Clinical presentation of influenza in children 6 to 35 months of age: findings from a randomized clinical trial of inactivated quadrivalent influenza vaccine

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Contributorship

All authors participated in the design or implementation or analysis, and interpretation of the study; and the development of this manuscript. All authors had full access to the data and gave final approval before submission. The Flu4VEC study group is shown in Supplemental Digital Content 1.

Data sharing statement

Anonymized individual participant data from this study plus the annotated case report form, protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset, and clinical study report are available for research proposals approved by an independent review committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access agreement will be required.

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Abstract

Background: In an exploratory analysis of an inactivated quadrivalent influenza vaccine (IIV4) trial in children 6–35 months without risk factors for influenza, we evaluated clinical presentation of influenza illness and vaccine impact on health outcomes.

Methods: This phase III trial was conducted in 13 geographically diverse countries across five influenza seasons (2011–2014). Children were randomized 1:1 to IIV4 or control. Active surveillance was performed for influenza-like episodes (ILE); influenza was confirmed by reverse transcription polymerase chain reaction (RT-PCR). The total vaccinated cohort was evaluated (N=12,018).

Results: 5702 children experienced ≥1 ILE; 356 (IIV4 group) and 693 (control group) children had RT-PCR-confirmed influenza. Prevalence of ILE was similar in RT-PCR-positive and RT-PCR-negative cases regardless of vaccination. Breakthrough influenza illness was attenuated in children vaccinated with IIV4; moderate-to-severe illness was 41% less likely to be reported in the IIV4 group than the control group (crude odds ratio: 0.59 [95% CI: 0.44–0.77]). Furthermore, fever >39°C was 46% less frequent following vaccination with IIV4 than with control (crude odds ratio: 0.54 [95% CI: 0.39–0.75]) in children with breakthrough illness. Health outcome analysis showed that, each year, IIV4 would prevent 54 influenza cases/1000 children and 19 children would need to be vaccinated to prevent one new influenza case.

Conclusion: In addition to preventing influenza in 50% of participants, IIV4 attenuated illness severity and disease burden in children who had a breakthrough influenza episode despite vaccination.

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Focus on patient

What is the context?

Morbidity and mortality caused by influenza are important global public health concerns. Children less than 5 years of age are highly susceptible to influenza disease leading to hospitalization and other healthcare resource use. Accurate clinical diagnosis of influenza is particularly difficult in young children because symptoms vary in severity and may overlap with symptoms caused by other respiratory pathogens. Timely diagnosis of influenza utilizing available diagnostic tests is particularly important for appropriate management of patients.

What is new?

In this paper, clinical presentation and impact of influenza vaccination on disease severity were evaluated in healthy children 6 to 35 months of age. Regardless of vaccination status, we confirmed that symptoms associated with influenza disease were similar to those associated with the other respiratory pathogens. However, we observed that children vaccinated against influenza were less susceptible to experience more severe disease. Most notably, prevalence of high fever was lower in vaccinated children.

What is the impact?

We aimed to characterize influenza disease and estimate the impact of influenza vaccination in young children. The severity of influenza illness is attenuated in

children who acquired infection despite vaccination, confirming the value of vaccinating children against influenza.

Introduction

In children, influenza attack rates are high[1] and influenza illness is associated with substantial hospitalization and other healthcare resource use.[2-5] Vaccination of children against influenza is now recommended in many countries. Although its main goal is prevention of influenza, there is some evidence that breakthrough illness is attenuated in people who acquire influenza despite vaccination. Studies in both adults and children have shown that vaccinated individuals with laboratory-confirmed influenza had lower death rates, fewer admissions to an intensive care unit, shorter hospital stay and less severe symptoms compared with non-vaccinated individuals.[6-9]

The lack of specificity in influenza symptoms means that a differential diagnosis from other illnesses associated with respiratory viruses remains a significant challenge, particularly in young children.[10-13] The increasing availability of technologies to detect and identify viruses has revealed that many cases of influenza-like illness (ILI) are in fact caused by viruses other than influenza.[14-16]

Between 2011 and 2014, we conducted a multinational, randomized, controlled clinical trial in healthy children 6 to 35 months of age to determine the efficacy of an inactivated quadrivalent influenza vaccine (IIV4) against reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza.[17] Vaccine efficacy (VE) was 63% against moderate-to-severe influenza illness and 50% against all influenza illness.[17] In this article, we present an exploratory analysis of the trial to evaluate the clinical presentation of influenza and influenza-like episodes (ILE) and to assess the

vaccine's impact on outcomes relevant to public health using a vaccine probe approach (see video, Supplemental Digital Content 2).

Materials and Methods

Detailed methods of this randomized, controlled, observer-blind phase III trial have been presented previously.[17] The study was funded by GlaxoSmithKline Biologicals SA and registered with ClinicalTrials.gov (NCT01439360) and received appropriate ethics approval (see Supplemental Digital Content 3).

Study design and participants

The study was conducted in 13 northern hemisphere and subtropical countries (see Supplemental Digital Content 3). Healthy children (6–35 months of age) without risk factors for complications of influenza illness were recruited in five independent cohorts and each study cohort was conducted during a different influenza season (see Supplemental Digital Content 3). Children were randomized 1:1 to IIV4 or non-influenza control vaccines (see Supplemental Digital Content 3).

Surveillance for illness and recording of symptoms

Influenza surveillance began for each individual child from 14 days after final vaccination and lasted until the end of the influenza season. The surveillance period covered the peak of the influenza season in each country.[17-19] Nasal swabs were collected according to the study protocol within 7 days (preferably within 24 hours) of the onset of an ILE that included influenza-like illness (ILI, which was 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 (AOM) or lower respiratory infection (LRI).

Influenza A or B was confirmed by RT-PCR. Further antigenic characterization was performed for influenza A subtype or B lineage as described previously.[17] Parents recorded temperature, symptoms (specified separately for ILI/LRI and AOM), and any medication used daily using an internet-based system or paper booklet (see Supplemental Digital Content 3). Symptoms were recorded until they resolved or a maximum of 13 days after onset. Study staff made a follow-up contact at the end of the episode at which they recorded its outcome; final physician diagnosis; medications; healthcare utilization; and absenteeism (see Supplemental Digital Content 3).

Study objectives

The primary objectives of the study (efficacy of IIV4 against the first occurrence of RT-PCR-confirmed influenza of any severity [all influenza] and moderate-to-severe influenza) have been previously reported.[17] Moderate-to-severe influenza was defined as any of the following: fever >39°C; physician-diagnosed AOM; physician-diagnosed LRI; physician-diagnosed serious extra-pulmonary complication (e.g. myositis, encephalitis, seizure, myocarditis/pericarditis or other serious medical condition); hospitalization in the intensive care unit (ICU); or supplemental oxygen for >8 hours. The latter three criteria defined severe influenza illness.

The objectives of the present analyses were (1) to describe the clinical characteristics of ILE in influenza-positive compared with influenza-negative (confirmed by RT-PCR) children, regardless of influenza vaccination status; (2) to compare the symptoms and symptom severity of RT-PCR-confirmed influenza in

children in the IIV4 group who experienced breakthrough illness versus children in the control group; (3) to evaluate the public health impact of the IIV4 using a vaccine probe approach (see figure, Supplemental Digital Content 4).

Statistical methods

All analyses conducted for this paper were exploratory and were conducted in the total vaccinated cohort (TVC), which included all vaccinated children with available data. VE was defined as the hazard ratio of cases of influenza A and/or B disease in children receiving IIV4 in contrast with children receiving non-influenza vaccine control, subtracted from 1. The Cox proportional hazard regression model included treatment group as the explanatory variable, age category as a covariate, and cohort as a stratification variable in the analysis. Full details on the regression modelling have been previously described.[17]

The crude odds ratio (OR) was calculated along with 95% confidence intervals (CI) to measure the association between children with RT-PCR-confirmed influenza experiencing moderate-to-severe versus mild illness for IIV4 versus control: (no. moderate-to-severe cases IIV4/no. moderate-to-severe cases control)/(no. mild cases IIV4/no. mild cases control). The crude OR for the proportion of children with RT-PCR-confirmed influenza with ILI or LRI as the primary event experiencing fever >39°C was calculated in the same way.

In an analysis attempting to further assess disease severity (in addition to categorization of influenza as mild and moderate-to-severe), a severity score for clinical symptoms was calculated based on the symptom diary for children in whom

ILI or LRI was the primary event triggering the nasal swab (see Supplemental Digital Content 3). A symptom score for AOM was not calculated because few children with RT-PCR-confirmed influenza experienced AOM as the event triggering the nasal swab.

Using established methods as described in Supplemental Digital Content 3,[20] we estimated the etiologic fraction (AF) of ILE caused by a pathogen, the vaccine prevention disease index (VPDI) and the number of vaccinees needed to prevent one new case of disease (NNV).

Results

A total of 12,018 children were included in the TVC; median age was 22 months, with approximately equal numbers of boys and girls. Most children were of South East Asian, White European, Central/South Asian or Hispanic ancestry. A total of 2,747 children in the IIV4 group experienced 4153 ILE episodes and 2955 children in the control group experienced 4411 ILE episodes (Figure 1). In the TVC, most (77.4%) events presented as ILI, 16.3% presented as LRI, and 6.3% presented as AOM.

Prevalence of symptoms defining ILI: influenza-positive versus influenza-negative episodes regardless of vaccination status

In total, 6625 ILI episodes were identified; 987 were RT-PCR-positive, 5464 were RT-PCR-negative, and 174 had a missing RT-PCR result (Figure 1). The frequency of episodes of any non-specific (before RT-PCR confirmation of influenza) ILI, LRI and AOM in the IIV4 group was similar to the control group. The prevalence of symptoms defining ILI was similar in RT-PCR-positive and RT-PCR-negative episodes (see figure, Supplemental Digital Content 5). All ILI cases were associated with fever, as this was part of the definition of ILI. Symptoms of at least fever, cough and runny nose were present in 73.4% and 74.9% of RT-PCR-positive and RT-PCR-negative cases, respectively (see figure, Supplemental Digital Content 5).

Comparison of RT-PCR-confirmed influenza symptoms in vaccinated and unvaccinated children

A total of 356 (IIV4) and 693 children (control) had RT-PCR-confirmed influenza (Figure 1).

Clinical symptoms in RT-PCR-confirmed influenza

Among children with RT-PCR-confirmed influenza who received IIV4, the event triggering the nasal swab was ILI in 92.3%, LRI in 6.3% and AOM in 1.4% (Figure 1). Corresponding values in the control group were 91.3%, 6.3% and 2.4%.

In children with ILI or LRI associated with RT-PCR-confirmed influenza, the frequency of symptoms and symptom duration were similar in both study groups (Table 1). Normal activities (parental absence from paid work or child absence from day-care) were disrupted in 78–79% of children with influenza-positive ILI or LRI in both study groups (Table 1). However, a lower prevalence of fever >39°C was observed in children in the IIV4 group than in the control group (17.7% [95% CI: 13.8, 22.1] vs 28.30% [25.0, 31.9]; crude OR: 0.54 (95% CI: 0.39, 0.75); Figure 2). Among children with AOM, the frequency of all symptoms was similar in both groups (data not shown).

Symptom severity and hospitalization in RT-PCR-confirmed influenza

Of children in the IIV4 group with RT-PCR-confirmed influenza, 25.8% experienced moderate-to-severe illness and 74.2% experienced mild illness; corresponding values in the control group were 37.2% and 62.8%. The crude OR (0.59 [95% CI:

0.44, 0.77]) demonstrated that breakthrough influenza illness was attenuated in children vaccinated with IIV4, with moderate-to-severe illness being 41% less likely to be reported in the IIV4 group versus the control group. However, the calculated severity scores for ILI and LRI showed little difference between the study groups (see table, Supplemental Digital Content 6).

Three children out of 356 (0.8%) with RT-PCR-confirmed influenza in the IIV4 group were hospitalized compared with nine out of 693 (1.3%) in the control group (see table, Supplemental Digital Content 7). Children remained in hospital for between 1 and 7 days, except for one child in the IIV4 group who was hospitalized for 19 days associated with pneumonia and sepsis. Two cases meeting the definition of severe influenza were reported in the IIV4 group (associated with sepsis and febrile convulsion) and three in the control group (two associated with febrile convulsion and one with febrile convulsion and typhoid fever).

At the time of hospitalization, children had concurrent symptoms of ILE, but it was unknown at admission whether they were RT-PCR-positive or -negative for influenza. The recorded diagnoses were based on clinical data, and the clinical presentation of each case was consistent with an episode of influenza. Further evaluation of each case identified a variety of medical conditions, including other infectious etiologies (RSV, roseola, typhoid fever and rotavirus), pneumonia (unknown etiology), febrile convulsion, and other respiratory conditions (see table, Supplemental Digital Content 7). Among those hospitalized with pneumonia (two in the IIV4 group and four in the control group), the events seemed consistent with secondary infections. Four cases of febrile convulsion prompting hospitalization were

recorded in children with confirmed influenza, one in the IIV4 group child and three in the control group. The case in the vaccinated child occurred after the child developed an upper respiratory tract infection. The cases in the control group occurred in conjunction with typhoid fever, pneumonia and upper respiratory tract infection. Thus, although these 12 hospitalized children presented with influenza-like symptoms and had influenza virus detected by RT-PCR, clinical tests performed during the hospital stay indicated that the hospitalization was associated with a medical condition in addition to influenza.

Public health impact of the IIV4 (vaccine probe analysis)

For RT-PCR-confirmed influenza of any severity, AF was 14.0%, VPDI was 5.4 per 100 children per year (i.e. IIV4 would prevent 54 influenza cases per 1000 children each year), and NNV was 19.0 (i.e. 19 children would need to be vaccinated to prevent one new influenza case each year). Other values are shown in Table 2.

Discussion

Our study recruited healthy young children without medical conditions that could place them at higher risk for influenza disease or complications, and excluded children with such conditions. These population characteristics should be borne in mind when interpreting the study results. We found that clinical symptoms did not distinguish between confirmed influenza cases (RT-PCR-positive) and cases unlikely to be influenza-related (RT-PCR-negative), providing further evidence of the difficulty of accurate clinical diagnosis of influenza in young children without the aid of diagnostic tests.[10-13] This likely results in underdiagnosis of influenza in children in real world settings, which in turn might lead to an underestimation of the impact of childhood influenza and the importance of vaccination.[21,22] The analysis of symptoms indicative of influenza was limited by the fact that only pre-specified symptoms were collected and therefore the whole clinical picture was not necessarily captured. A further limitation is that nasal swabs could be collected up to 7 days after symptom onset, which could decrease the positivity rate. However, parents were asked to report ILE symptoms as soon as they occurred, and every effort was made to collect swabs within 1 day of symptom onset. In fact, approximately 70% were collected within 0–1 days and approximately 90% within 3 days of symptoms onset.

Nevertheless, the symptoms observed in our study were consistent with those seen in other studies.[23,24] In a trial of live attenuated influenza vaccine (LAIV) among children 24–59 months of age, fever, cough or runny nose were reported in approximately 70% of children with confirmed influenza; fever was reported more frequently in children with confirmed influenza than those who were influenza-

negative.[23] A longitudinal active surveillance study in pre-school children found that children with febrile or respiratory illnesses testing positive for influenza were more likely to experience fever, headache, myalgia, runny nose, and loss of appetite than children testing negative for influenza.[24]

The control group of our study provides a global picture of influenza illness experienced in diverse locations over five influenza seasons in healthy young children. A study in Germany of unvaccinated children less than 5 years of age with laboratory-confirmed influenza reported a duration of 4 days for fever and 10–11 days for cough and runny nose.[25] This was longer than the median 2 days for fever, 6 days for cough and 7 days for runny nose observed in our study's control group. This difference might be due to differences in methodology. For example, our study excluded children at risk of influenza complications and included active follow-up for ILE, whilst the German study included all children presenting at outpatient pediatric practices with febrile acute respiratory infection.[25] Furthermore, the children enrolled in our study were younger than those enrolled in the German study (mean age of 22 months versus 43 months).

Higher VE against moderate-to-severe influenza versus influenza of any severity has been previously reported for this study.[17] Our analysis suggests that disease attenuation may occur in breakthrough cases. In children with RT-PCR-confirmed influenza, those vaccinated with IIV4 were 41% less likely to develop moderate-to-severe illness and 46% less likely to develop fever >39°C compared with unvaccinated children. Furthermore, there were fewer influenza-associated medically attended and emergency room visits among children who received IIV4. Several

other studies have reported attenuation of influenza severity following vaccination.[6-9,26,27] Another study of IIV4 in children 3–8 years of age reported higher vaccine efficacy against moderate-to-severe influenza (74%) than against influenza of any severity (59%).[26] A case-cohort study of children with confirmed influenza who died reported that 74% of deaths occurred among unvaccinated children.[6] Similarly, a trial of LAIV reported that vaccinated children missed substantially less day-care than unvaccinated children.[27] The latter has also been previously reported for the present study.[17]

The above findings emphasize the importance of selecting appropriate endpoints for the evaluation of influenza vaccine efficacy in clinical trials. The moderate-to-severe endpoint reflects clinical outcomes of LRI, ear infection, other serious non-pulmonary complications and high fever that are most likely to result in medical consultations.[28] Failure to distinguish moderate-to-severe influenza from mild influenza might mask the vaccine's ability to attenuate illness, and therefore its true benefit to individuals may be undervalued. The value of the moderate-to-severe endpoint has been confirmed using real-life data from community-based studies.[25,29,30] Perceived severity of disease influences the decision to vaccinate,[31] and thus raising awareness of the overall impact of influenza may help to improve vaccination rates. Furthermore, in low-resource settings with competing health priorities, an awareness of the impact of moderate-to-severe influenza and the benefits of vaccination may be required for prioritization of influenza among other vaccine-preventable diseases in young healthy children. We attempted to explore disease attenuation in the vaccine group by calculating a symptom severity score, but found that the score was not able

to differentiate between vaccinated and unvaccinated children. This might suggest that the symptoms collected in this study are unable to quantify or adequately describe the degree of illness severity experienced. Alternatively, the lack of difference in the score between study groups may be explained by methodology issues such as incomplete diaries, masking of the severity of influenza symptoms by co-infections, or recruitment of a population without pre-existing conditions putting them at risk for influenza. We concluded that the score as developed was not fit for the purpose of scoring influenza symptom severity.

Data from vaccine clinical trials can be used to assess the public health impact of vaccination by characterizing the disease burden and quantifying the reduction in disease outcomes through vaccination.[32] However, such analyses are limited to assessment of the direct impact of vaccination and are unable to evaluate any indirect effects. Thus, the true impact of vaccination is likely to be underestimated. We found that confirmed influenza contributed to 14% of all ILE episodes, indicating that 86% of episodes might result from other respiratory pathogens in this population of young children. Thus, the study suggests that IIV4 decreases the burden of RT-PCR confirmed influenza in young children, but has a limited net impact against non-specific ILE. However, evaluation of net impact was not the focus of the study, and the results should be interpreted with caution. The proportion of ILE associated with confirmed influenza depends upon the virulence of the circulating influenza strains, period of data collection since influenza is a seasonal disease, vaccine uptake, and, importantly, the susceptibility of the population against circulating influenza viruses.

The study showed that vaccination with IIV4 of 1000 children averted annually 54 influenza cases of any severity and 22 incidents of fever >39°C associated with influenza. The study findings are within the range of VPDI estimates by other studies and reflect the role of influenza vaccination in reducing the burden of influenza in children and preventing circulation of the virus in the community. In a review of studies in children, the VPDI ranged from 0 to 380 per 1000, with a mean value of 128/1000 children based on 17 studies or sub-studies.[33]

With regard to healthcare utilization, we estimated that, from our study population, 21 children would need to be vaccinated to prevent one new medically-attended visit and 36 to prevent one new event of antibiotic use (the NNV). A previous study has estimated that, assuming 50% VE based on data from previously published studies in a variety of settings and populations, 12–42 children 6–59 months of age would need to be vaccinated to prevent one outpatient visit, depending on the severity of the influenza season.[34] The NNV results from our study need to be taken in context because the estimates depend on several study-related factors such as location (multiple study centers in 13 countries in northern hemisphere and subtropical countries), disease prevalence over five seasons with three mostly mismatched seasons, demographic and clinical characteristics of the study population, and healthcare systems (westernized versus non-westernized countries). In addition, it is important to note that influenza disease in young children was indistinguishable from other respiratory infectious diseases and cannot be conclusively identified without the use of specific diagnostic tests. Without such tests, which are not readily

available in most settings, the burden of influenza-associated healthcare utilization cannot be reliably estimated.

In conclusion, our analysis showed that influenza is common and drives substantial use of healthcare resource even in healthy children without risk factors for influenza and influenza-related complications. The incidence of breakthrough illness was reduced, and disease was attenuated in breakthrough cases in vaccinated children. The public health impact assessment using a vaccine probe approach demonstrated that the IIV4 can help to reduce the burden of influenza in children and confirmed at the individual level the value of vaccinating children against influenza.

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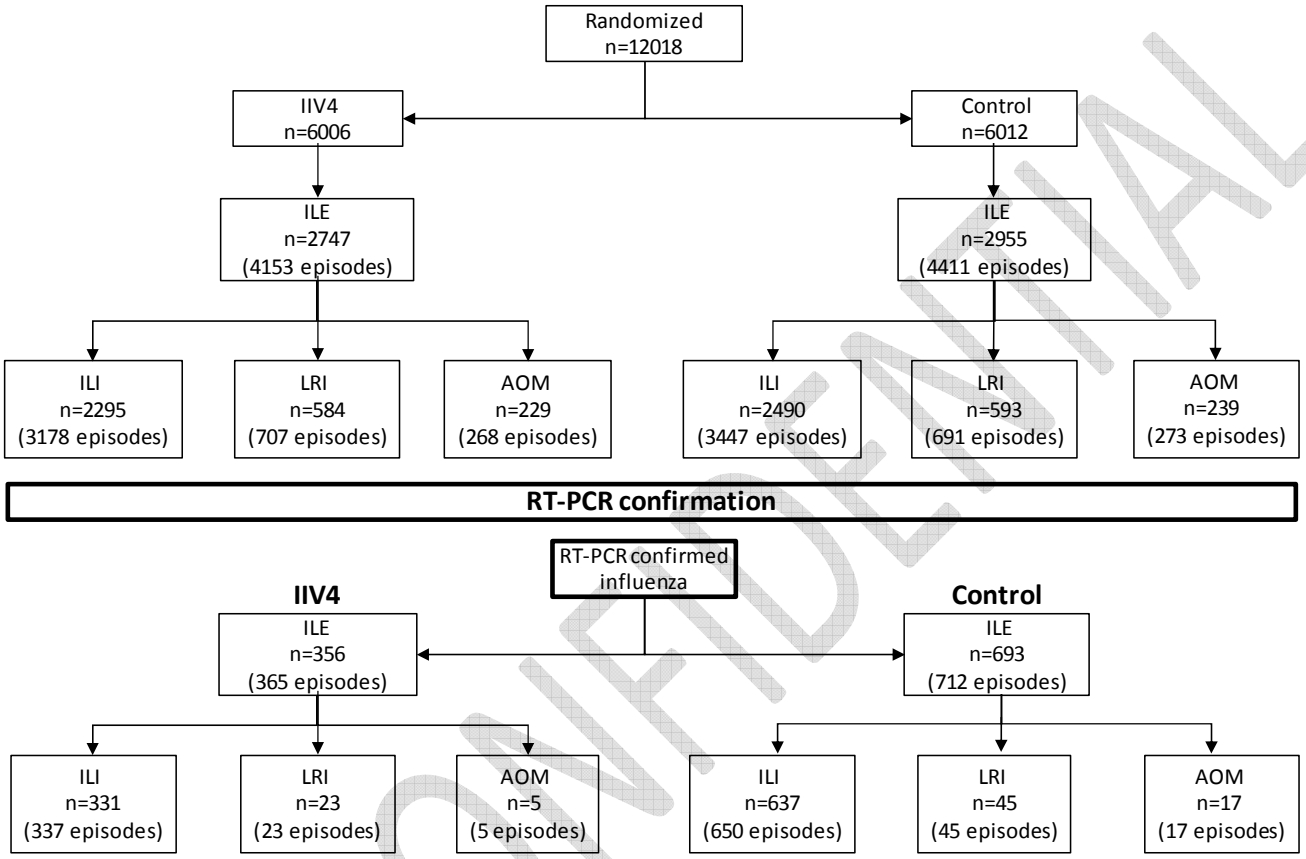
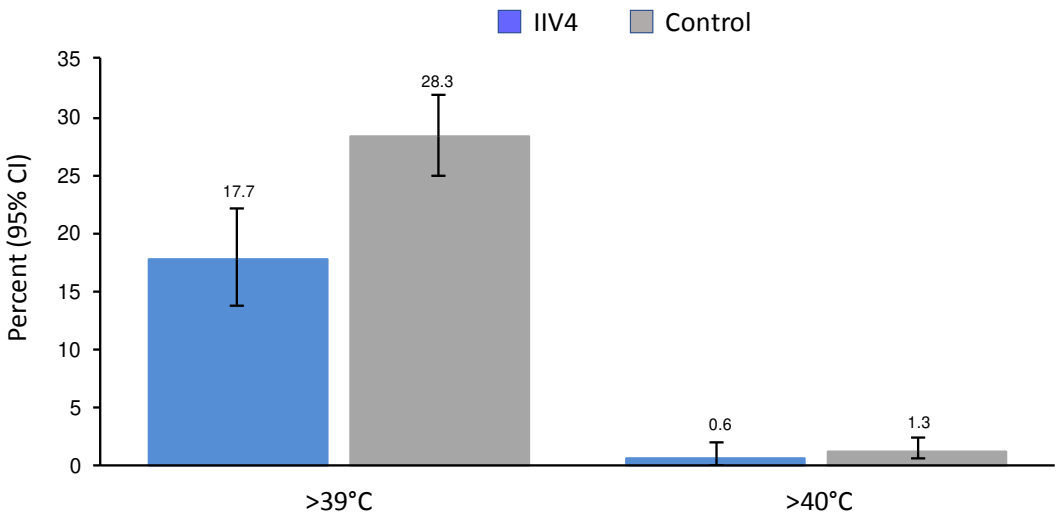
Figures

Figure 1. Disposition of influenza-like episodes



Three children in the IIV4 group and six children in the control group had two RT-PCR-confirmed infections that fell into different diagnostic categories (ILI, LRI and AOM) and are therefore counted twice in Figure 1. In the IIV4 group, all three children had one episode categorized as ILI and one episode categorized as LRI. In the control group, four children had one episode categorized as ILI and one episode categorized as LRI, and two children had one episode categorized as ILI and one episode categorized as AOM.
RT-PCR result missing (number of cases): ILI, n=94 and 80 for IIV4 and control, respectively; LRI, n=30 and 36 for IIV4 and control, respectively; AOM, n=27 and 24 for IIV4 and control, respectively.
AOM: acute otitis media; ILI: influenza-like illness; LRI: lower respiratory illness; RT-PCR: reverse transcription polymerase chain reaction

Figure 2. Fever >39°C and >40°C associated with ILI/LRI in children with RT-PCR-confirmed influenza



CI: confidence interval; ILI: influenza-like illness; LRI: lower respiratory illness; RT-PCR: reverse transcription polymerase chain reaction

Table 1. Clinical presentation of RT-PCR-confirmed influenza associated with ILI or LRI (day 0 to day 13 of episode)

Symptom[1]	IIV4 N=351			Control N=678		
	n	% (95% CI)	Median duration (range), days	n	% (95% CI)	Median duration (range), days
Fever ≥38°C	325	92.6 (89.3, 95.1)	2.0 (1–14)	614	90.6 (88.1, 92.7)	2.0 (1–8)
Cough	303	86.3 (82.3, 89.7)	6.0 (1–14)	608	89.7 (87.1, 91.9)	6.0 (1–14)
Runny nose or nasal congestion	340	96.9 (94.5, 98.4)	7.0 (1–14)	641	94.5 (92.6, 96.1)	7.0 (1–14)
Vomiting	71	20.2 (16.1, 24.8)	2.0 (1–8)	125	18.4 (15.6, 21.6)	2.0 (1–13)
Feeling unwell	322	91.7 (88.3, 94.4)	4.0 (1–14)	621	91.6 (89.2, 93.6)	4.0 (1–14)
Normal activities disrupted[2]	278	79.2 (74.6, 83.3)	3.0 (1–14)	531	78.3 (75.0, 81.4)	3.0 (1–14)

[1]Specified symptoms recorded by parents daily using an internet-based system or paper booklet

[2]The end of the period of disruption to normal activities was the last day (inclusive) on which a 'no' response was recorded for the question 'Return to normal activity'

Data for the first episode of infection are shown in the Table

N: number of children with RT-PCR-confirmed influenza and a diagnosis of ILI or LRI; n: number of children with specified symptom

CI: confidence interval; ILI: influenza-like illness; LRI: lower respiratory illness; RT-PCR: reverse transcription polymerase chain reaction

Table 2. Public health impact of the IIV4: vaccine probe analysis

	Attack rate, IIV4, %	Attack rate, control, %	Vaccine efficacy, %	Etiological fraction, %[1]	VPDI, % (95% CI)[2]	NNV[3]
Impact on manifestations of RT-PCR-confirmed influenza						
All influenza	5.88	11.24	49.5	14.0	5.4 (4.4, 6.4)	19
Moderate-to-severe influenza	1.52	4.14	63.9	10.9	2.6 (2.0, 3.2)	38
Mild influenza	4.45	7.25	39.9	17.4	2.8 (2.0, 3.6)	36
Severe influenza	0.03	0.05	34.0	20.4	0.02 (-0.06, 0.09)	6024
Influenza associated with AOM[4]	0.20	0.47	56.7	12.3	0.27 (0.06, 0.47)	376
Influenza associated with LRI[4]	0.47	1.03	54.9	12.7	0.57 (0.26, 0.87)	177
Fever >39°C	1.03	3.19	-	-	2.2 (1.6, 2.7)	46
Impact on healthcare resource associated with RT-PCR-confirmed influenza (any severity)						
Any medical care	5.2	10.0	-	-	4.8 (3.8, 5.7)	21
Visit to GP or pediatrician	5.2	9.7	-	-	4.5 (3.6, 5.5)	22
Visit to medical specialist	0.1	0.2	-	-	0.15 (0.02, 0.28)	668

ER visit	0.1	0.5	-	-	0.43 (0.23, 0.64)	231
Hospitalization	0.0	0.1	-	-	0.07 (-0.04, 0.17)	1504
Antibiotic use	2.9	5.7	-	-	2.8 (2.1, 3.5)	36
Antipyretic use	5.6	10.4	-	-	4.8 (3.8, 5.8)	21
Days of paid work missed by parents	0.4	0.9	-	-	0.5 (0.2-0.7)	215
Days of day care or school missed by child	0.8	1.8	-	-	1.0 (0.6-1.4)	102

[1]AF: VE against ILE divided by VE against RT-PCR-confirmed influenza

Calculation of VE against ILE: 1 minus the relative risk of ILE in vaccinated group versus unvaccinated group (1 minus [2747/6006]/[2955/6012])

AR against first ILE in IIV4 group: 2747/6006 = 45.7%

AR against first ILE in control group: 2955/6012 = 49.8%

VE against ILE: 1-(45.7/49.1) = 6.95% (95% CI: 3.4, 10.4)

[2]VPDI: incidence of RT-PCR-confirmed influenza in control group minus incidence of RT-PCR-confirmed influenza in IIV4 population (mathematically equivalent to the product of VE and incidence in the control population)

[3]NNV: 1 divided by VPDI

[4]Based on the clinical diagnosis of AOM or LRI rather than the documented reason for the initial swab taken on report of an ILE

AF: etiological fraction; AOM: acute otitis media; AR: attack rate; CI: confidence interval; ER: emergency room; GP: general practitioner; ILE: influenza-like episode; LRI: lower respiratory

infection; NA: not applicable; NNV: number needed to vaccinate; RT-PCR: reverse transcription

polymerase chain reaction; VE: vaccine efficacy; VPDI: vaccine-preventable disease incidence

Supplemental Digital Content

Supplemental Digital Content 1. Text

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