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

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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.

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.

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, 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 appears safe for use in egg-allergic children, including those with 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 is safe for use in 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 similar safety profile to inactivated influenza vaccines (IIVs).[5–9]

In common with other influenza vaccines licensed for use in children, LAIV is grown in hens' eggs and contains egg proteins.[10] 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.[11] Egg allergy is estimated to be 2.5% in this age group,[12] 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 that LAIV may induce wheezing in younger children.[13] 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.[14] Asthma was classified according to current therapy at time of immunisation using the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines.[15]

Participants were excluded if they had previously required invasive ventilation for anaphylactic reaction to egg, had severe unstable asthma, 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).[16] 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.[17] 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.[18]

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. Systemic allergic reaction (anaphylaxis) was defined according to the Brighton Collaboration Case definition.[19] Secondary outcomes were: incidence of delayed symptoms occurring up to 72 hours after LAIV administration (including those of non-allergic aetiology); change in ACT Test 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. Causality of adverse events was reviewed by an independent data monitoring committee (IDMC), 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; children with evidence of >95% likelihood of egg allergy (according to published criteria); prior history of anaphylaxis to egg; history of previous reaction to airborne traces of egg; tolerance to extensively heated egg; prior influenza administration (IIV or LAIV) and 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.

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 >1ng/ml ovalbumin.

All children were excluding egg from their diet at the time of immunisation. Three hundred and sixteen (40.6%) had experienced an allergic reaction to egg in the last 12 months. Forty (5.1%) had undergone formal, in-hospital food challenge within the previous 12 months to confirm their diagnosis. 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 for clinical egg allergy.[20] 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. Only 38 (5%) 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. Six were not consistent with a potential, IgE-mediated allergic response as defined by international consensus.[19] Two children reported skin symptoms (urticaria/angioedema) between 30 and 120 minutes following LAIV; both underwent subsequent specialist allergy testing four weeks later (both 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 following LAIV; 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%.

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, severity of egg allergy, previous influenza vaccination, 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).

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 6.3-10.3%) experienced lower respiratory symptoms within 72 hours, including 29 with parent-reported wheeze (3.8%, 95% CI for population 2.6-5.4%). 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 those over 5 years, although this did not reach statistical significance (22/149 (15%) 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 (Figure 2). There was no significant change in ACT score for children 12 years and over (p=0.12). In those aged 2-11 years, there was a small but significant improvement in ACT following LAIV (p<0.001). A similar improvement was also noted when the analysis was restricted to children under 5 years (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

We did not observe any systemic allergic reactions or anaphylaxis following administration of quadrivalent LAIV in egg-allergic children. Together with previous studies,[21,22] the literature now reports 955 egg-allergic children who have received at least one dose of LAIV without an acute systemic reaction (including anaphylaxis). 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. The incidence of possible local, IgE-mediated reactions is higher (1.2%) than that previously reported for non-egg-allergic individuals.[23] 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.[24] We have previously demonstrated that LAIV is unlikely to contain enough egg protein to trigger an IgE-mediated allergic reaction in egg-allergic individuals.[25] Quadrivalent LAIV therefore appears to be safe for administration to children with egg allergy, including those with a history of prior anaphylaxis to egg.

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;[21] 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).[4-7,9,23,24]

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,[13] due to concerns that LAIV might cause wheezing in susceptible children, something not consistent with published data.[4-6,23, 26,27] 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.[28] 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 LAIV is available, and 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 therefore chose to use 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 demonstrate the safety of LAIV in children with a history of asthma or recurrent wheeze, in whom symptoms are well-controlled.

In summary, this study provides evidence to support the revised Department of Health guidance for the 2015/16 season[18] that, with the exception of children with a history of very severe anaphylaxis to egg requiring intensive care, LAIV can be safely administered to egg-allergic children, including those with prior anaphylaxis in any setting (including primary care and schools). 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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References

1. Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds J. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modeling study. PLoS Med. 2013 Oct;10(10):e1001527.
2. JCVI statement on the routine annual influenza vaccination programme. https://www.gov.uk/government/publications/jcvi-statement-on-the-routine-annual-influenza-vaccination-programme. (Accessed 19 August 2015)
3. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12:36-44.
4. Ambrose CS, Wu X, Knuf M, Wutzler P. The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: a meta-analysis of 8 randomized controlled studies. Vaccine 2012;30:886-92.
5. Tennis P, Toback SL, Andrews E, McQuay LJ, Ambrose CS. A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in non-recommended children younger than 5 years. Vaccine. 2011;29(31):4947-52.
6. Ambrose CS, Yi T, Falloon J. An integrated, multistudy analysis of the safety of Ann Arbor strain live attenuated influenza vaccine in children aged 2-17 years. Influenza and other respiratory viruses. 2011;5(6):389-97.
7. Baxter R, Toback SL, Sifakis F, Hansen J, Bartlett J, Aukes L, et al. A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 5 through 17 years of age. Vaccine. 2012;30(19):2989-98.
8. Kelso JM. Safety of influenza vaccines. Current opinion in allergy and clinical immunology. 2012;12(4):383-8.
9. Tennis P, Toback SL, Andrews EB, McQuay LJ, Ambrose CS. A US postmarketing evaluation of the frequency and safety of live attenuated influenza

vaccine use in nonrecommended children younger than 5 years: 2009-2010 season. Vaccine. 2012;30(42):6099-102.

10. European Medicines Agency: Summary of Product Characteristics for Fluenz Tetra. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002617/WC500158412.pdf. Accessed 1 September 2015.
11. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/418428/Annual_flu_letter_ 24_03_15__FINALv3_para9.pdf (accessed 2 July 2015)
12. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines Group. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992-1007.
13. Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2015–16 Influenza Season. Morbidity and Mortality Weekly Report (MMWR) 2015; 64(30);818-825.
14. World Allergy Organization guidelines for the assessment and management of anaphylaxis. WAO J 2011;4:13-37.
15. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. Available at: https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/. Accessed September 30, 2014.
16. Bousquet PJ, Combescure C, Klossek JM, Daures JP, Bousquet J. Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. J Allergy Clin Immunol 2009;123:1349-54.

17. Jia CE, Zhang HP, Lv Y, Liang R, Jiang YQ, Powell H, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: Systematic review and meta-analysis. J Allergy Clin Immunol. 2013; 131:695-703.
18. Public Health England. Chapter 19: Influenza. In: Immunisation against infectious disease. Department of Health. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/347458/Green_Book_Chapter_19_v6_0.pdf. Accessed September 30, 2014
19. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675–84.
20. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. Pediatr Allergy Immunol 2004;15:435-41.
21. Turner PJ, Southern J, Andrews NJ, Miller E, Erlewyn-Lajeunesse M; SNIFFLE Study Investigators. Safety of live attenuated influenza vaccine in atopic children with egg allergy. J Allergy Clin Immunol. 2015;136:376-81.
22. Des Roches A, Samaan K, Graham F, Lacombe-Barrios J, Paradis J, Paradis L, et al. Safe vaccination of egg allergic patients with live attenuated influenza vaccine. J Allergy Clin Immunol Pract 2014;3:138-9.
23. Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med 2007;356:685-96.
24. Izurieta HS, Haber P, Wise RP, Iskander J, Pratt D, Mink C, et al. Adverse events reported following live, cold-adapted, intranasal influenza vaccine. JAMA 2005; 294:2720-5.
25. Turner PJ, Erlewyn-Lajeunesse M. Egg protein in the intranasal live-attenuated influenza vaccine (LAIV) is unlikely to cause egg-mediated allergic reactions in egg-allergic children. J Allergy Clin Immunol Pract 2015; 3:312-3.

26. Belshe RB, Ambrose CS, Yi T. Safety and efficacy of live attenuated influenza vaccine in children 2-7 years of age. Vaccine 2008;26(suppl 4):D10-6.

27. Gaglani MJ, Piedra PA, Riggs M, Herschler G, Fewlass C, Glezen WP. Safety of the intranasal, trivalent, live attenuated influenza vaccine (LAIV) in children with intermittent wheezing in an open-label field trial. Pediatr Infect Dis J 2008; 27:444-52.

28. Ambrose CS, Dubovsky F, Yi T, Belshe RB, Ashkenazi S. The safety and efficacy of live attenuated influenza vaccine in young children with asthma or prior wheezing. Eur J Clin Microbiol Infect Dis. 2012 Oct;31(10):2549-57.

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

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

Symptoms within 72hrs	- 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.[23]

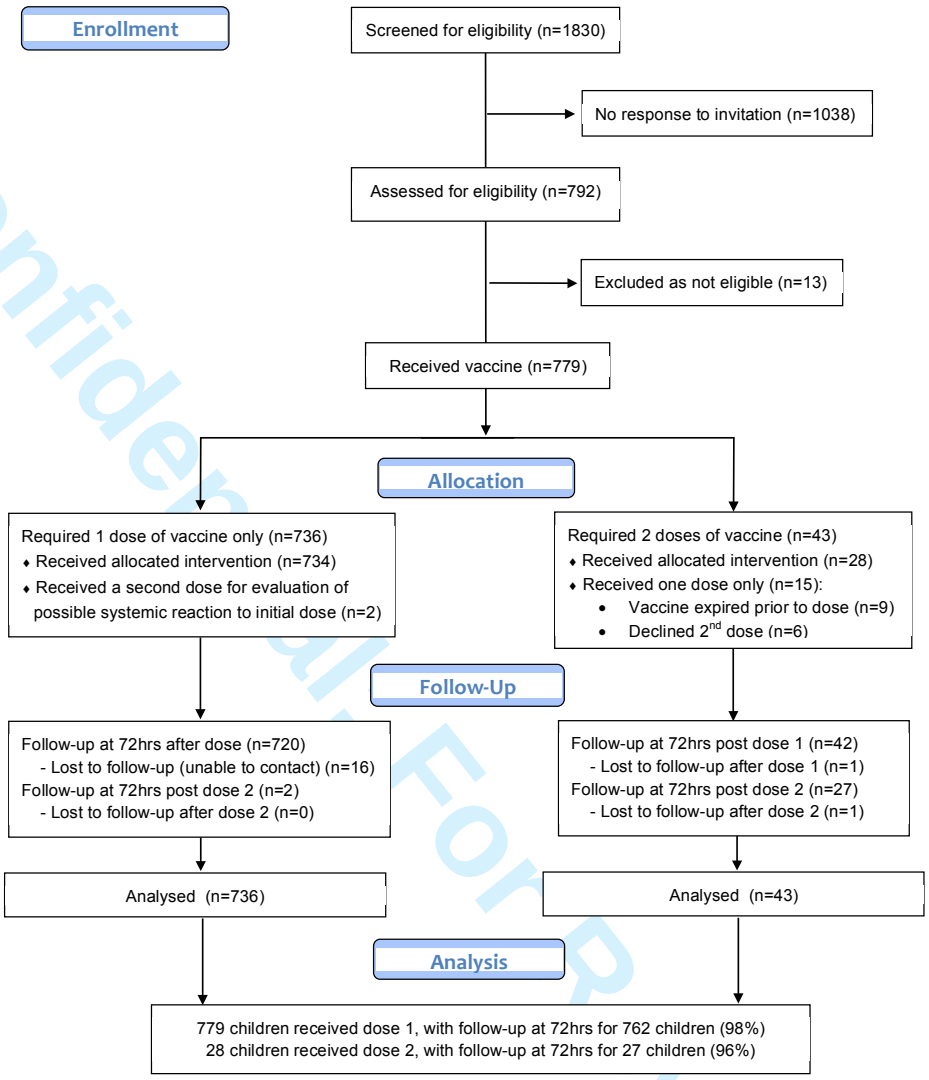

Figure 1: Participant flow diagram

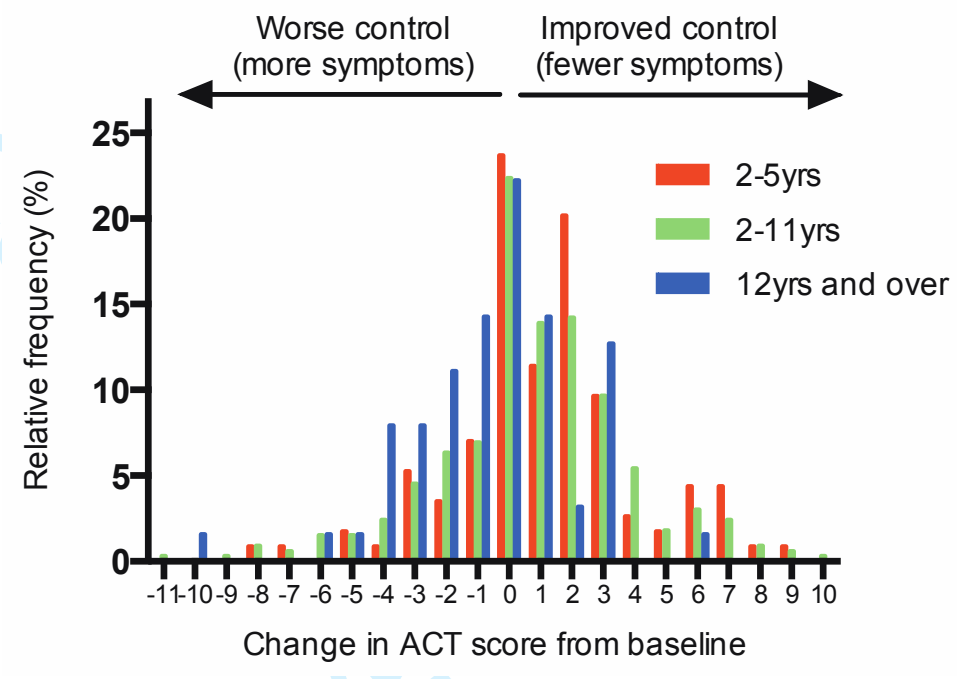

Figure 2: Change in Asthma Control Test (ACT) score at 4 weeks post LAIV, compared to baseline, in children with a history of asthma or recurrent wheeze.