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Incidence of live-attenuated influenza vaccine administration beyond expiry date in children and adolescents aged 2–17 years in the UK: a population-based cohort study

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ABSTRACT

Objectives To estimate the proportion of live-attenuated influenza vaccine (LAIV) doses administered beyond expiry date in children and adolescents during influenza seasons 2013–2014 and 2014–2015 in the UK.

Design This was a retrospective cohort study. Two cohorts of children and adolescents who received LAIV from 1 September 2013 to 31 March 2014 and from 1 September 2014 to 31 March 2015 and aged 2–17 years at time of LAIV administration were identified from the Clinical Practice Research Datalink (CPRD).

Setting More than 500 primary care practices in the UK.

Population Proportions of vaccine doses administered beyond expiry date were assessed among 47 396 and 67 099 LAIV recipients with a documented vaccine lot identifier in influenza seasons 2013–2014 and 2014–2015, respectively.

Intervention None.

Main outcome measure Administrations of expired LAIV were ascertained by comparison of vaccination dates in CPRD records with expiration dates in AstraZeneca/MedImmune lot distribution data.

Results Overall, 245 LAIV recipients, 80 in 2013–2014 and 165 in 2014–2015, received a dose after its expiration date, yielding proportion estimates of 1.7 per 1000 doses (95% CI 1.3 to 2.1) in season 2013–2014 and 2.5 per 1000 doses (95% CI 2.1 to 2.8) in season 2014–2015. This proportion increased above 1.0% after December during each season. Most (84% in influenza season 2013–2014 and 59% in influenza season 2014–2015) received an expired dose <30 days after its expiration date. The proportion was higher in London (relative risk 1.93 (95% CI 1.25 to 2.99)) and when the number of LAIV recipients registered in the practice was lower than the median number per practice (relative risk 2.69 (95% CI 1.99 to 3.62)).

Conclusions Administration of expired LAIV doses occurs infrequently.

Strengths and limitations of this study

- This is the first population-based study of the proportion of LAIV doses administered beyond expiry date.
- The Clinical Practice Research Datalink (CPRD) allows for analysis of a representative sample of the UK population.
- However, the incidence of expired dose administration may be overestimated, as there is evidence suggesting that the date recorded in the CPRD is in some cases the date of data entry, rather than the true date of vaccine administration, which may have occurred earlier.

INTRODUCTION

In July 2012, the Joint Committee on Vaccine and Immunisation recommended that the influenza vaccination programme in the UK should be extended to all healthy children aged 2–17 years, with live-attenuated influenza vaccine (LAIV) as the vaccine of choice.[1] The programme was introduced to children aged 2–3 years in the 2013–2014 influenza season and then extended to children aged 4 years in the 2014–2015 season, to children aged 5–6 years in the 2015–2016 season and to children aged 7–8 years in the 2016–2017 season.[2] Pilot programmes were also conducted in primary and secondary schools.[2]

As a live-attenuated vaccine, LAIV has a shorter expiration date (18 weeks after date of issue to distributors) than inactivated influenza vaccine (IIV), which typically expires on the 30 June.[3] It is important that healthcare providers are aware of LAIV's shorter expiration date to prevent the administration of expired vaccine. Safety surveillance by the manufacturer of LAIV (AstraZeneca/MedImmune) shows administration of an expired dose as the most frequent type of spontaneous report starting in January of each influenza season. However, spontaneous reports are not a reliable source for estimating actual incidence rates, and the

reported intervals between expiration and vaccine administration may not be representative of the distributions observed in the general population.

This population-based study examined the proportion of LAIV doses administered beyond the expiry date in children and adolescents aged 2–17 years during influenza seasons 2013–2014 and 2014–2015 in the UK. We also described the distributions of the intervals between dose expiration dates and LAIV administrations and investigated potential contributing factors.

METHODS

This study used data from the UK's Clinical Practice Research Datalink (CPRD), a government research service that maintains a database of anonymised longitudinal primary care medical records from over 500 practices in the UK.[4 5] The CPRD is considered representative of the UK population.[5] Vaccines administered to children and adolescents registered at a practice are documented, and school vaccination data are transferred to the practice where a child is registered.

Two cohorts of children and adolescents aged 2–17 years at the time of LAIV administration in season 2013–2014 (from 1 September 2013 to 31 March 2014) and in season 2014–2015 (from 1 September 2014 to 31 March 2015) were identified from CPRD. Subjects with invalid or missing LAIV lot (or batch) identifiers were excluded.

Demographic, clinical, referral, therapy and immunisation records were used for this analysis. Vaccine recipients as well as their vaccination dates and lot identifiers were retrieved from the immunisation, clinical and therapy records. High-risk groups recommended for vaccination were defined using the operational specifications published by PRIMIS at the University of Nottingham.[6]

Administration of expired LAIV was ascertained by comparing vaccination dates documented by all practices in CPRD records with expiration dates for each vaccine lot, as documented in AstraZeneca/MedImmune lot distribution data. Additionally, the CPRD reviewed medical records from four practices that reported 20 or more expired vaccine administrations, as this was an indication that the practices may have documented the date of data entry rather than the date of vaccine administration. All practices that contributed to CPRD in 2014–2015 also contributed to CPRD in 2013–2014; 70 practices that contributed in 2013–2014 did not report data in 2014–2015.

The proportion of LAIV doses administered beyond the expiry date was estimated as the number of individuals who received an expired dose divided by the total number of LAIV recipients aged 2–17 years with a valid LAIV lot identifier during each influenza season. The 95% CIs were estimated under the assumption that the number of administrations of expired LAIV vaccine followed a Poisson distribution. Associated factors were assessed by a stepwise multivariate logistic regression.

A preliminary analysis identified over 64 000 children aged 2–17 years as having received LAIV vaccination during influenza season 2013–2014, before submission of the study protocol to the Independent Scientific Advisory Committee (ISAC). Therefore, it was assumed that the proportion of expired administrations could be estimated with a 95% CI range smaller than 0.1%, even if the point estimate were as low as 0.2%.

The study protocol was approved by ISAC on 25 November 2015. Data were extracted from the databases released by the CPRD in July 2015. All analyses were conducted with SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A total of 69 093 and 86 863 LAIV recipients aged 2–17 years at the time of administration were identified in influenza seasons 2013–2014 and 2014–2015, respectively. After CPRD's review of source data from two practices with high apparent frequencies of expired vaccine administrations, 596 children vaccinated in influenza season 2013–2014 and 630 vaccinated in influenza season 2014–2015 were excluded from the analysis for the following reasons:

- Practice A: The practice explained that a number of vaccines were administered outside of the practice at local schools. Relevant data for these vaccines were subsequently entered into the CPRD records, and the date of administration was incorrectly documented as the date the vaccine information was entered, rather than the date the vaccine was actually administered.
- Practice B: This practice explained that it had been using a third-party macro to facilitate entering multiple data items. The practice subsequently discovered that the macro was not collecting the correct batch information, and it incorrectly appeared that the vaccines were being administered from a batch that had already expired. Subsequently, the practice stopped using the macro in question and now uses another system, containing macros that run dependably.

In both cases, the CPRD was satisfied that an administrative or technical error was the cause of the vaccines appearing to have been administered after their expiry dates.

After excluding information for these two practices, vaccine lot identifier data were missing in 21 101 and 19 134 LAIV recipients in influenza seasons 2013–2014 and 2014–2015, respectively. LAIV recipients with a missing lot identifier were more often school-aged children from 5 to 8 years old: 17% versus 10% among LAIV recipients with a complete vaccination record in season 2013–2014 and 39% versus 13% in season 2014–2015 (table 1). Practice size was directly related to the frequency of finding LAIV recipients with missing lot identifiers. Other differences by time of administration, gender, region and length of registration at practice varied between seasons and were less substantial.

Table 1 Distributions of live-attenuated influenza vaccine (LAIV) recipients' characteristics as a function of lot documentation

	2013–2014 season				2014–2015 season			
	Documented lot (n=47 396)		Missing lot (n=21 101)		Documented lot (n=67 099)		Missing lot (n=19 134)	
Time of administration								
September	5%	(2211)	4%	(848)	1%	(534)	<1%	(44)
October	46%	(21 947)	53%	(11 226)	43%	(29 087)	40%	(7656)
November	36%	(16 844)	34%	(7196)	38%	(25 217)	41%	(7787)
December	11%	(5211)	7%	(1557)	15%	(10 206)	17%	(3220)
January	2%	(1136)	1%	(251)	3%	(1697)	2%	(331)
February	<1%	(38)	<1%	(18)	1%	(353)	<1%	(83)
March	<1%	(9)	<1%	(5)	<1%	(5)	<1%	(13)
Age (years)								
2–4	76%	(35 813)	57%	(12 061)	69%	(46 070)	28%	(5371)
5–8	10%	(4686)	17%	(3647)	13%	(8753)	39%	(7382)
9–17	14%	(6897)	26%	(5393)	18%	(12 276)	33%	(6381)
Gender								
Female	47%	(22 510)	48%	(10 221)	48%	(31 934)	49%	(9351)
Male	53%	(24 886)	52%	(10 880)	52%	(35 165)	51%	(9783)
Length of registration at practice								
<1 year	10%	(4547)	15%	(3219)	9%	(5874)	9%	(1789)
≥1 year	90%	(42 849)	85%	(17 882)	91%	(61 225)	91%	(17 345)
Region								
North	16%	(7355)	20%	(4303)	12%	(8368)	8%	(1558)
England/Midlands	14%	(6467)	10%	(2023)	17%	(11 196)	11%	(2200)
England/South	29%	(13 913)	19%	(4022)	9%	(5868)	4%	(827)
England/London	13%	(6291)	13%	(2658)	5%	(3358)	1%	(97)
Northern Ireland	7%	(3123)	5%	(1044)	15%	(10 239)	60%	(11 409)
Scotland	11%	(5290)	27%	(5701)	11%	(7145)	3%	(624)
Wales	10%	(4957)	6%	(1350)	31%	(20 925)	13%	(2419)
North	16%	(7355)	20%	(4303)	12%	(8368)	8%	(1558)
Number of LAIV recipients by practice								
Lower than per-practice median*	24%	(11 220)	19%	(3951)	25%	(16 804)	12%	(2354)
Per-practice median or higher	76%	(36 176)	81%	(17 150)	75%	(50 295)	88%	(16 780)

*The median numbers of LAIV recipients by practice were 107 and 152 in influenza seasons 2013–2014 and 2014–2015, respectively.

The proportion of LAIV doses administered beyond the expiry date could therefore be assessed among 47 396 and 67 099 LAIV recipients who received vaccine with a valid lot identifier in influenza seasons 2013–2014 and 2014–2015, respectively. A total of 245 LAIV recipients, 80 in 2013–2014 and 165 in 2014–2015, received a dose after its expiration date, yielding proportion estimates of 1.7 per 1000 doses (95% CI 1.3 to 2.1) in influenza season 2013–2014 and 2.5 per 1000 doses (95% CI 2.1 to 2.8) in influenza season 2014–2015. The majority of these children (84% in influenza season 2013–2014 and 59% in influenza season 2014–2015) received an expired dose less than 30 days after its expiration date (figure 1).

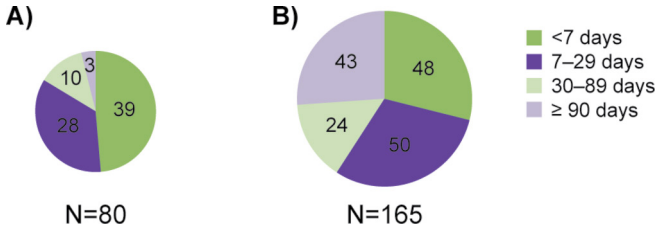

Figure 1 Distribution of the number of days between expiration date and administration date. (A) Influenza season 2013–2014: 80 doses. (B) Influenza season 2014–2015: 165 doses. The number of doses administered 7 to 29 days after expiration: 28 in 2013–2014 and 50 in 2014–2015.

Table 2 Proportion of live-attenuated influenza vaccine (LAIV) recipients who received an expired dose as a function of time of administration and recipient characteristics

	2013–2014 season (n=47 396)		2014–2015 season (n=67 099)	
Distribution by month of administration				
September	0.0%	(0/2211)	0.2%	(1/534)
October	<0.1%	(3/21 947)	<0.1%	(14/29 087)
November	0.0%	(0/16 844)	0.1%	(17/25 217)
December	0.3%	(15/5211)	0.2%	(23/10 206)
January	4.6%	(52/1136)	5.2%	(88/1697)
February	21.1%	(8/38)	4.8%	(17/353)
March	22.2%	(2/9)	100%	(5/5)
Distribution by recipient age (years)				
2–4	0.2%	(56/35 813)	0.2%	(108/46 070)
5–8	0.3%	(12/4686)	0.3%	(24/8753)
9–17	0.2%	(12/6897)	0.3%	(33/12 276)
Distribution by gender				
Female	0.1%	(29/22 510)	0.3%	(84/31 934)
Male	0.2%	(51/24 886)	0.2%	(81/35 165)
Distribution by comorbidities*				
Recipient with high-risk medical condition	0.2%	(14/6903)	0.2%	(19/10 012)
Recipient without high-risk medical condition	0.1%	(37/33 336)	0.2%	(111/47 819)
Distribution by length of registration at practice				
<1 year	0.4%	(16/4547)	0.3%	(18/5874)
≥1 year	0.1%	(64/42 849)	0.2%	(147/61 225)
Distribution by region				
North	0.1%	(8/7355)	0.3%	(27/8368)
England/Midlands	0.1%	(9/6467)	0.1%	(15/11 196)
England/South	0.1%	(18/13 913)	0.2%	(50/20 925)
England/London	0.3%	(20/6291)	0.6%	(36/5868)
Northern Ireland	0.1%	(4/3123)	<0.1%	(1/3358)
Scotland	0.3%	(14/5290)	0.1%	(13/10 239)
Wales	0.1%	(7/4957)	0.3%	(23/7145)
Distribution by number of LAIV recipients by practice				
Below per-practice median	0.3%	(36/11 220)	0.4%	(73/16 804)
At or above per-practice median	0.1%	(44/36 176)	0.2%	(92/50 295)

*This analysis was restricted to children and adolescents with at least 12 months of medical history documented in CPRD before vaccination; high-risk conditions were defined as those listed in the annual influenza letter issued by Public Health England (PRIMIS specifications) and included chronic (long-term) respiratory disease, such as severe asthma, chronic obstructive pulmonary disease or bronchitis; chronic heart disease, such as heart failure; chronic kidney disease at stage 3, 4 or 5; chronic liver disease; chronic neurological disease, such as Parkinson's disease or motor neuron disease, or learning disability; diabetes; splenic dysfunction; and a weakened immune system due to disease (such as HIV/AIDS) or treatment (such as cancer treatment).

Table 2 presents the proportions of LAIV recipients who received an expired dose as a function of month of vaccine administration, age group, gender, high-risk comorbidity and duration of registration in the practice, as well as practice characteristics of geographic region and number of LAIV recipients (lower or greater than the median among all practices contributing to the CPRD).

The proportion of LAIV doses administered beyond the expiry date increased above 1.0% after December in both influenza seasons. This proportion varied significantly by the geographic region of the practice, with a higher estimate in London (relative risk 1.93 (95% CI 1.25 to 2.99)). The proportion was also higher when the number of LAIV recipients registered in the practice was relatively low, that is, lower than the median calculated from all

CPRD practices (relative risk 2.69 (95% CI 1.99 to 3.62)). No additional significant associations were found with age, gender, comorbidities or length of registration at practice.

Despite exclusion of data from two practices described above, a review of the source data for the final analysis showed that the date of vaccine administration and the date of data entry were the same for 170 of the 245 patients identified as having received an expired dose (69%). This proportion was significantly higher than that observed among children and adolescents who received a dose before its expiration date (58 282 of 114 250 LAIV recipients, or 51%). Of special note, all but one of the 46 LAIV recipients identified as having received a dose 90 days or more after the expiration date had the same vaccination date and date of data entry into CPRD.

DISCUSSION

Statement of principal findings

This study provides evidence that administration of an expired LAIV dose is rare. The proportion of LAIV doses administered beyond the expiry date increased from 2013 to 2014 (0.17% (95% CI 0.13 to 0.21)) to 2014–2015 (0.25% (95% CI 0.21 to 0.28)), when the UK's national influenza vaccination programme was extended from all 2- and 3-year-olds in 2013–2014 to all 4-year-olds through general practice, with pilots in primary and secondary school-aged children (in years 7 and 8) in 2014–2015. The proportion of LAIV doses administered beyond the expiry date was also higher in London and in practices that vaccinated a relatively small number of children and adolescents.

Strengths and weaknesses of the study

CPRD allows for analysis of a representative sample of the UK population. Detection of expired LAIV administrations could be ascertained among almost three-quarters of all LAIV recipients as 74%—104 495 out of a total of 154 730 LAIV recipients—had a documented valid lot identifier.

However, there is evidence suggesting that the date recorded in the CPRD databases is in some cases the date of data entry, rather than the true date of vaccine administration, which may have occurred earlier. Therefore, the proportion of LAIV doses administered beyond the expiry date may be overestimated. Children and adolescents with a documented valid lot identifier are also not fully representative of all LAIV recipients, with more missing lot identifiers in school-aged children from 5- to 8-years-old and in practices that document a large number of vaccinated children. This could possibly be a result of children being vaccinated off-site at school or community clinics. CPRD does not document the site of vaccination (eg, general practice, school or community clinic), so this could not be investigated further. However, these associations are not strong enough to markedly bias the study findings.

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

A publication by the US Centers for Disease Control and Prevention (CDC) showed that expired LAIV administrations accounted for a disproportionately high fraction of all spontaneous adverse event reports to the Vaccine Adverse Event Reporting System: 18.4% of reports which describe administration of LAIV versus 0.02% of all spontaneous reports with IIV.[3] Our study could not compare the proportions of vaccine doses administered beyond the expiry date for LAIV versus IIV because the UK has a policy of preferential LAIV use for children and adolescents aged 2–17 years. However, we found much lower proportions of expired LAIV dose administrations in these population-based CPRD data than might be expected from spontaneous reports.

Meaning of the study: possible explanations and implications for clinicians and policymakers

The findings from this study suggest that the administration of expired LAIV is rare, despite being the most frequent type of medication error spontaneously reported to AstraZeneca/MedImmune starting in January of each influenza season. Nevertheless, as the UK's childhood influenza vaccination programme is rolled out across older age groups, it is important that healthcare providers are aware of the shorter lifespan of LAIV compared with IIV and the potential risk for expired doses to be administered. As vaccine doses only gradually lose potency, minimally expired vaccine may still protect against wild-type influenza of strains in the vaccine.[7] However, the CDC recommends revaccination with non-expired vaccine, stating

> "Doses of expired vaccines that are administered inadvertently generally should not be counted as valid and should be repeated. Inactivated vaccines should be repeated as soon as possible. Live vaccines should be repeated after a 28 day interval from the invalid dose to reduce the risk for interference from interferon on the subsequent doses."[8]

In the 2015–2016 and 2016–2017 seasons, AstraZeneca/MedImmune took steps to improve the visibility of the expiry date on the LAIV packaging and provided educational materials to healthcare providers on good practice regarding expiry dates.

Unanswered questions and future research

This study shows that the proportion of LAIV doses administered beyond the expiry date increased slightly but significantly from 2013–2014 to 2014–2015, as the UK's influenza vaccination programme was extended to older children. As the national vaccination programme expands further, we will keep monitoring reports of expired vaccine administration.

CONCLUSIONS

These findings confirm that administration of expired LAIV occurs rarely in the UK population. While the

proportion of LAIV doses administered beyond the expiry date was low, it increased from 0.17% (95% CI 0.13 to 0.21) in 2013–2014 to 0.25% (95% CI 0.21 to 0.28) in the 2014–2015 season when the UK's national influenza vaccination programme was extended to older children. However, this difference needs to be interpreted with caution as the proportion of school-aged children among LAIV recipients increased from 2013–2014 to 2014–2015, with more frequent missing information about the lot expiration date in this age group. In subsequent influenza seasons, AstraZeneca/MedImmune took steps to improve the visibility of the expiry date on the LAIV packaging and provided educational materials to healthcare providers on good practice regarding expiry dates to reduce the risk of healthcare providers administering expired LAIV.

Correction notice This article has been corrected since it first published. The statement "*MedImmune is a member of the AstraZeneca group." has been moved from the author list to the affiliations.

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Contributors HC, RB and RW were involved in the study design. AS provided primary programming and statistical analyses. All authors were involved in developing the manuscript and approved the final version for submission.

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Competing interests HC is an employee of MedImmune, the biologics arm of AstraZeneca, and AS is a contractor for MedImmune. RW was an employee of AstraZeneca during the study. RB is an employee of AstraZeneca.

Patient consent Consent was not required, as retrospective observational study using the Clinical Practice Research Datalink.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data were obtained retrospectively from the Clinical Practice Research Datalink.

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