/California/7/2009 (H1N1) pdm09 - **100%**	A/California/7/2009 (H1N1) pdm09 - **100%**	A/California/7/2009 (H1N1) pdm09 - **100%**
A(H3)	A/Perth/16/2009 (H3N2) - **86.36%** A/Victoria/361/2011 (H3N2) - 13.64%	A/Perth/16/2009 (H3N2) - **0%** A/Victoria/361/2011 (H3N2) - 100%	A/Victoria/361/2011(H3N2) or A/Texas/50/2012(H3N2)* - **100%**
B	B/Brisbane/60/2008 (Victoria) **83.7%** B/Florida/60/2008 (Yamagata) 3.7% B/Wisconsin/01/2010 (Yamagata) 12.6%	B/Brisbane/60/2008 (Victoria) **26.3%** B/Wisconsin/01/2010 (Yamagata) 45.4% B/Massachusetts/2/2012 (Yamagata) 28.3%	B/Wisconsin/01/2010 (Yamagata) **15.4%** B/Brisbane/60/2008 (Victoria) 13.2% B/Massachusetts/2/2012 (Yamagata) 71.4%

**A/Texas/50/2012 is an A (H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011.*
Bold fonts signify % vaccine strain matching with the circulating strains in each year.