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Evaluation of the safety of live attenuated influenza vaccine (LAIV) in children and adolescents with asthma and high-risk conditions: a population-based prospective cohort study conducted in England with the Clinical Practice Research Datalink

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ABSTRACT

Objectives To assess the safety of live attenuated influenza vaccine (LAIV) in children in high-risk groups.

Design Non-interventional cohort study.

Setting England during 2013–2014 and 2014–2015 influenza seasons.

Participants LAIV recipients identified from the Clinical Practice Research Datalink, aged 2–17 years, and with at least one underlying high-risk condition. LAIV recipients were matched with inactivated influenza vaccine (IIV) recipients and unvaccinated controls.

Primary outcome measures Primary safety endpoints were any hospitalisation documented in the linked Hospital Episodes Statistics database within 42 days and up to 6 months after vaccination.

Results 11 463 children and adolescents were included: 4718 received the trivalent LAIV formulation during the 2013–2014 influenza season and 6745 received the quadrivalent formulation during the 2014–2015 influenza season. The risks of hospitalisation within 42 days were 231 per 1000 person-years (95% CI 193 to 275) in season 2013–2014 and 231 (95% CI 198 to 267) in season 2014–2015. These risks were not significantly different when compared with matched unvaccinated children (relative risks (RR) 0.96 (95% CI 0.78 to 1.19) in season 2013–2014, 0.90 (95% CI 0.76 to 1.07) in season 2014–2015) and consistently lower than after IIV administration (RR 0.47 (95% CI: 0.37 to 0.59) in season 2013–2014, 0.42 (95% CI 0.35 to 0.51) in season 2014–2015). A similar pattern was observed up to 6 months postvaccination with a risk of hospitalisation after LAIV administration that did not differ from what was observed in unvaccinated controls and was lower than after IIV administration.

Conclusions This study did not identify new safety concerns associated with the administration of LAIV in children and adolescents with high-risk conditions. However, as with any other observational study, treatment administration was not randomly assigned and our findings may be confounded by differences between the groups at baseline.

Strengths and limitations of this study

- The study enrolled all eligible live attenuated influenza vaccine (LAIV) recipients with at least one high-risk condition in a population-based data set that is generally considered representative of the UK population in influenza seasons 2013–2014 and 2014–2015.
- The sample size was large enough to detect a doubling in the rate of hospitalisations within 42 days, and a 50% increase within 6 months versus unvaccinated matched controls or inactivate influenza vaccine (IIV) recipients.
- The primary outcome (all-cause hospital admission) was assessed from a database managed independently from the practices and schools where vaccine decisions were made, and regularly audited for data validity.
- Treatment administration was not controlled and observed differences between LAIV recipients, IIV recipients and unvaccinated controls may be confounded by differences between the groups at baseline.

Trial registration number EUPAS18527.

INTRODUCTION

An Ann Arbor-based live attenuated influenza vaccine (LAIV) was initially approved in the USA in 2003 and later approved for use in the European Union (EU) in 2011 in eligible children and adolescents aged from 24 months to <18 years. LAIV was originally distributed as a trivalent formulation (LAIV3) containing an A(H1N1) strain, an A(H3N2) strain and a B strain from either the Victoria or Yamagata lineage, as per recommendations updated

annually by WHO and national regulators. A quadrivalent formulation (LAIV4) containing a B/Victoria and a B/Yamagata strain replaced LAIV3 in the USA in the 2013–2014 influenza season and in most other countries, including the UK, in 2014–2015, with global use of LAIV4 in all countries where licensed from the 2015–2016 influenza season.

The safety of LAIV (Fluenz in the EU, FluMist in the USA and the rest of the world) has been extensively documented.[1] At the beginning of 2013–2014 influenza season, >50 000 patients had received LAIV in its clinical development programme and >80 million doses had been distributed, mostly in the US. However, the use of LAIV in children and adolescents with asthma or other underlying medical conditions has been relatively limited. In the USA, the 'Warnings and Precautions' section of the LAIV package insert indicates that persons with asthma might be at increased risk for wheezing after administration of LAIV, and notes that the safety of LAIV has not been established in persons with other underlying medical conditions that might predispose them to complications after wild-type influenza infection.[2] The US Advisory Committee on Immunisation Practices also states that LAIV use is contraindicated in 'children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a healthcare provider has told them during the preceding 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the preceding 12 months' .[3 4]

In contrast to US guidance from the Food and Drug Administration and the Advisory Committee on Immunization Practices (ACIP), in Europe, the 'Special Warnings and Precautions for Use' section of the Summary of Product Characteristics states that LAIV should not be administered to children or adolescents with severe asthma or active wheezing because the vaccine has not been adequately studied in these patient groups in clinical trials.[1] There is no warning or contraindication against use in children with mild to moderate asthma, based on the safety results from two open-label randomised studies that compared LAIV and IIV in children 6 to 72 months of age with recurrent respiratory tract infections and children 6 to 17 years of age with asthma, respectively. Additionally, there is no warning or precaution against use in children with other high-risk underlying medical conditions given that there is no evidence of adverse outcomes in that population.

With the initial approval of LAIV in the EU, the European Medicines Agency requested a postauthorisation safety study to describe the safety of LAIV in children and adolescents with high-risk underlying medical conditions for whom safety data were limited. The study protocol was submitted for review to the European Medicines Agency and was agreed on as part of the Fluenz risk management plan.

MATERIALS AND METHODS

This was a prospective, non-interventional cohort study as it was planned before LAIV became available in the UK and before implementation of the UK's national childhood immunisation programme, which aimed to raise rates of vaccination against influenza in all children aged 2 years and older with the use of LAIV. It was conducted during two influenza seasons: 2013–2014, when only LAIV3 was distributed, and 2014–2015, when only LAIV4 was distributed. Subjects were identified using the Clinical Practice Research Datalink (CPRD), which maintains a database of anonymised longitudinal primary care medical records from over 500 practices in the UK. The database documents vaccine administration to children and adolescents at the primary care practice; school vaccination data are also transferred to the practice where the child is registered. Data were extracted for each participant for a total of 18 months: from 12 months before to 6 months after receiving LAIV or inactivated influenza vaccine (IIV), or the index date for unvaccinated controls.

Children who received LAIV between 1 September 2013 and 31 March 2014 and between 1 September 2014 and 31 March 2015 were included in the analysis. LAIV recipients had to be aged from 2 to 17 years at the time of vaccination and have at least one high-risk underlying medical condition. High-risk conditions identified as per the operational definitions that were specified by PRIMIS at the University of Nottingham[5] were derived from the list of medical serious conditions that are listed in the National Health Services (NHS) influenza annual letter.[6] Hospitalisation data were obtained from the NHS Hospital Episode Statistics (HES) database and were provided already anonymised, after a list of encrypted subject identifiers was submitted to CPRD; as this database only includes information from England, LAIV recipients registered in Northern Ireland, Scotland and Wales were excluded from all analyses.

LAIV recipients were matched to IIV recipients and unvaccinated controls by:

- medical condition
- age
- calendar date of vaccination (with the index date for unvaccinated controls defined as the vaccination date for the referent-matched LAIV recipient)
- healthcare utilisation in the past 12 months (referral in past 12 months (yes/no), if asthmatic: oral steroid prescription and/or hospital admission in past 12 months (yes/no))
- and geographic location (North, Midlands, South and London).

LAIV recipients were matched 1:1 with IIV recipients and 1:3 with unvaccinated controls, with replacement (ie, with the same control who could be selected for more than one LAIV recipient).

Primary safety endpoints were any hospitalisation within 42 days and up to 6 months after vaccination (or index date for unvaccinated controls). Secondary endpoints were hospitalisation for lower respiratory

events (discharge diagnosis of asthma, croup, wheezing, bronchiolitis, pneumonia or acute respiratory failure) and other medically attended events of interest, including all seizure/convulsion events, incident diagnosis of hypersensitivity, Guillain-Barre syndrome, Bell's palsy, encephalitis, neuritis, vasculitis and narcolepsy. Hospitalisations for lower respiratory events were assessed within 42 days and up to 6 months after vaccination. Other medically attended events of interest were also assessed within 42 days except hypersensitivity (3 days) and narcolepsy (6 months).

The incidence of hospitalisation and medically attended events among LAIV recipients were compared with IIV recipients and unvaccinated controls (between cohorts analysis), respectively. The incidence of hospitalisation within 42 days after administration of LAIV was also compared with a reference period later in the follow-up: days 43–84 (within cohort analysis).

Incidence was reported as the number of subjects with an incident event per 1000 person-years. Relative risks and corresponding 95% CI were estimated by conditional Cox's proportional hazards models. All statistical analyses were conducted with SAS V.9.3 (SAS Institute, North Carolina, USA).

The study was planned to stop when at least 10 000 LAIV recipients were identified. A feasibility study was conducted on individuals aged 2 to 17 years that estimated the risk of hospitalisations for any event in season 2008–2009 at 102 and 92 per 1000 person-years among IIV recipients and unvaccinated controls, respectively. Assuming a hospitalisation rate of 100 per 1000 person-years in the IIV recipients and unvaccinated group, the study had >80% statistical power to detect a relative risk (RR) of 2.0 for hospitalisation within 42 days among LAIV recipients, and >90% statistical power to detect an RR of 1.5 during an observation period of 6 months.

Patient and public involvement

The research question, study design and primary outcome were specified so that they documented relevant safety events in a usual care setting, did not require any additional information from the patients and addressed a critical question of interest from the public perspective: is there any safety risk associated with LAIV versus no vaccination or IIV in children and adolescents with high-risk conditions? Dissemination of the results to the study participants was planned indirectly via the manuscript submission to a peer-reviewed journal with a large readership among primary care practitioners in the UK.

RESULTS

Data from two seasons, 2013–2014 and 2014–2015, were necessary to identify at least 10 000 eligible LAIV recipients. From 17 September 2013 to 30 March 2015 (per each previously described season), a total of 14 287 eligible LAIV recipients were identified from the CPRD database. As 2824 children (20%) could not be linked to the HES database, a total of 11 463 LAIV recipients were enrolled in the study: 4718 LAIV3 recipients in 2013–2014 and 6745 LAIV4 recipients in 2014–2015. The reasons why a child enrolled in CPRD could not be linked with the HES database were generally administrative in nature, for example, children could only be linked if the practitioner gave agreement for the linkage. The 6-month follow-up in the CPRD database was completed for 10 476 children (91%): 4294 in 2013–2014 and 6182 in 2014–2015.

The demographics and medical conditions of LAIV recipients at enrolment are presented in table 1. The population is distributed over all age groups (2–3, 4–8 and 9–17 years), with an over-representation of 2–3 year olds in the 2013–2014 season and of 4–8-year-olds in the 2014–2015 season. This likely is due to the specific recommendations of the UK national childhood immunisation programme for each season. There were more male (59%) than female recipients. The most prevalent high-risk condition was asthma (74%), followed by heart disease (12%). A total of 4716 IIV recipients and 14 085 unvaccinated controls were matched to the 4718 LAIV recipients in 2013–2014. Similarly, 6738 IIV recipients and 20 163 unvaccinated controls were matched to the 6745 LAIV recipients in 2014–2015.

Table 2 compares the incidence and relative risk of hospitalisation between LAIV recipients, matched IIV recipients and matched unvaccinated controls. The risk of any hospitalisation after LAIV administration (first 42 days: 231 hospitalisations per 1000 person-years (95% CI 193 to 275) and 231 (95% CI 198 to 267) in seasons 2013–2014 and 2014–2015, respectively. Up to 6 months: 183 hospitalisations per 1000 person-years (95% CI 166 to 202) and 178 (95% CI 164 to 193) in seasons 2013–2014 and 2014–2015, respectively) and the risk of hospitalisation for lower respiratory events (first 42 days: 106 hospitalizations per 1000 person-years (95% CI 80 to 136) and 98 (95% CI 77 to 122) in seasons 2013–2014 and 2014–2015, respectively. Up to 6 months: 80 hospitalisations per 1000 person-years (95% CI 69 to 93) and 75 (95% CI 66 to 85) in seasons 2013–2014 and 2014–2015, respectively) did not significantly differ compared with matched unvaccinated controls, and were lower after LAIV 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. No significant differences were observed in the incidence of hospitalisation within the cohort of LAIV recipients between a period at risk of 42 days after vaccine administration and days 43–84 (table 3).

Table 4 compares the incidence of other medically attended events of interest between LAIV recipients, matched IIV recipients and matched unvaccinated controls. No cases of Guillain-Barre syndrome, Bell's palsy, encephalitis or neuritis were 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

Table 1 Description of LAIV recipients at enrolment: demographics and high-risk medical conditions

Descriptor	Season 2013–2014 (n=4718)	Season 2014–2015 (n=6745)	Total population (n=11 463)
Age, years			
2–3	22% (1033)	12% (799)	16% (1832)
4–8	35% (1644)	37% (2533)	36% (4177)
9–17	43% (2041)	51% (3413)	48% (5454)
Gender			
Male	58% (2722)	58% (3893)	58% (6615)
Female	42% (1996)	42% (2852)	42% (4848)
High-risk medical conditions*			
Asthma	73% (3442)	74% (5016)	74% (8458)
Cystic fibrosis	1% (38)	1% (47)	1% (85)
Congenital lung abnormalities	<1% (15)	<1% (23)	<1% (38)
Other chronic respiratory disease	1% (36)	1% (39)	1% (75)
Chronic heart disease	13% (631)	12% (799)	12% (1430)
Chronic renal disease	2% (73)	1% (88)	1% (161)
Sickle cell anaemia	1% (62)	1% (90)	1% (152)
White blood cell disorders	<1% (15)	<1% (24)	<1% (39)
Immunosuppressive disorders (excluding malignancy)	1% (66)	2% (119)	2% (185)
Malignancy	2% (71)	1% (95)	1% (166)
Diabetes mellitus	4% (188)	4% (304)	4% (492)
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)
Chronic liver disease	<1% (7)	<1% (8)	<1% (15)
Chronic neurological disease	2% (106)	2% (131)	2% (237)
Any medical condition chronically treated with aspirin	<1% (18)	<1% (18)	<1% (36)
Pregnancy	<1% (1)	<1% (1)	<1% (2)

*Several high-risk medical conditions could be present at baseline.
LAIV, live attenuated influenza vaccine.

Table 2 Risk of hospitalisation: comparisons between LAIV recipients and matched unvaccinated children and IIV recipients (between cohorts analysis)

Season 2013–2014	Period at risk	Incidence (per 1000 person-years) (95% CI) LAIV recipients (n=4718)	Matched unvaccinated children (n=14 085)	Matched IIV recipients (n=4716)	Relative risk (95% CI) LAIV versus no vaccine	LAIV versus IIV
Any hospitalisation	42 days	231 (193 to 275) n*=127	227 (203 to 253) n*=325	470 (415 to 531) n*=260	0.96 (0.78 to 1.19)	0.47 (0.37 to 0.58)
Hospitalisation for lower respiratory event		106 (80 to 136) n*=58	91 (76 to 108) n*=130	197 (162 to 238) n*=109	1.07 (0.77 to 1.46)	0.53 (0.39 to 0.73)
Any hospitalisation	6 months	183 (166 to 202) n*=412	157 (147 to 168) n*=818	251 (230 to 272) n*=567	1.09 (0.96 to 1.23)	0.69 (0.60 to 0.79)
Hospitalisation for lower respiratory event		80 (69 to 93) n*=180	67 (60 to 74) n*=346	125 (111 to 141) n*=283	1.13 (0.94 to 1.37)	0.64 (0.53 to 0.78)
Season 2014–2015	**Period at risk**	**Incidence (per 1000 person-years) (95% CI) LAIV recipients (n=6745)**	**Matched unvaccinated children (n=20 163)**	**Matched IIV recipients (n=6738)**	**Relative risk (95% CI) LAIV versus no vaccine**	**LAIV versus IIV**
Any hospitalisation	42 days	231 (198 to 267) n*=182	251 (230 to 273) n*=518	503 (455 to 555) n*=395	0.90 (0.76 to 1.07)	0.42 (0.35 to 0.51)
Hospitalisation for lower respiratory event		98 (77 to 122) n*=77	112 (98 to 128) n*=232	199 (169 to 232) n*=156	0.85 (0.65 to 1.10)	0.46 (0.35 to 0.61)
Any hospitalisation	6 months	178 (164 to 193) n*=575	164 (155 to 173) n*=1242	311 (292 to 331) n*=999	1.08 (0.97 to 1.20)	0.53 (0.47 to 0.59)
Hospitalisation for lower respiratory event		75 (66 to 85) n*=241	74 (68 to 80) n*=558	120 (108 to 133) n*=385	1.01 (0.87 to 1.18)	0.59 (0.50 to 0.70)

*Number of incident cases.
IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine.

of LAIV, both in seasons 2014 and 2015. Neither case resulted in hospitalisation and the incidence did not significantly differ compared with IIV recipients and matched unvaccinated controls. 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 (both in 2014–2015 season) were observed within 42 days after administration of LAIV. The incidence of these medically attended events did not significantly differ from those observed in IIV recipients and matched unvaccinated controls, with the exception of the risk of seizures/convulsions which was lower in LAIV recipients than in IIV recipients in 2014–2015 (RR of 0.42 (95% CI 0.25 to 0.69)).

DISCUSSION

Statement of principal findings

This study investigated safety events in 11 463 children and adolescents from 2 to 17 years old with high-risk underlying medical conditions who received LAIV: 4718 received the trivalent formulation in influenza season 2013–2014 and 6745 received the quadrivalent formulation in influenza season 2014–2015. The risk of hospitalisation after LAIV administration did not vary significantly compared with matched unvaccinated controls in both seasons—that is, with LAIV3 in 2013–2014 and LAIV4 in 2014–2015—and was consistently lower than after IIV administration, within 42 days or in the first 6 months postvaccination, whether all hospitalisations were retained for analysis or only

Table 3 Risk of hospitalisation: comparison within the LAIV cohort between period at risk and control period (within-cohort analysis)

Season 2013–2014 (n*=4560)	Incidence rate per 1000 person years (95% CI) Period at risk (days 0–42)	Control period (days 43–84)	Relative risk (95% CI)
Any hospitalisation	225	238	0.93 (0.71 to 1.23)
Hospitalisation for lower respiratory event	104 (79 to 135) n†=56	95 (71 to 126) n†=50	1.09 (0.73 to 1.63)
Season 2014–2015 (n*=6514)	**Incidence rate per 1000 person years (95% CI) Period at risk (Days 0–42)**	**Control Period (Days 43 to 84)**	**Relative risk (95% CI)**
Any hospitalisation	232 (199 to 269) n†=178	236 (203 to 274) n†=177	1.00 (0.79 to 1.26)
Hospitalisation for lower respiratory event	99 (78 to 124) n†=76	91 (70 to 115) n†=68	1.12 (0.79 to 1.60)

*Number of LAIV recipients who completed follow-up for the two time periods, that is, until day 84.
†Number of incident cases.
LAIV, live attenuated influenza vaccine.

hospitalisations for lower respiratory events. The risk of hospitalisation during the first 42 days following LAIV administration and days 43–84 was also comparable. None of the specific medically attended events of interest that were examined occurred at an increased rate among LAIV recipients.

Strengths and weaknesses of the study

This study enrolled all eligible LAIV recipients that could be identified in a population-based data set that is generally considered representative of the UK population.[7] The sample size was large enough to detect a doubling in the rate of hospitalisations within 42 days and a 50% increase within 6 months versus unvaccinated matched controls or LAIV recipients. In addition, the primary outcome—all-cause hospital admission—was assessed from a database that is managed independently from the practices and schools where vaccine decisions were made, and regularly audited for data validity.[8]

As with any other observational study, treatment administration was not controlled and observed differences between LAIV recipients, IIV recipients and unvaccinated controls may be confounded by differences between the groups at baseline. In particular, it is likely that asthmatic LAIV recipients had less severe disease than IIV recipients at baseline, as the Fluenz label specifies that the vaccine should not be administered to children and adolescents with severe asthma or active wheezing.[1] To minimise this risk, LAIV and IIV recipients with a diagnosis of asthma were matched on use of oral steroids and hospital admission during the past 12 months, both of which are indicators of asthma severity. Still, it is likely that residual confounding explains the higher risk of hospitalisation and possibly the higher risk of seizures/convulsions among IIV recipients versus LAIV recipients.

Although >10 000 LAIV recipients with high-risk medical conditions were enrolled and followed for up to 6 months, the power of this study is insufficient to detect a significant increase in very rare events like Guillain-Barre syndrome or narcolepsy, if the increased incidence is still lower than one event per 1500 patient-years.

Strengths and weaknesses in relation to other studies, discussing important differences in results

The safety of LAIV in children with underlying medical conditions such as cystic fibrosis, infections with the HIV and cancer has generally been evaluated in small clinical studies focused on individuals with a particular illness.[9–11] Children with underlying conditions have also been included as part of a larger phase 3 clinical trial comparing LAIV and IIV vaccines,[3] and two relatively large LAIV efficacy studies focused on children with recurrent respiratory tract infections and asthma have been conducted.[12 13] In this section, we review these key studies of LAIV safety to provide context to our results.

Hospitalisation

In a phase 3 trial of LAIV versus IIV, an increase in all-cause hospitalisation was noted in a subset of LAIV3 recipients aged 6 to 11 months of age, that is, in patients younger than the recommended age for LAIV use (≥2 years of age).[3] Larger postmarketing studies using vaccine administration and safety data from the Kaiser Permanente integrated medical care system have evaluated the risk of hospitalisation in children (≥2 years of age) following the receipt of LAIV3[14 15] and LAIV4.[16] A total of more than

Table 4 Risk of medically attended events: comparisons between LAIV recipients and matched unvaccinated children and IIV recipients

Season 2013–2014	Period at risk	Incidence rate per 1000 person-years (95% CI)			Relative risk (95% CI)	
		LAIV recipients (n=4718)	Matched unvaccinated children (n=14 085)	IIV recipients (n=4716)	Versus unvaccinated children	Versus IIV recipients
Hypersensitivity	3 days	–	7 (0 to 37) n*=1	19 (0 to 108) n*=1	–	–
Seizures/convulsions	42 days	24 (13 to 40) n*=13	21 (14 to 30) n*=30	36 (22 to 56) n*=20	1.11 (0.56 to 2.10)	0.65 (0.32 to 1.29)
Vasculitis		–	–	–	–	–
Season 2014–2015	**Period at risk**	**Incidence (per 1000 person-years) (95% CI)**			**Relative risk (95% CI)**	
		LAIV recipients (n=6745)	**Matched unvaccinated children (n=20 163)**	**IIV recipients (n=6738)**	**Versus unvaccinated children**	**Versus IIV recipients**
Hypersensitivity	3 days	27 (3 to 98) n*=2	14 (3 to 40) n*=3	41 (8 to 119) n*=3	2.00 (0.26 to 12.07)	0.66 (0.02 to 2.60)
Seizures/convulsions	42 days	28 (17 to 42) n*=22	17 (12 to 24) n*=36	66 (49 to 87) n*=52	1.65 (0.95 to 2.80)	0.42 (0.25 to 0.69)
Vasculitis		3 (0 to 9) n*=2	1 (0 to 4) n*=3	–	3.00 (0.20 to 9.94)	–

*Number of incident cases.
IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine.

70 000 paediatric LAIV recipients were documented and, while an elevated risk of hospitalisation was not seen in either of the studies, it is worth noting that they documented mostly healthy children. A recently published study using a large commercial claims database examined the risk of hospitalisation within 14 days after LAIV administration in >99 000 children (2–18 years) with underlying medical conditions, excluding asthma or immunocompromising conditions, and found no evidence of differences compared with healthy children.[17]

Of note, this study did not find lower rates of hospitalisation among vaccine recipients versus unvaccinated controls: rates did not differ between LAIV recipients and unvaccinated controls and were higher in IIV recipients than in unvaccinated controls. These findings may be explained by residual confounding, with vaccine recipients more at risk of hospitalisation than unvaccinated controls at baseline.

Anaphylaxis, Guillain-Barre syndrome and encephalitis

The risk of anaphylaxis, Guillain-Barre syndrome and encephalitis has also been investigated in 200 000 paediatric LAIV3 recipients using the US Vaccine Safety Datalink.[18] Two cases of encephalitis, one case of Guillain-Barre syndrome and no case of anaphylaxis were identified following LAIV administration; no significant differences were found between rates observed after vaccination and rates observed during a control period later in the follow-up.

Use in children with asthma

Concern about use of LAIV in asthmatic children was raised after an early preapproval randomised clinical trial conducted during the 2000–2001 influenza season identified a higher risk of International Classification of Diseases, Ninth Revision-coded asthma events within 42 days after administration of LAIV in children aged 18–35 months.[19] A similar finding was noted in children aged 6–23 months in a large, randomised, double-blind study conducted in 2004–2005, in which children receiving LAIV experienced a higher rate of medically significant wheezing in the 42 days following vaccination.[12] However, no study conducted specifically in children with an underlying diagnosis of asthma has confirmed the initial findings from these studies. A randomised open-label study conducted in children (6–17 years old) with a clinical diagnosis of asthma during the 2002–2003 season found no significant differences between LAIV and IIV recipients in the incidence of asthma

exacerbations, mean peak expiratory flow rate findings and asthma symptom scores.[13] A more recent observational study that analysed all Kaiser Permanente Northern California LAIV and IIV recipients aged 2 to <18 years with a history of asthma from 2007–2008 to 2013–2014 found no increased risk of asthma exacerbation immediately after LAIV or IIV administration compared with later in the follow-up, and a decreased risk when LAIV recipients were compared with IIV recipients.[20] In addition, two studies conducted in Senegal and Bangladesh in children between the ages of 2 and 5 with a live attenuated influenza vaccine based on the Russian Leningrad backbones did not show an increase in protocol-defined wheezing.[21 22]

Overall, in the paediatric age group recommended for LAIV use (≥2 years), studies to date have not identified an increase in hospitalisations, nor an increase in the rates of anaphylaxis, Guillain-Barre syndrome and encephalitis; and no recent studies have found any increased risk of asthma exacerbation following LAIV administration. The results of our study are in agreement with these previous findings: the risk of hospitalisation after LAIV administration did not vary significantly compared with matched unvaccinated controls, and no increase in specific medically attended events of interest (eg, Guillain-Barre syndrome, Bell's palsy, encephalitis or neuritis) was noted. This study is not powered to detect extremely small increases in very rare events, as previously discussed. Nevertheless, it adds to the body of evidence that LAIV does not increase the risks of hospitalisation, medically attended events of interest or asthma exacerbation.

Unanswered questions and future research

The safety of LAIV will continue to be assessed through regular monitoring of spontaneous adverse event reports and annual enhanced safety surveillance studies.

CONCLUSION

This study did not identify any new safety concerns associated with the administration of LAIV, either as a trivalent formulation in the 2013–2014 influenza season or as a quadrivalent formulation in the 2014–2015 season, in children and adolescents with underlying diagnoses of asthma or other high-risk medical conditions.

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Disclaimer AstraZeneca did not have any additional role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests HC, RMM and CSA are full-time employees of AstraZeneca. Amy Steffey is an independent contractor who received funding from AstraZeneca for the data management and analysis of this study.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All source data were obtained from the Clinical Practice Research Datalink (CPRD) and linked with the Hospital Episodes Statistics database. Those data sources are made available for scientific and medical research after submission of a study protocol to be reviewed and approved by the CPRD Independent Scientific Advisory Committee (ISAC). All aggregate data from the study were presented in this manuscript. The only relevant data that were not shared are patient-level data for children presenting adverse events, consistently with the data privacy rules set up by CPRD/ISAC.

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