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Quadrivalent Influenza Vaccine Prevents Illness and Reduces Healthcare Utilization Across Diverse Geographic Regions During Five Influenza Seasons

A Randomized Clinical Trial

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Background: We evaluated an inactivated quadrivalent influenza vaccine (IIV4) in children 6–35 months of age in a phase III, observer-blind trial.

Methods: The aim of this analysis was to estimate vaccine efficacy (VE) in preventing laboratory-confirmed influenza in each of 5 independent seasonal cohorts (2011−2014), as well as vaccine impact on healthcare utilization in 3 study regions (Europe/Mediterranean, Asia-Pacific and Central America). Healthy children were randomized 1:1 to IIV4 or control vaccines. VE was estimated against influenza confirmed by reverse transcription polymerase chain reaction on nasal swabs. Cultured isolates were characterized as antigenically matched/mismatched to vaccine strains.

Results: The total vaccinated cohort included 12,018 children (N = 1777, 2526, 1564, 1501 and 4650 in cohorts 1−5, respectively). For reverse transcription polymerase chain reaction confirmed influenza of any severity (all strains combined), VE in cohorts 1−5 was 57.8%, 52.9%, 73.4%, 30.3% and 41.4%, respectively, with the lower limit of the 95% confidence interval >0 for all estimates. The proportion of vaccine match for all strains combined in each cohort was 0.9%, 79.3%, 72.5%, 24.1% and 28.6%, respectively. Antibiotic use associated with influenza illness was reduced with IIV4 by 71% in Europe, 36% in Asia Pacific and 59% in Central America.

Conclusions: IIV4 prevented influenza in children 6−35 months of age in each of 5 separate influenza seasons in diverse geographical regions. A possible interaction between VE, degree of vaccine match and socioeconomic status was observed. The IIV4 attenuated the severity of breakthrough influenza illness and reduced healthcare utilization, particularly antibiotic use.

Key Words: vaccine efficacy, influenza, seasonal variation, healthcare utilization, disease attenuation

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PLAIN LANGUAGE SUMMARY?

What Is the context?

- Influenza is a global public health concern. Young children are especially susceptible, leading to high rates of illness and substantial utilization of healthcare resources.
- The influenza virus changes rapidly, and the circulating virus strains can vary across seasons and geographical regions. Therefore, vaccine composition needs to be revisited for every Northern and Southern hemisphere season to ensure match to circulating virus strains.
- Vaccine mismatch can occur when its composition is not closely related to the circulating virus, potentially reducing its effectiveness.
- Information is lacking on how vaccine efficacy varies in different geographical regions or depending on the virus strains in circulation.

What Is new?

- We reported the efficacy of an influenza vaccine in children 6−35 months of age, across 5 different seasons, from several temperate and sub-tropical countries.
- Vaccine efficacy was observed in all seasons and regions.
- Efficacy was influenced by how well the vaccine composition matched the circulating virus.
- Efficacy was higher in countries with high socioeconomic status than in countries with a lower socioeconomic status.
- Vaccination reduced the healthcare utilization in all regions.

What Is the impact?

- Influenza vaccine prevented illness in children 6−35 months of age in each of the 5 influenza seasons and reduced healthcare utilization, including antibiotic use, in temperate and sub-tropical countries.
- Vaccine efficacy and its impact on healthcare resource were influenced by the degree of vaccine match/mismatch in each cohort. There also appeared to be some effect on vaccine efficacy of the socioeconomic status of the countries included in the study, although this needs to be further explored.

Influenza illness in children is associated with substantial hospitalization and other healthcare resource use.[1–4] Vaccination of children against influenza is now recommended in many countries, and the World Health Organization (WHO) has prioritized vaccination in children <5 years of age and particularly in those <2 years.[5,6] However, few studies investigating vaccine prevention of influenza have been reported in children <2 years of age, and estimates of vaccine efficacy (VE) vary.[7–12]

The influenza virus is subject to considerable antigenic drift, and therefore circulating virus strains vary from season to season and from one geographical region to another. The WHO recommends which strains are to be included in the vaccine annually in the Northern and Southern hemispheres to ensure that the influenza strains used in the seasonal vaccine are closely related to the predominant circulating viruses.[5,6] Nevertheless, vaccine mismatch occurs in some seasons when antigenic drift or vaccine virus mutation during production in embryonated eggs results in the vaccine strains not being closely related to the circulating strains. Substantially reduced VE can occur during vaccine mismatched seasons in all age groups.[5,6] Information is lacking on how influenza VE varies according to the virus strains in circulation in different geographical regions, and data from high quality studies are desired, particularly in young children. In addition, the impact of vaccine mismatch on efficacy needs to be better understood.

We have carried out a Phase III, observer-blind, randomized, multinational, controlled clinical trial to evaluate the efficacy of an inactivated quadrivalent influenza vaccine (IIV4) in healthy children 6−35 months of age; the study was conducted in separate seasonal cohorts over 5 influenza seasons in 3 geographically diverse locations. We have previously reported VE of 50% against reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza of any severity and 63% against RT-PCR-confirmed moderate-to-severe influenza in the entire study population inclusive of the 5 cohorts.[13] In this article, we report the efficacy of the IIV4 in preventing laboratory-confirmed influenza in each individual seasonal cohort of the study, as well as its impact on healthcare utilization in different study regions.

METHODS

Detailed methodology of this randomized, controlled, observer-blind phase III trial has been previously published.[13] The study was funded by GlaxoSmithKline Biologicals SA, registered with Clinical-Trials.gov (NCT01439360) and received appropriate ethics approval (Supplemental Digital Content 1; http://links.lww.com/INF/D682).

Study Design and Participants

The study enrolled healthy children from 13 countries in northern hemisphere and subtropical countries. The northern hemisphere included countries in Europe (Belgium, the Czech Republic, Poland, Spain and the United Kingdom) and the Mediterranean region (Lebanon and Turkey); subtropical countries included the Asia-Pacific region (Bangladesh, India, the Philippines and Thailand) and Central America (the Dominican Republic and Honduras) (Fig. 1). The study was conducted during 5 independent influenza seasons: cohort 1—October 2011 to July 2012 (northern hemisphere); cohort 2—April 2012 to December 2012 (subtropical countries); cohort 3—October 2012 to July 2013 (northern hemisphere); cohort 4—March 2013 to December 2013 (subtropical countries); and cohort 5—March 2014 to December 2014 (subtropical countries) (Fig. 1). Children participated in only one seasonal cohort, that is, each participant contributed only once to the study.

Children 6−35 months of age were recruited and randomized 1:1 to IIV4 or non-influenza control vaccines (Supplemental Digital Content 1; http://links.lww.com/INF/D682). The IIV4 strain composition followed WHO recommendations for the northern hemisphere influenza vaccine (note that a mutation in the egg-adapted A/H3N2 vaccine virus seed occurred in the 2012−2013 season[14]). Only healthy children without risk factors for complications of influenza illness were included in the study.

Surveillance for Illness and Recording of Symptoms

Vaccination was performed before the start of the influenza season or very early in the season in European and Mediterranean countries, and prior to the peak of the influenza season in subtropical countries. The surveillance period covered the peak influenza season in each country. The timing of vaccination and surveillance was based on influenza surveillance activities conducted by public health bodies and information from study sites.[13,15,16] For each study participant, surveillance began from 14 days after final vaccination and continued until the end of the influenza season. Parents were asked to contact the study center within 24 hours if their child developed an influenza-like episode (ILE), and study staff contacted parents weekly with a reminder. ILE included influenza-like illness (ILI, defined as temperature ≥38°C in combination with one or more of the following: cough, runny nose, nasal congestion or breathing difficulty), physician-diagnosed acute otitis media or lower respiratory infection (LRI). For children experiencing an ILE, parents kept a daily record of temperature, symptoms and medication using an internet-based system or paper booklet until symptoms resolved or a maximum 13 days after onset (Supplemental Digital Content 1; http://links.lww.com/INF/D682). A follow-up contact was made at the end of the episode at which study staff recorded outcome, final physician diagnosis, medications, healthcare utilization and absenteeism (Supplemental Digital Content 1; http://links.lww.com/INF/D682).

The study protocol specified collection of a nasal swab within 7 days of ILE onset, preferably within 24 hours of the episode being reported. Detailed methodology of virus detection in nasal swabs has been published previously.[13] In brief, influenza A or B was confirmed by RT-PCR. Positive samples underwent viral culture with immunostaining, followed by antigenic characterization to identify them as matched or mismatched compared with the vaccine strain.

COHORT 1 Northern hemisphere	COHORT 2 Subtropical countries	COHORT 3 Northern hemisphere	COHORT 4 Subtropical countries	COHORT 5 Subtropical countries
Study period 1 Oct 2011 to 7 July 2012[1]	Study period 9 April 2012 to 12 Dec 2012[1]	Study period 8 Oct 2012 to 16 July 2013[1]	Study period 7 March 2013 to 2 Dec 2013[1]	Study period 11 March 2014 to 31 Dec 2014[1]
Influenza surveillance period End-date: 30 April 2012[2]	Influenza surveillance period End-date: 31 Oct 2012[2]	Influenza surveillance period End-date: 30 April 2013[2]	Influenza surveillance period End-date: 15 Nov 2013[2,3]	Influenza surveillance period End-date: 31 Oct 2014[2]
Belgium N=117 Czech Republic N=254 Poland N=659 Spain N=513 UK N=234	Bangladesh N=819 Dominican Republic N=1138 Honduras N=569	Belgium N=30 Czech Republic N=162 Lebanon N=250 Poland N=606 Spain N=344 Turkey N=37 UK N=135	Bangladesh N=492 Dominican Republic N=113 Honduras N=228 Philippines N=502 Thailand N=166	Bangladesh N=1600 Dominican Republic N=694 Honduras N=513 India N=464 Philippines N=944 Thailand N=435
Total N=1777	**Total N=2526**	**Total N=1564**	**Total N=1501**	**Total N=4650**
Median age: 21.0 months	Median age: 19.0 months	Median age: 19.0 months	Median age: 27.0 months	Median age: 24.0 months
Vaccine strain	Vaccine strain	Vaccine strain	Vaccine strain	Vaccine strain
A/H1N1: California/7/2009[4]	A/H1N1: California/7/2009[4]	A/H1N1: Christchurch/16/2010[4]	A/H1N1: Christchurch/16/2010[4]	A/H1N1: Christchurch/16/2010[4]
A/H3N2: Victoria/210/2009	A/H3N2: Victoria/210/2009	A/H3N2: Victoria/361/2011	A/H3N2: Victoria/361/2011	A/H3N2: Texas/50/2012
B Victoria: Brisbane/60/2008	B Victoria: Brisbane/60/2008	B Victoria: Brisbane/60/2008	B Victoria: Brisbane/60/2008	B Victoria: Brisbane/60/2008
B Yamagata: Brisbane/3/2007	B Yamagata: Hubei-Wujiagang/158/2009	B Yamagata: Hubei-Wujiagang/158/2009	B Yamagata: Hubei-Wujiagang/158/2009	B Yamagata: Massachusetts/2/2012

[1]Date that the first vaccine dose was administered to the first child in the cohort to the date of the last visit of the last child in the cohort
[2]Influenza surveillance began in each individual child 2 weeks after they had received their final vaccine dose
[3]The end of the surveillance period was 15 November 2013 in Bangladesh, Honduras and the Philippines, and 31 October 2013 in the Dominican Republic and Thailand
[4]A/H1N1: Christchurch/16/201 is a California/7/2009-like strain

FIGURE 1. Study cohorts.

Antigenic characterization was done by a standard hemagglutination inhibition (HI) assay for A/H1N1 and B lineages and by microneutralization (MN) assay for A/H3N2.[17] For samples that could not be evaluated for technical reasons (eg, insufficient virus titer), the outcome was categorized as an indeterminate result. A vaccine-matched strain was defined as ≤4-fold difference in HI or MN titer relative to a reference serum; similarly, a mismatch was defined as a >4-fold difference in HI or MN titer relative to reference serum.

Study Objectives

The 2 primary objectives of the overall study were evaluation of VE against the first occurrence of RT-PCR-confirmed moderate-to-severe influenza or any influenza (regardless of disease severity) associated with any seasonal influenza strain during the influenza season following vaccination. Moderate-to-severe influenza was defined as a subset of "any" RT-PCR-confirmed influenza disease with any of the following: fever >39°C; physician-diagnosed acute otitis media; physician-diagnosed LRI; physician-diagnosed serious extra-pulmonary complication (eg, myositis, encephalitis, seizure, myocarditis/pericarditis or other serious medical condition); hospitalization in the intensive care unit; or supplemental oxygen for >8 hours. The latter 3 criteria defined severe influenza illness. Secondary objectives of the overall study are described in Supplemental Digital Content 1 (http://links.lww.com/INF/D682). The principal analysis of the primary and secondary objectives in the overall study has been published previously.[13]

The aims of the present publication are to present the: (1) VE estimate in each seasonal cohort and the impact of vaccine match/mismatch; and (2) impact of the vaccine on healthcare utilization within different study regions with different healthcare systems (Europe/Mediterranean, Asia-Pacific and Central America).

Statistical Methods

The primary efficacy analysis was conducted on the per-protocol cohort of the entire study population, as reported previously.[13] The present exploratory analyses in individual seasonal cohorts and in different geographical regions were descriptive, and no power calculation was performed. Because the analyses were exploratory, they were conducted on the total vaccinated cohort (TVC). VE was calculated with a time-to-event model based on a Cox proportional hazard regression model, with 2-sided 95% confidence intervals (CI) calculated. No pre-set criteria, for statistical significance of the estimate, were set; however, VE was considered meaningful if the lower limit (LL) of the 95% CI was >0 with no adjustment for multiplicity. Vaccine impact on healthcare utilization associated with influenza of any severity and moderate-to-severe influenza was evaluated in the TVC in all children with available data. Evaluation of VE by cohort was pre-planned, while evaluation of vaccine impact on healthcare utilization in different regions was done post-hoc.

In the time-to-event model, children were censored for the following reasons from the date of occurrence: randomization code broken, administration of a concomitant vaccine or medication not allowed by the protocol, underlying medical condition not allowed by the protocol, or concomitant infection that might have influenced the immune response.

RESULTS

A total of 12,018 children were included in the TVC, 1777 in cohort 1, 2526 in cohort 2, 1564 in cohort 3, 1501 in cohort 4 and 4650 in cohort 5 (Fig. 1). Median age ranged from 19 to 27 months in the individual cohorts, with approximately equal numbers of boys and girls (Table 1; Table S1, Supplemental Digital Content 1, http://links.lww.com/INF/D682). Most children were of South East Asian, White European, Central/South Asian or Hispanic ancestry,

TABLE 1. Baseline Demographics by Cohort (TVC)

	Cohort 1		Cohort 2		Cohort 3		Cohort 4		Cohort 5	
	IIV4; N = 884	Control; N = 893	IIV4; N = 1260	Control; N = 1266	IIV4; N = 788	Control; N = 776	IIV4; N = 751	Control; N = 750	IIV4; N = 2323	Control; N = 2327
Age at first vaccination, mo										
Median (range)	21.0 (6, 35)	21.0 (6, 35)	19.0 (6, 35)	19.0 (6, 35)	19.0 (6, 35)	19.0 (6, 35)	27.0 (6, 35)	27.0 (6, 35)	24.0 (6, 35)	24.0 (6, 43)
Female, n (%)	422 (47.7)	426 (47.7)	606 (48.1)	616 (48.7)	391 (49.6)	367 (47.3)	387 (51.5)	351 (46.8)	1127 (48.5)	1165 (50.1)
Geographic ancestry, n (%)										
South East Asian	1 (0.1)	2 (0.2)	408 (32.4)	408 (32.2)	0 (0.0)	0 (0.0)	332 (44.2)	334 (44.5)	920 (39.6)	922 (39.6)
Central or South Asian	9 (1.0)	5 (0.6)	0	1 (0.1)	7 (0.9)	2 (0.3)	246 (32.8)	246 (32.8)	800 (34.4)	799 (34.3)
Other Asian	1 (0.1)	1 (0.1)	2 (0.2)	0	0	0	1 (0.1)	0	0	0
White, Caucasian/European heritage	832 (94.1)	851 (95.3)	0	0	639 (81.1)	630 (81.2)	0	0	0	0
White, Arabic/North African heritage	11 (1.2)	16 (1.8)	0	0	131 (16.6)	133 (17.1)	0	0	0	0
African/African American heritage	16 (1.8)	13 (1.5)	4 (0.3)	2 (0.2)	4 (0.5)	4 (0.5)	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.0)	1 (0.0)
American Indian or Alaskan Native	0	0	0	0	0	0	0	0	0	0
Other*	14 (1.6)	6 (0.7)	845 (67.1)	854 (67.5)	7 (0.9)	7 (0.9)	171 (22.8)	170 (22.7)	602 (25.9)	605 (26.0)

*Mainly mixed race or Hispanic origin.

but the proportion varied according to the countries included in the individual cohort (Fig. 1; Table 1). Cohort 1 was based entirely in Europe and >90% of children were of European heritage. Cohort 3 also included Lebanon and Turkey, with a corresponding increase in the number of children with Middle Eastern heritage. Cohorts 2, 4 and 5 were based in Asia Pacific and Central America. Approximately two-thirds of children in cohort 2 were of mixed race or Hispanic origin and one-third were of South East Asian origin. Cohorts 4 and 5 were composed mainly of children with South East Asian, Central and South Asian, and mixed race or Hispanic origin (Table 1).

Vaccine Efficacy by Cohort

In cohort 1, RT-PCR-confirmed influenza was identified in 43 and 100 children in the IIV4 and control groups, respectively. Corresponding values were 38 and 81 in cohort 2; 35 and 123 in cohort 3, 71 and 98 in cohort 4 and 166 and 274 in cohort 5 (Table 2). VE against RT-PCR-confirmed influenza of any severity for all strains combined was between 30.3% and 73.4% in each cohort, with the LL of the 95% CI >0 for each estimate (Table 2). VE against RT-PCR-confirmed moderate-to-severe influenza for all strains combined was 42.8% to 83.9%; again, the LL of the 95% CI of each estimate was >0 (Table 2).

Few A/H1N1 infections were reported in individual cohorts except cohort 3; few B/Victoria infections were reported in any cohort (Table 2). For A/H3N2, VE estimates against influenza of any severity ranged between 35.8% and 68.5%, with all LLs of the CI >0 except for cohort 2 (−0.7%) (Table 2). High efficacy was also observed against B/Yamagata. The analysis of VE against moderate-to-severe influenza associated with individual A subtypes and B lineages was limited by the low number of cases; however, the pattern of VE estimates favoring IIV4 was similar to the analysis of influenza of any severity (Table 2). Table (Table S2, Supplemental Digital Content 1, http://links.lww.com/INF/D682) shows the VE estimates for the remaining endpoints analyzed; estimates with the LL of the CI >0 were observed in some cohorts.

Vaccine Efficacy in Vaccine-matched and -mismatched Cases

In cohort 1, only 0.9% of culture-confirmed cases (any subtype or lineage) matched the vaccine strains. Influenza A/H3N2 predominated in cohort 1, but no cases at all were matched to the A/H3N2 virus used in the vaccine. The overall vaccine match in cohort 2 was 79.3%. Influenza B/Yamagata was the most common virus identified in cohort 2, with almost all B/Yamagata cases (96.2%) being matched to the vaccine. The overall vaccine match in cohort 3 was 72.5%. Influenza A/H1N1 and B/Yamagata predominated, both of which were well matched to the vaccine virus (85.4% and 98.2%, respectively). Overall vaccine match was lower in cohort 4, at 24.1%. Influenza A/H1N1 and A/H3N2 predominated; vaccine match was 74.4% for A/H1N1 but only 1.7% for A/H3N2. In cohort 5, the overall vaccine match was 28.6%. Influenza A/H3N2 and B/Yamagata were the most commonly identified viruses. Influenza A/H3N2 was poorly matched to the vaccine (5.0%), while half of all B/Yamagata cases were matched to the vaccine (vaccine match 50%). The number of culture-confirmed cases of any severity that were matched or mismatched to the vaccine strain is shown in Figure S1 (Supplemental Digital Content 1, http://links.lww.com/INF/D682).

VE estimates with the LL of the 95% CI >0 were observed against both matched and mismatched A/H1N1, A/H3N2 and B/Yamagata viruses (Figure S1, Supplemental Digital Content 1, http://links.lww.com/INF/D682). Very few cases associated with B/Victoria were identified in any cohort.

Impact on Healthcare Utilization Related to RT-PCR-confirmed Influenza

The impact of vaccination on healthcare utilization related to RT-PCR-confirmed influenza is shown in Figure 2 (influenza of any severity) and Figure 3 (moderate-to-severe influenza) for each study region (Europe and the Mediterranean, Asia-Pacific and Central America). The IIV4 reduced the risk of a child receiving any medical care, a general practitioner or pediatrician visit, or an antibiotic in all regions for both influenza of any severity and moderate-to-severe influenza. The risk of an emergency room visit was also reduced in Europe by >80%, but was not estimable in Asia-Pacific or Central America. The analysis of the vaccine's impact on influenza-related medical specialty visits or hospitalization in the 3 regions was inconclusive because of the low number of events.

DISCUSSION

We have previously reported the overall efficacy of the IIV4 observed in the present study, combining data from 13 temperate and sub-tropical countries across 5 influenza seasons.[13] Here, we report VE in each seasonal cohort and the impact of vaccine match/mismatch, as well as the impact of the vaccine on healthcare utilization within different study regions. Investigating the impact of influenza vaccines in single seasons and distinct regions covering Northern and Southern hemispheres is important because temporal and geographical variability in influenza epidemiology can affect VE and effectiveness.[18,19] Influenza cases consistently peak over a short period in the winter months in Northern and Southern hemispheres, but in tropical and sub-tropical countries, the peak is less pronounced and can occur at almost any time.[18,20] The characteristics of influenza epidemics are more variable in tropical and sub-tropical areas than in temperate areas, and different virus subtypes and lineages are more likely to circulate independently.[18,21] The emergence of antigenic variants also varies from season to season, and it is well recognized that effectiveness declines in seasons where the vaccine is poorly matched to circulating strains.[6]

This study demonstrated meaningful VE of IIV4 against all strains combined in each individual cohort, despite vaccine mismatch in some cohorts. We also identified VE against some individual influenza A subtypes or B lineages, although the analysis was limited by a low number of cases in some cohorts. The efficacy achieved against mismatched strains probably reflects a broad immune response to the IIV4. We have previously observed that the vaccine induces both neutralizing and anti-neuraminidase antibodies,[22] which might contribute towards protection against influenza even when circulating strains are vaccine-mismatched by HA antigenicity. However, the VE estimates and associated 95% CIs varied substantially between cohorts. We speculate that there might be an interaction between VE, degree of vaccine match, and socioeconomic status. In cohorts situated in the Northern hemisphere, comprising countries of high socioeconomic status, cohort 3 had the highest VE (73.4%) and the highest vaccine match (72.5%), and cohort 1 had VE of 57.8%, despite a vaccine match of only 0.9%. In the cohorts situated in subtropical countries with lower socioeconomic status, the highest VE was observed in cohort 2 (52.9%), which also had the highest vaccine match (79.3%). Lower VE was observed in cohorts 4 and 5 (30.3% and 41.4%), which corresponded to vaccine match of 24.1% and 28.4%. Thus, a generally higher level of VE was observed with higher proportion of vaccine match and in cohorts with countries of higher socioeconomic status. Children from lower socioeconomic settings might be exposed to various factors that increase the risk of influenza despite vaccination. The Global Burden of Disease 2016 study demonstrated a higher risk of LRI in low-income countries among children <5

TABLE 2. Vaccine Efficacy Against RT-PCR-Confirmed Influenza (TVC, Time-to-Event Analysis, VE)

	IIV4		Control		
	n	Attack rate, %	n	Attack rate, %	VE, % (95% CI)
Influenza of any severity					
All strains					
Cohort 1	43	4.86	100	11.20	57.8 (40.2, 70.8)
Cohort 2	38	3.02	81	6.40	52.9 (31.2, 68.3)
Cohort 3	35	4.44	123	15.85	73.4 (61.7, 82.0)
Cohort 4	71	9.45	98	13.07	30.3 (5.5, 48.8)
Cohort 5	166	7.15	274	11.77	41.4 (29.0, 51.7)
A/H1N1					
Cohort 1	1	0.11	2	0.22	50.0 (−422.4, 97.7)
Cohort 2	5	0.40	12	0.95	57.6 (−14.3, 86.5)
Cohort 3	11	1.40	60	7.73	82.3 (67.7, 91.2)
Cohort 4	14	1.86	24	3.20	43.0 (−8.7, 71.3)
Cohort 5	4	0.17	5	0.21	21.5 (−196.6, 80.6)
A/H3N2					
Cohort 1	40	4.52	93	10.41	57.7 (39.3, 71.1)
Cohort 2	10	0.79	21	1.66	51.4 (−0.7, 78.1)
Cohort 3	7	0.89	22	2.84	68.5 (29.8, 87.5)
Cohort 4	38	5.06	60	8.00	38.0 (7.3, 59.0)
Cohort 5	88	3.79	135	5.80	35.8 (16.2, 51.0)
B/Victoria					
Cohort 1	0	0.00	0	0.00	—
Cohort 2	3	0.24	8	0.63	62.0 (−31.2, 91.7)
Cohort 3	2	0.25	5	0.64	60.3 (−84.3, 94.3)
Cohort 4	19	2.53	16	2.13	−17.0 (−130.4, 39.8)
Cohort 5	5	0.22	9	0.39	45.4 (−57.9, 83.2)
B/Yamagata					
Cohort 1	0	0.00	3	0.34	100 (13.4, −)
Cohort 2	21	1.67	37	2.92	42.4 (2.5, 66.8)
Cohort 3	15	1.90	42	5.41	64.8 (38.0, 81.1)
Cohort 4	1	0.13	1	0.13	1.9 (−2377.8, 96.1)
Cohort 5	69	2.97	127	5.46	47.0 (29.2, 60.6)
Moderate-to-severe influenza					
All strains					
Cohort 1	23	2.60	41	4.59	42.8 (5.6, 66.2)
Cohort 2	8	0.63	28	2.21	71.1 (39.5, 87.7)
Cohort 3	10	1.27	60	7.73	83.9 (69.9, 92.2)
Cohort 4	17	2.26	35	4.67	52.2 (16.0, 73.9)
Cohort 5	33	1.42	85	3.65	61.9 (43.6, 74.9)
A/H1N1					
Cohort 1	1	0.11	1	0.11	−2.3 (−2485.7, 96.0)
Cohort 2	1	0.08	3	0.24	66.1 (−164.9, 98.3)
Cohort 3	3	0.38	32	4.12	90.8 (74.3, 97.8)
Cohort 4	5	0.67	9	1.20	45.1 (−59.0, 83.1)
Cohort 5	3	0.13	1	0.04	−199.1 (−5945.6, 61.7)
A/H3N2					
Cohort 1	22	2.49	37	4.14	39.3 (−2.1, 64.7)
Cohort 2	3	0.24	8	0.63	61.8 (−32.1, 91.6)
Cohort 3	1	0.13	7	0.90	85.7 (19.4, 99.2)
Cohort 4	11	1.46	18	2.40	39.3 (−26.7, 72.2)
Cohort 5	16	0.69	42	1.80	62.3 (34.4, 79.4)
B/Victoria					
Cohort 1	0	0.00	0	0.00	—
Cohort 2	0	0.00	3	0.24	100 (8.6, −)
Cohort 3	1	0.13	2	0.26	50.6 (−415.8, 97.7)
Cohort 4	2	0.27	7	0.93	71.8 (−16.7, 95.8)
Cohort 5	0	0.00	3	0.13	100 (13.0, −)
B/Yamagata					
Cohort 1	0	0.00	1	0.11	100 (−508.0, −)
Cohort 2	4	0.32	12	0.95	66.1 (2.7, 90.5)
Cohort 3	5	0.63	20	2.58	75.2 (38.6, 91.7)
Cohort 4	0	0.00	1	0.13	100 (−470.9, −)
Cohort 5	13	0.56	39	1.68	67.1 (40.1, 83.1)

n, number of children with at least one case of the influenza event considered.

Europe
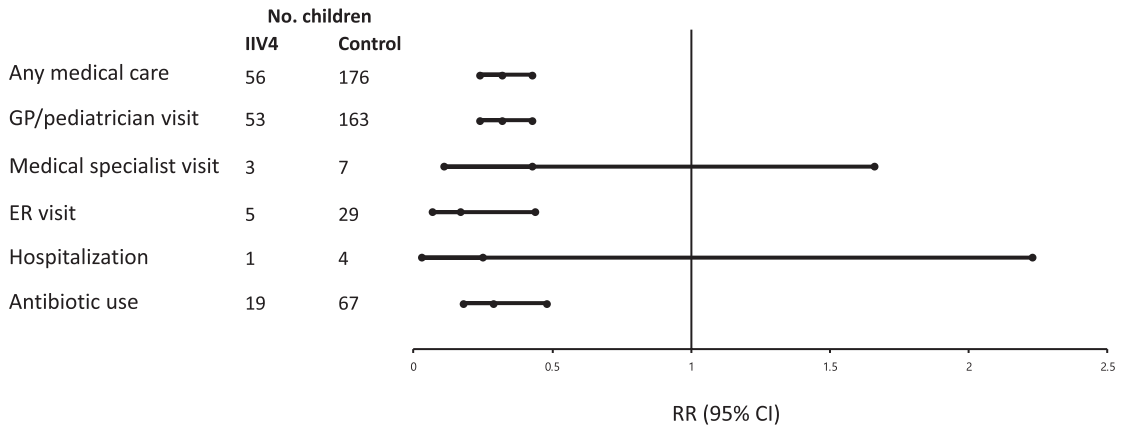
No. children with at least one RT-PCR-confirmed influenza episode: 81 (IIV4), 240 (control)

Asia Pacific
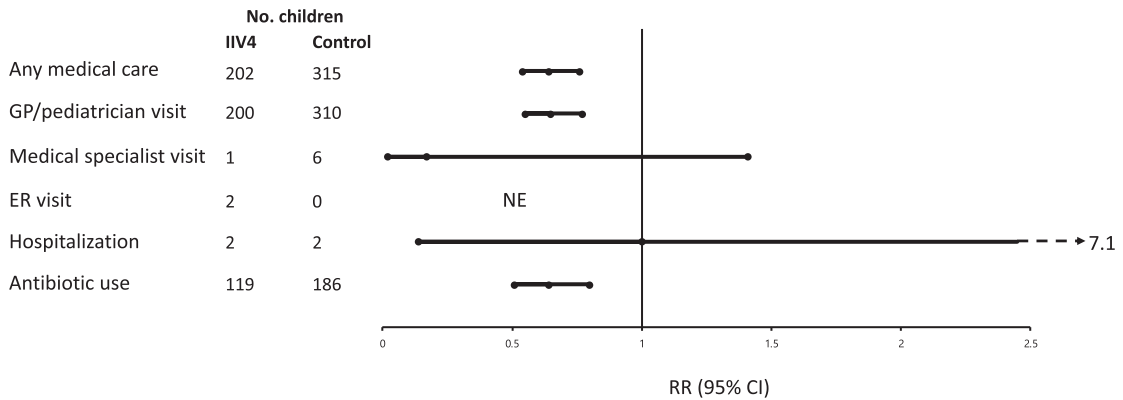
No. children with at least one RT-PCR-confirmed influenza episode: 212 (IIV4), 327 (control)

Central America

No. children with at least one RT-PCR-confirmed influenza episode: 63 (IIV4), 126 (control)

FIGURE 2. Impact of vaccination on healthcare utilization related to RT-PCR-confirmed influenza of any severity by region (TVC).

Europe

	No. children	
	IIV4	Control
Any medical care	26	94
GP/pediatrician visit	24	84
Medical specialist visit	2	5
ER visit	2	16
Hospitalization	1	4
Antibiotic use	12	51

RR (95% CI)

No. children with at least one RT-PCR-confirmed moderate-to-severe influenza episode: 34 (IIV4), 114 (control)

Asia Pacific

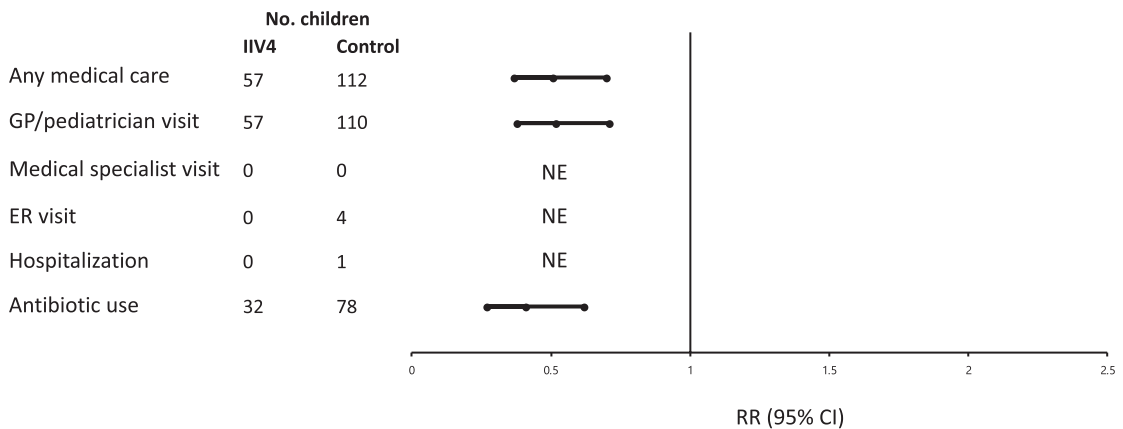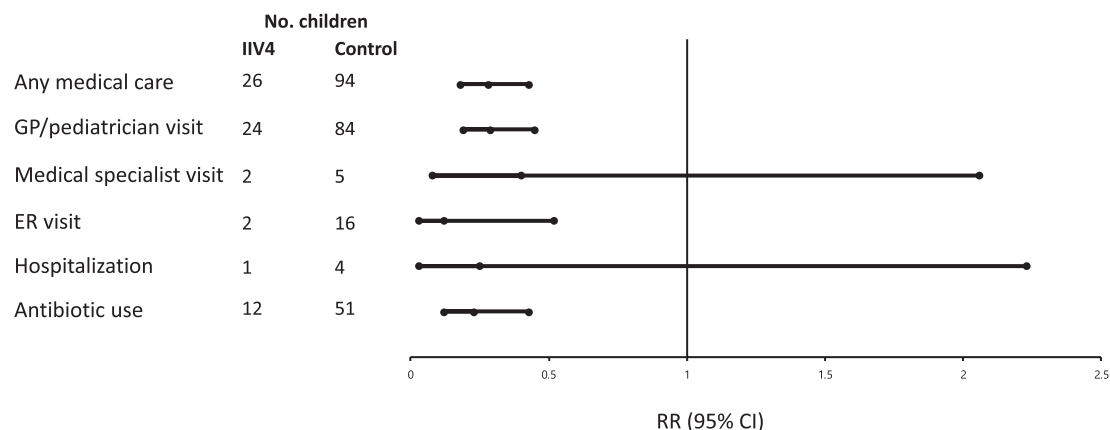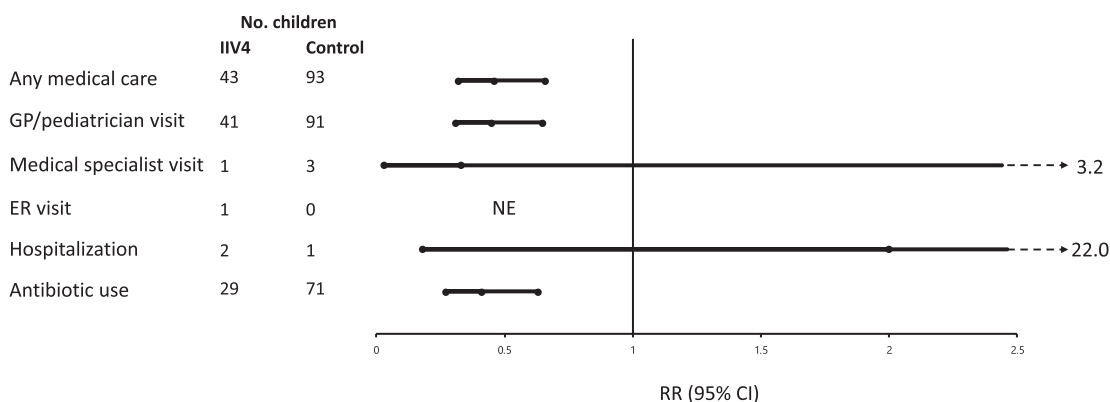|	No. children	
	IIV4	Control
Any medical care	43	93
GP/pediatrician visit	41	91
Medical specialist visit	1	3
ER visit	1	0
Hospitalization	2	1
Antibiotic use	29	71

RR (95% CI)

No. children with at least one RT-PCR-confirmed moderate-to-severe influenza episode: 47 (IIV4), 97 (control)

Central America

	No. children	
	IIV4	Control
Any medical care	10	48
GP/pediatrician visit	10	47
Medical specialist visit	0	0
ER visit	0	2
Hospitalization	0	1
Antibiotic use	6	33

RR (95% CI)
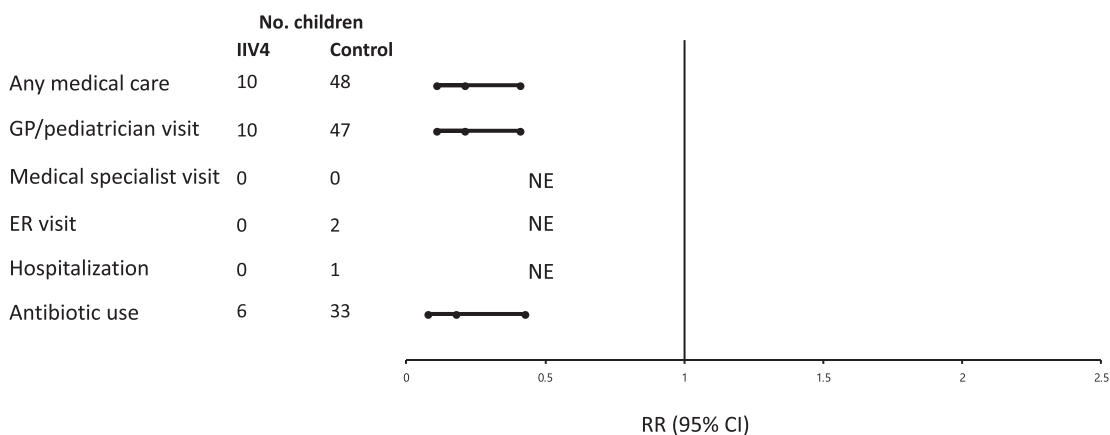
No. children with at least one RT-PCR-confirmed moderate-to-severe influenza episode: 11 (IIV4), 51 (control)

FIGURE 3. Impact of vaccination on healthcare utilization related to RT-PCR-confirmed moderate-to-severe influenza by region (TVC).

years of age, and indicated that improved outcomes were associated with increasing socioeconomic development.[23]

We observed VE against moderate-to-severe influenza (all strains combined) of between 42.8% and 83.9%. A community-based, case-control study in the United States during the 2010−2012 seasons has previously shown vaccine effectiveness of 82% against influenza-associated intensive care unit admission in children 6 months to 17 years of age (in the case and control groups, respectively, median age was 4.3 and 3.0 years, with 55% and 62% of children <5 years).[24] Higher VE was achieved against moderate-to-severe influenza than against influenza of any severity for all strains combined in each cohort except cohort 1, in line with previous observation of overall efficacy across all cohorts in the present study and for a similar IIV4 in a study of children 3−8 years of age.[13,25] The difference in the magnitude of the VE estimates suggests that the IIV4 not only prevents influenza illness but also attenuates breakthrough illness. Analysis of moderate-to-severe illness is important because it captures the clinical outcomes that are most likely to result in medical consultations, such as fever, LRI, ear infections and serious non-pulmonary complications.[26] In our study, fever was the most common presentation of moderate-to-severe influenza, as previously described.[13] The value of the moderate-to-severe endpoint has been confirmed using real-life data from community-based studies.[27–29] We have previously reported attenuation of breakthrough illness in vaccinated children in this study; compared with unvaccinated children, vaccinated children were less likely to develop moderate-to-severe illness and fever, and had fewer medical and emergency room visits.[30] Attenuation of illness severity following vaccination has also been demonstrated in a case cohort study of children with fatal laboratory-confirmed influenza; of 291 deaths, 74% occurred in children who were not vaccinated.[31]

Vaccination reduced the risk of medical visits and antibiotic use in all regions of the study (Europe, Asia Pacific and Central America). Antibiotic use associated with influenza illness of any severity was reduced by 71% in Europe, 36% in Asia Pacific and 59% in Central America. The reduction in antibiotic use associated with moderate-to-severe illness was even higher: 77% in Europe, 59% in Asia Pacific and 82% in Central America. Antibiotics continue to be prescribed frequently in young children with influenza,[32] despite their use in childhood respiratory infections being associated with development of resistance.[33,34] A reduction in antibiotic use following influenza vaccination could therefore have important public health implications.

Study strengths and limitations have been discussed previously.[13] Briefly, strengths included the large randomized trial design in 5 independent cohorts during 5 influenza seasons in 3 regions including temperate and sub-tropical countries, use of active surveillance and laboratory assays, and capture of moderate-to-severe influenza endpoints that reflect the most clinically relevant illness. The study recruited children in stable health with no conditions that could increase the risk of complications of influenza illness; therefore, the results might not be generalizable to the overall population including at-risk children. Other limitations of the study included heterogeneous access to medical facilities, including patient care and use of antibiotics; variability in the available information on circulating strains in different countries in the study; no information was collected on the socioeconomic status of individual participants; and not all RT-PCR-positive specimens were able to be antigenically characterized. The analyses reported here were limited by their exploratory nature and lack of power calculation, and no formal analysis of the relationship between VE and exact degree of match/mismatch was conducted (either for the overall study or by cohort).

In conclusion, the IIV4 prevented influenza in children 6−35 months of age in each of 5 separate influenza seasons in diverse geographical regions. A possible interaction between VE, proportion of vaccine match and socioeconomic status was observed. The IIV4 attenuated the severity of breakthrough influenza illness and reduced healthcare utilization, particularly antibiotic use.

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