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Effectiveness of the 2013 and 2014 Southern Hemisphere Influenza Vaccines Against Laboratory-Confirmed Influenza in Young Children Using a Test-Negative Design, Bangkok, Thailand

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Abstract

Background—The Thai Advisory Committee on Immunization Practices recommends annual influenza vaccination for children six months through two years of age, although older children may be vaccinated on request. We evaluated effectiveness of the 2013 and 2014 inactivated influenza vaccines to reduce medically-attended laboratory-confirmed influenza illness among Thai children aged 7–60 months.

Methods—From September 2013–May 2015, children with influenza-like illness (ILI) were screened with a rapid influenza diagnostic test. Enrolled children had nasal and throat swabs tested for influenza viruses using polymerase chain reaction (PCR). Cases and controls were subjects testing positive and negative, respectively, for influenza viruses by PCR. Vaccination status was ascertained from vaccination cards. Vaccine effectiveness (VE) was calculated as 100%*(1−odds ratio of vaccination among cases versus controls).

Results—Of 1,377 children enrolled, cases (n=490) and controls (n=887) were similar in demographic characteristics. Cases were less likely to receive influenza vaccine than controls in 2013 (6% vs. 14%; p=0.02), but not in 2014 (6% vs. 7%; p=0.57). Among cases, 126 (26%) were positive for influenza A(H1N1)pdm09 virus, 239 (49%) for influenza A(H3N2) and 124 (25%) for influenza B. One specimen was positive for both influenza A(H3N2) and B viruses. VE for full

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vaccination against all viruses was 64% (95% confidence interval [CI], 21%, 84%) in 2013 and 26% (95% CI, −47%, 63%) in 2014.

Conclusions—Influenza vaccination was low among Thai children in our study, and VE varied by year, highlighting the need for annual monitoring of VE to better understand vaccine program effectiveness.

Keywords

influenza; vaccination; effectiveness; Thailand; children

Background

Influenza is an important cause of morbidity and mortality worldwide. Children, particularly those less than two years old,[1] are among those at highest risk for severe influenza virus illness and influenza-associated complications.[1–5] A systematic review of the global disease burden of influenza in children less than five years of age estimated that there were 90 million new cases of seasonal influenza globally in 2008; the majority of the cases (97%) occurred in developing countries.[6]

Influenza vaccination is currently recommended by the World Health Organization to prevent influenza in high-risk groups (e.g., prematurity, congenital heart disease, chronic lung disease, neuromuscular disease).[1, 7] Influenza vaccine effectiveness (VE) varies from season to season depending upon the antigenic match between circulating influenza viruses and the influenza strains represented in the vaccine, which are chosen seven to nine months prior to the current influenza season.[8] Since influenza viruses may experience antigenic drift during the influenza season, mismatches between vaccine strains and the predominant circulating viruses can occur and reduce protection from the vaccine.[9, 10]

Randomized-controlled trials are considered the gold standard for evaluating influenza vaccine efficacy but are expensive and challenging to perform in populations for which influenza vaccines are already recommended. While vaccine efficacy may be optimal in a clinical trial, vaccine performance in target populations under field conditions may differ. A test-negative case-control observational study design is now widely used to estimate influenza VE.[11] In this approach, patients seeking care for an acute respiratory illness are tested for influenza and vaccination status is compared between those testing positive for an influenza virus (cases) and those testing negative (test-negative controls). Compared to traditional case-control or cohort studies, the test-negative case-control design has the added advantage of better controlling for confounding because of differences in health care seeking behaviors between persons who received influenza vaccine versus those who did not.[12, 13]

In Thailand, the burden of influenza disease in children less than five years of age is considerable, with an average annual incidence of influenza-associated pneumonia of 236 per 100,000 population during 2002–2008[14] and an estimated incidence of influenza A(H1N1)pdm09-associated hospitalization of 477 per 100,000 population during the 2009–2010 influenza pandemic.[15] Since 2009, the Thai Ministry of Public Health (MOPH) has recommended annual influenza vaccination for children aged six months through two years

of age (i.e., 6–35 months). In addition, children older than this age are occasionally vaccinated by Thai clinicians upon parents' request. Annual evaluation of influenza VE is needed to assess the impact of the influenza vaccine program on various age and risk groups. Although the number of studies evaluating VE in children has increased worldwide in recent years, VE studies among Thai children are limited. We report on the effectiveness of the 2013 and 2014 inactivated Southern Hemisphere influenza vaccines to prevent medically-attended, laboratory-confirmed influenza illness in Thai children aged 7–60 months using a test-negative case-control design.

Method

Setting

In Thailand, influenza viruses circulate year-round, with a large peak during June–November (when approximately 60% of the cases occur)[16] and a small peak during January–March.[17] The Thai MOPH recommends that seasonal influenza vaccination begin in May each year, although the start of national vaccination campaigns with trivalent Southern Hemisphere influenza vaccine varies each year from early May through June depending upon the timing of vaccine delivery from manufacturers. All government-purchased vaccine is Southern Hemisphere, but Northern Hemisphere trivalent vaccine is also available on the private market starting in January or February. Figure 1 shows influenza vaccine composition[18] and influenza circulating strains in Thailand for the 2013 and 2014 seasons.

The study was conducted at the Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok. The QSNICH is Thailand's largest tertiary medical facility dedicated to treatment and care of pediatric patients (from birth to 18 years of age). The hospital serves around 350,000 outpatients and 15,000 inpatients each year.

Enrollment and data collection

From September 2013–May 2015, children aged 7–60 months with influenza-like illness (ILI) seeking medical care at QSNICH's outpatient clinic or those admitted to QSNICH's inpatient wards with other non-respiratory illness, but coincidentally had mild respiratory symptoms, were recruited. By study design, children six months old were given one month to receive influenza vaccination, if their parents chose to, before being eligible for study enrollment from seven months of age. In this study, we adopted a broad definition of ILI to capture possible influenza-associated complication such as pneumonia. For those aged 7–24 months, ILI was defined as tympanic temperature >38°C and one or more of the following symptoms: nasal discharge or congestion, cough, conjunctivitis, respiratory distress (tachypnea or retractions), sore throat, or recent seizure. For those aged >24 months, ILI was defined as tympanic temperature >38°C and cough or sore throat in the absence of another explanation. During study screening, children were excluded if their caregivers indicated they could not provide a copy of the children's vaccination cards. Consenting children with ILI were screened for influenza virus by rapid influenza diagnostic test (RIDT; QuickVue, Quidel, California, USA). Results were shared with the children's attending physicians

within 15–20 minutes following specimen collection for use in clinical management, which could have included oseltamivir prescription.

Each child with ILI and a positive RIDT and the next two children with ILI in the same age group (7–23 and 24–60 months) with negative RIDT results were eligible for enrollment. Study nurses interviewed caregivers using a structured questionnaire to document the children's demographic characteristics, ILI onset date, symptoms, and general health status. All enrolled children had combined nasal and throat swabs collected using sterile polyester tipped plastic applicator swabs for influenza virus testing by real-time reverse transcription polymerase chain reaction (rRT-PCR) at the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok using U.S. Centers for Disease Control and Prevention's standard protocol (specimens with a cycle threshold ≤38 were classified as positive).[19] Influenza A virus specimens were subtyped by rRT-PCR as H1N1 or H3N2 and the lineage (Yamagata or Victoria) was determined for influenza B virus specimens.[19] If illnesses were not resolved three days after enrollment, caregivers were encouraged to bring their children to the hospital for treatment. Seven days following enrollment, study nurses interviewed each caregiver by phone to collect information on clinical illness course, outcomes, and total expenses related to the child's illness (direct and indirect cost). Study participants were compensated for their time and subsequent travel for bringing a copy of vaccination cards back to the clinic.

Definitions

For the purpose of this analysis, we defined an influenza season as June through May of the following year (e.g., the 2013 influenza season was June 2013–May 2014).[16] Children were considered immunized 14 days after vaccination.[11] They were considered fully vaccinated if they received two vaccine doses administered ≥28 days apart in the current season or two doses administered ≥28 days apart in any previous season and one dose in the current season.[20] Children who received one dose of influenza vaccine in the current season and were never fully vaccinated in any previous season were considered partially vaccinated. All children in our study had their influenza vaccination status verified against vaccination cards or medical records.

Ethical consideration

Two written informed consents were obtained from children's caregivers: one for screening using RIDT and another, if eligible, for study enrollment. This study was approved by the ethics committee of the QSNICH (Bangkok, Thailand). The Institutional Review Board of the U.S. Centers for Disease Control and Prevention (Atlanta, GA) relied on the ethics committee of the QSNICH.

Data analysis

Once results of rRT-PCR testing for influenza viruses were available, children were classified as a case or test-negative control. Cases and test-negative controls were compared with respect to baseline demographic, socio-economic, and clinical characteristics using Pearson's chi-square test or Wilcoxon rank-sum test, as appropriate. In the 2013 season, the required sample size with 80% power to detect a VE of 60% assuming 30% vaccination

coverage in controls and a Type I error rate of 5% was 156 cases and 156 controls for children aged 7–23 months and 205 cases and 205 controls for children aged 24–60 months. The sample size was re-calculated for the 2014 season with a 10% vaccination coverage because of low vaccination rates observed in 2013 (10%); the required sample size in 2014 was 266 cases and 532 controls for children aged 7–23 months and 405 cases and 810 controls for children aged 24–60 months.

Logistic regression models were used to estimate odds ratios (ORs) comparing vaccination (full or partial) between cases and test-negative controls. Previously reported confounders (age at ILI [7–23 and 24–60 months] and presence of underlying medical conditions) were considered. Additional potential confounders, including breastfeeding status and daycare attendance, and interactions among variables of interest (e.g., 2-way interaction of: presence of medical condition and breastfeeding status, age and breastfeeding status, age and doses of vaccine receipt) were also explored.[21–23] VE was estimated as 100% × (1-OR of vaccination among cases compared to controls). Confidence intervals were calculated from standard errors derived from maximum likelihood estimation.[24] Separate VE estimates for any influenza virus, influenza A(H1N1)pdm09, influenza A(H3N2), influenza B (Yamagata), and influenza B (Victoria) were generated.

Expense related to influenza illness was calculated by summing medical expenses subsidized by health insurance, over-the-counter medicines, other medical expenses not subsidized by health insurance, transportation cost, and caregiver's reported actual income loss and productivity loss for caring for the ill child (days caregiver skipped work due to the child's illness or days child skipped daycare multiplied by daily wages). Expense due to illnesses managed as outpatients were compared to those requiring hospitalization. Expense estimates are reported in USD using the conversion rate averaged across study period of 1 USD=31.4 Thai Baht.[25] Statistical analyses were conducted using Stata software version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of study participants

A total of 2,822 children were screened; 1406 (50%) were eligible. Of these, 24 (2%) refused, 5 (<1%) could not provide vaccination cards, and 1,377 (98%) were enrolled in the study (459 positive and 918 negative by RIDT). After rRT-PCR confirmation, there were 490 influenza cases (200 in the 2013 season and 290 in the 2014 season) and 887 test-negative controls (341 in the 2013 season and 546 in the 2014 season). Compared to rRT-PCR, RIDT had a sensitivity of 85% (95% confidence interval [CI], 82% to 88%) and a specificity of 95% (95% CI, 94% to 97%). Of all enrolled children, 1,360 (480 cases and 880 controls) were recruited from the outpatient department and 17 (10 cases and 7 controls) from the inpatient department. Table 1 shows detailed characteristics of the enrolled children by influenza season and case-control status. Table 2 shows the percentage of children with underlying medical condition considered as high-risk for severe influenza virus infection and complications. In both seasons, the median time from ILI onset to specimen collection for both cases and controls was two days (interquartile range [IQR], 1–3 days).

Clinical course, outcomes, and expenses of influenza illness

Among 490 influenza cases, 445 (91%) could be contacted for the 7-day follow-up interview. Of which, 293 (66%) resolved their illness (i.e., caregivers reported children no longer had any symptoms) by this interview. Among those resolved, the median duration from symptom onset to resolution was three days (IQR, 2–5 days). Thirty (6%) patients with influenza were hospitalized during the course of their illness; 20 of these were recruited from the outpatient department, but had progression of respiratory illness resulting in hospitalization. The median duration of hospital admission was four days (IQR, 3–5 days). Oseltamivir treatment was prescribed for 428 (87%) cases. Among 231 cases with known dates of oseltamivir prescription, 150 (65%) received treatment within two days of illness onset. One hundred and sixty-four cases who received oseltamivir had illness solution dates available; duration of the illness was significantly shorter for those starting oseltamivir within two days of the illness onset compared to those starting after two days (median, 2 days; IQR, 2–3 days vs. median, 5 days; IQR, 5–7 days; $p<0.01$). The median total expense related to laboratory-confirmed influenza illness was 28 USD (IQR, 22–40 USD) if managed as an outpatient (2–3% of monthly household income)[26] and 158 USD (IQR, 124–286 USD) if hospitalized ($p<0.01$; 10–19% of monthly household income).[26]

Influenza vaccination

In the 2013 season, the overall vaccination coverage (either full or partial vaccination) was 11%; cases were less likely to have received an influenza vaccine compared to controls (6% vs. 14%; $p=0.02$). Among 235 children aged 7–23 months, 212 (90%) were unvaccinated, 6 (3%) partially vaccinated, and 17 (7%) fully vaccinated. Among 306 children aged 24–60 months, 270 (88%) were unvaccinated, 10 (3%) partially vaccinated, and 26 (9%) fully vaccinated. Of all enrolled children, those with underlying medical conditions were more likely to be vaccinated (either fully or partially) compared to healthy children (22% vs. 9%; $p<0.01$). Forty-nine (83%) of 59 vaccinated children likely received the Southern Hemisphere formulation (i.e., received the vaccine before or on December 31, 2013 when Southern Hemisphere vaccine formulation was available in Thailand and before the Northern Hemisphere vaccine had become available). Of all vaccinated children, 37 (63%) reported paying or co-paying for the vaccine cost.

In the 2014 season, the overall vaccination coverage (either full or partial vaccination) was 7%; similar proportions of cases and control were vaccinated (6% vs. 7%; $p=0.57$). Among 326 children aged 7–23 months, 304 (93%) were unvaccinated, 6 (2%) partially vaccinated, and 17 (5%) fully vaccinated. Among 510 children aged 24–60 months, 477 (93%) were unvaccinated, 8 (2%) partially vaccinated, and 25 (5%) fully vaccinated. Similar to the 2013 season, those with underlying medical conditions were more likely to be vaccinated compared to healthy children (14% vs. 7%; $p=0.01$). Fifty-one (91%) of 56 vaccinated children received the vaccine before or on December 31, 2014. Of all vaccinated children, 42 (75%) reported paying or co-paying for the vaccine cost.

Influenza type, subtype, and lineage

Of the 200 specimens collected from cases in the 2013 season, 144 (72%) were positive for influenza A viruses and 56 (28%) for influenza B viruses (Figure 2). Among all influenza A

positive specimens, 78 (54%) were influenza A(H1N1)pdm09 and 66 (46%) were influenza A(H3N2). Among all influenza B positive specimens, 49 (88%) were Yamagata and 7 (12%) were Victoria lineage.

Of the 290 specimens collected from cases in the 2014 season, 221 (76%) were positive for influenza A viruses and 68 (23%) for influenza B viruses (Figure 2). One specimen was positive for both influenza A(H3N2) and B viruses. Among all influenza A positive specimens, 48 (22%) were influenza A(H1N1)pdm09 and 173 (78%) were influenza A(H3N2). Among all influenza B positive specimens, 48 (70%) were Yamagata, 19 (27%) were Victoria lineage, and 2 (3%) could not be lineage typed.

Vaccine effectiveness

No covariates were found to confound or modify the association between medically-attended laboratory confirmed influenza illness and vaccination; therefore, the final models did not include these variables. In the 2013 season, VE was 64% (95% CI, 21% to 84%) among fully vaccinated children and 48% (95% CI, −64% to 83%) among partially vaccinated children (Figure 3). Among children who were fully vaccinated, VE against influenza A(H1N1)pdm09 was 77% (95% CI, 2% to 95%); influenza A(H3N2), 73% (95% CI, −14% to 94%); and influenza B (Yamagata), 25% (95% CI, −120% to 75%) (Figure 4). VE for influenza B (Victoria) could not be calculated due to low numbers.

In the 2014 season, the VE was 26% (95% CI, −47% to 63%) among fully vaccinated children and −3% (95% CI, −211% to 66%) among partially vaccinated children (Figure 3). Among children who were fully vaccinated, VE against influenza A(H1N1)pdm09 was 64% (95% CI, −170% to 95%); influenza A(H3N2), 6% (95% CI, −103% to 56%); and influenza B (Yamagata), 23% (95% CI, −236% to 82%) (Figure 4). VE against influenza B (Victoria) could not be calculated due to low numbers. VE for full vaccination against any influenza virus was 38% (95% CI, 8% to 59%) during June 2014 through November 2014 (large influenza peak).

Discussions

During the 2013 season, vaccination among children aged 7–60 months was moderately effective against medically-attended, laboratory-confirmed influenza illness. However, in the 2014 season, our estimate of influenza VE was not statistically significant. Based on the timing of vaccine receipt among children in our study, it is likely that the majority of vaccinated children received the Southern Hemisphere formulation. During both seasons, influenza vaccination coverage was low among study participants.

In this study, VE estimates for 2013 indicated moderate protection from influenza, consistent with estimates for the 2013 Southern Hemisphere vaccine from other countries.[27, 28] Data from the Thai national virologic surveillance showed that the A(H1N1) and A(H3N2) virus components of the 2013 Southern Hemisphere vaccine were well matched to the predominant circulating strains whereas the influenza B virus component was not (although the B virus components in vaccines and the predominating B viruses that were in circulation throughout the season both belonged to Yamagata lineage). For the 2014

season, all vaccine components of the 2014 Southern Hemisphere vaccine were well matched with the predominant circulating viruses until influenza A/Switzerland (H3N2) and influenza B/Phuket viruses emerged in September 2014. Children exposed to influenza vaccine after September would had suboptimal projection against circulating A/Switzerland (H3N2) or influenza B/Phuket viruses; a condition that could be partially responsible for the poor VE identified during that year.

Two prior studies have evaluated influenza VE among young children in Thailand. A prospective cohort study of respiratory illness among children aged ≤36 months found influenza VE ranging from 55% (95% CI, −72% to 88%) to 64% (95% CI, 13% to 85%) during the 2011 and 2012 seasons despite a poor match between the A(H3N2) virus component of the 2012 vaccine and predominant circulating viruses.[29] A test-negative, case-control study among hospitalized patients in Bangkok during 2009–2012 estimated an influenza VE of 56% among children aged 6–35 months.[30] Estimates from these studies are similar to the estimate of influenza VE during the 2013 season in our study. However, VE estimated for the 2014 season was low in our study as well as in published studies from Northern Hemisphere countries, likely due to a poor match between the A(H3N2) component of both the 2014 Southern Hemisphere and 2014–2015 Northern Hemisphere vaccines and the circulating A(H3N2) viruses which predominated in many countries.[31–35]

Influenza vaccination coverage was low among children in our study. In absolute terms, the coverage is higher than the national estimate of 1–2%,[36] but lower than the report from an earlier cohort study conducted in Thai children aged 0–36 months who regularly visited the QSNICH for care and treatment (39–44%).[29] In Thailand, government purchase of influenza vaccine increased from 520,000 doses in 2009 to 3.3 million doses in 2012,[36] and the purchased doses did not change through 2015 (Tawee Chotpitayasunondh, personal communication). However, over time the National Advisory Committee on Immunization Practice has expanded influenza vaccine recommendation to various high-risk groups (i.e., healthcare personnel, poultry cullers, persons aged ≥65 years, persons with chronic diseases, pregnant women, obese persons, mentally disabled persons, and children aged six months to two years), covering 11 million individuals.[36] Of these, two million were children aged six months to two years.[37] A program evaluation is needed to determine whether supply or demand (or both) results in low coverage.

There are a few limitations when interpreting the study findings. First, we could only infer the type of vaccine (Northern or Southern) that enrolled children received because it was not documented on the vaccination cards or medical records. Compositions of the 2013–2014 Northern Hemisphere and 2013 Southern Hemisphere vaccines were the same for the A(H1N1) and A(H3N2) virus components, but different for influenza B, while those of 2014–2015 Northern Hemisphere and 2014 Southern Hemisphere vaccines were identical. The vaccination card should accommodate recording of information regarding vaccine formulation (Northern vs. Southern Hemisphere) and future studies should collect this information to improve the accuracy of VE estimates. Second, despite conducting the study at the largest pediatric hospital in Thailand, the study did not have adequate statistical power to assess VE by age or influenza type because of low virus activity and vaccination coverage. Future evaluations of influenza VE in Thailand should consider using a multi-site

network approach to optimize the chances of enrolling a sample size large enough to evaluate VE by age and virus type/subtype. Lastly, we only reported influenza type, subtype, and lineage of influenza virus detected in the study, but antigenic characterization of influenza viruses detected was not performed.

Our study has some important strengths. First, we verified children's vaccination status and date against documentation for accurate exposure classification, reducing the bias from under- or over-reporting of children's vaccination uptake by the caregivers.[38] Second, we used the most sensitive and specific test (rRT-PCR) and a standard testing protocol with recommended cycle threshold for classifying a specimen as positive for influenza viruses.[19, 39] Third, we used a test-negative case-control study design that is less prone to confounding by health care seeking behavior[12] and is widely accepted as the standard approach for routinely assessing VE.[11]

In this study, influenza vaccine provided moderate protection against medically-attended influenza during the 2013 season but no significant benefit during the 2014 season, likely due to a mismatch between the vaccine and circulating A(H3N2) viruses.[40] Influenza vaccination coverage among children aged 7–60 months was low during both seasons. Thailand requires strategies to increase vaccination coverage in young children to take full advantage of vaccine protection to prevent influenza virus infection among this vulnerable target group. There is an urgent need to explore whether this is a vaccine supply (e.g., insufficient procurement versus not enough vaccine at the right place and at the right time issues) or demand issue (e.g., undervalued by pediatricians, unknown or undervalued by parents, etc.).

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Abbreviations

ILI	Influenza-Like Illness

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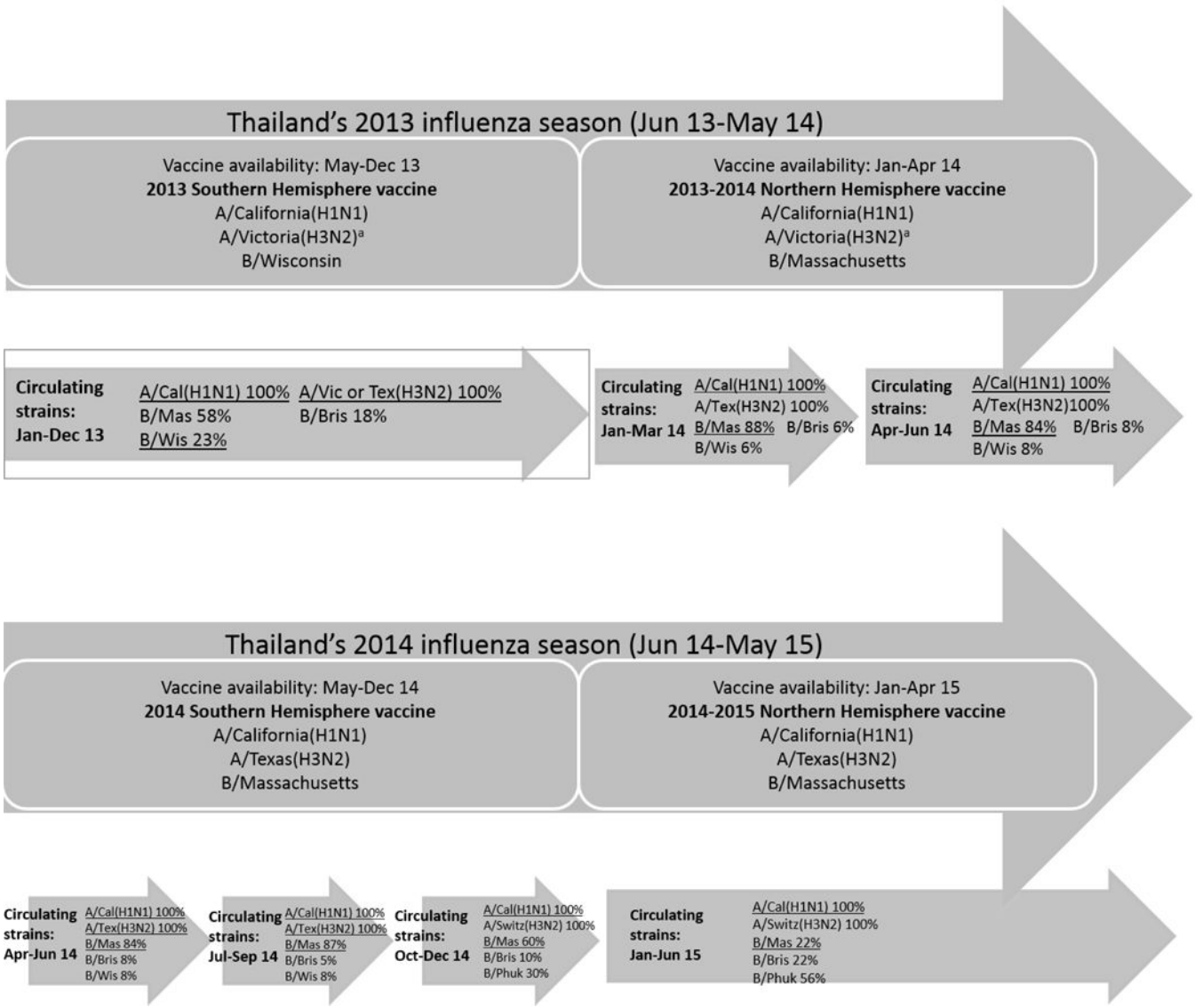

Figure 1. Influenza vaccine composition[18] and circulating strains in 2013 and 2014 seasons

Cal, California; Tex, Texas; Mas, Massachusetts (Yamagata lineage); Bris, Brisbane (Victoria lineage); Wis, Wisconsin (Yamagata lineage); Phuk, Phuket (Yamagata lineage); percentage indicates proportion of influenza virus among all influenza viruses identified during a given time period; underline indicates influenza circulating strain that was matched to vaccine strain; data are available from Thai National Influenza Center's website (http://www.thainihnic.org/influenza/main.php?option=pnewsletter)

[a]A/Texas/50/2012 is an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011

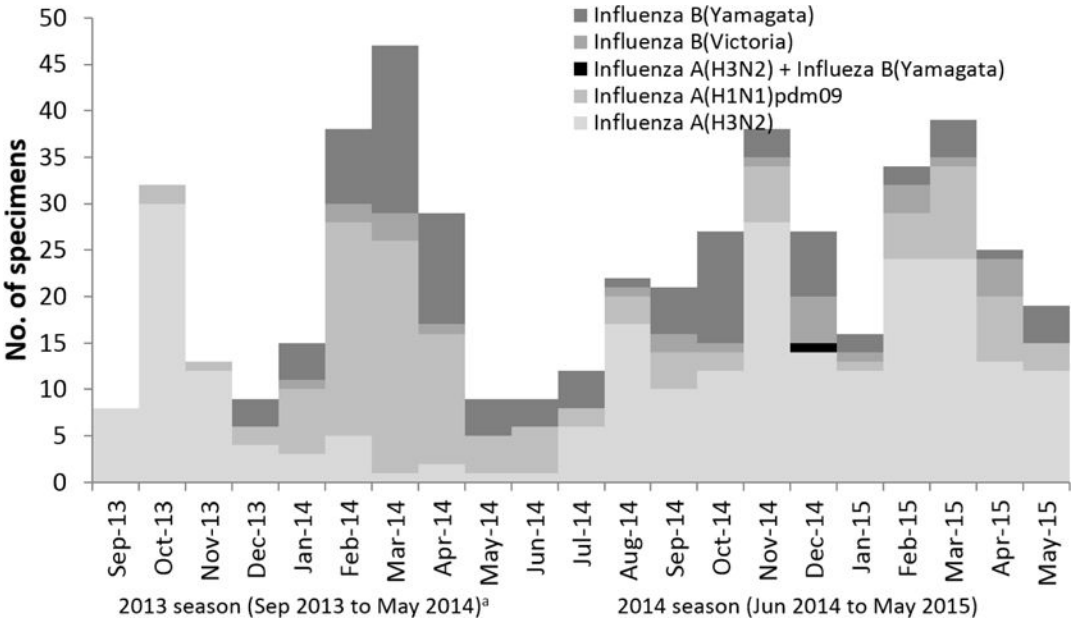

Figure 2. Influenza type and subtype detected in specimens collected from children enrolled in a test-negative case-control study in Bangkok, Thailand (2013 and 2014 seasons)

[a]Not full season, study started from September 2013

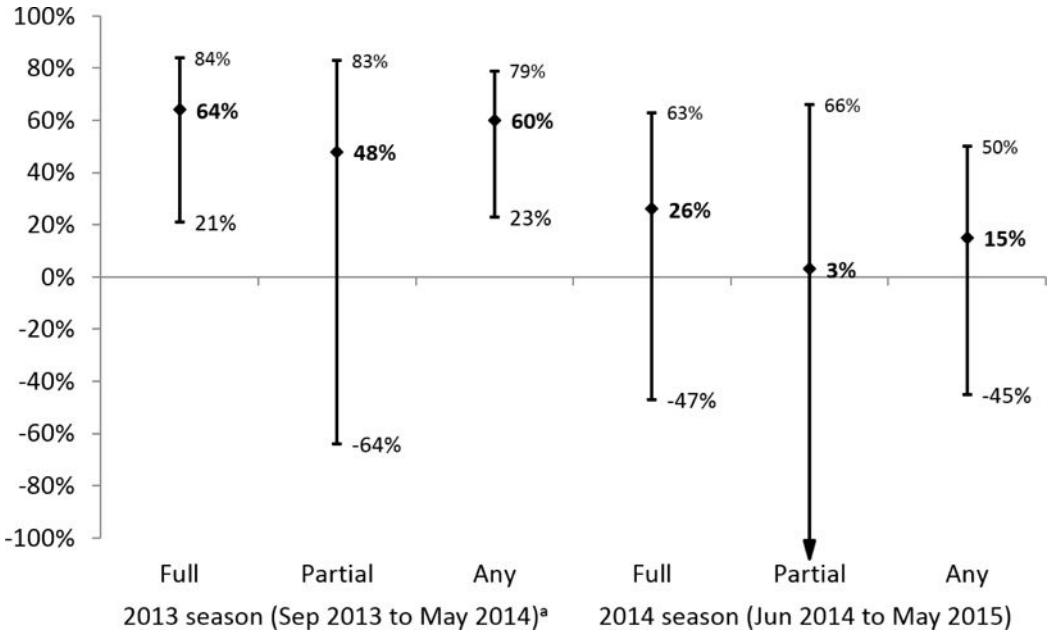

Figure 3. Influenza vaccine effectiveness of Southern Hemisphere inactivated influenza vaccines, trivalent, in 2013 and 2014 seasons

Full vaccination is defined as having received two vaccine doses administered ≥28 days apart in the current season or two doses administered ≥28 days apart in any previous season and one dose in the current season; partial vaccination is defined as having received one dose of influenza vaccine in the current season and having never been fully vaccinated in any previous season; any vaccination is defined as vaccinated either fully or partially; bold type indicates point estimate

[a]Not full season, study started from September 2013

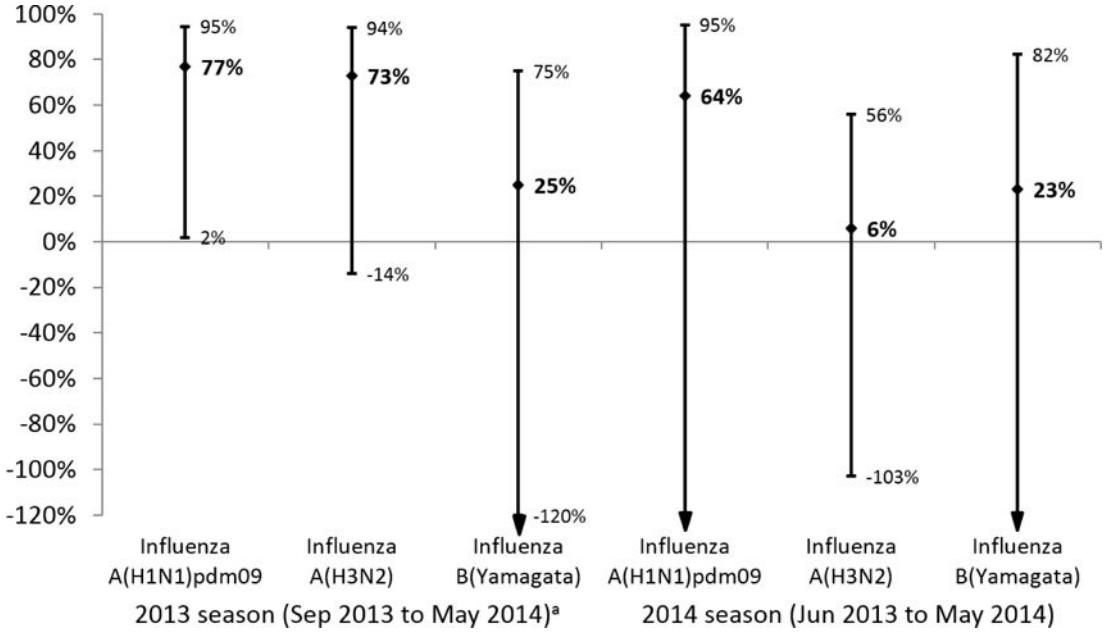

Figure 4. Influenza vaccine effectiveness of Southern Hemisphere inactivated influenza vaccines, trivalent, in 2013 and 2014 seasons by type and subtype

Bold type indicates point estimate for full vaccination defined as having received two vaccine doses administered ≥28 days apart in the current season or two doses administered ≥28 days apart in any previous season and one dose in the current season

[a]Not full season, study started from September 2013

Table 1

Characteristics of children aged 7–60 months enrolled in a test-negative case-control study in Bangkok, Thailand (2013 and 2014 seasons)

	2013 season (Sep 2013 to May 2014)[d]		2014 season (Jun 2014 to May 2015)	
	Case (N=200) Number (%)	Control (N=341) Number (%)	Case (N=290) Number (%)	Control (N=546) Number (%)
Age at enrollment				
7–23 months	84 (42)	151 (44)	112 (39)	214 (39)
24–60 months	116 (58)	190 (58)	178 (61)	332 (61)
Male	105 (53)	196 (57)	163 (56)	294 (54)
Underlying medical condition[a]	23 (12)	54 (16)	42 (14)	83 (15)
Recruitment venue				
Outpatient department	193 (96)	337 (99)	287 (99)	543 (99)
Inpatient department	7 (4)	4 (1)	3 (1)	3 (1)
Attended daycare	57 (29)	119 (35)	98 (34)	242 (44)[d]
Currently breastfed	14 (7)	33 (10)	27 (9)	46 (8)
Lived in Bangkok or surrounding province	190 (95)	328 (96)	282 (97)	530 (97)
Household income <30,000 Baht per month	127 (63)	209 (61)	187 (64)	320 (59)
Received influenza vaccination[b]	12 (6)	47 (14)[d]	17 (6)	39 (7)
Full	8 (4)	35 (10)	12 (4)	30 (5)
Partial	4 (2)	12 (4)	5 (2)	9 (2)
Occurrence of influenza-like illness[c]				
<4 months of influenza vaccination	6 (50)	22 (47)	9 (53)	27 (69)
4–12 months of influenza vaccination	6 (50)	25 (53)	8 (47)	12 (31)
Vaccination venue[c]				
QSNICH	10 (83)	23 (49)	10 (48)	19 (41)
Other government hospitals	1 (8)	9 (19)	6 (29)	14 (30)
Private hospitals/clinics	0 (0)	14 (15)	3 (14)	12 (26)
School	1 (8)	1 (2)	2 (9)	1 (2)
Vaccination cost[c]				
Free of charge	6 (50)	16 (34)[d]	4 (19)	14 (30)
Out of pocket (pay or co-pay)	6 (50)	31 (66)	17 (81)	32 (70)

[a] Some children had >1 underlying medical condition

[b] At least 14 days before onset of influenza-like illness

[c] Percentage calculated among those vaccinated only

[d] Not full season, study started from September 2013

[d] Statistically different between cases and controls (p-value≤0.05)

Table 2

Underlying medical condition of 202 children considered as high-risk for severe influenza virus infection and complications at study enrollment[a]

Underlying medical condition	Case (N=65) Number (%)	Control (N=137) Number (%)
Born at <37 weeks gestation or birth weight <2,500 grams	30 (46.1)	58 (42.3)
Asthma	6 (9.2)	18 (13.1)
Developmental delay (e.g., Down's syndrome)	9 (13.8)	10 (7.3)
Hemoglobinopathy including thalassemia	7 (10.8)	8 (5.8)
Heart and circulatory disease (excluding hypertension)	5 (7.7)	6 (4.4)
Abnormality of the upper airway	5 (7.7)	2 (1.4)
Neurologic/Neuromuscular disorder (including muscular dystrophy, cerebral palsy)	5 (0.4)	1 (0.7)
Chronic lung disease	1 (1.5)	3 (2.2)
Metabolic disease (including diabetes)	1 (1.5)	3 (2.2)
Kidney disease	1 (1.5)	2 (1.4)
Known case HIV-positive	0 (0)	1 (0.7)

[a]A child could have more than one condition