Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Ensuring safe access to the influenza vaccination programmes in the UK and US for children with egg allergies and asthma.

Period when the underpinning research was undertaken: 2013 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Paul Turner	Reader	2012 - present
John Tregoning	Reader in Respiratory Infections	2011 - present

Period when the claimed impact occurred: September 2013 - present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum of 100 words)

Anaphylaxis to egg was a documented contraindication for the live attenuated influenza vaccine (LAIV), produced in eggs. In the USA, asthma was a relative contraindication. Egg allergy (with risk of anaphylaxis) and/or asthma affects over 10% of children, so the impact on national vaccination programmes has been very significant. The SNIFFLE studies were undertaken to generate evidence of the safety of LAIV in children with egg allergy and/or asthma, resulting in changes in vaccine policy, both in the UK (2015, 2019) and North America. Following concerns over vaccine efficacy in the USA, the SNIFFLE studies (and associated mechanistic work) also generated critical efficacy data to support the ongoing inclusion of LAIV in the UK.

2. Underpinning research (indicative maximum of 500 words)

Seasonal influenza causes over 500,000 deaths each year. Epidemiological data and mathematical modelling indicate children are the main spreaders of influenza infection; thus, a vaccination programme targeting children provides the most effective method for interrupting transmission and achieving disease control.

Annual influenza vaccination for children was introduced to the UK in 2013, using the intranasal live attenuated influenza vaccine (LAIV). However, in common with other influenza vaccines, LAIV is grown in hens' eggs and contains egg proteins; the vaccine was thus contraindicated for use in children with egg allergy. On the basis of UK 2013 census data, there are over 60,000 egg-allergic children eligible for vaccination in whom LAIV would be contraindicated. US guidelines further recommended against LAIV in children with recurrent wheeze and asthma (estimated to affect up to one third of preschool children), due to limited evidence from a single clinical trial. These contraindications represented significant barriers to achieving successful implementation of the immunisation programme in the UK. Researchers at Imperial College therefore sought to assess the safety of LAIV in children with egg allergy and/or asthma in a series of multicentre, interventional studies.

SNIFFLE-1 (2013/14) & SNIFFLE-2 (2014/15) were interventional studies in which 887 egg-allergic children across 30 paediatric centres in the UK were given LAIV and then monitored for adverse events following vaccination. The studies, led and coordinated by Paul Turner at Imperial College, demonstrated the safety of LAIV in children with egg allergy, with no cases of systemic allergic reaction observed (1, 2). The INATE study (2013/14) provided further evidence of the safety of LAIV in this cohort by demonstrating that the maximum amount of egg protein in LAIV

was some 10-100 times less than that needed to trigger even the mildest local allergic response in children with egg allergy (3).

SNIFFLE-2 also generated reassuring data that the vaccine could be safely used in children with mild-moderate asthma with well-controlled symptoms. However, a concern remained as to its safety in children with more significant asthma. The SNIFFLE-3 study (2015/16) was designed to pilot tools to monitor immune response and asthma and generate data to help demonstrate the ongoing efficacy of LAIV in the UK (4,5). This was essential due to data from USA that efficacy of the vaccine may have fallen from >85% pre-2009 to <5% in 2015/16 season. In SNIFFLE-4 478 children were recruited across 14 UK centres nationally, to assess the safety of LAIV in children with severe asthma. The study confirmed that the vaccine can be safely used in children with asthma across the severity spectrum (6).

Imperial College were the central coordinating site for the studies, as well as host institution for Dr Turner, who wrote the protocols and established a new research network in order to carry out the study. SNIFFLE-1 and -2 were also facilitated by co-chief investigator Dr Erlewyn-Lajeunesse of University Southampton Hospitals. Members of the National Vaccine Evaluation Committee (NVEC) at Public Health England (Lead, Prof Elizabeth Miller) contributed to all 4 studies in terms of study support and data analysis.

3. References to the research (indicative maximum of six references)

(1) Turner, P.J., Southern, J., Andrews, N.J., Miller, E., Erlewyn-Lajeunesse, M.; on behalf of the SNIFFLE Study Investigators. (2015). Safety of live attenuated influenza vaccine in atopic children with egg allergy. *J Allergy Clin Immunol*; 136: 376-81. DOI.

(2) Turner, P.J., Southern, J., Andrews, N.J., Miller, E., Erlewyn-Lajeunesse, M.; SNIFFLE-2 Study Investigators. (2015). Safety of live attenuated influenza vaccine in young people with egg allergy: multicentre prospective cohort study. *BMJ*; 351:h6291. DOI.

(3) Turner, P.J., Erlewyn-Lajeunesse, M. (2015). Intranasal live-attenuated influenza vaccine (LAIV) is unlikely to cause egg-mediated allergic reactions in egg-allergic children. *J Allergy Clin Immunol Practice*; 3: 312-3. DOI.

(4) Hoschler, K., Maharjan, S., Whitaker, H., Southern, J., Okai, B., Baldevarona, J., Turner, P.J., Andrews, N.J., Miller, E., Zambon, M. (2020). Use of traditional serological methods and oral fluids to assess immunogenicity in children aged 2-16 years after successive annual vaccinations with LAIV. *Vaccine*; 38(12): 2660-2670. DOI.

(5) Turner, P.J., Abdulla, A.F., Cole, M.E., Javan, R.R., Gould, V., O'Driscoll, M.E., Southern, J., Zambon, M., Miller, E., Andrews, N.J., Höschler, K., Tregoning, J.S. (2020). Differences in nasal immunoglobulin A responses to influenza vaccine strains after live attenuated influenza vaccine (LAIV) immunization in children. *Clin Exp Immunol*; 199(2): 109-118. DOI.

(6) Turner, P.J., Fleming, L., Saglani, S., Southern, J., Andrews, N.J., Miller, E.; SNIFFLE-4 Study Investigators. (2020). Safety of live attenuated influenza vaccine (LAIV) in children with moderate to severe asthma. *J Allergy Clin Immunol*; 145(4): 1154-1164.e6. DOI.

4. Details of the impact (indicative maximum of 750 words)

These Imperial-led studies have resulted in policy changes to the annual 'flu vaccination programme in the UK, facilitating uptake amongst pre- and primary school age children and contributing to uptake of over 60% in the UK paediatric population.

Following review of the SNIFFLE-1 and -2 studies by the Joint Committee for Vaccination and Immunisation (JCVI; an independent expert advisory committee which provides advice to the UK Departments of Health on matters pertaining to immunisation) in June 2015, JCVI recommended

changes to UK vaccine guidance whereby the contraindication of egg allergy was effectively removed. This facilitated the roll out of seasonal influenza vaccination in UK children [**A**; see page 4, point 12; **B**; see page 19]. A similar process was followed for SNIFFLE-4 in 2019, resulting in further changes in guidance with respect to children with asthma [**B**; see page 18; and **C**; see pages 13-14]. The guidance now states, as a result of the SNIFFLE-4 data, "*children with asthma on inhaled corticosteroids may safely be given LAIV, irrespective of the dose prescribed*" [**C**; see page 18]. Importantly, this has resulted in a shift towards use of LAIV in children of all ages with asthma. Given the evidence that LAIV induces a higher level of immunity than injected influenza in children, this shift may offer better protection to older children with asthma.

Changes in practice were further reinforced through presentations at a number of national and international meetings. Public Health England (PHE) have credited the SNIFFLE studies as having been one factor facilitating the roll-out of LAIV amongst eligible children, achieving uptake exceeding 60% [**D**: see page 4].

While there was emerging evidence from the UK and Canada that injected influenza vaccines are safe in children with egg allergy, evidence was lacking for LAIV. Thus, egg-allergic children in USA could only be offered the injected vaccine. Data generated from SNIFFLE-1 and -2 studies were also presented to the Centers for Disease Control and Prevention (CDC), the USA's health protection agency, in turn resulting in a change in US and Canadian guidance [**E, F, G**; see section new developments] whereby LAIV is no longer contraindicated for the majority of egg-allergic children, and so "*Persons reporting symptoms other than hives after exposure to egg (such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention) may also receive any licensed and recommended influenza vaccine [including LAIV] that is otherwise appropriate*" [**E**].

SNIFFLE-3 and SNIFFLE-4 studies generated biological samples (nasal swabs, saliva and serum samples) that were used by both Imperial College London researchers and PHE to assess the response to changes in vaccine strains included in LAIV. This was due to concerns in the USA, which had reported that vaccine efficacy might have fallen from >85% pre-2009 to <5% in 2015/16 season, and led to a change in the strains included for the 2017/18 season. The collaboration between Imperial and PHE allowed the collection of biological samples from patients participating in the SNIFFLE and FLUSHED studies (also run at Imperial), which facilitated further mechanistic work evaluating both vaccine efficacy and local mucosal immunity following LAIV [**H, I**]. These results contributed to the assessment by the UK's JCVI that LAIV continued to demonstrate efficacy (midseason vaccine efficacy in 2018/19 of 87%) [**C**], thus supporting the ongoing use of LAIV in the UK's National Immunisation Programme.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Minutes of the Joint Committee on Vaccination And Immunisation, June 2015 meeting. Available at: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/229171865007 (see page 4, point 12). Archived here.

[**B**] Public Health England. Influenza: the green book, chapter 19. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/931139/Green_book_chapter_19_influenza_V7_OCT_2020.pdf (see page 18 - 19). Archived here.

[**C**] Minutes of the Joint Committee on Vaccination And Immunisation, February 2019 meeting. Available at: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/424913874479 (see pages 13-14, 18). Archived here.

[**D**] Public Health England. Seasonal influenza vaccine uptake in children of primary school age

Winter season 2019 to 2020. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/894772/Childhood_flu_annual_report_2019_20.pdf (see page 4). Archived here.

[**E**] Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2018-19. Available at: https://www.cdc.gov/flu/professionals/acip/2018-2019/2018-19summary.htm (archived here) & https://www.cdc.gov/flu/professionals/acip/2018-2019/background/safety-vaccines.htm#EggAllergy

[**F**] National Advisory Committee on Immunization (NACI) Canada. LAIV Use in Egg Allergic Individuals Advisory Committee Statement. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=14&ved=2ahUKEwj0lc3w0szdAhWLbMAKHfHZC_IQFjANegQIBhAC&url=https%3A%2F%2Fwww.canada.ca%2Fcontent%2Fdam%2Fphac-aspc%2Fmigration%2Fphac-aspc%2Fnaci-ccni%2Fassets%2Fpdf%2Ffinal-addendum2016-17-laiv-egg-allergy-eng.pdf&usg=AOvVaw3WTkB_vR6XfiTirp1llkui (Archived here).

[**G**] Greenhawt, M., Turner, P.J., Kelso, J.M. Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017. DOI.

[**H**] Jackson, D., Pitcher, M., Hudson, C., Andrews, N., Southern, J., Ellis, J., Höschler, K., Pebody, R., Turner, P.J., Miller, E., Zambon, M. (2020). Viral Shedding in Recipients of Live Attenuated Influenza Vaccine in the 2016-2017 and 2017-2018 Influenza Seasons in the United Kingdom. *Clin Infect Dis*; 70(12): 2505-2513. DOI.

[**I**] Cole, M.E., Kundu, R., Abdulla, A.F., Andrews, N., Hoschler, K., Southern, J., Jackson, D., Miller, E., Zambon, M., Turner, P.J., Tregoning, J.S. (2020). Pre-existing influenza-specific nasal IgA or nasal viral infection does not affect live attenuated influenza vaccine immunogenicity in children. *Clin Exp Immunol*; 204(1): 125-133. DOI.