A POSTMARKETING OBSERVATIONAL EVALUATION

OF THE SAFETY OF LIVE ATTENUATED INFLUENZA VACCINE (LAIV)

IN CHILDREN AND ADOLESCENTS WITH HIGH-RISK CONDITIONS

Final Study Report

Protocol Number:	MI-MA194
Product:	Fluenz® – trivalent formulation of live attenuated influenza vaccine (LAIV3) Fluenz® Tetra – quadrivalent formulation of LAIV (LAIV4)
Sponsor:	MedImmune, LLC, a wholly owned subsidiary of AstraZeneca
Date of Report	09DEC2016

1. SUMMARY OF THE STUDY PROTOCOL

1.1. Country and Site(s):

There were 505 general practitioner practices distributed across the United Kingdom (UK) contributing to the Clinical Practice Research Datalink (CPRD) on 01Sep2013 and 447 practices on 01Sep2014.

1.2. Objective:

The primary objective of this study was to assess the safety of live attenuated influenza vaccine (LAIV) among children 2 to 17 years of age who have high-risk underlying medical conditions.

1.3. Study Design:

This was a post-marketing, observational, prospective cohort study.

Incidence rates of events of interest during a period at risk following LAIV administration were compared with rates during a reference period later in the follow-up (within-cohort analysis) and with rates observed in matched inactivated influenza vaccine (IIV) recipients and unvaccinated controls.

1.4. Subject Population:

LAIV recipients, IIV recipients, and unvaccinated controls were identified from records made available by the Clinical Practice Research Datalink (CPRD), which maintains a large computerized database of anonymized longitudinal medical records from primary care in the UK.

LAIV recipients were selected based on receipt of LAIV, age 2 to 17 years at the time of vaccination, and the presence of at least one high-risk underlying medical condition.

LAIV recipients were matched with replacement to IIV recipients and unvaccinated controls by high-risk medical condition, age, calendar date of vaccination (index date for unvaccinated controls), healthcare utilization in the past 12 months, and geographic location.

Data extracted for this analysis were collected for each enrollee for 18 months (12 months before and 6 months after LAIV or IIV receipt, or index date for unvaccinated controls). Hospitalisation data were obtained from the National Health Service (NHS) Hospital Episode Statistics (HES) database.

The study was completed after enrollment of more than 10,000 LAIV recipients in influenza seasons 2013-2014 and 2014-2015. Of note, LAIV recipients enrolled in influenza season 2013-2014 received the trivalent formulation (or Fluenz®) while those enrolled in 2014-2015 received the quadrivalent formulation (or Fluenz Tetra®), which then fully replaced the trivalent formulation in the UK.

1.5. Safety Endpoints:

Table 1.5-1 presents the list of all safety endpoints as well as the periods at risk and the reference periods specified in the study protocol.

Table 1.5-1 Safety Endpoints, Study MI-MA194

Event	Period at Risk	Reference Period
Any hospitalisation Hospitalisation for lower respiratory event [a]	Days 0-42 and Days 0-180	Days 43-84 [c]
Hypersensitivity	Days 0-3	Days 4-42
Guillain-Barre syndrome Bell's palsy Seizures/convulsions [b] Encephalitis Neuritis Vasculitis	Days 0-42	Days 43-84
Narcolepsy	Days 0-180	--

[a] Lower respiratory events are those associated with diagnoses of asthma, croup, wheezing, bronchiolitis, pneumonia, or acute respiratory failure.

[b] All seizure/convulsion events occurring after the index date are considered incidence events.

[c] Results to be compared with the Days 0-42 risk period only.

The study primary endpoint was the rate of all-cause hospitalisations. The incidence rates of hospitalisation for lower respiratory events as well as the incidence rates of other medically attended events (MAEs) of interest, identified as potential safety concerns in the LAIV risk management plan, were secondary endpoints.

Hospitalisations with a discharge diagnosis of pneumonia (as a proxy for hospitalisations related to influenza) was added as a secondary endpoint based on feedback from the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's assessment of the annual report dated 14Jan2016.

The ICD10 diagnosis codes retained for the identification of hospitalisations for lower respiratory event and pneumonia are presented in Appendix 1.

1.6. Statistical Analysis:

Incidence rates were reported as number of subjects with an incident event per 1,000 person-years. If a subject had more than one event in the time period, only the incident event was counted and the child censored afterwards.

When comparing LAIV recipients with matched IIV recipients or unvaccinated controls, relative risks, and corresponding 95% confidence intervals (CI) were estimated using conditional Cox proportional hazards models. A period effect defined as a time-varying covariate was added to the model for within-cohort analyses.

2. RESULTS

2.1. Study Enrollment and Disposition:

Enrollment into Study MI-MA194 began on 17Sept2013 when the first subject documented in CPRD was administered LAIV in season 2013-2014 and ended on 30Mar2015, when the last eligible subject was administered LAIV in season 2014-2015.

Table 2.1-1 presents the population of LAIV recipients retained for analysis.

Table 2.1-1 Study Enrollment and Disposition by Season, Study MI-MA194

Study Enrollment	**2013-2014**	**2014-2015**
All LAIV recipients 2 to 17 years of age at time of vaccination	64,260	86,100
Exclusion for < 12 months of prior history in CPRD	4,311	5,783
Exclusion for absence of high-risk conditions	50,209	67,741
Exclusion for child enrolled outside of England[a]	3,836	4,193
Exclusion for absence of matching record in the HES database	1,186	1,638
Total eligible LAIV recipients	**4,718**	**6,745**
Disposition at Day 42		
Death between Day 0 and Day 42	0	0
Administration of IIV or unknown influenza vaccine as a second vaccination	12	4
Loss to follow up in CPRD since administration of LAIV	112	124
Completion of 42 days of follow up	**4,594**	**6,617**
Disposition at Day 180		
Death between Day 42 and Day 180	0	1
Administration of IIV or unknown influenza vaccine as a second vaccination after Day 42	8	2
Loss to follow up in CPRD since Day 42	292	432
Completion of 180 days of follow up	**4,294**	**6,182**

CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; IIV = inactivated influenza vaccine.

[a] Only children enrolled in CPRD in England can be documented in HES

A total of 11,463 LAIV recipients - 4,718 in 2013-2014 and 6,745 in 2014-2015 - were eligible for analysis.

The 6-month follow up in the CPRD was completed for 10,476 of these 11,463 children: 4,294 in 2013-2014 and 6,182 in 2014-2015.

Enrollment and follow up in the study is considered complete as more than 10,000 eligible LAIV recipients have been documented for 6 months.

2.2. Description of the LAIV recipients at enrollment:

The following tables present the LAIV recipient enrollees' demographics, vaccination date, and region (Table 2.2-1), high-risk conditions (Table 2.2-2) and medical history within 12 months prior to LAIV administration (Table 2.2-3).

LAIV recipients were more often 4 years and older in season 2014-2015 than in 2013-2014 (Table 2.2-1) as the the national vaccination programme that began in 2013-2014 with all two- and three-year-olds being offered vaccination through general practice and geographic pilots in primary school-aged children was extended in 2014-2015 to four-year-olds through general practice, with pilots in primary and secondary school-aged children (in years 7 and 8; Public Health England, 2016).

More than half of all LAIV recipients were boys (59%), vaccinated in October (55%), and enrolled in England/South or London (56%).

Table 2.2-1 Description of LAIV Recipients at Enrollment: Demographics, Vaccination Date and Region

Descriptor	Season 2013-2014 N = 4,718	Season 2014-2015 N = 6,745	Total population N = 11,463
Age (years)			
2 to 3	22%(1,033)	12%(799)	16%(1,832)
4 to 8	35%(1,644)	37%(2,533)	36%(4,177)
9 to 17	43%(2,041)	51%(3,413)	48%(5,454)
Gender			
Male	58%(2,722)	58%(3,893)	59%(6,715)
Female	42%(1,996)	42%(2,852)	41%(4,848)
Month of vaccination			
September	5%(224)	<1%(20)	2%(244)
October	56%(2,630)	54%(3,636)	55%(6,266)
November	29%(1,372)	30%(2,045)	30%(3,417)
December	9%(402)	12%(841)	11%(1,243)
January	2%(88)	2%(156)	2%(244)
February	<1%(2)	1%(45)	<1%(47)
March	0	<1%(2)	<1%(2)
Region			
England/North	20%(930)	20%(1,332)	20%(2,262)
England/Midlands	23%(1,088)	25%(1,691)	24%(2,779)
England/South	40%(1,877)	42%(2,805)	40%(4,682)
England/London	17%(823)	14%(917)	15%(1,740)

LAIV = live attenuated influenza vaccine

The list of diagnosis codes qualified as "per study protocol" (Table 2.2.-2) was used to estimate the number of children and adolescents 2 to 17 years of age with high-risk conditions in CPRD according to the original specifications of the study protocol. The extended list includes operational definitions that were specified by PRIMIS at the University of Nottingham. The operational definitions specified by PRIMIS are well accepted by the medical community.[1] Using the PRIMIS-specified definition of high-risk conditions ensured that approximately 5% more children were included in the analysis that would have been missed if only the protocol-specified definitions were used.

A large majority of enrollees (74%) were diagnosed with asthma.

Table 2.2-2 Description of LAIV Recipients at Enrollment: High-risk Conditions

Condition	Season 2013-2014 N = 4,718	Season 2014-2015 N = 6,745	Total Population N = 11,463
High-risk conditions as per study protocol	**95%(4,473)**	**95%(6,440)**	**95%(10,913)**
Asthma	73%(3,442)	74%(5,016)	74%(8,458)
Cystic fibrosis	1%(38)	1%(47)	1%(85)
Congenital lung abnormalities	<1%(15)	<1%(23)	<1%(38)
Chronic heart disease	12%(577)	11%(728)	11%(1,305)
Chronic renal disease	1%(58)	1%(72)	1%(130)
Sickle cell anemia	1%(62)	1%(90)	1%(152)
White blood cell disorders	<1%(15)	<1%(24)	<1%(39)
Immunosuppressive disorders (excluding malignancy)	1%(32)	1%(78)	1%(110)
Malignancy	2%(71)	1%(95)	1%(166)
Diabetes mellitus	4%(188)	4%(299)	4%(487)
Lipid metabolism disorders	<1%(1)	<1%(7)	<1%(8)
Cerebral palsy	3%(118)	2%(137)	2%(255)
Down syndrome	1%(63)	1%(98)	1%(161)
Any medical condition being treated with chronic aspirin therapy	<1%(18)	<1%(18)	<1%(36)
Additional subjects recommended for vaccine as per NHS	**5%(245)**	**5%(305)**	**5%(550)**
Chronic respiratory disease	1%(36)	1%(39)	1%(75)
Chronic heart disease	1%(54)	1%(71)	1%(125)
Chronic kidney disease	<1%(15)	<1%(16)	<1%(31)
Chronic liver disease	<1%(7)	<1%(8)	<1%(15)
Chronic neurological disease	2%(106)	2%(131)	2%(237)
Diabetes	0	<1%(5)	<1%(5)
Immunosuppression	1%(34)	1%(41)	1%(75)
Pregnancy	<1%(1)	<1%(1)	<1%(2)

LAIV = live attenuated influenza vaccine; NHS = National Health Service

A large majority of enrollees (73%) had visited their primary care physician practice at least 3 times within one year prior to LAIV receipt (Table 2.2.-3). Other indicators of severity are the proportion of enrollees who had been referred to a secondary care practice or had been hospitalized (19%), and the proportion of asthmatic children treated with oral steroids or admitted to an emergency room (23%) that remained stable over the two seasons.

Table 2.2-3 Description of LAIV Recipients at Enrollment: Medical History Within 12 Months Prior to LAIV Administration

Medical History Descriptor	Season 2013-2014 N = 4,718	Season 2014-2015 N = 6,745	Total Population N = 11,463
Number of office visits			
0	4%(205)	5%(348)	5%(553)
1	9%(422)	11%(731)	10%(1,153)
2	11%(515)	13%(853)	12%(1,368)
3 or more	76%(3,576)	71%(4,813)	73%(8,389)
Referral/hospitalisation			
Yes	18%(869)	20%(1,328)	19%(2,197)
No	82%(3,849)	80%(5,417)	81%(9,266)
Asthma treatment in prior 12 months[a]	n=3,442	n=5,016	n=8,458
Inhaled steroids, no oral steroids	76%(2,603)	77%(3,875)	77%(6,478)
Oral steroids/emergency room visit	24%(839)	23%(1,141)	23%(1,980)

LAIV = live attenuated influenza vaccine

[a] Among asthmatics as per study protocol.

2.3. Matching:

2.3.1. Matching LAIV recipients to IIV recipients:

LAIV recipients were matched 1:1 with IIV recipients with replacement by at least two of the following criteria:

1. High-risk condition
2. Vaccination date within +/-14 days
3. Age group (years): 2-3, 4-8, 9-17
4. Healthcare utilization:
   a. referral in past 12 months: yes/no
   b. if asthmatic: inhaled steroids only vs. oral steroid prescription or hospital admission in past 12 months
5. Region: England/North, Midlands, England/South, London

A total of 4,716 of the 4,718 LAIV recipients in season 2013/2014 could be matched with an IIV recipient:

- 4,355 could be matched by all 5 criteria
- 254 could be matched by criteria 1 to 4 only
- 50 could be matched by criteria 1 to 3 only
- 48 could be matched by criteria 1 and 2 only

A total of 6,738 of 6,745 LAIV recipients in season 2014/2015 could be matched also with replacement with an IIV recipient:

- 6,035 could be matched by all 5 criteria
- 474 could be matched by criteria 1 to 4 only
- 135 could be matched by criteria 1 to 3 only
- 94 could be matched by criteria 1 and 2 only

2.3.2. Matching LAIV recipients to unvaccinated children:

LAIV recipients were matched 1:3 with unvaccinated children with replacement also by at least two criteria:

1. High-risk condition
2. Age group (years)
3. Healthcare utilization:
4. Region

Unvaccinated children were also to be under follow up when the referent LAIV recipients was vaccinated.

All 4,718 LAIV recipients in season 2013/2014 could be matched with at least one unvaccinated child:

- 4,701 could be matched by all 4 criteria
- 16 could be matched by high risk condition, age and region only
- 1 could be matched by criteria 1 and 2 only

All 6,745 LAIV recipients in season 2014/2015 could also be matched with at least one unvaccinated child:

- 6,728 could be matched by all 4 criteria
- 15 could be matched by criteria 1, 2 to 4 only
- 2 could be matched by criteria 1 and 2 only

Of note, due to the matching with replacement, the same IIV recipient or unvaccinated control could be matched to more than one LAIV recipient. However, no IIV recipient or unvaccinated control was matched more than once to the same LAIV recipient.

2.4. Safety Assessments:

2.4.1. Hospitalisations:

Table 2.4.1-1 compares the incidence rates of hospitalisations between LAIV recipients, matched IIV recipients, and matched unvaccinated controls and presents the relative risk estimates.

The risk of any hospitalisation and the risk of hospitalisation for lower respiratory events consistently did not significantly differ after LAIV administration versus matched unvaccinated controls and were lower after LAIV administration than after IIV administration both in the 2013-2014 and the 2014-2015 seasons, whether enrollees were followed up for the first 42 days or the first 6 months after vaccination.

In season 2013-2014, the incidence of hospitalisation for pneumonia was significantly higher during the 42 days and 6 months after vaccination with LAIV versus unvaccinated controls, with relative risks of 4.34 [1.47;14.29] and 2.25 [1.21;4.21], respectively. The incidence of hospitalisation was also higher than during the 42 days after vaccination with IIV, with a relative risk of 5.00 [1.32;32.53]. However, the number of children hospitalized for pneumonia remained small in absolute terms; out of 4,718 LAIV recipients, 10 were hospitalized for pneumonia during the first 42 days and 23 during the first 6 months after vaccination. Also, the risk of hospitalisation for pneumonia within 6 months after vaccination did not differ between LAIV and IIV recipients (relative risk of 0.64 [0.36;1.09]), and was lower after administration of LAIV than IIV in 2014-2015 during the first 42 days (relative risk of 0.19 [0.06;0.50]) and the first 6 months (relative risk of 0.30 [0.15;0.53]) after vaccination. No difference in the risk of hospitalisation for pneumonia was observed in 2014-2015 during the 42 days and 6 months after vaccination by LAIV versus unvaccinated controls, with relative risks of 0.44 [0.13;1.16] and 0.93 [0.47;1.71], respectively.

Table 2.4.1-1 Risk of Hospitalisation by Season: Comparisons Between LAIV Recipients and Matched Unvaccinated Children and IIV Recipients

Season 2013-2014	Period at Risk	Incidence Rate (per 1000 person-years) and 95% CI			Relative Risk 95% CI	
		LAIV Recipients N = 4,718	Matched Unvaccinated Children N = 14,085	Matched IIV Recipients N = 4,716	Versus Unvaccinated Children	Versus IIV Recipients
Any hospitalisation	42 days	231 [193;275] n = 127	227 [203;253] n = 325	470 [415;531] n = 260	0.96 [0.78;1.19]	0.47 [0.37;0.58]
Hospitalisation for lower respiratory event		106 [80;136] n = 58	91 [76;108] n = 130	197 [162;238] n = 109	1.07 [0.77;1.46]	0.53 [0.39;0.73]
Hospitalisation for pneumonia		18 [9;33] n = 10	3 [1;8] n = 5	4 [0;13] n = 2	4.34 [1.47;14.29]	5.00 [1.32;32.53]
Any hospitalisation	6 months	183 [166;202] n = 412	157 [147;168] n = 818	251 [230;272] n = 567	1.09 [0.96;1.23]	0.69 [0.60;0.79]
Hospitalisation for lower respiratory event		80 [69;93] n = 180	67 [60;74] n = 346	125 [111;141] n = 283	1.13 [0.94;1.37]	0.64 [0.53;0.78]
Hospitalisation for pneumonia		10 [6;15] n = 23	4 [2;6] n = 20	15 [11;22] n = 35	2.25 [1.21;4.21]	0.64 [0.36;1.09]
Season 2014-2015	**Period at Risk**	**Incidence Rate (per 1000 person-years) and 95% CI**			**Relative Risk 95% CI**	
		LAIV Recipients N = 6,745	**Matched Unvaccinated Children N = 20,163**	**Matched IIV Recipients N = 6,738**	**Versus Unvaccinated Children**	**Versus IIV Recipients**
Any hospitalisation	42 days	231 [198;267] n = 182	251 [230;273] n = 518	503 [455;555] n = 395	0.90 [0.76;1.07]	0.42 [0.35;0.51]
Hospitalisation for lower respiratory event		98 [77;122] n = 77	112 [98;128] n = 232	199 [169;232] n = 156	0.85 [0.65;1.10]	0.46 [0.35;0.61]
Hospitalisation for pneumonia		6 [2;15] n = 5	12 [7;17] n = 24	27 [17;41] n = 21	0.44 [0.13;1.16]	0.19 [0.06;0.50]
Any hospitalisation	6 months	178 [164;193] n = 575	164 [155;173] n = 1,242	311 [292;331] n = 999	1.08 [0.97;1.20]	0.53 [0.47;0.59]
Hospitalisation for lower respiratory event		75 [66;85] n = 241	74 [68;80] n = 558	120 [108;133] n = 385	1.01 [0.87;1.18]	0.59 [0.50;0.70]
Hospitalisation for pneumonia		4 [2;7] n = 14	5 [4;7] n = 38	15 [11;20] n = 47	0.93 [0.47;1.71]	0.30 [0.15;0.53]

CI = confidence interval; IIV = inactivated influenza vaccine; LAIV = live attenuated influenza vaccine;
Note: n = number of incident cases.

Table 2.4.1-2 compares the incidence rates of hospitalisation within the cohort of LAIV recipients, between a period at risk of 42 days after vaccine administration and a control period later during the follow-up (Days 43-84).

No significant change in the risk of hospitalisation was observed between Days 0-42 and Days 43-84 after LAIV vaccination.

Table 2.4.1-2 Risk of Hospitalisation by Season: Comparison Within the LAIV Cohort Between Period at Risk and Control Period

Season 2013-2014 (N[a] = 4,560)	**Incidence Rate (per 1,000 Person[a] years)**		**Relative Risk 95% CI**
	Period at risk (Days 0-42)	**Control Period (Days 43-84)**	
Any hospitalisation	225 [187;269] n = 121	238 [198;284] n = 125	0.93 [0.71;1.23]
Hospitalisation for lower respiratory event	104 [79;135] n = 56	95 [71;126] n = 50	1.09 [0.73;1.63]
Hospitalisation for pneumonia	17 [8;32] n = 9	8 [2;21] n = 4	2.25 [0.73;8.30]
Season 2014-2015 (N[a] =6,514)	**Incidence Rate (Per 1000 Person[a] years)**		**Relative Risk 95% CI**
	Period at Risk (Days 0-42)	**Control Period (Days 43-84)**	
Any hospitalisation	232 [199;269] n = 178	236 [203;274] n = 177	1.00 [0.79;1.26]
Hospitalisation for lower respiratory event	99 [78;124] n = 76	91 [70;115] n = 68	1.12 [0.79;1.60]
Hospitalisation for pneumonia	7 [2;15] n = 5	7 [2;16] n = 5	1.00 [0.24;4.23]

LAIV = live attenuated influenza vaccine
[a] Number of LAIV recipients who completed follow up for the two time periods, ie, until Day 84.
Note: n = number of incident cases.

2.4.2. Other Medically Attended Events of Interest:

Table 2.4.2-1 compares the incidence rates of other medically attended events of interest (MAE) between LAIV recipients, matched IIV recipients, and matched unvaccinated controls.

No case of Guillain Barre syndrome, Bell's palsy, encephalitis, or neuritis was observed during the first 42 days after administration of LAIV and no case of narcolepsy was observed during the first 6 months.

Two cases of hypersensitivity were observed within 3 days after administration of LAIV in season 2014-2015. Neither case resulted in hospitalisation and the incidence rate did not significantly differ versus matched unvaccinated children and IIV recipients.

A total of 35 cases of seizures/convulsions (13 in the 2013-2014 season and 22 in 2014-2015 season) and two cases of vasculitis (in 2014-2015 season) were observed within 42 days after administration of LAIV. The incidence rates did not significantly differ from those observed in matched unvaccinated children and were lower than those observed among IIV recipients.

Table 2.4.2-1 Risk of MAEs by Season: Comparisons Between LAIV Recipients and Matched Unvaccinated Children and IIV Recipients

Season 2013-2014	**Period At Risk**	**Incidence Rate (Per 1,000 Person-years)**			**Relative Risk 95% CI**	
		LAIV Recipients N = 4,718	**Matched Unvaccinated Children N = 14,085**	**IIV Recipients N = 4,716**	**Versus Unvaccinated Children**	**Versus IIV Recipients**
Hypersensitivity	3 days	-	7 [0;37] n = 1	19 [0;108] n = 1	-	-
Seizures/convulsions	42 days	24 [13;40] n = 13	21 [14;30] n = 30	36 [22;56] n = 20	1.11 [0.56;2.10]	0.65 [0.32;1.29]
Vasculitis		-	-	-	-	-
Season 2014-2015	**Period at risk**	**Incidence rate (per 1,000 person*years)**			**Relative Risk 95% CI**	
		LAIV Recipients N = 6,745	**Matched Unvaccinated Children N = 20,163**	**IIV Recipients N = 6,738**	**Versus Unvaccinated Children**	**Versus IIV Recipients**
Hypersensitivity	3 days	27 [3;98] n = 2	14 [3;40] n = 3	41 [8;119] n = 3	2.00 [0.26;12.07]	0.33 [0.02;2.60]
Seizures/convulsions	42 days	28 [17;42] n = 22	17 [12;24] n = 36	66 [49;87] n = 52	1.65 [0.95;2.80]	0.42 [0.25;0.69]
Vasculitis		3 [0;9] n = 2	1 [0;4] n = 3	-	1.59 [0.20;9.94]	-

LAIV = live attenuated influenza vaccine; MAE = medically attended event.
Note: n = number of incident cases.

Table 2.4.2-2 compares the incidence rate of other medically attended events of interest within the cohorts of LAIV recipients, between a period at risk of 42 days after vaccine administration (3 days for hypersensitivity; 42 days for other medically attended events) and a control period later during the follow-up (Days 4 to 42 for hypersensitivity; Days 43 to 84 for other medically attended events). The populations retained for this analysis were LAIV recipients who completed both the period at risk and the control period.

No significant change in the incidence of MAEs was observed between the period at risk and the control period.

Table 2.4.2-2 Risk of MAEs by Season: Comparison Within the LAIV Cohort Between Period at Risk and Control Period

Season 2013-2014 (N[a] = 4,594; 4,560)	**Incidence Rate (Per 1,000 Person[a] years) (Per 1000 Person-years)**		**Relative Risk 95% CI**
	Period at Risk	**Control Period**	
Hypersensitivity [b]	-	8 [2;21] n = 4	-
Seizures/convulsions [c]	24 [13;41] n = 13	15 [7;30] n = 8	1.83 [0.70;5.32]
Vasculitis [c]	-	-	-
Season 2014-2015 (N[a] = 6,617; 6,514)	**Incidence Rate (per 1,000 Person[a] years) (Per 1000 Person-years)**		**Relative Risk 95% CI**
	Period at risk	**Control period**	
Hypersensitivity [b]	28 [3;100] n = 2	7 [2;17] n = 5	NS
Seizures/convulsions [c]	29 [18;43] n = 22	21 [12;35] n = 16	1.55 [0.73;3.40]
Vasculitis [c]	3 [0;9] n = 2	3 [0;10] n = 2	1.00 [0.12;8.33]

NS = not significant
Note: n = number of incident cases.
[a] Number of LAIV recipients who completed both the period at risk and the control period (Days 0-42 for hypersensitivity; Days 0-84 for all other events); the period at risk for hypersensitivity was the first 3 days.
[b] Period at risk = Days 0-3; control period = Days 4-42.
[c] Period at risk = Days 0-42; control period = Days 43-84.

3. SUMMARY AND DISCUSSION

This study investigated safety events in 11,463 children and adolescents 2 to 17 years of age presenting with high-risk underlying medical conditions who were administered LAIV: 4,718 who were administered the trivalent formulation in influenza season 2013-2014 and 6,745 who were administered the quadrivalent formulation in influenza season 2014-2015. Rates of events were compared within cohort during a period at risk after vaccine administration versus a reference period later during the follow up, and between cohorts: rates of events were compared between LAIV recipients and matched IIV recipients or matched unvaccinated controls.

The risk of hospitalisation after LAIV administration did not vary significantly versus matched unvaccinated controls and was consistently lower than after IIV administration, within 42 days or 6 months of vaccination, whether all hospitalisations were retained for analysis or only hospitalisations for lower respiratory events. Within-cohort analyses of risk of hospitalisation during the first 42 days following LAIV administration or later during the follow-up were also comparable.

A significant increase in the risk of hospitalisation for pneumonia was observed 42 days and 6 months after administration of LAIV versus unvaccinated controls in 2013-2014; the risk was not significantly increased during the first 42 days versus the next 42 days retained as a control period. There was also no risk increase in influenza season 2014-2015, when the risk of hospitalisation for pneumonia was actually lower after administration of LAIV than IIV.

No incident case of Guillain Barre syndrome, Bell's palsy, encephalitis, or neuritis was observed during the first 42 days after administration of LAIV, and no case of narcolepsy was observed during the first 6 months after vaccination. The risk of hypersensitivity, seizures/convulsions, and vasculitis did not significantly differ from those observed in matched unvaccinated children and were actually lower than those observed among IIV recipients.

The study presents several limitations:

- The incomplete linkage of the Hospital Episode Statistics (HES) database could affect the final results:

  The reasons why a child enrolled in CPRD could not be linked with HES were a priori administrative in nature: children could be linked only if they were enrolled in a practice located in England or if the practitioner gave her/his agreement for linkage. Table A in Appendix 2 of the Clinical Study Report compares the demographic characteristics - age and gender - as well as the distributions by vaccination date and region between eligible LAIV recipients linked or not to HES in English practices. The proportions of children and adolescents enrolled in practices from England/South was higher among those would could not be linked to HES (55% versus 40%). There was no substantial difference in the distributions of age, gender and vaccination date..

- Matching with replacement is acceptable in observational studies, especially when the number of controls (here IIV recipients) is low compared to the number of treated subjects (here LAIV recipients). However, due to the fact that IIV recipients can be used more than once as control, the incidence of hospitalisation in the matched IIV group may differ from the incidence of hospitalisation in the source IIV population of the same age and presenting with high-risk medical condition:

  The incidence rates of hospitalisations and other MAEs in matched IIV recipients and in the source population of IIV recipients are presented in table B in Appendix 2. The table shows that the risk of any hospitalisation and the risk of hospitalisation for lower respiratory events were higher among matched IIV recipients than in the source population of IIV recipients in season 2013-2014: 470 [415;531] versus 368 [330;409] patient-years and 197 [162;238] versus 107 [87;130] patient-years, respectively. The confidence intervals overlapped in 2014-2015 but there was still a trend towards higher incidence rates of

hospitalisation among matched IIV recipients versus the source population. This finding shows an association between the matching variables and the risk of hospitalisation, and justifies a posteriori the matching procedure.

- The incidence of hospitalisations in LAIV recipients was significantly lower than the incidence of hospitalisations in the IIV recipients. However, as discussed above, due to the use of the method of matching with replacement, the incidence of hospitalisation in the matched IIV group may differ from the incidence of hospitalisation in the source population. That said, the relative risk indicates a significant statistical difference, which may be due to an actual difference in the hospitalisation rates or to some difference of the severity of the high-risk condition at baseline.

  To control for the severity of the high-risk condition, LAIV recipients were matched to IIV recipients and to unvaccinated controls presenting with the same condition. Asthmatic children were matched as a function of oral steroid use and admission to an emergency department within the last 12 months. It is acknowledged that these two variables - nature of the condition and medical history within the last 12 months for asthmatics are imprecise indicators of severity and that there may still be residual confounding. However, a more precise indicator of severity that would be also systematically documented in CPRD was not identified.

- Choosing a period of control outside the period of high circulation of respiratory pathogens, eg, before vaccination, could eventually lead to other conclusions. The MAH is recommended to conduct within-cohort analysis using also a control period before vaccination with confidence from those results.

  A within-cohort analysis using a control period before vaccination is presented in table C of Appendix 2. It confirms there was no significant increase in the incidence of all cause hospitalization and hospitalisation for lower respiratory events after administration of LAIV. The incidence of hospitalisation for pneumonia was higher during the 42 days after LAIV administration versus the 42 days prior in season 2013-2014 (relative risk: 5.00 [1.32;32.53]). This finding can be related to the comparison between the 42 days after LAIV administration and the next 42 days that showed no significant difference and suggests a seasonal effect. Also the rate of hospitalisation for pneumonia did not vary significantly before and after LAIV administration in season 2014-2015 (relative risk: 1.67 [0.41;8.12]).

This discussion about the study limitations was informed by the feedback from the PRAC Rapporteur's assessment of the annual report dated 14Jan2016.

In conclusion, this study did not identify any new safety signal associated with the administration of LAIV, either as a trivalent formulation in influenza season 2013-2014 or as a quadrivalent formulation in influenza season 2014-2015, in children and adolescents with high-risk medical conditions.

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APPENDIX 1

ICD-10 discharge diagnoses code retained for a diagnosis of pneumonia

ICD-10 code	Description
J10.0	Influenza with pneumonia, seasonal influenza virus identified
J11.0	Influenza with pneumonia, virus not identified
J12*	Viral pneumonia, not elsewhere classified
J13*	Pneumonia due to Streptococcus pneumoniae
J14*	Pneumonia due to Haemophilus influenzae
J15*	Bacterial pneumonia, not elsewhere classified
J16*	Pneumonia due to other infectious organisms, not elsewhere classified
J17*	Pneumonia in diseases classified elsewhere
J18*	Pneumonia, organism unspecified

*includes more specific diagnoses below this code in the hierarchy.

ICD-10 discharge diagnoses code retained for a diagnosis of other lower respiratory events

ICD-10 code	Description
A37*	Whooping cough
J05	Acute obstructive laryngitis [croup] and epiglottitis
J05.0	Acute obstructive laryngitis [croup]
J09-J18*	Influenza and pneumonia
J20-J22*	Other acute lower respiratory infections
J45*	Asthma
J46	Status asthmaticus
J96	Respiratory failure, not elsewhere classified
J96.0	Acute respiratory failure
J96.9	Respiratory failure, unspecified
R06.2	Wheezing

*includes more specific diagnoses below this code in the hierarchy

APPENDIX 2/COMPLEMENTARY ANALYSES

	Eligible LAIV recipients linked to HES n=11,463	Eligible LAIV recipients not linked to HES n=2,824
Age (years)		
2 to 3	16%(1,832)	18%(518)
4 to 8	36%(4,177)	38%(1,074)
9 to 17	48%(5,454)	44%(1,232)
Gender		
male	59%(6,715)	60%(1,689)
female	41%(4,848)	40%(1,135)
Vaccination date		
September	2%(244)	3%(83)
October	55%(6,266)	50%(1,399)
November	30%(3,417)	32%(905)
December	11%(1,243)	12%(334)
January	2%(244)	3%(90)
February	<1%(47)	<1%(12)
March	<1%(2)	0
April	0	<1%(1)
Region		
England/North	20%(2,262)	16%(462)
England/Midlands	24%(2,779)	18%(499)
England/South	40%(4,682)	55%(1,546)
England/London	15%(1,740)	11%(317)

Table A

Comparison between eligible LAIV recipients linked or not to HES in English practices

	2013-2014		2014-2015	
	Matched IIV recipients n=4,716	Source population of IIV recipients n=7,834	Matched IIV recipients n=6,738	Source population of IIV recipients n=3,822
Any hospitalisation	470 [415;531] n*=260	368 [330;409] n*=338	503 [455;555] n*=395	447 [387;513] n*=199
Hospitalisation for lower respiratory event	197 [162;238] n*=109	107 [87;130] n*=98	199 [169;232] n*=156	139 [107;179] n*=62
Hospitalisation for pneumonia	4 [0;13] n*=2	4 [1;11] n*=4	27 [17;41] n*=21	11 [4;26] n*=5
Hypersensitivity	19 [0;108] n*=1	23 [3;84] n*=2	41 [8;119] n*=3	96 [26;245] n*=4
Seizures/convulsions	36 [22;56] n*=20	27 [18;40] n*=25	66 [49;87] n*=52	29 [16;50] n*=13

* number of individuals with incident event.

Table B

Incidence rates of hospitalisations and other medically attended events (/per 1,000 patient-years) in matched IIV recipients and in the source population of IIV recipients

The incidence rates were estimated during the first 42 days after administration of IIV (first 3 days for hypersensitivity).

Season 2013-2014 (n=4,594)	Incidence rate (per 1,000 person-years)		Relative risk
	Period at risk (D.0-D.42)	Control period (D.-42-D.0)	
Any hospitalisation	225 [187;269] n**=121	257 [216;304] n**=136	0.85 [0.65;1.12]
Hospitalisation for lower respiratory event	104 [79;135] n**=56	119 [92;152] n**=63	0.86 [0.58;1.26]
Hospitalisation for pneumonia	17 [8;32] n**=9	4 [0;14] n**=2	5.00 [1.32;32.53]
Season 2014-2015 (n=6,617)	Incidence rate (per 1000 person-years)		Relative risk
	Period at risk (D.0-D.42)	Control period (D.-42-D.0)	
Any hospitalisation	232 [199;269] n**=178	260 [225;299] n**=198	0.88 [0.70;1.10]
Hospitalisation for lower respiratory event	99 [78;124] n**=76	121 [97;148] n**=92	0.78 [0.56;1.09]
Hospitalisation for pneumonia	7 2;15] n**=5	4 [1;12] n**=3	1.67 [0.41;8.12]

* number of incident cases.

Table C

Risk of hospitalisation

Comparison within the LAIV cohort between period at risk and a control period before vaccination