

## Impact case study (REF3)

<b>Institution:</b> King's College London		
<b>Unit of Assessment:</b> 1		
<b>Title of case study:</b> Revolutionising the understanding of childhood food allergy to halt the epidemic		
<b>Period when the underpinning research was undertaken:</b> 2000 – 2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Prof Gideon Lack	Professor of Paediatric Allergy	2006-present
Dr Alexandra Santos	Reader in Paediatric Allergy	2010-present
<b>Period when the claimed impact occurred:</b> 2014 – 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> N		

**1. Summary of the impact**

King's College London researchers have conclusively shown (i) that childhood peanut allergy is a largely preventable disease, and (ii) that early introduction of peanut in the diets of high-risk infants can prevent tens of thousands of children from developing peanut allergy every year. This breakthrough research has reversed global public health strategy and led to new international guidelines on infant weaning advocating early introduction of peanut products into infants' diets for the prevention of peanut allergy. This research provides a compelling rationale for exploring similar approaches to preventing other food allergies and autoimmune diseases. The impact of this work will also have a lasting effect on generations to come.

**2. Underpinning research**

**Peanut allergy is common and can be fatal.** The incidence of childhood food allergy has risen in recent decades, and peanut allergy (PA) has more than doubled in the last 10 years in the UK and North America; PA now affects 1 in 50 schoolchildren in the UK and is a global public health concern. PA develops early in life and there is currently no cure. It is a major cause of paediatric anaphylaxis and living with PA impacts negatively on the quality of life of patients and their families. Three King's led RCTs have conclusively demonstrated that early consumption of peanuts in infancy prevents the majority of peanut allergy developing in the population. This research has shown that the previous advice of peanut avoidance during infancy was not only incorrect but was a major cause of the rise in peanut allergy witnessed over previous decades.

**King's research found that consumption of peanuts in infancy is associated with low rates of peanut allergy.** The possibility of inducing tolerance to peanuts by eating them (oral tolerance) was explored in a King's study that compared the prevalence of PA in more than 10,000 Jewish children in the UK and Israel **(1)**. Both groups shared a common ancestral background, which meant that any differences found were likely to be due to nurture, not nature. PA was 10-fold more prevalent in UK children than in Israeli children. Paradoxically, Israeli infants consume large quantities of peanuts in the first year of life, whereas UK health guidance (until 2014) advised parents that children should avoid peanuts.

**King's researchers showed that environmental exposure is linked to developing peanut allergy, but also that early dietary exposure has a protective effect.** Evidence suggested that skin exposure to peanuts increased allergy risk: both eczema in the first 6 months of life (especially severe eczema), and the application to skin of creams containing peanut oil were known to be important independent risk factors in the development of PA. King's research showed, in a large case-controlled study of more than 12,000 infants, that high household exposure to peanut in the environment is associated with PA **(2)**; this supports the hypothesis that sensitisation to peanut occurs by exposure via the skin (especially via inflamed or broken skin). Although children exposed to high levels of environmental peanut had a high risk of developing PA, conversely, they appeared to be protected against developing PA if they had also eaten peanuts in the first year of

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life. These findings strongly suggested that guidelines to avoid giving peanuts to babies in the UK and the US were not only incorrect but also potentially harmful.

**King's research demonstrates that more than 80% of peanut allergy can be prevented.** The LEAP (Learning Early About Peanut allergy) study was a randomised controlled study where 640 highly atopic children with eczema and/or egg allergy were randomised at 4-11 months to consumption of peanut (6g protein per week) or complete avoidance. They were followed until 5 years of age, when they were determined to have either peanut allergy or peanut tolerance **(3)**. The rate of peanut allergy in the children who avoided peanut was 17.2%, and in the children consuming peanut it was 3.2% - an 81% reduction in the prevalence of peanut allergy. This finding conclusively demonstrated for the first time that early exposure to peanuts is an effective strategy in preventing allergy from developing in children.

In 2019 this paper **(3)** was chosen by the Editor-in-Chief of NEJM as one of the most influential articles published in the journal out of 4000 articles in the last 19 years. The LEAP study received the prestigious international David Sackett Clinical Trial of the Year Award for 2015, from the Society for Clinical Trials, for "the randomized clinical trial published in the previous year that best fulfils the following standards: improves the lot of humankind; provides the basis for a substantial, beneficial change in health care; reflects expertise in subject matter, excellence in methodology, and concern for study participants; overcomes obstacles in implementation; presentation of its design, execution, and results is a model of clarity and intellectual soundness."

**King's show that protection against peanut allergy is stable and long term despite cessation of peanut.** The question remained whether children in the LEAP study consuming peanuts had been transiently desensitised through ongoing peanut exposure, or whether they had acquired long-term tolerance independent of continuing peanut consumption. The LEAP-On study asked all participants in LEAP to completely cease peanut consumption for 12 months **(4)**. At the end of this year the six-year-old children were assessed, and the same differences in tolerance vs. allergy were found between groups: the original peanut consuming group remained tolerant of peanuts despite complete avoidance of peanut for a year – in other words, as a result of consuming peanuts in their first year of life, these children had acquired long-term stable protection against peanut allergy.

**King's further demonstrate that early introduction of other allergenic foods reduces the prevalence of a range of food allergies in children.** In the subsequent EAT (Enquiring About Tolerance) randomised controlled study of 1306 infants, the group demonstrated that early infant weaning on to six allergenic solids (egg, peanut, fish, milk, wheat, sesame) at three months compared with six months of age was associated with (i) reduced prevalence of all food allergies at three years of age and (ii) a 66% reduction in the overall burden of food allergy in the population who were able to adhere to the study intervention **(5)**.

### 3. References to the research

1. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher H, Fox AT, Turcanu V, Amir T, Zadik-Menuhin G, Cohen A, Livne I, Lack G. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008 Nov;122(5):984-91.
2. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol*. 2009 Feb;123(2):417-423.
3. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, Turcanu V, Sever ML, Gomez Lorenzo M, Plaut M, Lack G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015 Feb 26;372(9):803-13.
4. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, Brough HA, Santos AF, Harris KM, Radulovic S, Basting M, Turcanu V, Plaut M, Lack G; Immune Tolerance Network LEAP-On Study Team. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. *N Engl J Med*. 2016 Apr 14;374(15):1435-43.

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5. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, Brough H, Marrs T, Radulovic S, Craven J, Flohr C, Lack G; EAT Study Team. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. *N Engl J Med.* 2016 May 5;374(18):1733-43.

**4. Details of the impact**

Every year more than 15,000 babies in the UK will develop peanut allergy; King's research has shown that at least 12,000 of these cases can be prevented. This fundamental shift in our understanding of childhood allergy has reversed infant weaning policy worldwide, and has directly led to new national and international guidelines recommending early peanut consumption for the prevention of peanut allergy. This impact case follows on from a REF2014 case covering the early impact of this research that led to a shift in the guidelines to withdraw the recommendation to actively avoid food allergens in the infants' diet. Since 2014, King's research has subsequently led international guidelines to be rewritten to recommend active introduction of allergenic foods, namely peanut and egg, in infants' diet during weaning; a fundamental shift in the understanding of food allergy, and associated change in clinical practice; and direct benefit to children and families around the world

**King's trial results immediately reversed the global consensus on allergenic foods in infant diets.** The LEAP findings were deemed so convincing that a statement was immediately published simultaneously (from August 2015) in eight journals recommending that the LEAP strategy should be put into practice, based on consensus among the 10 major international allergy specialist organisations: American Academy of Allergy, Asthma & Immunology (AAAAI), American Academy of Pediatrics (AAP), American College of Allergy, Asthma & Immunology (ACAAI), Australasian Society of Clinical Immunology and Allergy (ASCIA), Canadian Society of Allergy and Clinical Immunology (CSACI), European Academy of Allergy and Clinical Immunology (EAACI), Israel Association of Allergy and Clinical Immunology (ISACI), Japanese Society for Allergology (JSA), Society for Pediatric Dermatology (SPD), and World Allergy Organization (WAO). This was considered interim guidance whilst national and international guidelines were formalised **[A]**.

**New national clinical guidelines for the prevention of childhood peanut allergy are being developed around the world.** In January 2017, the National Institute of Allergy and Infectious Diseases (USA) published new clinical practice guidelines for the prevention of peanut allergy which were endorsed by 26 federal agencies, professional societies, foundations, and advocacy groups **[B]**. In March 2019, the American Academy of Paediatrics updated its guidelines on how to prevent food allergies in children, saying there was not enough evidence to prove that delaying the exposure of children as young as four to six months old to allergenic foods helps keep them from developing food allergies. On the contrary, based on strong evidence from the LEAP study they endorsed the evidence showing that purposeful early introduction of peanuts may prevent peanut allergies in high-risk infants, resulting in the recommendation to introduce peanut protein as early as between four and six months **[B]**. Independently, scientific societies such as the Australasian Society of Clinical Immunology and Allergy have also produced their own guidelines **[B]**. As a result of these findings, the European Guidelines (from the European Academy of Allergy and Clinical Immunology, EAACI) have been re-written and are under submission for publication; these are followed by clinicians in the UK **[B]**.

**New clinical guidelines are already leading to a significant change in clinical practice.** Implementation of the ASCIA guidelines in Australia has resulted in a dramatic shift in infant feeding, documented very rigorously: prior to 2011 fewer than 30% of 12-month-old infants were eating peanuts, whereas after the guidelines were introduced in 2017, almost 90% of infants were eating peanuts (of more than 6000 infants surveyed) **[C]**.

**Clinical programs are now being set up nationally and internationally to implement the findings of the LEAP study:**

- (i) **The first NHS food allergy prevention clinic has been established.** The research findings resulted in the first NHS food allergy prevention clinics being established at Guy's & St. Thomas' NHS Trust in 2018, with community liaison using Skype video consultations to promote early intervention in the first 12 months of life. In the last two years, more than 500 infants at risk of peanut allergy have been seen in this clinic and peanut has been introduced successfully in their diet in the vast majority, either at home or in hospital **[D]**.

- (ii) Harvard clinicians Wayne Shreffler and colleagues at **Massachusetts General Hospital have instituted a similar programme in the Boston area**. This focuses on identifying infants at risk of developing food allergies and facilitating early introduction of peanut and other allergenic foods, under medical supervision if needed. Since the establishment of the prevention programme in 2017, 862 new patient visits for evaluation of eczema or egg allergy in infants under one year of life have taken place. Over 616 food challenges have been conducted to a variety of foods, including 100 peanut challenges on patients under 18 months of life, where the allergenic food is introduced under medical supervision to assess for possible allergic reaction. 68 children did not react, allowing the incorporation of peanut in the diet [E].

**King's research has improved the lives of children at risk of food allergy, and their families.**

This patient-focused research has improved the lives of children worldwide by providing clear guidance on the age of dietary introduction of peanut to reduce allergies via simple, low-cost, safe, and practical means. Looking locally within our prevention clinic at who has been assessed and established on peanut consumption, this will have prevented more than 80 new cases in our community in the last couple of years [D]. This practice is now expanding to our Institutions in the four UK nations. The testimonials from parents of children identified as being at risk of peanut allergy who had the opportunity to attend our clinic and have medically supervised introduction of peanut into the diet have expressed how much difference it has made to their lives. For instance: *"I am and will be forever grateful for the care you bestowed on baby (child's name) when she was driven to madness by her eczema and the subsequent improvement in her health once she was found to be allergic to breast milk, eggs and wheat by your excellent team. Knowing now how lucky she is to hopefully be peanut tolerant for the rest of her life (she loved her Bamba) I feel so very grateful."* [F.1]. King's has also improved the lives of children with allergies and their families through charities. The Anaphylaxis Campaign, for example, widely disseminated King's papers on the LEAP and EAT studies. After that, they received feedback, via their helpline, from *"parents who have changed their strategy for introducing solid food in order to ensure early introduction of allergenic foods that they would otherwise have avoided based on outdated advice"* [F.2]. Additionally, the Head of Clinical Services at another organisation - Allergy UK - has said: *"This is such important research and I have no doubt has given much more structure to our advice as a charity and helping parents make informed decisions."* [F.3]

**The paradigm shift resulting from King's RCTs is being transmitted to the medical community and trainees through teaching and professional development, transforming clinical practice and approach to treating and preventing childhood food allergy [G]:**

- (i) *Medical students*: Textbooks have been rewritten to include the new evidence and recommendations. Locally, at Kings the Paediatric Allergy Service has two medical students allocated per year who often focus their case study reports on early food introduction; and other groups of medical students covering paediatric specialties in their rotations (approximately eight students per week) who learn about food allergy prevention during their clinic placements.
- (ii) *Paediatricians*: There have been articles in general paediatrics journals about early introduction of allergenic foods in infants, which target a large and broad readership within the medical community. As part of the training in Paediatrics, the UK national curriculum now includes illustrations such that general paediatric trainees need to provide evidence of understanding of the principles of allergy prevention.
- (iii) *GPs and other health professionals*: In the UK this work is being communicated to the medical community beyond the Allergy specialty through courses about prevention of food allergy run by the KCL Allergy Academy. This was set up by King's researchers and is directed at GPs, general paediatricians, nurses and dietitians. The Children's Allergy Service at the Evelina London also hosts international courses and two visiting professionals per year from around the world who come to learn about food allergy prevention, among other aspects of Paediatric Allergy. An allergy trainee from Portugal said: *"I have had a wonderful experience at St Thomas'. I have learnt so much that I can take back into my own practice back home."* A visiting paediatrician commented: *"I have gained so much from my year here and was exposed to so much, from so many different*

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*areas of allergy. I now feel confident to develop a service when I return to Greece” and a Clinical fellow from the Children’s Hospital of Fudan University, China said: “The learning experience in St Thomas Hospital was very helpful for my professional career. I plan to do the skin prick test, food challenge and sublingual immunotherapy in our hospital in the future, which we do not do now. I think this work will benefit patients.”*

**King’s raised public awareness on how to prevent childhood peanut allergy [H].** This work has been widely disseminated to the public through multiple national and international media outlets such as BBC, ITV, Sky, Channel 4, CNN, NHK, Al Jazeera, Canadian Broadcasting Corporation, ABC News, CBS, The Wall Street Journal, The New York Times, The Guardian, Daily Mail, The Times, and many more.

### 5. Sources to corroborate the impact

**[A]. Interim consensus guidance (published simultaneously in 8 different journals) - Fleischer DM et al.** Consensus Communication on Early Peanut Introduction and Prevention of Peanut Allergy in High-Risk Infants: Annals of Allergy, Asthma & Immunology, World Allergy Organization Journal, Allergy, Asthma & Clinical Immunology, European Journal of Allergy and clinical immunology, The Journal of Allergy and Clinical Immunology, Official Journal of the American Academy of Pediatrics, Pediatric Dermatology [PDF]

**[B]. New national and international clinical guidelines: B.1** The National Institute of Allergy and Infectious Diseases Addendum Guidelines for the Prevention of Peanut Allergy in the United States (2017); **B.2.** Australasian Society of Clinical Immunology and Allergy guidelines (2017); **B.3** Joint guidelines from American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology; **B.4** Recommendations from the British Society of Allergy and Clinical Immunology; **B.5** New guidelines for the prevention of food allergy by the European Academy of Allergy and Clinical Immunology [PDF]

**[C]. Evidence of change in clinical practice: data from Australia on shift in infant peanut consumption 2011 vs 2017:** Soriano VX, Peters RL, Ponsonby AL, Dharmage SC, Perrett KP, Field MJ, Knox A, Tey D, Odoi S, Gell G, Camesella Perez B, Allen KJ, Gurrin LC, Koplin JJ. Earlier ingestion of peanut after changes to infant feeding guidelines: The EarlyNuts study. J Allergy Clin Immunol. 2019 Nov;144(5):1327-1335.e5. doi: 10.1016/j.jaci.2019.07.032. [PDF]

**[D].** Testimonial from the Director of the Allergy Academy at Guy’s & St. Thomas’ NHS Trust

**[E].** Testimonial from the Director of Food Allergy Advocacy and the Chief of Pediatric Allergy and Immunology at Massachusetts General Hospital and Harvard Medical School [PDF]

**[F]. Testimonials from patient organisations in the UK and abroad: F.1** LEAP Study Parent Feedback Quotes; **F.2** CEO, Anaphylaxis Campaign, UK; **F.3** Head of Clinical Services, Allergy UK; **F.4** Professor of Pediatrics and Medicine, Northwestern University, USA [PDF]

**[G]. Evidence of training and professional development work (books, curricula, courses) influenced by King’s research: G.1** Lack G. An Innovative Treatment for Food Allergy. Landmark Papers in Allergy: Seminal Papers in Allergy with Expert Commentaries. 28 Feb 2013. Edited by Aziz Sheikh, Thomas Platts-Mills, and Allison Worth; **G.2** Du Toit G, Fleischer DM, Lack G. (2014) Prevention of Food Allergy in Food Allergy - Adverse Reaction to Foods and Food Additives 5e. pp237-267. Edited by Dean D. Metcalfe, Hugh A. Sampson, Ronald A. Simon, Gideon Lack; **G.3** Lack G, Santos A, Penagos M, Allen K (2015). Antiallergic Strategies: Induction of Tolerance to Food in Allergy, Immunity and Tolerance in Early Childhood: The First Steps of the Atopic March. Edited by: Ulrich Wahn and Hugh A. Sampson; **G.4** Lack G. Food Allergy Management. Middleton’s Allergy, 8<sup>th</sup> (2012) and 9<sup>th</sup> Edition (2018) edited by A Wesley Burks, Stephen T Holgate, Robyn O’Hehir, David H Broide, Leonard B Bacharier, Gurjit (Neeru) K Khurana Hershey, Ray Stokes Peebles; **G.5** Quotes from health professionals who received training from the Allergy Academy [PDF]

**[H].** Evidence of impact on public awareness and dissemination of knowledge – diverse examples of media engagement (TV, online, radio) [PDF]