Institution: University of Oxford

Unit of Assessment: 5 – Biological Sciences

Title of case study: Better protection against influenza through national childhood vaccination programmes

Period when the underpinning research was undertaken: 2000 to 2003

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:
Ervin Fodor	Academic Fellow, now Professor	1998 - present
George Brownlee	Professor	1998 - 2008

Period when the claimed impact occurred: 1 August 2013 to 31 December 2020

Is this case study continued from a case study submitted in 2014? Y

1. Summary of the impact

Reverse genetics technology invented by University of Oxford researchers has been used to generate influenza vaccine strains for the production of influenza vaccines used worldwide. MedImmune (now part of AstraZeneca) used the patented technology to generate FluMist Quadrivalent, an intranasal live attenuated vaccine protective against four influenza virus strains, for use in children. The trivalent formulation Fluenz was made available as the influenza vaccine of choice in the expansion of the UK National Vaccination Programme to include healthy children aged 2 to <17 years. The European branded version of the quadrivalent vaccine, Fluenz Tetra, was introduced in the UK in 2013. During the current REF period, it remained the vaccine of choice for the National Childhood Vaccination Programme, providing protection to these children and also to vulnerable members of the population by reducing community transmission. The Programme has resulted in 20,000,000 children being vaccinated in the UK. It has significantly reduced the incidence of influenza in primary care and influenza hospital admissions in children and in the wider community and has led to a reduction in the excess respiratory mortality. The vaccine has also been introduced as part of national childhood vaccination programmes in other countries including the US, Canada, Finland and South Korea.

2. Underpinning research

The World Health Organization estimates that 290,000 to 650,000 deaths occur worldwide every year from flu-related illnesses. In the UK alone, annual outbreaks of seasonal flu affect 5 to 20% of the population. On average, an estimated 17,000 people die from flu each year in England; however, in a bad flu year, deaths can be much higher, such as in 2014/15 when there were over 28,000 deaths. Flu has particularly serious consequences for the elderly. Hospital costs for influenza-related admissions are approximately GBP100,000,000 per season, with the 65+ year group associated with the highest costs and proportion of in-hospital deaths. Flu also results in more than 400,000 GP appointments annually in England and Wales. In addition to healthcare costs, flu also places a heavy burden on productivity and the economy; more than 6,000,000 working days are estimated to be lost in the UK due to seasonal influenza every year.

Ervin Fodor in Professor George Brownlee's laboratory at the University of Oxford, working in collaboration with Palese and Garcia-Sastre (Mount Sinai School of Medicine, New York) devised a method for producing a wide range of influenza viruses within the laboratory. In this approach, recombinant influenza viruses are generated after plasmid transfection using reverse genetics. In 2003 a patent was granted to Palese, Garcia-Sastre, Brownlee and Fodor describing the technology, which enhances the specificity, reliability, safety and efficiency with which new vaccine strains can be produced [1].

Fodor and Brownlee, in collaboration with Subbarao at the Centre for Disease Control, Atlanta, applied the method to generate a series of vaccine candidates. The method was particularly powerful because, combined with the relative ease of manipulating DNA plasmids, it enabled any desired mutation to be introduced into any of the eight individual RNA segments that comprise the influenza RNA genome. A key achievement was generation of a candidate vaccine against the highly pathogenic H5N1 avian influenza as proof of principle, showing that new vaccine strains could be generated rapidly, simply and reproducibly [2]. The study also reported that the method allows the genetic modification of the virus to eliminate determinants of high pathogenicity, an important safety consideration during vaccine production particularly against pandemic vaccine strains.

The body of research described here is the same as in the impact case study 'Revolution in influenza vaccine production', submitted by the University of Oxford in REF2014.

3. References to the research (University of Oxford employees in bold)

1. *Patent:* Palese P, García-Sastre A, **Brownlee GG** and **Fodor E** (2003) Helper-free rescue of negative strand RNA virus. United States Patent 6649372. First published on 18.01.01. Application granted 18.11.03. https://patents.google.com/patent/US6649372

2. *Journal Article:* Subbarao K, Chen H, Swayne D, **Mingay L**, **Fodor E**, **Brownlee G**, Xu X, Lu X, Katz J, Cox N and Matsuoka Y (2003) Evaluation of a genetically modified reassortant H5N1 influenza A virus vaccine candidate generated by plasmid-based reverse genetics. *Virology* 305:192-200. DOI:10.1006/viro.2002.1742

The research at the University of Oxford was supported by two **Medical Research Council** grants to G. Brownlee,: a Programme Grant for GBP1,128,390 (reference G9523972, commenced 1998) entitled 'The role of the RNA fork in the transcription and replication of influenza A virus', and a Cooperative Component Grant for GBP224,904 (G9901312, 2001) entitled 'Identification of cap-binding and endonuclease domains in the PB2 subunit of the RNA polymerase of influenza A virus.'

4. Details of the impact

Context and pathway to impact

The reverse genetics technology covered by the patent to Fodor, Brownlee and colleagues [1] is used by AstraZeneca to manufacture its seasonal flu vaccine each year, ensuring that it contains the most relevant and up-to-date virus strains [A]. The technology was licensed to MedImmune Inc. (now part of AstraZeneca) to improve production of the initially licensed trivalent formulation vaccine, branded as FluMist in the U.S. and Fluenz in Europe, which is a live attenuated influenza vaccine (LAIV) and given intranasally. The technology was first applied to generate FluMist as trivalent (LAIV) vaccine for the 2008 and following seasons. In 2012, it was used to generate the quadrivalent vaccine (FluMist Quadrivalent, LAIV4) protecting against four flu virus strains. FluMist Quadrivalent and Fluenz Tetra, licensed in the US and Europe respectively, have been in use worldwide since 2013.

Prior to 2008, LAIV vaccine virus strains were generated by an inefficient empirical process of natural genetic reassortment between the wild-type influenza virus and the LAIV Master Donor Virus. The helper-free reverse genetics technology in the patent granted to the University of Oxford researchers [1] was described by AstraZeneca as vital to the success of FluMist and Fluenz:

"This technology has been of critical importance to the success of Flumist/Fluenz as it is a quicker, simpler and more robust way of generating the vaccine strains than previous technology. This is important as the timelines to manufacture seasonal influenza vaccines are incredibly challenging. This technology has increased the speed of the vaccine to market, ensuring that the maximum number of patients are able to receive the vaccine before the start of the Flu season." [Ai]

The REF2014 impact case study described the health benefits from use of FluMist in the U.S. from 2008 to July 2013, the economic benefits to MedImmune from FluMist sales and the impact of the reverse genetics technology for the production of vaccines against the 2009 swine-origin pandemic influenza virus. This impact case study describes wider health benefits to populations from use of FluMist and Fluenz in national childhood vaccination programmes the UK and other countries from August 2013 to 2020.

Introduction and uptake of the UK's childhood influenza national vaccination programme

In 2012, the Joint Committee on Vaccination and Immunisation (JCVI) recommended the stepwise roll-out of a universal childhood influenza vaccine programme with the trivalent vaccine Fluenz [B]. The programme was recommended to cover all children 2-17 years of age because children experience some of the highest rates of infection during seasonal epidemics and also play a key role in the spread of the virus. Recommendation of the programme was based on its predicted direct and indirect impact, with the aim to provide individual protection to children themselves and, by reducing transmission across all age groups, protection to vulnerable members of the population. The commonly used trivalent inactivated influenza vaccine was documented to have poor immunogenicity in children and therefore the intranasally administered LAIV, which early efficacy studies suggested provides excellent protection for children, was recommended. The LAIV vaccine is suitable for all children except those who are clinically immunosuppressed.

Flu vaccination has been offered to children in a phased roll-out since 2013. The programme was initiated with the trivalent LAIV and then changed to LAIV4 following European approval in 2013. Fluenz was introduced in the 2013-14 flu season, UK-wide, to all children aged 2 and 3 years [C]. The vaccine was subsequently rolled out to include older children, starting in 2014/15 with school year 1 and expanding by a single year group each season up to the current 2020/21 season when it has been offered to children who have just started secondary school in year 7. The programme combined stepped roll-out nationally with geographical school-based pilots covering the full 4-11 age range and additionally, in some cases, secondary school children (11-13 years). Over 20,000,000 children in the UK aged 2-17 have been vaccinated since the programme was rolled out in 2013 [A]. Vaccine uptake has generally increased over the period of introduction of the vaccine and ranges from 30% to 80% [D]. The intranasal formulation may have helped to make vaccination more acceptable in this age group by overcoming needle phobia, which is estimated to affect at least 10% of children.

Health impact of the UK's childhood influenza national vaccination programme

Since its introduction in 2013/14, the programme has been shown to positively impact influenza-related outcomes in children and the community as a whole, with the greatest impact observed in pilot areas where children in *all* primary school years have been offered vaccination. Early results from the school-based pilot in England in the 2013/14 season followed by an evaluation of the impact of the programme and continuation of the pilots in the 2014/15 season informed the programme's national roll-out. The early results indicated that the programme in the pilot areas had a significant impact on flu in multiple age groups [E]. Evaluation of the 2014/15 season confirmed this [F]; vaccinating primary school-aged children resulted in direct protection in children aged 5–10 years, with significant reductions in cumulative GP influenza-like illness (ILI) consultations (94% reduction), emergency department respiratory attendances (74% reduction) and confirmed influenza hospital admissions (93%) as well as a reduction in excess respiratory mortality. These changes were also associated with indirect protection of other age groups. Information captured by the Royal College of General Practitioners network for the 2014/15 season showed that cumulative GP ILI consultation rates in individuals aged 50-70 years were lower in pilot areas that vaccinated primary and secondary (children aged 11–13 years) school children compared with non-pilot areas (consultation rate: 3.4 per 100,000 versus 17.4 per 100,000, respectively); similar results were also seen for swab positivity (7.7% positive versus 29.5% positive, respectively) [D]. These changes were accompanied by a significant reduction in cumulative GP ILI consultations at a population level i.e. in individuals aged 17 years or more (59% reduction) [F].

A review of clinical impact of the programme across all UK nations over six influenza seasons provided further data about vaccine effectiveness and influenza-related outcomes in different

age groups [D]. Vaccine effectiveness against laboratory-confirmed influenza in children aged 2-17 in primary care in the UK varied from year to year. Whilst the data were not available for the first two seasons, the vaccine prevented 58% of flu cases in 2015/16, 66% of flu cases in 2016/17, 27% of flu cases in 2017/18, 49% of flu cases in 2018/19 and 45% of flu cases in 2019/20 [D,G]. In the 2015/16 season, vaccinating primary school-aged children was associated with lower ILI GP consultations and swab positivity in children of primary school age and those aged <5 years for pilot versus non-pilot areas. In addition, these changes were associated with significant indirect protection of the wider population, with reductions in the adjusted cumulative primary care indicators for ILI (63% reduction) and swab positivity (estimated 48% reduction) in individuals aged 17 years or more from pilot areas compared with those from non-pilot areas. In Northern Ireland, significant reductions were observed in GP in-hours consultations and out-of-hour calls for ILI both overall (61% reduction in GP in-hours; 51% reduction in out-of-hours) and in children aged <14 years (38% reduction in GP in-hours; 39% reduction in out-of-hours), in seasons with full implementation of the programme (2014/15 to 2016/17) compared with pre-programme seasons (2010/11 to 2012/13).

There is also evidence that vaccination in young children through the programme may contribute to a reduction in prescribing of amoxicillin in children. Amoxicillin is one of the most prescribed antibiotics in primary care and is indicated for two common complications of influenza: community-acquired pneumonia and acute otitis media. Whilst further studies are needed to confirm the size of the effect, a study in 2017 found a 12.8% to 14.5% reduced rate of amoxicillin prescribing during periods of LAIV-induced immunity in preschool children [H].

As the UK's programme expanded beyond the pilot areas and to older children, it has become more challenging to fully capture the benefits of the vaccination programme especially those on the wider community. Nevertheless, the data available to date demonstrate a positive impact of the UK's programme for a range of key surveillance indicators. In addition, an economic analysis of influenza vaccination in England found that vaccination (across all age groups) helped to avert between 5,678 and 8,800 premature deaths per year [I].

Cost-effectiveness of the UK's childhood influenza national vaccination programme
Cost-effectiveness studies were amongst those that provided evidence supporting extending the UK influenza vaccination programme to children in 2012. These studies continue to support the vaccination of children to optimise the benefits of influenza vaccination programmes. A recent cost-benefit assessment of influenza vaccination in England concluded that "*public policy should focus on improving coverage rates among young people aged 15 years or under, as the most efficient approach to improving overall benefits relative to costs*" [I].

Impact of use of Fluenz/FluMist vaccine worldwide
Influenza vaccination of healthy children with Flumist/Fluenz has been introduced through national vaccination programmes in the United States, Canada, Finland and other European countries, and South Korea. Up to 22,000,000 doses of Flumist/Fluenz are manufactured in Liverpool, UK each season and used to vaccinate people in the US, Europe, Israel, Canada and South Korea [A].

FluMist has been used in the US since before 2013 in children from the age of 2 upwards. FluMist Quadrivalent is approved for use in healthy individuals aged 2-49 and was first introduced in the 2013/14 season. The US Advisory Committee on Immunization Practices recommends annual influenza vaccination for everyone aged 6 months and older with any licensed, influenza vaccine that is appropriate for the recipient's age and health status. FluMist has been used in most seasons since 2013/14 and from 2018/19 onwards [J].

In Finland, influenza vaccine has been given free of charge to all eligible children (6-35 months) since 2007. To enhance vaccine uptake, Fluenz (Fluenz Tetra) was introduced in the 2015/16 season. Since then, all 2-year-old children have been eligible for vaccination with either Fluenz or trivalent inactivated influenza vaccine, without a recommended preference. Vaccination coverage has increased steadily following Fluenz introduction – from 11% of children aged 6–35 months in 2014/15 to 24% in 2017/18 [K]. Vaccine effectiveness of Fluenz measured over three seasons (2015/16 to 2017/18) was comparable with that in the UK – between 20% and 54%. Since the 2018/19 season, children aged between 2 and 6 years have been offered the Fluenz

vaccine free of charge as part of the national vaccination programme. For the 2020/21 season, 116,000 doses of Fluenz were procured for the programme which is sufficient for four out of ten children in this age range [L].

With COVID-19 putting pressure on hospitals in winter 2020/21, Ireland offered Fluenz for the first time to children aged between 2 and 12 years from October to December 2020 [M].

5. Sources to corroborate the impact

A. Letter (i) and email (ii) from Director of Virology and Vaccines Discovery, Biopharm R&D, AstraZeneca, corroborating the company's use of the technology covered by patent [1] in manufacturing the LAIV influenza vaccine and vaccinations given in the UK.

B. JCVI statement on the annual influenza vaccination programme – extension of the programme to children, 25 July 2012. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012.pdf

C. Department of Health, Public Health England and NHS England letter: Influenza immunisation programme 2013-14 – extension to children. 26 July 2013. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/225360/Children_s_flu_letter_2013.pdf

D. Journal article: Kassianos G et al. (2020). Implementation of the United Kingdom's childhood influenza national vaccination programme: A review of clinical impact and lessons learned over six influenza seasons.' *Vaccine* 38(36) DOI: 10.1016/j.vaccine.2020.06.065

E. Journal article: Pebody RG et al (2014). Uptake and impact of a new live attenuated influenza vaccine programme in England: early results of a pilot in primary-school age children, 2013/14 influenza season' *Euro Surveill.* 19(22):20823 https://www.eurosurveillance.org/content/10.2807/ese.19.22.20823-en

F. Journal article: Pebody RG et al (2015) Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. *Euro Surveill.* 20(39):30029. DOI:10.2807/1560-7917.ES.2015.20.39.30029

G. Information about the Nasal Flu Vaccine, Vaccine Knowledge Project, University of Oxford, updated 12/8/2020. http://vk.ovg.ox.ac.uk/vk/nasal-flu-vaccine

H. Journal article: Hardelid P et al (2017), Effectiveness of LAIV in preventing amoxicillin prescribing in preschool children: a self-controlled case series study. *Journal of Antimicrobial Chemotherapy* 73(3) DOI: 10.1093/jac/dkx463

I. An economic analysis of flu vaccination. Report from the International Longevity Centre UK, 5 July 2018. https://ilcuk.org.uk/wp-content/uploads/2018/07/An_economic_analysis_of_flu_vaccination_-_ILC-UK.pdf

J. Live Attenuated Influenza Vaccine (The Nasal Spray Flu Vaccine). Centers for Disease Control and Prevention website. https://www.cdc.gov/flu/prevent/nasalspray.htm

K. Journal article: Baum U et al. (2020). Effectiveness of 2 influenza vaccines in nationwide cohorts of Finnish 2-year old children in the seasons 2015-2016 through 2017-2018. *Clinical Infectious Diseases* 71(8). DOI: 10.1093/cid/ciaa050

L. Nasal Spray Influenza Vaccine for Children, Finnish Institute for Health and Welfare website, August 2020. https://thl.fi/en/web/infectious-diseases-and-vaccinations/vaccines-a-to-z/influenza-vaccine/nasal-spray-influenza-vaccine-for-children

M. Newspaper article 'The flu vaccine and children: Here is everything parents need to know'. September 28, 2020. https://www.thejournal.ie/flu-vaccine-children-ireland-5211677-Sep2020/