Safety of Live Attenuated Influenza Vaccine in Children with Egg Allergy: a multi-centre, non-randomised intervention study

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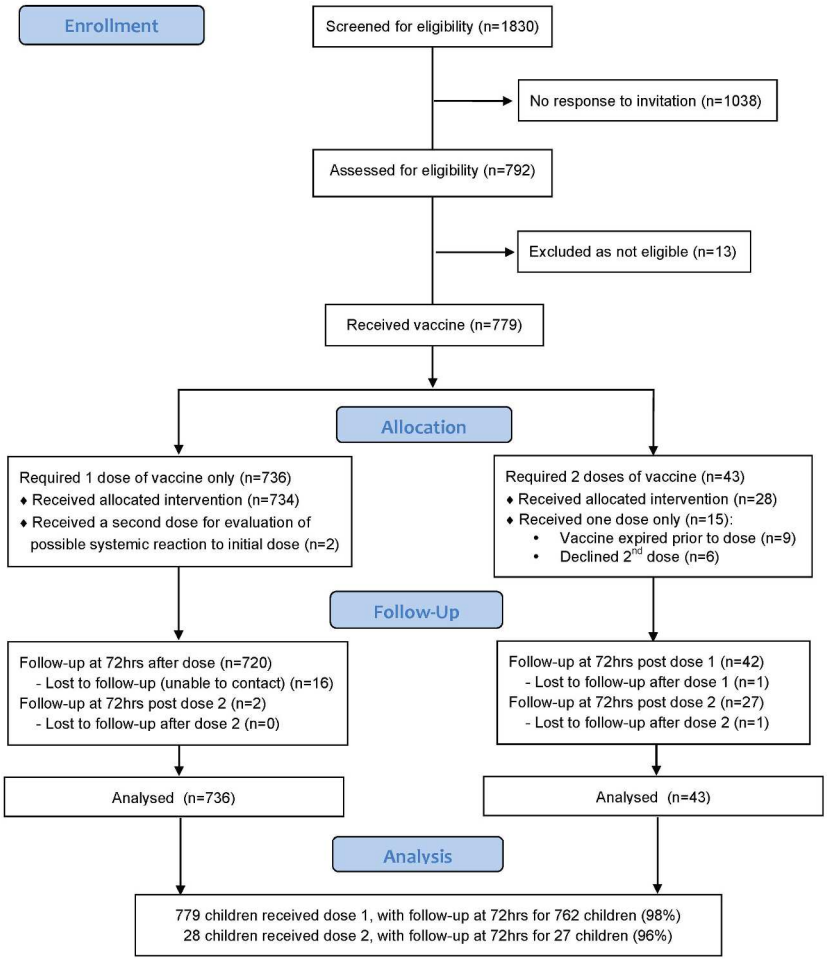

Figure 1: Participant flow diagram
13 children were consented but were not eligible for the study: 6 due to recent antihistamine use (family declined a further study appointment); 5 refused after parental consent had been obtained; 2 with unstable asthma (and who were given IIV instead).
215x279mm (300 x 300 DPI)

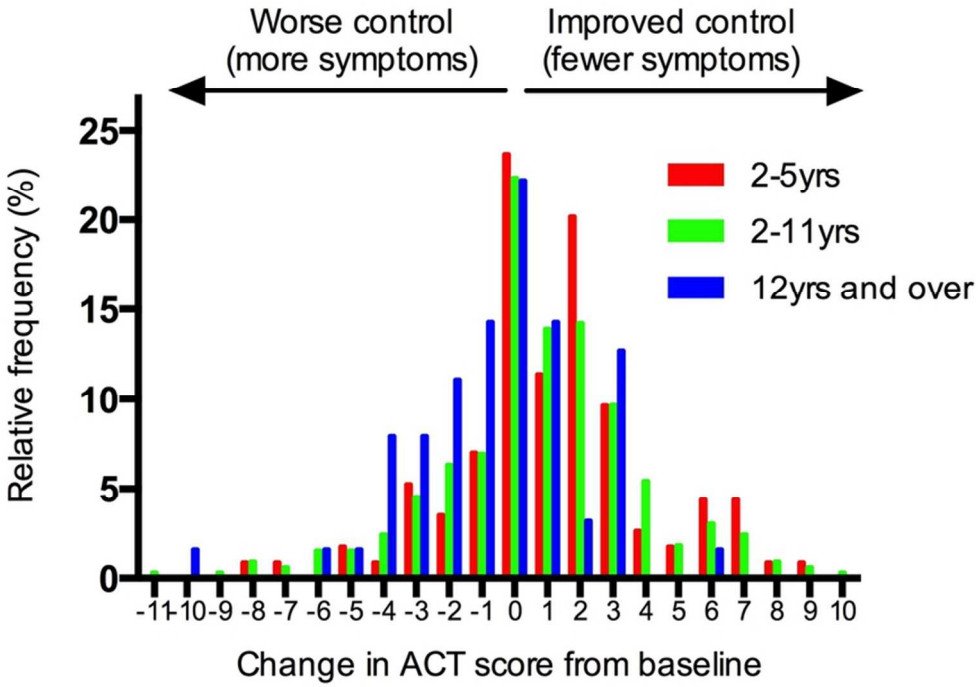

Figure 2: Change in Asthma Control Test (ACT) score at 4 weeks post LAIV, compared to baseline, in children with a history of asthma or recurrent wheeze.
75x53mm (300 x 300 DPI)

Table E1: AEFI reported within 2 hours of LAIV administration

Study ID number	Time to symptoms (minutes)	Description of events	IDMC review: possible allergic aetiology?	Causality
BR/005	20-60	Generalised urticarial following LAIV. Negative allergy testing and tolerated 2nd dose of LAIV. Reaction attributed to milk present in ingredients of snack eaten following 1st dose of LAIV (child has milk allergy).	NO	
CA/011	5-20	Red itchy nose	YES	Probable
ED/054	5-20	Itchy naso-oropharynx. Facial flushing; no hives	YES	Probable
LE/005	5-20	Felt as if wanted to sneeze, but no actual sneezing. No significant change in TNSS.	NO	
LE/020	5-20	Pre-existing nasal symptoms due to mild cold.	NO	
LP/001	5-20	Large hive on face-disappeared in minutes. Scratching both sides of face, transient	YES	Possible
LP/016	20-60	Itchy erythema/ hives on forehead; eczema flare on arms 30 mins post LAIV	YES	Probable
NW/018	20-60	Local rhinitis symptoms at 30 mins post LAIV	YES	Possible
OX/006	1-5	Itchy nose and skin - ?due to contact reaction, no visible urticaria	YES	Possible
OX/020	20-60	Single episode of vomiting, 45 mins after LAIV. Does not meet BCC criteria for systemic reaction.	NO	
OX/022	5-20	Contact urticarial reaction	YES	Probable
RL/031	5-20	Mother reported mild R facial swelling. Negative allergy testing and tolerated 2nd dose of LAIV without any similar symptoms.	NO	
SF/025	20-60	3 hives on chin 25 mins post LAIV, resolved in <15mins	YES	Probable
UC/006	5-20	Mild nasal itch, no change in TNSS. No objective symptoms. Tolerated 2nd dose without issue.	NO	
UC/001	60-120	Itchy tongue and neck	YES	Possible
SM/066	20-60	Sore 'tummy' 40mins post LAIV, onset shortly after eating a take-away from local restaurant. Family member (not receiving LAIV) had same symptoms.	NO	
MA/023	60-120	Not Itchy	NO	

Table E2: Incidence of AEFI of allergic aetiology, by factor of interest.

Factor	Level	n/N	P value
Age group (years)	2-4	5/360	0.24
	5-11	2/334	
	12-18	2/85	
Physician-assessed clinical reaction to egg in previous 12 months	No	4/464	0.50
	Yes	5/315	
95% PPV criteria met for egg allergy within previous 12months	No	3/326	0.74
	Yes	6/453	
Previous anaphylaxis to egg	No	7/622	1.00
	Yes	2/157	
Previous reported reaction to aerosolised egg	No	6/709	0.04
	Yes	3/70	
Tolerance to baked egg in diet	No	5/436	1.00
	Yes	4/343	
Previous influenza vaccine (any)	No	3/410	0.32
	Yes	6/369	
Previous LAIV	No	7/591	1.00
	Yes	2/188	
Diagnosis of asthma or recurrent wheeze	No	3/334	0.74
	Yes	6/445	
Batch ovalbumin content >1.0 ng/ml	No	2/268	0.73
	Yes	7/511	
Batch ovalbumin content >0.3 ng/ml	No	1/112	1.00
	Yes	8/667	

Table E3: Incidence of delayed events within 72 hours of LAIV administration, by factor of interest.

Factor	Level	n/N	P value
Age group (years)	2-4	112/360	0.07
	5-11	93/334	
	12-18	16/85	
Physician-assessed clinical reaction to egg in previous 12 months	No	140/464	0.20
	Yes	81/315	
95% PPV criteria met for egg allergy within previous 12months	No	101/326	0.17
	Yes	120/453	
Previous anaphylaxis to egg	No	180/622	0.55
	Yes	41/157	
Previous reported reaction to aerosolised egg	No	199/709	0.58
	Yes	22/70	
Tolerance to baked egg in diet	No	120/436	0.58
	Yes	101/343	
Previous influenza vaccine (any)	No	123/410	0.30
	Yes	98/369	
Previous LAIV	No	176/591	0.14
	Yes	45/188	
Diagnosis of asthma or recurrent wheeze	No	92/334	0.69
	Yes	129/445	
Batch ovalbumin content >1.0 ng/ml	No	80/268	0.51
	Yes	141/511	
Batch ovalbumin content >0.3 ng/ml	No	28/112	0.43
	Yes	193/667	

TITLE PAGE

Safety of Live Attenuated Influenza Vaccine in Children with Egg Allergy: a multi-centre, non-randomised intervention study

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: PJT and MEL had financial support from the Department of Health for the submitted work; PJT has received research grants from the Medical Research Council and NHS National Institute for Health Research. All authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors: The study was conceived by PJT, MEL, JS and EM. PJT and MEL designed and managed the trial. NJA contributed to the statistical design, and together with PJT undertook data analysis. PJT and MEL drafted the report. All authors contributed to and reviewed the final report. PJT is guarantor for this work.

Ethics approval: The study was approved by the West Midlands-Edgbaston Research Ethics Committee (14/WM/0159) and the parent/guardian of each participant gave written informed consent.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. This report is independent research commissioned and funded by the Department of Health Policy Research Programme (National Vaccine Evaluation Consortium, 039/0031). The views expressed in this publication are those of the authors and not necessarily those of the Department of Health. The study received additional local support through the NIHR Clinical Research Networks, with additional funding for the Edinburgh site from Health Protection Scotland and the Belfast site from Health & Social Care Services in Northern Ireland. The study design and data collection were performed independently of the funder; data analysis was performed in conjunction with Public Health England, who also contributed to the writing of this report. The study chief investigators (PJT and MEL) had full access to all the data in the study, and final responsibility for the decision to submit for publication.

Transparency declaration

PJT affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: no additional data available.

This report follows the TREND guidelines for the reporting quality of non-randomised evaluations of a public health intervention. [Des Jarlais, D. C., Lyles, C., Crepaz, N., & the TREND Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. American Journal of Public Health, 94, 361-366].

ABSTRACT

Objective: Live attenuated influenza vaccine (LAIV), an intranasal vaccine, was recently incorporated into the UK immunisation schedule for all children. However, in common with other influenza vaccines currently licensed for use in children, LAIV contains egg protein and is contraindicated in egg allergy. In addition, LAIV may induce wheezing in younger children, thus some guidelines recommend against its use in children with recurrent wheeze.

Design: Prospective, multi-centre, open label, phase IV intervention study involving 30 secondary/tertiary UK centres.

Participants: 779 children with physician-diagnosed egg allergy, including those with prior analphylaxis to egg not requiring management on an intensive care unit.

Intervention: LAIV was administered under medical supervision, with observation for one hour and telephone follow-up 72 hours later. Children with a history of recurrent wheeze/asthma underwent further follow-up 4 weeks post-vaccination. Children without prior influenza vaccination and in a high-risk clinical group received a second dose of LAIV 4 weeks later. Vaccination was deferred in children with poorly-controlled asthma.

Main outcome measures: Incidence of allergic reaction as an adverse event following immunisation (AEFI) occurring within 2 hours of LAIV administration in egg-allergic children.

Results: 809 doses were administered to 779 egg-allergic children (median 5.3 years, range 2-18 years); 270 (35%) had experienced prior anaphylaxis to egg. A physician-diagnosis of asthma/recurrent wheeze was noted in 445/779 (57%) participants: 361 (46%) were receiving regular preventer therapy (Step 2+, British Thoracic Society (BTS) classification). There were no systemic allergic reactions (upper 95% CI for population <0.47%). Nine children experienced mild self-limiting symptoms, potentially consistent with an IgE-mediated allergic reaction. 62 children (8.1%, 95% CI for population 6.3-10.3%) experienced lower respiratory symptoms

within 72 hours, including 29 with parent-reported wheeze. This prompted medical assessment by a general practitioner in five cases, with no resulting hospital admissions. LAIV did not increase lower respiratory symptoms (assessed using the Asthma Control Test) in the 4 weeks following administration.

Conclusions: LAIV is unlikely to trigger a systemic allergic reaction in egg-allergic children and appears safe for use in most egg-allergic children, including those with a history of anaphylaxis, well-controlled asthma or recurrent wheeze.

Trial registration: ClinicalTrials.gov registration NCT02111512, EU Clinical Trials registration 2014-001537-92.

What this paper adds

What is already known on this subject

- Egg allergy is common, affecting 2-6% of preschool children
- An intranasal vaccine (Live Attenuated Influenza Vaccine, LAIV) has been introduced into the UK paediatric vaccination schedule, but there is limited safety data for LAIV in children with egg allergy and/or asthma.
- Some guidelines recommend against using LAIV in non-egg allergic children under 5 years with a history of recurrent wheeze or asthma

What this study adds

- LAIV did not cause any systemic allergic reactions in this cohort of egg-allergic children.
- LAIV appears to be well-tolerated in children with a diagnosis of asthma or recurrent wheeze providing that respiratory symptoms are well controlled.

INTRODUCTION

Epidemiological data and mathematical modelling indicate children are the main spreaders of influenza infection.[1] Vaccinating children therefore provides the most effective method for interrupting transmission and achieving disease control. This was recognised by the Joint Committee for Vaccination and Immunisation (JCVI), an independent expert advisory committee to the Departments of Health, which in 2012 recommended annual vaccination of all children aged 2-16 years of age with the live attenuated influenza vaccine (LAIV).[2] LAIV is given via the intranasal route, and has high efficacy against influenza in children aged 2-17 years,[3, 4] with a good safety profile, similar to that of inactivated influenza vaccines (IIVs).[5-9] The JCVI considered that extending the influenza vaccine programme to include both high risk and low risk children was likely to be safe and cost-effective, providing both direct protection to the vaccinated child, as well as indirect protection by lowering influenza transmission from vaccinated children to other children, adults and those in clinical risk groups.[2]

In common with other influenza vaccines licensed for use in children, LAIV is grown in hens' eggs and contains egg proteins, such as ovalbumin.[10] There is now a consensus that IIV with low ovalbumin content (below 0.12 µg/ml, equivalent to 0.06 µg for a 0.5 ml dose) are safe for use in egg-allergic individuals,[11, 12] with the proviso that "in all settings providing vaccination, facilities should be available and staff trained to recognise and treat anaphylaxis."[11] Until recently, there was no safety data on the use of LAIV in egg-allergic children, and egg allergy remains listed as a contraindication for LAIV in the Summary of Product Characteristics.[10] For the 2015/16 influenza season, seasonal influenza vaccination will be offered to all 2 to 4 year olds, and those in school years 1 and 2, ideally using quadrivalent LAIV.[13] Egg allergy is estimated to be 2.5% in this age group,[14] so on the basis of UK 2013

population data, there are 100,000 egg-allergic children in whom LAIV would therefore be contraindicated.

Children with egg allergy often have concomitant diseases including eczema and recurrent wheeze. Some guidelines recommend against LAIV in children with recurrent wheeze, due to limited evidence from a clinical trial [15] that LAIV may induce wheezing in younger children.[16] These are significant barriers to achieving successful implementation of the immunisation programme in community and primary care environments. To address this and provide data to underpin an evidence-based change to guidance, we sought to assess the safety of administering LAIV to egg-allergic children in a large, multi-centre, interventional study.

METHODS

We undertook a Phase IV open label study of LAIV in egg-allergic children during the influenza season (September 2014 – February 2015) across 30 hospitals (specialist and non-specialist clinics) in the UK. Eligible participants were aged 2-18 years, with a current physician diagnosis of egg allergy. Patients with a history of prior anaphylaxis to egg or a history of severe but stable asthma were also included. Anaphylaxis was defined using World Allergy Organization (WAO) criteria.[17] Asthma was classified according to current therapy at time of immunisation using the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines.[18]

Participants were excluded if they had previously required invasive ventilation for anaphylactic reaction to egg, had severe asthma (defined as BTS/SIGN step 5 therapy with poor control, assessed either by the attending specialist or with an Asthma Control Test score of less than 20),[19] or contraindication to LAIV (other than egg allergy). Vaccination was deferred for acute febrile illness; wheeze in the preceding 72 hours or acute asthma symptoms requiring corticosteroids in the previous 2 weeks; and receipt of antihistamine within the previous 4 days (due to the possibility that any allergic symptoms might be masked).

The study was approved by the West Midlands-Edgbaston Research Ethics Committee (14/WM/0159) and the parent/guardian of each participant gave written informed consent. Children over 8 years were encouraged to provide assent. The study sponsor was University Hospital Southampton NHS Foundation Trust (study number RHM CHI0714). This study was registered with ClinicalTrials.gov (NCT02111512) and the EU Clinical Trials Register EudraCT 2014-001537-92).

Procedures

Baseline measurements (blood pressure, heart rate, respiratory rate, oxygen saturations) were recorded, with simultaneous clinical respiratory and dermatological assessment. Quadrivalent LAIV (Fluenz Tetra, produced for the 2014/15 influenza season) was administered according to the approved summary of product characteristics.[10] Participants were observed for at least 30 minutes for symptoms of local or systemic allergic reaction, with clinical observations and symptom scoring (Total Nasal Symptom Score, TNSS),[20] documented on a dedicated study case report form. Parents were telephoned after at least 72 hours to document any delayed symptoms. In participants with a history of asthma or recurrent wheeze, the asthma control test (ACT) was administered both prior to vaccination and 4 weeks later. The ACT is a validated tool providing an assessment of asthma symptoms over the preceding 4 weeks.[19] Participants in a high risk clinical group and who had not received seasonal influenza vaccine in previous years were offered a second dose of LAIV at least 4 weeks later, in line with national guidelines.[12]

Outcomes

The primary outcome was the incidence of allergic reaction as an adverse event following immunisation (AEFI) occurring within 2 hours of LAIV administration in egg-allergic children, according to symptoms listed in the Brighton Collaboration Case definition for systemic allergic reaction (anaphylaxis) as an AEFI.[21] Any reaction not meeting the case definition for anaphylaxis was defined as a possible non-anaphylactic reaction. A change in TNSS of 3 or more was taken as indicative of a possible local (nasal) allergic response.[20] Secondary outcomes were: incidence of delayed symptoms occurring up to 72 hours after LAIV administration (including those of non-allergic aetiology); change in ACT score prior to, and 1 month after vaccination in participants with a history of asthma and/or recurrent wheeze. In children under 12 years, only the score relating to parental assessment of symptoms was compared at the 4 week time point. All adverse events were reviewed by an

independent data monitoring committee (IDMC), and causality assigned in conjunction with local study teams.

Statistical analyses

Analyses were planned prospectively and detailed in a statistical analysis plan. The incidence of reactions to LAIV (both immediate and delayed) was estimated with two-sided exact 95% confidence intervals. For subgroup analyses, incidence of reactions was compared between different cohorts using a two-sided Fisher's exact test. Sub-group analyses included: age group (2-5, 6-11, 12-17 years); certainty of true clinical allergy (on the basis of reaction to egg within the previous 12 months and/or evidence of >95% likelihood of egg allergy according to published criteria);[22, 23] prior history of anaphylaxis to egg; history of previous reaction to airborne traces of egg; tolerance to extensively heated egg; prior receipt of any influenza vaccine (IIV or LAIV) or LAIV alone; presence of physician-diagnosed asthma / recurrent wheeze; ovalbumin content of LAIV batch used. Change in ACT score was assessed using McNemar's exact test.

Sample size was considered with respect to a historical comparison and also based on the precision around an estimate of zero. If there were no allergic reactions in a sample size of 730, then this would provide confidence (based on the upper end of the two-sided 95% CI) that the true rate of allergic reaction to LAIV in egg-allergic children within the population is no more than 0.5%. The analysis dataset was as treated and with the relevant safety data measured.

Patient involvement

Parents of egg-allergic children were involved in the design of the study and the development of study information leaflets, and in setting the research question. Results of the study will be disseminated through patient support organisations

(Alllergy UK and the Anaphylaxis Campaign) through electronic newsletters and social media.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The study was funded centrally through a National Vaccine Evaluation Consortium Grant awarded by the UK Department of Health to Public Health England. The study received additional local support through the NIHR Clinical Research Networks, with additional funding for the Edinburgh site from Health Protection Scotland and the Belfast site from Health & Social Care Services in Northern Ireland. The study design and data collection were performed independently of the funder; data analysis was performed in conjunction with Public Health England colleagues, who also contributed to the writing of this report. The study chief investigators (PJT and MEL) had full access to all the data in the study, and final responsibility for the decision to submit for publication.

RESULTS

779 children with egg allergy were enrolled and received at least one dose of LAIV between September 2014 and February 2015. The median age of the cohort was 5.3 years (range 2-18 years) and 508 (65%) were male. Three hundred and sixty-nine (47%) had received influenza vaccination in previous years, of whom 188 had been given LAIV. The majority of LAIV in circulation in the UK does not contain detectable ovalbumin (personal communication, Department of Health). For this study, we sourced vaccine with detectable ovalbumin. In 667 (86%) children, the LAIV batch used contained >0.3 ng/ml ovalbumin, of whom 511 (66%) received a dose containing 1-1.93 ng/ml ovalbumin.

All children were excluding egg from their diet at the time of immunisation. Three hundred and fifteen (40.4%) had experienced an allergic reaction to egg in the last 12 months, including 40 (5.1%) at formal, in-hospital food challenge. A total of 138 (18%) had not reacted to egg in the last 12 months, but had evidence of sensitisation above the published criteria for >95% positive predictive values (PPV) for clinical egg allergy.[22, 23] Thus, 453 (58%) children met criteria consistent with >95% likelihood of clinical egg allergy within the 12 months prior to vaccination. The diagnosis of egg allergy had been verified by an allergy specialist in 673 (86%) children. Of the remainder, 90 had been diagnosed by a general paediatrician and 16 by their GP; within this subgroup, only 42 (5.3% of total cohort) did not meet 95% PPV criteria.

The cohort included 270 (35%) children with a history of prior anaphylaxis to egg, of whom 157 (20%) had experienced respiratory and/or cardiovascular symptoms with egg ingestion. Fifty-three (6.8%) children had experienced WAO Grade 3+ reactions (stridor with respiratory compromise, wheeze not responsive to initial bronchodilator therapy, or collapse/hypotension). Only 56 (7.2%) had never eaten egg and were diagnosed on the basis of predictive allergy testing alone. Four hundred and forty-

five children (57%) had a physician-diagnosis of asthma or recurrent wheeze, of whom 361 (46% of total cohort) were using daily preventer therapy (BTS/SIGN Step 2+) and 143 (18%) on BTS/SIGN Step 3+ therapy. Three hundred and seventy-seven (48%) had allergic rhinitis, 463 (59%) had atopic eczema while 435 (56%) were allergic to 3 or more food groups.

A second LAIV dose was administered to 30 children: 28 vaccine-naïve children who required a further dose according to clinical risk, and two children who underwent subsequent allergy skin testing including nasal challenge with vaccine, due to possible systemic allergic reaction to LAIV (Figure 1). A further 15 children were eligible for a second dose, but did not receive it due to expiry of the vaccine (9 children) or the family declining a second visit for a further dose (6 children).

Immediate Adverse Events following immunisation (AEFI)

There were 17 recorded adverse events in 17 different children reported within 2 hours of vaccine administration (Table E1). Six were not consistent with a potential, IgE-mediated allergic response as defined by international consensus criteria.[21] Two children reported skin symptoms (urticaria/angioedema) between 30 and 120 minutes following LAIV; both underwent subsequent specialist allergy testing four weeks later (to LAIV and excipients, all of which were negative), and given a second dose of LAIV which was tolerated without any observed adverse symptoms in the two hours following administration. In one case, the initial reaction could be attributed to accidental consumption of cow's milk, to which the child was allergic. Therefore, no child experienced a systemic reaction attributed to LAIV administration; the 95% upper confidence interval for the incidence of a systemic allergic reaction (including anaphylaxis) to LAIV in egg-allergic children was therefore 0.47%. In children with a history of anaphylaxis, the equivalent 95% upper CI interval was 1.36%.

Nine subjects (1.2%, 95% CI: 0.5% to 2.2%) experienced an immediate AEFI of possible allergic aetiology. These reactions (4 rhinitis, 4 localised/contact urticaria, 1 oropharyngeal itch) were mild, self-limiting and occurred within 30 minutes of LAIV administration. Children with a history of reaction to aerosolized egg had a higher incidence of possible reaction (3/70 vs 6/709, p=0.04), but otherwise no risk factors were identified for occurrence of an acute adverse event, allergic or otherwise, when assessed for age, previous anaphylaxis to egg, previous influenza vaccination (any or previous LAIV), presence of physician-diagnosed asthma / recurrent wheeze or allergic rhinitis, or level of ovalbumin in the LAIV dose given (p>0·05 for all comparisons, Table E2).

Delayed Adverse Events (occurring between 2 and 72 hours after vaccine administration)

No SAEs attributable to LAIV occurred during the study. Delayed events potentially related to LAIV were reported in 221 children (table 1). Sixty-two children (8.1%, 95% CI for population 6.3 to 10.3%) experienced lower respiratory symptoms within 72 hours, including 29 with parent-reported wheeze (3.8%, 95% CI for population 2.6 to 5.4%). No risk factors were identified for occurrence of delayed events, although there was a trend towards an increased rate of lower respiratory symptoms in younger children (p=0.07, Table E3). Some guidelines have suggested that children under 5 years with a history of wheezing are at risk of developing wheeze following LAIV. To assess this, in an additional exploratory analysis, we compared the rate of lower respiratory symptoms in children with asthma or recurrent wheeze: children under 5 years were slightly more likely to develop lower respiratory symptoms compared to older children, although this did not reach statistical significance (22 of 149 (15%) children under 5 years vs 26/296 (8.7%), P=0.07). Medical review by the child's primary care physician was sought in five cases, with a change in medication

in three; one child was referred to hospital for further assessment, but was discharged after review.

Given the concern regarding wheeze post LAIV, we analysed the change in ACT score for the four weeks following LAIV administration, from baseline. ACT was determined at both time points for 394/445 (89%) children with a history of asthma or recurrent wheeze. There was no significant change in ACT score for children 12 years and over (median change 0, p=0.12, Figure 2). In those aged 2-11 years, there was a small but significant improvement in ACT following LAIV (median change +1, p<0.001). A similar improvement was also noted when the analysis was restricted to children under 5 years (median change +1, p<0.001).

In the 29 children who received a second dose of LAIV and in whom follow-up was complete, 4 experienced an AEFI within 72 hours. Two children experienced a flare in eczema; in one this also occurred after the first dose of LAIV.

DISCUSSION

Principal findings: Systemic allergic reactions

We did not observe any systemic allergic reactions or anaphylaxis following administration of quadrivalent LAIV in egg-allergic children. Anaphylaxis is defined as a “severe, life-threatening generalized or systemic hypersensitivity reaction”.[24, 25] Thirty-five percent of study participants had a history of anaphylaxis to egg: 20% had experienced respiratory and/or cardiovascular involvement. In this study, children with previous anaphylaxis to egg allergy were not found to be at higher risk of AEFI (either of allergic aetiology, or otherwise) following LAIV.

Together with previous studies,[26, 27] the literature now reports 955 egg-allergic children (including 338 (35%) with prior anaphylaxis to egg) who have received at

least one dose of LAIV without an acute systemic reaction. This gives an upper 95% CI for the incidence of acute systemic allergic reaction in egg-allergic children in the general population of 0.39%, or under 1 in 256 egg-allergic children vaccinated. In children with prior anaphylaxis to egg, the upper 95% CI for the incidence of acute systemic reaction is 1.09%. The incidence of possible local, IgE-mediated reactions is higher (1.2%) than that previously reported for non-egg-allergic individuals.[15] However, these reactions were all mild, localised and self-limiting. Anaphylaxis to LAIV has been reported in adults (at a rate of 0.3 reactions per 100,000 doses), but none were related to egg allergy.[28] We have previously reported that LAIV is unlikely to contain enough egg protein to trigger an IgE-mediated allergic reaction in egg-allergic individuals.[29] The risk of causing a systemic allergic reaction with quadrivalent LAIV therefore appears to be no greater in children with egg allergy (including those with a history of prior anaphylaxis to egg) compared to non-egg-allergic individuals.

Following discussions with our local patient and public involvement (PPI) teams, we chose to use an open design for this Phase IV study, in order to maximize recruitment to the study. Our PPI input indicated that it would not be as acceptable to include a placebo arm, nor would many parents consent to IIV when an non-injectable alternative was available. Thus, we can only make comparisons to historical data in terms of risk of adverse events.

This study confirms our previous findings that trivalent LAIV is safe in egg-allergic children, with a number of important additions. Our earlier study provided initial data relating to the safety of LAIV in 282 egg-allergic children;[26] however, the trivalent LAIV used in that study did not have detectable egg protein, thus the safety profile may have been due to a lack of egg protein in the batches of vaccine used. In this study, the majority of LAIV batches used contained detectable ovalbumin. This,

combined with the larger cohort size and more representative egg-allergic paediatric population achieved by inclusion of non-tertiary allergy clinics provides a stronger evidence base to support the safety of LAIV in egg allergic children. In theory, it is possible that LAIV administration in previous years might cause sensitization and an increased risk of subsequent reaction in future years. In this study, 24% of the cohort received LAIV in 2013/14, and this was not associated with an increased risk of adverse events. Reassuringly, the rate of delayed adverse events in this study is similar to that previously reported following LAIV administration in non-atopic children (Table 2).[4-7, 9, 15, 28]

Principal findings: Wheeze post LAIV

Guidelines from North America currently recommend against the use of LAIV in children under 5 years with a history of an episode of wheezing in the previous 12 months,[16] due to concerns that LAIV might cause wheezing in susceptible children, something not consistent with published data.[4-6, 15, 35, 36] An analysis of two randomized, multinational trials, in 1940 children aged 2–5 years with asthma or a history of wheezing, found no difference in the incidence of wheezing following vaccination between those who received LAIV versus TIV.[37] However, both trials excluded children with wheeze in the 42 days prior to receiving LAIV. Furthermore, previous studies have used 'medically-significant wheeze' in the 42 days post vaccination as the outcome measure for lower respiratory symptoms. While this may be a measure of more concerning wheeze, it is insensitive, as many parents of children with recurrent wheezing will manage their child's symptoms at home without recourse to a medical professional. Parent-reported wheeze is common in the autumn/winter months (when immunization with LAIV is indicated). In this study, we only excluded children with acute wheezing in the previous 3 days, a more feasible scenario in terms of a targeted immunization campaign. We did observe a higher rate of parent-reported lower respiratory symptoms in children age 2 to 5 years, but this

did not reach statistical significance. To explore this further, we used the ACT questionnaire to assess asthma symptoms including wheeze, in the 4 weeks pre- and post LAIV administration. We did not observe an significant increase in lower respiratory symptoms in children under 5 years of age receiving LAIV, nor was there a worsening in ACT scores. These data suggest that LAIV is safe in children with a history of asthma or recurrent wheeze, in whom symptoms are well-controlled.

Strengths and limitations of study

Our study population was recruited from a large number of secondary and tertiary allergy centres in the UK, and may therefore represent a cohort of individuals with more severe allergy requiring specialist input. We therefore expect our findings to be applicable to a wider egg-allergic population of children, including those with more mild allergy managed in primary care. We excluded children who had previously required ventilation on intensive care following an anaphylaxis triggered by egg. This, however, is a very atypical occurrence, and no child was excluded due to this criterion. Anaphylaxis to food is not uncommon, with an estimated incidence in food-allergic children of 0.20 (95%CI 0.09-0.43) cases per 100 person-years.[30] In contrast, fatal anaphylaxis is a rare event (although unpredictable), with an estimated incidence of 1.81 (95%CI 0.94-3.45) cases per million person-years.[31] There are approximately 10 fatalities due to food anaphylaxis in the UK per annum,[32] compared with an annual average of 30-40 admissions to intensive care due to food anaphylaxis (data obtained from UK Health and Social Care Information Centre).[33] The published data indicates that egg-allergic children with a history of anaphylaxis are not more sensitive to lower doses of egg than those with only prior mild reactions.[34] Taken together, these data suggest that LAIV is likely to be well-tolerated even in those few children with prior anaphylaxis to egg requiring intensive care, although arguably it is reasonable to expect such children to be vaccinated within an appropriate healthcare facility.

Conclusions and policy implications

This study provides evidence to support the revised Department of Health guidance for the 2015/16 season that, with the exception of children "with severe anaphylaxis to egg which has previously required intensive care, children with an egg allergy can be safely vaccinated with Fluenz Tetra® in any setting (including primary care and schools)".[12] As with all settings providing vaccination, facilities should be available and staff trained to recognise and treat anaphylaxis. Furthermore, the vaccine is appropriate for use in children at risk of wheeze, whose symptoms are well controlled with no evidence of active wheezing in the 72 hours prior to LAIV.

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Adverse event:	No. children	Rate (95% CI) in this cohort
Upper Respiratory		
• Upper respiratory (any)	141	18.5% (15.8 to 21.4%)
• Isolated symptoms only, <24hrs duration	72	9.4% (7.5 to 11.8%)
• Isolated symptoms only, >24hrs duration	69	9.1% (7.1 to 11.3%)
• Nasal symptoms with ocular involvement	1	0.1% (0.0 to 0.7%)
Lower Respiratory		
• Lower respiratory (any)	62	8.1% (6.3 to 10.3%)
• Parent-reported wheeze	29	3.8% (2.6 to 5.4%)
Constitutional		
• Any	53	7.0% (5.2 to 9.0%)
• Fever <24hrs	30	3.9% (2.7 to 5.6%)
• Fever >24hrs	9	1.2% (0.5 to 2.2%)
• Other: lethargy, headache, dizziness, myalgia	19	2.5% (1.5 to 3.9%)
Dermatological		
• Flare in eczema	22	2.9% (1.8 to 4.3%)
• Non-specific rash, no response to antihistamine	8	1.0% (0.5 to 2.1%)
Abdominal symptoms		
• Vomiting, nausea, abdominal pain	2	0.3% (0.0 to 0.9%)
• Loose stools	1	0.1% (0.0 to 0.7%)
Ear–nose–throat		
• Mild nose bleed	6	0.8% (0.3 to 1.7%)
Ocular		
• Itch, redness	1	0.1% (0.0 to 0.7%)
Neurological		
• Any	0	0% (0.0 to 0.5%)
Cardiovascular		
• Any	0	0% (0.0 to 0.5%)

Table 1: Delayed adverse events 2-72 hours post immunisation as reported by parents from 762 children with 72 hour follow-up.

Symptoms within 72 hours	- This Study -		Reported
Allergic reaction (mild symptoms) only	9/779	1.2%	0·02%
Allergic reaction: anaphylaxis	0/779	0%	0%
Fever	39/779	5.0%	5·4%
Nasal symptoms	141/779	18.1%	31%
Wheeze (parent reported)	29/779	3.7%	Not reported
Wheeze requiring treatment by physician	3/779	0.4%	0.2%
Lower respiratory symptoms	62/779	8.0%	Not reported
Eczema flare	22/779	2.8%	Not reported

Table 2: Rates of adverse events occurring within 72 hours after LAIV administration in SNIFFLE-2, compared to the published rates in the literature. Rates are reported as a proportion of total number of doses given, to be consistent with the method of reporting used in the existing literature.[15]

FIGURE LEGENDS

Figure 1: Participant flow diagram

13 children were consented but were not eligible for the study: 6 due to recent antihistamine use (family declined a further study appointment); 5 refused after parental consent had been obtained; 2 with unstable asthma (and who were given IIV instead).

Figure 2: Change in Asthma Control Test (ACT) score at 4 weeks post LAIV, compared to baseline, in children with a history of asthma or recurrent wheeze.