Imperial College London Consultants

Evidence base for risks and best management of food-allergic individuals on commercial airliners: a systematic review

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Executive summary

The Civil Aviation Authority (CAA) commissioned a report from the Health and Safety Laboratory (HSL) in 2018, entitled "A Review of Evidence: Passenger Exposure to Peanut and Tree Nut Allergens on Airlines". Subsequently, CAA commissioned Dr Paul Turner and Imperial Consultants (ICON) to undertake an update and synthesis of the evidence, in order to provide an evidence-based interpretation of the risks of allergic reactions in food-allergic individuals during commercial flights.

A systematic search of relevant scientific articles was undertaken, published from 1 January 1980 until 31 December 2022. Additional relevant studies identified during the search were also included in a subsequent quantitate and qualitative analysis. This was undertaken according to international standards which included an assessment of potential bias. The project was registered in advance at the International prospective register of systematic reviews (PROSPERO, reference CRD42022384341).

The key findings of this report are:

1. The rate of "in-flight medical events" due to allergic reactions is low: for a typical food-allergic passenger on a commercial flight, the risk is around 10-100 times lower than when "on the ground". However, this needs to be interpreted in the context of food-allergic passengers reporting high levels of anxiety when travelling by air, resulting in them taking significant precautions that are likely to reduce the risk of in-flight allergic reactions.
2. One of the most effective measures to reduce risk is for passengers to wipe down their seat area, including the tray table and the seat-back entertainment system. The proteins which cause food allergy are often "sticky" and can adhere to these surfaces, from where they are easily transferred to a person's hands and on to food that may be consumed. Airline companies should support passengers in wiping down their seating area, for example through pre-boarding. The United States of America Department of Transportation already requires airlines to allow food-allergic passengers with peanut and tree nut allergies (and their caregiver) to preboard in order to wipe down their seating area, where this is requested.
3. In practice, this could be achieved by providing food-allergic passengers with non-latex disposable gloves and suitable wipes, which can then be discarded. This would avoid the need for passengers to then have to visit the bathrooms to wash their hands after wiping down their seat area (which could slow cabin boarding).
4. Research studies, including aircraft simulations, demonstrate that there is no evidence to support airborne transmission of peanut/tree nut allergens as a likely phenomenon. On this basis, general "nut bans" or announcements requesting passengers not to consume nuts on a specific flight are not supported. Local "buffer" zones may help limit potential exposure, but evidence is lacking; nonetheless, their implementation may provide additional reassurance to food-allergic passengers.
5. Food-allergic individuals at risk of anaphylaxis should be prescribed two adrenaline autoinjector devices which they should carry on their person at all times, including when on board aircraft. Nonetheless, given the need for additional training when using adrenaline from the on-board medical kit for managing allergic reactions, airlines should consider stocking a separate supply of "general use" adrenaline autoinjectors to be included in the on-board medical kit for use in an emergency. In the UK-setting, this is likely to be a cost-effective measure.

6. All airlines should have clear policies relating to food allergies which are easily available from their websites or on request. These policies should be applied consistently by both ground staff and cabin crew, in order to provide reassurance to food-allergic passengers and their caregivers.

Contents

1. Introduction

1.1 Background

In 2018, the Civil Aviation Authority (CAA) commissioned a report from the Health and Safety Laboratory (HSL) to evaluate the evidence base regarding the risks of in-flight medical emergencies due to severe allergic reactions caused by exposure to peanuts and tree nuts. The purpose of the review was to develop an evidence base to inform the guidance relating to food allergy that the CAA provides to airlines and other bodies responsible for civilian aircraft flight safety.

Airlines, aviation regulatory bodies and allergy support networks have developed guidance for the travelling public at risk of food allergic reactions [1]. A number of different measures might be implemented by Operators to mitigate against risk of allergic reaction, including (but not limited to):

- Notification prior to flying.
- Food-allergic passengers being asked to prepare their own food to take onto the flight, and to carry appropriate emergency rescue medication (injectable adrenaline).
- Preboarding (for example, to allow for passengers to clean their seat area).
- Not serving peanuts during in-flight service.
- On-board announcements requesting all passengers to not eat a food to which another a passenger is allergic (must commonly peanut or tree nuts).
- Use of “exclusion” or “buffer zones,” where passengers seated immediately adjacent to a food-allergic passenger are asked not to consume the relevant food allergen.

However, the evidence-base underpinning these strategies, and their effectiveness, is unclear.

Following publication of the 2018 HSL report [2], the CAA commissioned Dr Paul Turner, an expert in Food Allergy at Imperial College London, to update and review the evidence base in order to inform any guidance the CAA may wish to provide.

1.2 Food hypersensitivity and food allergy

Food hypersensitivity (FHS) affects around 2-5% of children and 1-2% of adults in the UK [3], and is a complex, multifactorial disease of concern to multiple stakeholders including consumers with FHS, their families, clinicians, regulatory agencies and policy makers, scientists, food manufacturers and food business operators. FHS encompasses both immune-mediated food hypersensitivity (such as food allergy) and non-immune food intolerances (Figure 1).

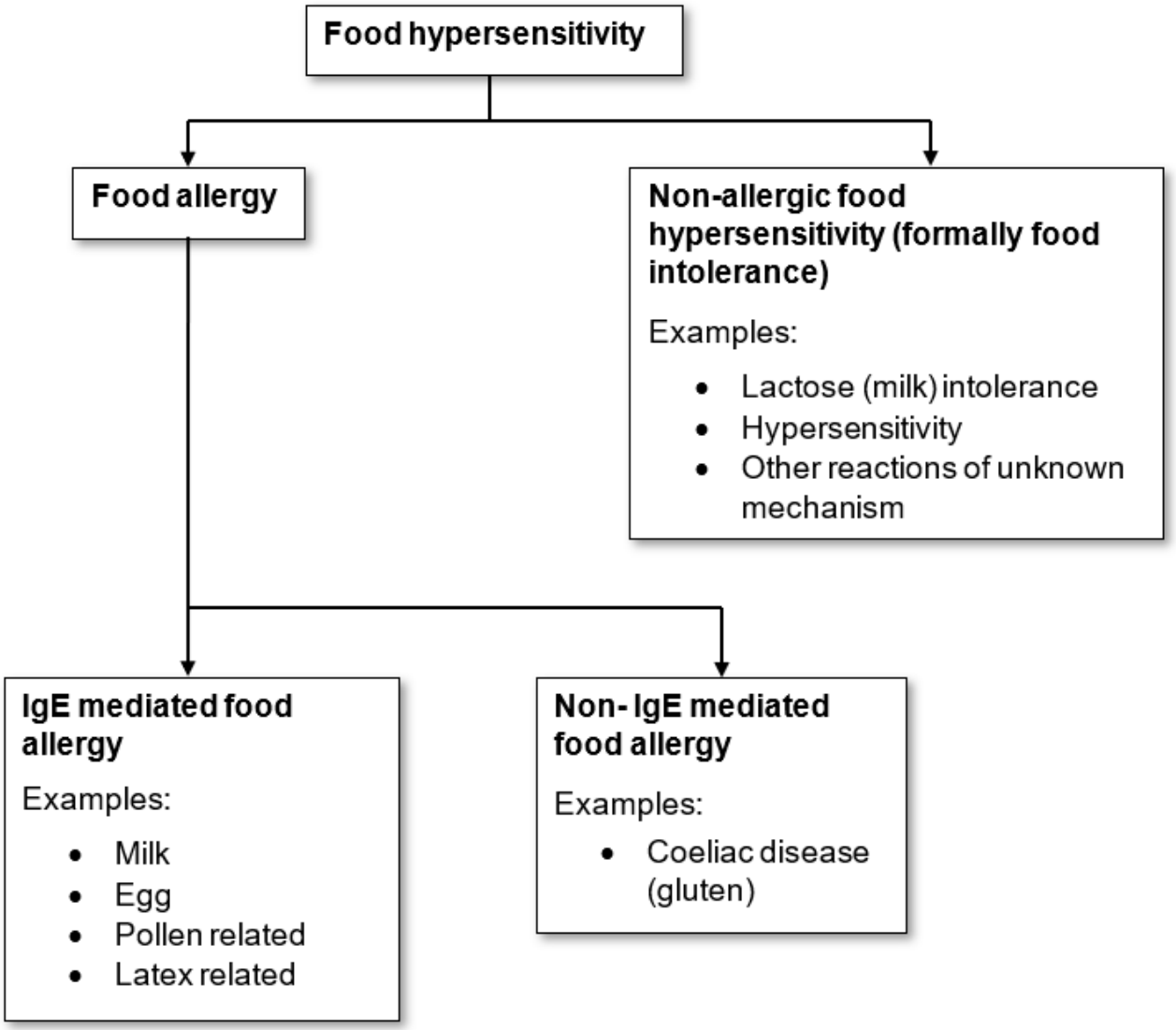
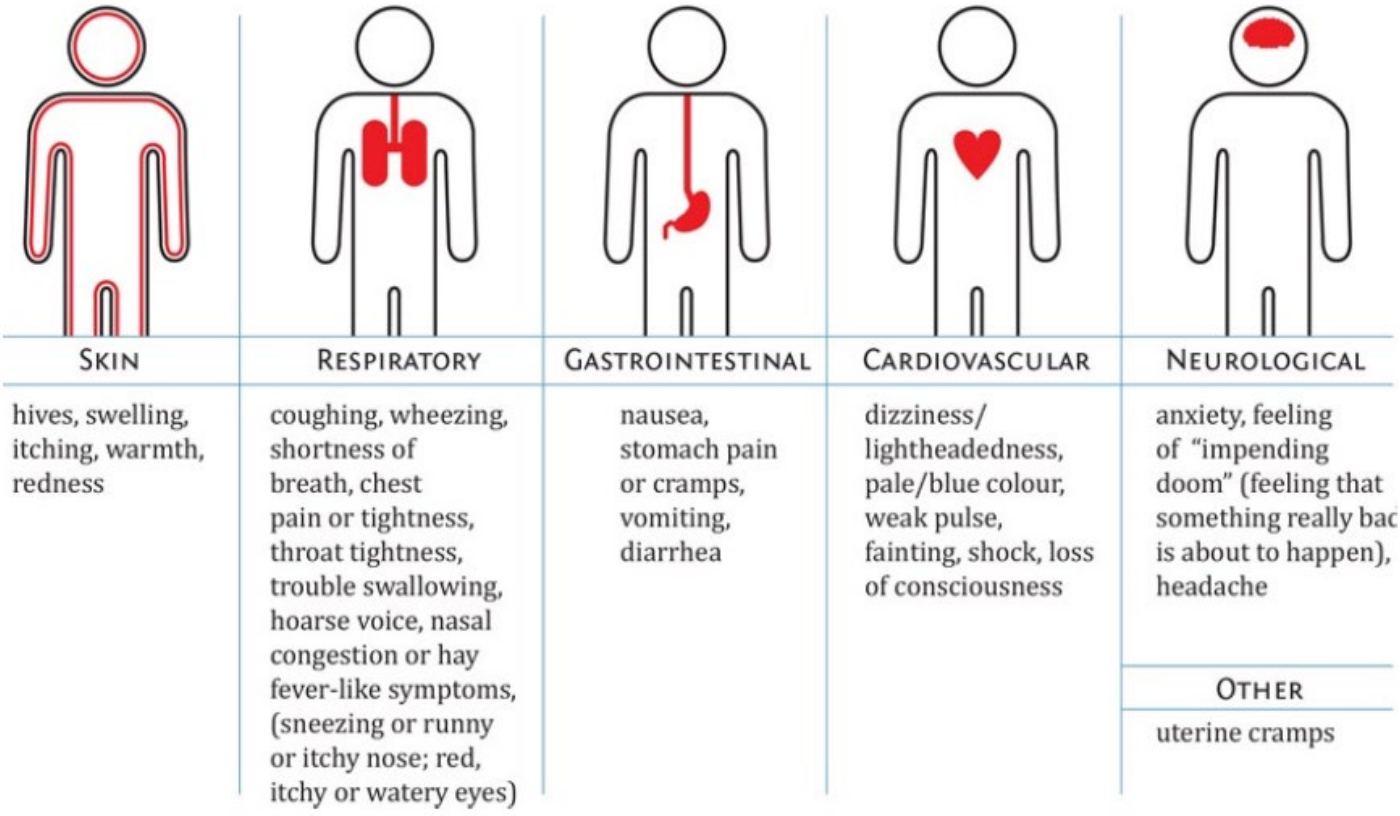


Figure 1: FHS encompasses both food intolerances (which do not involve the immune system) and immune-mediated hypersensitivity.

IgE-mediated food allergy is the most common immune-mediated FHS in children and adults. Food allergy is not the same as food intolerance: food allergies are caused by the immune system reacting to an otherwise harmless food protein, something known as an **allergen**. Non-allergic food hypersensitivity reactions (which include food intolerances) are usually caused by the gut being unable to breakdown certain food sugars, resulting in abdominal discomfort for example, lactose intolerance, which is caused by too little enzyme in the gut which breaks down lactose sugar. The key distinction is that the immune system is not involved, so food intolerances do not result in life- threatening, immune-mediated reactions.

On the other hand, food allergy – especially that caused by the IgE antibody – triggers an immune response (almost like a domino effect) which can cause symptoms of an allergic reaction, ranging from mild skin itch to life-threatening reactions which can (rarely) cause death (Figure 2). Unfortunately, severe reactions are unpredictable, so everyone with IgE-mediated food allergy must be managed as potentially being at risk of severe reactions.



SKIN	RESPIRATORY	GASTROINTESTINAL	CARDIOVASCULAR	NEUROLOGICAL
hives, swelling, itching, warmth, redness	coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, trouble swallowing, hoarse voice, nasal congestion or hay fever-like symptoms, (sneezing or runny or itchy nose; red, itchy or watery eyes)	nausea, stomach pain or cramps, vomiting, diarrhea	dizziness/ lightheadedness, pale/blue colour, weak pulse, fainting, shock, loss of consciousness	anxiety, feeling of "impending doom" (feeling that something really bac is about to happen), headache

OTHER
uterine cramps

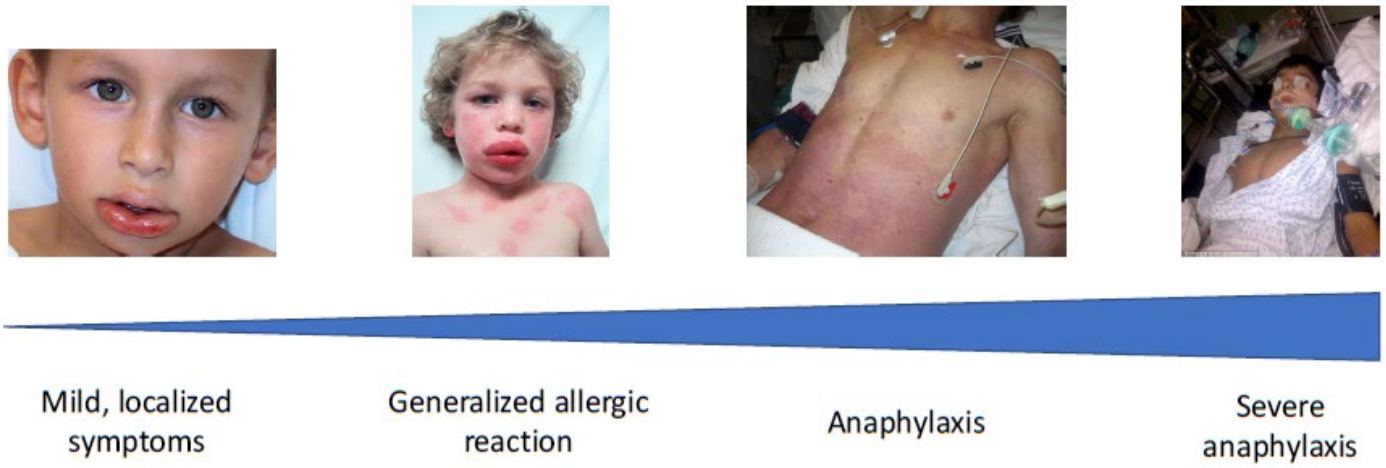


Figure 2: Symptoms experienced during IgE-mediated allergic reactions due to food (upper panel). In practice, symptoms lie on a spectrum of severity [4], ranging from mild localised symptoms (for example, itchy mouth) to near-fatal and even fatal anaphylaxis (lower panel). Reproduced with permission.

1.3 Anaphylaxis

If a reaction involves Airway/Breathing/Consciousness problems, then the reaction is called anaphylaxis [4]. The World Allergy Organization describes anaphylaxis as “a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterised by potentially life-threatening compromise in airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present” [5].

1.3.1 Epidemiology

Accurately determining the incidence of anaphylaxis is difficult, due to a number of reasons. The lack of consensus over clinical criteria to define anaphylaxis, together with lack of biomarker to define such cases, is a significant confounder. Estimates often rely on diagnostic coding for hospital visits which can be very inconsistent or use retrospective assessment which is prone to recall bias, incomplete reporting and the potential to overexaggerate rates when using self-report [6]. Moreover, many episodes of anaphylaxis may not be reported to health authorities.

Estimates for the incidence of anaphylaxis range from 50 and 112 episodes per 100 000 person-years, with an estimated lifetime prevalence of 0.3–5.1% [5]. Global datasets imply an increase in rates of anaphylaxis due to food over the past 20-30 years [7]. Fortunately, mortality due to anaphylaxis remains low and is a rare outcome, estimated at 0.03–0.32 per million people/year for food-induced reactions [7]. Therefore, while anaphylaxis is not uncommon, severe outcomes from anaphylaxis are fortunately rare.

1.3.2 Treatment of anaphylaxis

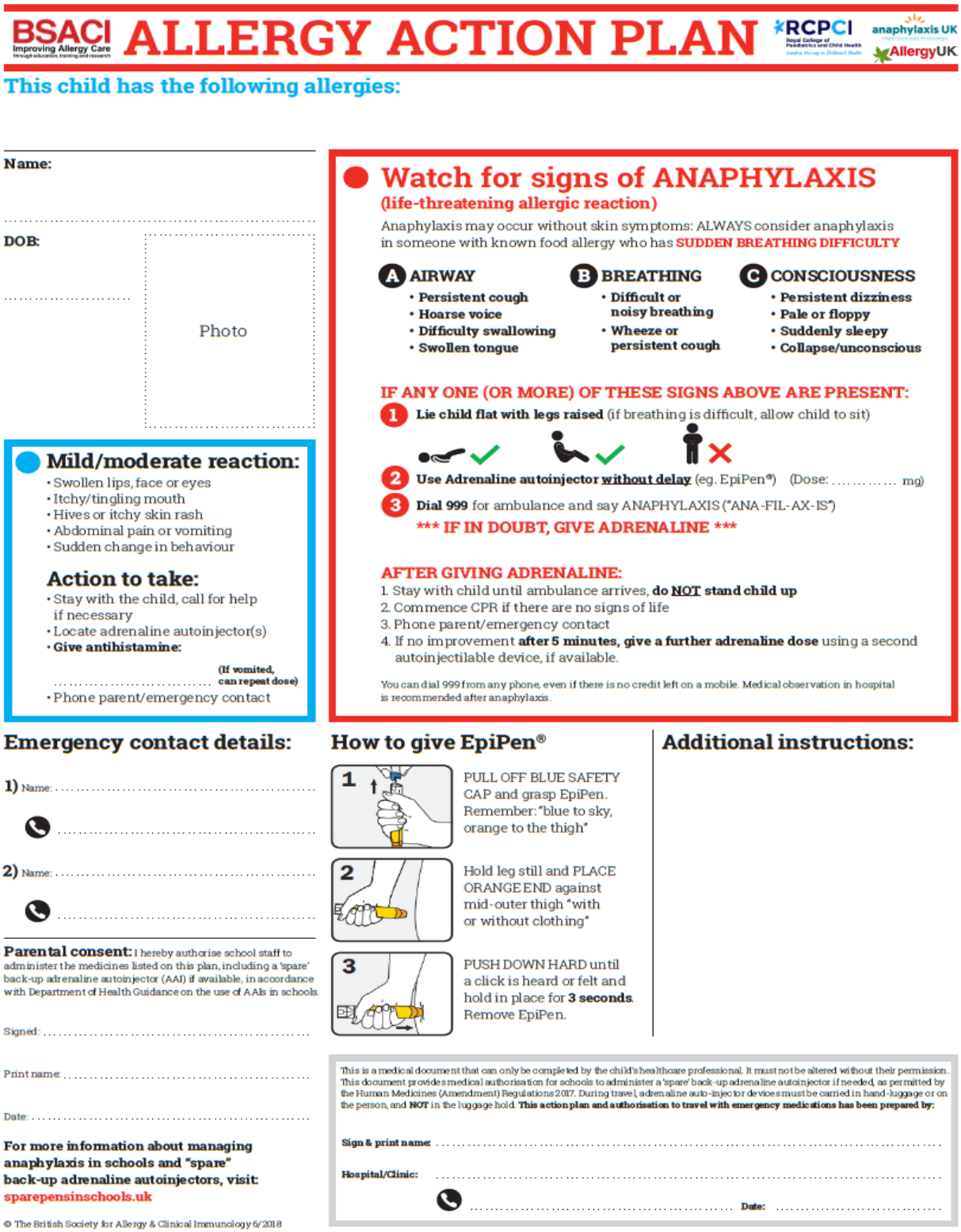
Anaphylaxis always requires an emergency response, as it can be life threatening [5]. The treatment of choice for anaphylaxis is an injection of adrenaline (epinephrine) into the upper outer thigh muscle. To facilitate safe management, people at risk of anaphylaxis are often prescribed self-injectable adrenaline (as an autoinjector, such as Epipen®, Jext® or Emerade®). Other medicines which might be needed include oxygen and intravenous fluids. Antihistamines can be useful to treat skin rashes but are not effective for anaphylaxis [4,5].

Most (90%) anaphylaxis reactions get better with a single dose of adrenaline [8]; around 10% of reactions need treatment with more than one dose. Official UK government advice is for individuals at risk of anaphylaxis to be prescribed two auto-injector devices, to keep with them at all times [9]. In addition, individuals should be provided with an Action Plan (example in Figure 3) which details which symptoms should prompt adrenaline administration. In the UK, the Action Plan from the British Society for Allergy & Clinical Immunology (BSACI) includes authorisation from a healthcare professional for the individual to carry their adrenaline autoinjector devices with them in their hand luggage, when travelling (although under UK legislation, medical authorisation is not needed for individuals who are prescribed autoinjector devices to carry these during travel; similarly, permission is not needed from airlines or UK government agencies prior to travel).

Around 1-2% of anaphylaxis reactions need more than two doses of adrenaline for resolution to occur [8]. Of note, fatal reactions can occur despite timely administration of adrenaline [4].

Following resolution of symptoms, in around 2-3% of reactions, there can be a recurrence

of symptoms after many hours; in around half of such cases, this occurs more than 12 hours after the initial reaction [4]. Such reactions are called “biphasic” reactions. Evidence suggests that biphasic reactions following a food-induced allergic reaction are less common than for non-food allergens [10].



BSACI Improving Allergy Care

ALLERGY ACTION PLAN

RCPCH anaphylaxis UK AllergyUK

This child has the following allergies:

Name: .....

DOB: .....

Photo

Mild/moderate reaction:

- Swollen lips, face or eyes
- Itchy/tingling mouth
- Hives or itchy skin rash
- Abdominal pain or vomiting
- Sudden change in behaviour

Action to take:

- Stay with the child, call for help if necessary
- Locate adrenaline autoinjector(s)
- **Give antihistamine:** ..... **(If vomited, can repeat dose)**
- Phone parent/emergency contact

Watch for signs of ANAPHYLAXIS

(life-threatening allergic reaction)

Anaphylaxis may occur without skin symptoms: ALWAYS consider anaphylaxis in someone with known food allergy who has **SUDDEN BREATHING DIFFICULTY**

A AIRWAY	B BREATHING	C CONSCIOUSNESS
• Persistent cough	• Difficult or noisy breathing	• Persistent dizziness
• Hoarse voice	• Wheeze or persistent cough	• Pale or floppy
• Difficulty swallowing		• Suddenly sleepy
• Swollen tongue		• Collapse/unconscious

IF ANY ONE (OR MORE) OF THESE SIGNS ABOVE ARE PRESENT:

1. **Lie child flat with legs raised** (if breathing is difficult, allow child to sit)
2. **Use Adrenaline autoinjector without delay** (eg. EpiPen®) (Dose: ..... mg)
3. **Dial 999** for ambulance and say ANAPHYLAXIS (“ANA-FIL-AX-IS”)

*** IF IN DOUBT, GIVE ADRENALINE ***

AFTER GIVING ADRENALINE:

1. Stay with child until ambulance arrives, **do NOT stand child up**
2. Commence CPR if there are no signs of life
3. Phone parent/emergency contact
4. If no improvement **after 5 minutes, give a further adrenaline dose** using a second autoinjectilable device, if available.

You can dial 999 from any phone, even if there is no credit left on a mobile. Medical observation in hospital is recommended after anaphylaxis.

Emergency contact details:

1) Name: .....

.....

2) Name: .....

.....

Parental consent: I hereby authorise school staff to administer the medicines listed on this plan, including a ‘spare’ back-up adrenaline autoinjector (AAI) if available, in accordance with Department of Health Guidance on the use of AAIs in schools.

Signed: .....

Print name: .....

Date: .....

For more information about managing anaphylaxis in schools and “spare” back-up adrenaline autoinjectors, visit: sparepensinschools.uk

How to give EpiPen®

1. PULL OFF BLUE SAFETY CAP and grasp EpiPen. Remember: “blue to sky, orange to the thigh”
2. Hold leg still and PLACE ORANGE END against mid-outer thigh “with or without clothing”
3. PUSH DOWN HARD until a click is heard or felt and hold in place for **3 seconds**. Remove EpiPen.

Additional instructions:

This is a medical document that can only be completed by the child’s healthcare professional. It must not be altered without their permission. This document provides medical authorisation for schools to administer a ‘spare’ back-up adrenaline autoinjector if needed, as permitted by the Human Medicines (Amendment) Regulations 2017. During travel, adrenaline auto-injector devices must be carried in hand-luggage or on the person, and **NOT** in the luggage hold. **This action plan and authorisation to travel with emergency medications has been prepared by:**

Sign & print name: .....

Hospital/Clinic: .....

..... **Date:** .....

Figure 3: Example of an Allergy Action Plan from the British Society for Allergy & Clinical Immunology.

1.4 Common food allergens

While food allergy has been reported to almost every known food (including fruit and vegetables), in most countries, over 90% of food allergy is caused by the following eight foods [11]:

- Cow's milk
- Hen's egg
- Peanuts
- Tree nuts and seeds, for example, sesame
- Fish
- Shellfish
- Soya
- Wheat

Many individuals with an allergy to one food are also allergic to other foods – this is due to structural similarities between different food proteins, so the immune system can react to other related food proteins (something known as cross-reactivity). Common cross-reactivities are shown in Figure 4.

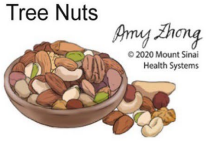
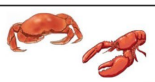
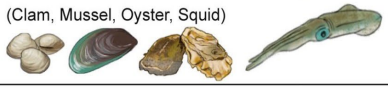
Primary Food Allergy	**Cross Reactive Food**	**Risk** (varies with region)
Peanut 	Tree Nuts (co-allergy)	~33%
	Lupine	~20%
	Sesame (co-allergy)	10-15%
	Green Bean, Pea, Soy 	5-20%
Tree Nuts 	Other Tree Nuts	15-33%
	Sesame (co-allergy)	10-15%
If Walnut	Pecan 	~66-75%
If Pecan	Walnut 	>95%
If Cashew	Pistachio 	~66-83%
If Pistachio	Cashew 	>95%
If Peanut and Tree Nut	Sesame (co-allergy) 	50%
Milk (Cow) 	Milk (Sheep, Goat) 	>90%
	Milk (Camel, Mare) 	<5%
Crustacean Shellfish 	Other Crustaceans 	~75%
	Mollusks/Bivalves (Clam, Mussel, Oyster, Squid) 	<50%
Finned Bony Fish 	Other Finned Bony Fish	~50%
	Cartilaginous Fish (Dogfish, Ray, Shark) 	<5%

Figure 4: Common cross-reactivities in food allergy (adapted from reference 11).

ICON Ref: DH13088

1.5 Food allergy in the context of commercial flights

1.5.1 Routes of exposure

There are two key stages involved in food allergy:

1. **Sensitisation**: no allergic reaction occurs when the immune system is first exposed to an allergen. This is because before an allergic reaction can occur, the immune system must become "sensitised," a process whereby immune cells known as "B cells" produce IgE- antibodies which can bind to the food allergen.
2. **Elicitation and the allergic reaction**: Only once sensitisation has occurred can an allergic response be elicited, whereby cells to which the IgE-antibody binds to can become activated if exposed to the food allergen, resulting in cell activation and the release of chemical mediators (such as histamine) which cause the allergic reaction (Figure 5) [12].

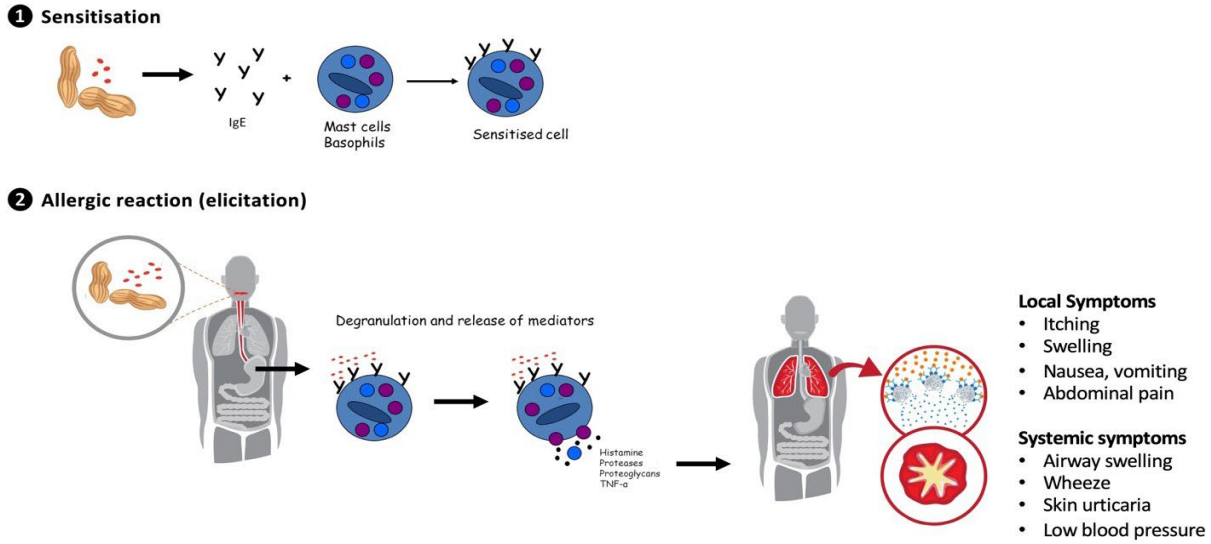


Figure 5: There are two stages involved in the development of an allergic reaction: sensitisation and then elicitation. Only once sensitisation has occurred can an allergic reaction occur.

While there is no doubt that allergic sensitisation can occur via multiple routes, including the skin, airways, and gut [13], whether systemic ("whole body") allergic reactions to food can be elicited via non-oral routes is more controversial.

Respiratory reactions to aerosolized foods have been described in the literature, but with a few notable exceptions (for example, fish/seafood and occupational allergen exposure, such as baker's asthma, fish market workers), these are limited to anecdotal case reports, which in the majority of cases are not subsequently verified through re-exposure. This is important: often, there are alternative explanations, for example, due to occult allergen presence on hands which is subsequently ingested during eating. A number of reviews have been published in this area [14-18]; these purport that reactions due to aerosolised food allergens may be increasing, but there is no evidence for this in the scientific literature, including from prospective studies of food-allergic individuals. With the notable exception of fish/seafood allergy, allergic reactions due to non-occupational exposure to aerosolised foods would seem to be rare.

There is a common perception that reactions due to aerosolised peanut are common, particularly on commercial aircraft; however, evidence for this is very limited, which suggests that such instances are rare exceptions [19]. This perception may have arisen due to a combination of a number of factors:

a. An assumption that all foods are "equal" in terms of propensity to induce allergic reactions due to aerosolised exposures. Reports of allergic reactions and even anaphylaxis to **fish/seafood** vapours (for example, due to a fish counter in a shop or cooking fumes) in people allergic to fish/seafood are common. In a prospective survey of 167 children with recent history of clinical reaction to seafood and/or positive food challenge, 16% reported symptoms to exposure to fish vapours [20]. Reassuringly, patients with a history of symptoms due to vapours were not more likely to report anaphylaxis on consumption.

   Many proteins in fish/seafood are volatile amines, which are readily aerosolised at room temperature and are therefore "bioavailable" to induce symptoms: these are typically ocular or upper respiratory (rhinorrhoea, nasal itch) [20] but lower respiratory symptoms are also reported in the literature [21] (though whether these represent a local reaction or true systemic reaction with respiratory involvement i.e., anaphylaxis is unclear).

b. Upper and lower respiratory symptoms are common in occupational allergen exposure to foods. The best characterised presentations are those due to wheat/yeast exposure in "baker's asthma" and in fish/seafood market workers [22,23].

c. There are a limited number of case reports of airway reactions to food allergens when cooked in a confined area, but such occurrences are uncommon in the vast majority of food- allergic individuals (Table 1). Roberts et al reported that out of a cohort of 750 food-allergic children, twelve (1.6%) presented with a history of asthma symptoms following inhalational exposure to their trigger food allergen. Nine subsequently underwent bronchial challenge using a blinded, placebo-controlled methodology where possible: only five developed objective wheeze and changes in lung function at bronchial food challenge [26].

Table 1: Studies reporting the incidence of allergic reactions due to potential, non-occupational inhalation of aerosolised food. HCP, healthcare professional.

Study	Methodology	Population sampled	n	Food allergen	Proportion reporting reactions via inhaled route
Sicherer, 2001 [24]	Registry, self-report	School-aged children	100 out of a cohort of 750 reporting reactions	Peanut, tree nuts	16 (16%)
Eigenmann, 2002 [25]	Online survey	Age 1-61y	51	All	3 (6%)
Roberts 2002 [26]	Prospective study of clinic patients	Children	750	Fish, chickpea, cow's milk, egg, buckwheat	12 (1.6%)
Turner, 2011 [20]	Postal survey with telephone interview by training HCP	Children/ young people	167	Fish/seafood	26 (16%)
Fleischer, 2012 [27]	Prospective observational study	Children aged 3-15m with possible FA	512, reporting 1171 (unverified) reactions	Cow's milk, egg, peanut	14 (1.2%)
Nguyen-Luu, 2012 [28]	Retrospective clinic cohort	Children <18y	1411, reporting 266 reactions	Peanut	13 (0.9%)

1.5.2 Altitude and cabin air control systems

Commercial aircrafts typically operate at cruising altitudes of 33,000 to 40,000 feet (10,000 – 12,000m), and the cabin must be maintained at a state whereby this provides a safe and comfortable environment for staff and passengers. This is achieved through an Environmental Control System (ECS) which manages cabin air pressure, air supply, and temperature while providing for adequate removal of carbon dioxide, odours, and other contaminants. Regulations (such as the European Aviation Safety Agency Certification Specification for Large Aeroplanes, CS-25III or the Federal Air Regulations Part 25IV in the United States) require that the cabins of passenger-carrying aircraft operating at altitudes above 5000–8000 feet are pressurized to allow civilian passengers to breathe normally and move freely in the cabin during flight. In practice, cabin air pressure is maintained to at least that occurring at an altitude of 8000 feet (2,438 m) during normal operations [29].

ECS might impact on risk of allergic reactions in two ways. First, at an altitude of 8000 feet, the partial pressure of oxygen is approximately 120 mmHg (16.0 kPa), 75% of its level at sea level. As a result, in healthy adults, normal oxygen saturations fall from 97% (arterial oxygen pressure, PaO_2 of 12.7 kPa) to 85-91% (PaO_2 of 7.0-8.5 kPa) – something well tolerated by healthy individuals but can lead to hypoxia in some individuals with underlying respiratory disease, for example, Chronic Obstructive Pulmonary Disease. In theory, therefore, altitude could worsen the severity of any respiratory symptoms caused by an allergic reaction. However, in practice, hypoxia as a presenting feature of food-induced anaphylaxis at sea-level is very rare [30,31], and if present while in-flight, could be addressed through administration of oxygen. Although humidity levels are lower in aircraft (5-20%, compared to indoor levels of 30-60% in temperate climates), this does not impact adversely upon oxygenation [29].

The second consideration is the ventilation dynamics (and filtration) that are used in ECS to ensure adequate removal of carbon dioxide and airborne contaminants including pathogens. This requires high flow rates of air within the cabin. Adequate ventilation is

achieved by air being supplied into the cabin through overhead distribution outlets which run the length of the cabin. The system is designed to create a controlled circular pattern of airflow, with air continuously extracted through vents at floor level. This results in air circulating across the aircraft, rather than along the cabin (Figure 6), which minimises the potential for spreading passenger-generated contaminants through the passenger cabin.

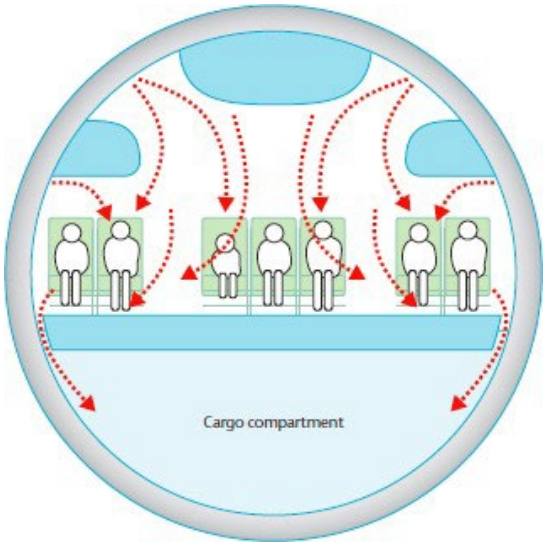


Figure 6: Model of air circulation in a passenger cabin on commercial aircraft [32]. Copyright © 2005 Elsevier Ltd. Re-use granted by Elsevier as part of the Elsevier COVID-19 resource centre.

The cabin air supply is sourced from outside “bleed air” (drawn from the pre-combustion stage of the engines) which is then conditioned to the desired temperature and pressure, before being mixed with recirculated air and distributed into the cabin (the Boeing 787 aircraft is an exception, as outside air is sourced via a separate intake and not from the engines). Typically, ECS are designed to provide approximately 20 cubic feet (566 litres) of air per minute per passenger, resulting in a complete cabin air exchange every 3-4 minutes [32].

In modern large commercial aircraft, around half of the air is recirculated air (in contrast, modern buildings have a typical recirculation rate of 80%). While outside air is assumed to be sterile at normal cruising altitudes, high efficiency particulate air (HEPA) filters are used to filter recirculated air, before delivery into the cabin. In general, the HEPA filters used on commercial airlines have a particle- removing efficiency of 99·97% at 0·3 microns, which effectively remove dust, vapours, potential microbial pathogens – and, in all likelihood, reduce the chance of inhaling airborne allergens.

1.5.3 Access to emergency medical services

Another key issue is the challenge of providing medical assistance while in-flight. The International Civil Aviation Organization (ICAO) provides standards and recommendations on the provision of first- aid training for cabin crew and contents of first-aid and onboard medical kits [33]. National aviation authorities specify detailed regulations with which airlines are required to comply: these typically include adrenaline in the onboard medical kit as stock vials [34,35]. There are no specific requirements for carriage of adrenaline autoinjectors (although many larger international airlines choose to include these in the medical kit). It is therefore important that travellers at risk of anaphylaxis and who have been prescribed adrenaline autoinjectors have these readily available in the cabin when flying [36]. In some

instances (and where permitted by national regulations), cabin crew may be permitted to administer adrenaline autoinjector to an individual experiencing potential anaphylaxis.

Clearly, there are challenges in requesting emergency medical assistance, thus aircraft have robust procedures in the event of a medical emergency which includes cabin crew first-aid training, access to medical equipment and typically, ground-support from a specialist remote medical care provider.

1.5.4 Impact of a diagnosis of food allergy on affected passengers

In a global survey of 4704 food-allergic passengers and their caregivers, 98% of food-allergic individuals (and their families) reported increased anxiety when flying; high anxiety levels were reported by two thirds of respondents [37]. Over one third reported unprofessional or insensitive behaviour from airline staff (including this being directed at children). Reported issues ranged from home-made food being "ruined" during routine airport inspections (in 25% of cases) to over 10% being asked to provide a medical note to verify the need to carry an adrenaline auto-injector with the devices sometimes being confiscated [37].

At the same time, allergic individuals also report of positive experiences from airline staff, including not selling or serving peanuts, announcements to stop other passengers eating nuts and ‘keeping an eye out’ for a food-allergic passenger [37,38]. Such experiences are reassuring and tend to impact the choice of airline when arranging future trips [37].

2. Methods

We sought to answer the following two research questions:

- What is the incidence of unintended allergic reactions in individuals with food allergy while travelling on commercial aircraft?
- What are the mechanisms of unintended allergic reactions in individuals with food allergy while travelling on commercial aircraft, and how can the risk posed by food allergens be reduced?

Methods and analyses were planned a priori, and registered at the International prospective register of systematic reviews (PROSPERO, reference CRD42022384341).

2.1 Search strategy

We systematically searched MEDLINE, Embase, PsycINFO, TRANSPORT and the Cochrane Register of Controlled Trials, including all primary records from 1 January 1980 and 31 December 2022. We used the following search strategy:

1. (food or peanut or milk or egg or wheat or LTP or nut or fish or seafood or crustac*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm, an]
2. (allerg* or anaphyla*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm, an]
3. 1 and 2
4. limit 3 to human
5. (air* or flight*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm, an] AND react*.af
6. 4 and 5

We also reviewed reference lists of included studies and review articles to identify other relevant studies. There were no language restrictions. Studies were only included if they included original data relating to at least 10 subjects with the outcome of interest. All studies were assessed for risk of bias, and those at high risk of bias were excluded from inclusion.

2.2 Study selection

The inclusion criteria were:

- **Population**: Individuals with a physician diagnosis of IgE-mediated food allergy, travelling on commercial aircraft

  Exclusion: Non-IgE-mediated food allergy

- **Exposure(s):** Exposures (all routes) to:
  - to food allergens while travelling on commercial aircraft
  - to food allergens in simulated settings which reflect commercial aircraft environments

  Exclusion: Intentional consumption of food/drink products containing a trigger food allergen

- **Main outcome:** Estimated incidence (events per person years) of unintended IgE-mediated food-induced allergic reactions while travelling on commercial aircraft

- **Additional outcomes:** Data relating to the route of exposure:
  - risks of aerosolised allergen resulting in allergic reactions
  - risks of allergen exposure due to cross-contact (for example, on aircraft surfaces) causing allergic reactions

Abstracts were independently screened by at least two authors to identify relevant studies. We included only published, peer-reviewed full papers or research letters, and excluded conference abstracts. Where repeated reports of the same study were identified, we included the most up-to- date or detailed report. We extracted data in duplicate, assessed the risk of bias and undertook meta- analysis where appropriate.

2.3 Risk of bias of individual studies

Pairs of authors independently assessed the risk of bias in individual studies. Studies reporting incidence of in-flight medical events due to allergic reactions were evaluated using the approach of Hoy et al [39], which assesses internal and external validity. Internal validity reflects the degree of systematic data collection and potential bias due to how this data was obtained (for example, direct from patients, contemporaneous medical notes, historical case notes). External validity assesses for whether selection bias impacts on whether the study data are generalizable to the overall food-allergic population. For other studies, the Risk of Bias in Non-randomized Studies - of Exposure (ROBINS-E) tool [40] was used, which provides a structured approach to assessing the risk of bias in observational epidemiological studies. Risk of bias assessments are shown in Appendix 1.

2.4 Synthesis of results

For incidence of in-flight medical events, we undertook a random effects meta-analysis. Study heterogeneity was assessed using the I2 statistic. Meta-analysis was performed using Meta Package, R project, version 4.0.3a (random-effects model, REML). For all other data, we synthesised findings narratively because the data were insufficient or too heterogeneous to undertake meta-analysis.

3. Results

1362 reports were initially identified and screened, resulting in 141 full-text articles assessed for eligibility and 32 studies deemed eligible for inclusion (Figure 7).

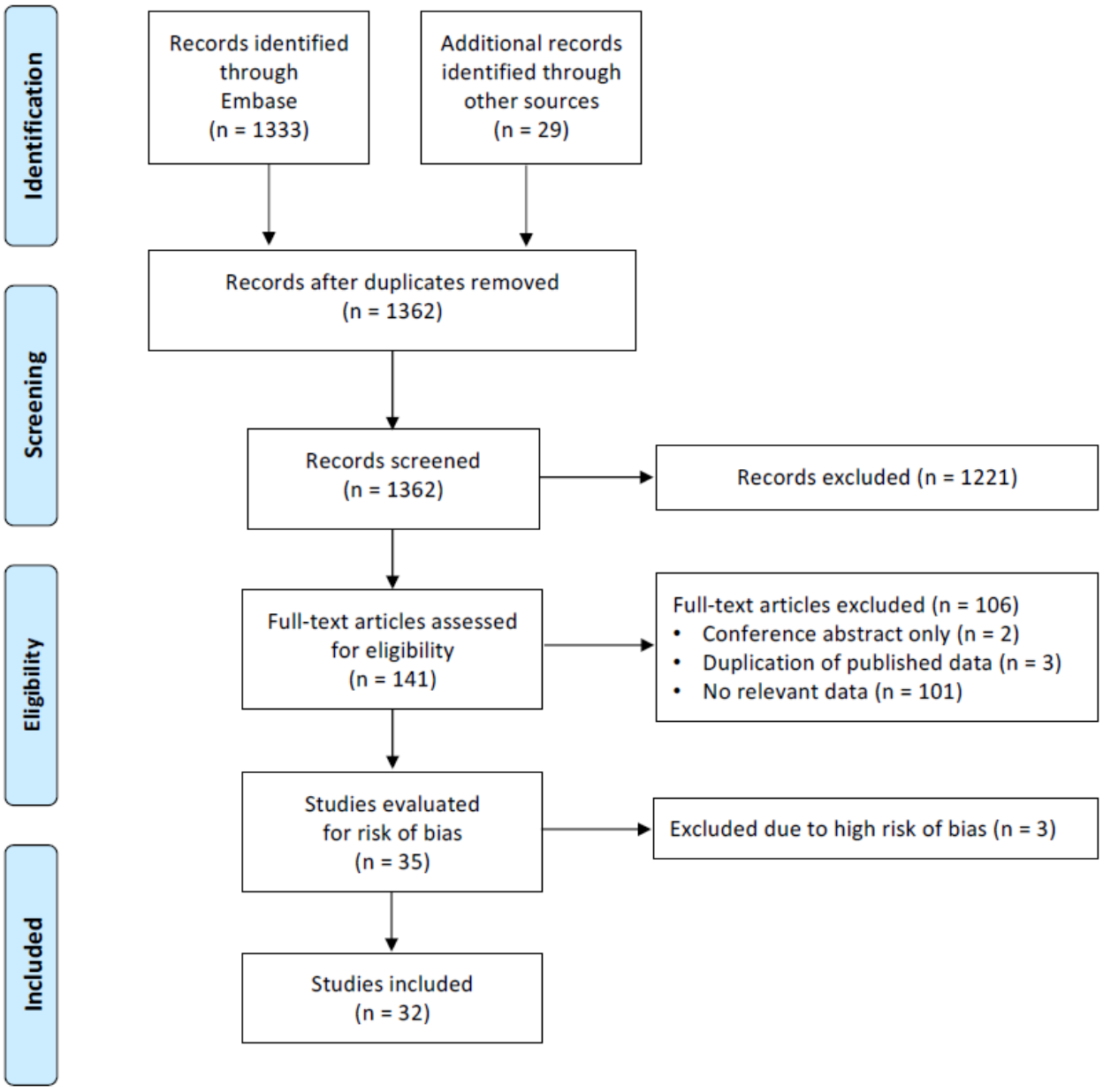


Figure 7: PRISMA diagram.

3.1 Incidence of unintended allergic reactions in food-allergic individuals while travelling on commercial aircraft

Two types of data were identified from the literature: data reporting the proportion in in-flight medical events reported to be due to “allergy,” and studies evaluating how frequently food-allergic individuals report allergic incidents during air travel. These studies were considered separately.

3.1.1 Incidence of in-flight medical events due to allergy

A total of 17 publications described rates of in-flight medical events (IMEs) of allergic aetiology (Table 2). All studies were assessed as being at low-moderate risk of bias (Table S1, Appendix 1). There was no obvious evidence of publication bias (see funnel plot in Figure S1, Appendix 1).

Table 2: Studies included for meta-analysis of incidence of in-flight medical events due to allergy.

Study	Data source	Location	Study period	No. of revenue passengers	Number of IMEs		Incidence of IMEs due to allergy		Risk of Bias
					Overall	Allergy	% overall	per million passengers	
Donaldson 1996 [41]	Airline records	Australia	1993	4 million	454	5	1.1%	1.25	Low
DeJohn 2000 [42]	Ground-to-air provider	USA	1996-1997	N/A	1132	27	2.4%	–	Low
Szmajer 2001 [43]	Ground-to-air provider	France	1989-1999	70 million	374	9	2.4%	0.13	Low
Sirven 2002 [44]	Ground-to-air provider	USA	1995-2000	312.1 million	2,042	71	3.5%	0.23	Moderate
Delaune 2003 [45]	Airline records	Unknown	1999-2000	100.8 million	2,279	63	2.8%	0.62	Low
Moore 2005 [46]	Ground-to-air provider	USA	1995-2002	N/A	169	15	8.9%	–	Moderate
Baltsezak 2008 [47]	Ground-to-air provider	China	2006	N/A	191	7	3.7%	–	Moderate
Sand 2009 [48]	Airline records	Europe	2002-2007	N/A	10,189	222	2.2%	–	Moderate
Mahony 2011 [49]	Airline records	Oceania	1996-2004	71.4 million	11,326	257	2.3%	3.60	Low
Peterson 2013 [50]	Ground-to-air provider	Global	2008-2010	744 million	11,920	265	2.2%	0.36	Low
Kesapli 2015 [51]	Airline records	Eurasia	2011-2013	10.1 million	1,312	10	0.76%	0.99	Low
Kim 2017 [52]	Airline records	Asia	2009-2013	115 million	2,818	132	4.7%	1.15	Low
Alves 2019 [53]	Ground-to-air provider	Global	2009-2013	N/A	114,222	1052	0.92%	–	Low
Pauline 2020 [54]	Airline records	Europe	2017	N/A	581	5	0.86%	–	Moderate
Rotta 2020 [55]	Ground-to-air medical	Global	2015-2016	N/A	11,719	643	5.5%	–	Low
Ceyhan 2021 [56]	Airline records	Unknown	2018-2020	177.4 million	19,313	138	0.71%	0.78	Low
Kodoth 2022 [57]	Ground-to-air provider	Global	2017-2019	6313 million	140,579	4230	3.0%	0.67	Low

See Table S1 (Appendix 1) for risk of bias evaluation

At meta-analysis, a pooled estimate of 2.2% (95%CI 1.6%-3.1%) of IMEs were coded as being due to allergic reactions (Figure 8A). Limiting the analysis to those studies reporting data in children, the rate of IMEs due to allergic reactions was 3.1% (95%CI 1.5%-6.6%). Most studies reported IMEs across a range of ages (both children and adults), thus these data should be interpreted accordingly. Analysing those studies where data was published corresponding to the number of flights taken (revenue passengers), the rate of IMEs due to allergic reactions was 0.66 (95%CI 0.38-1.14)) per million passengers (Figure 8B).

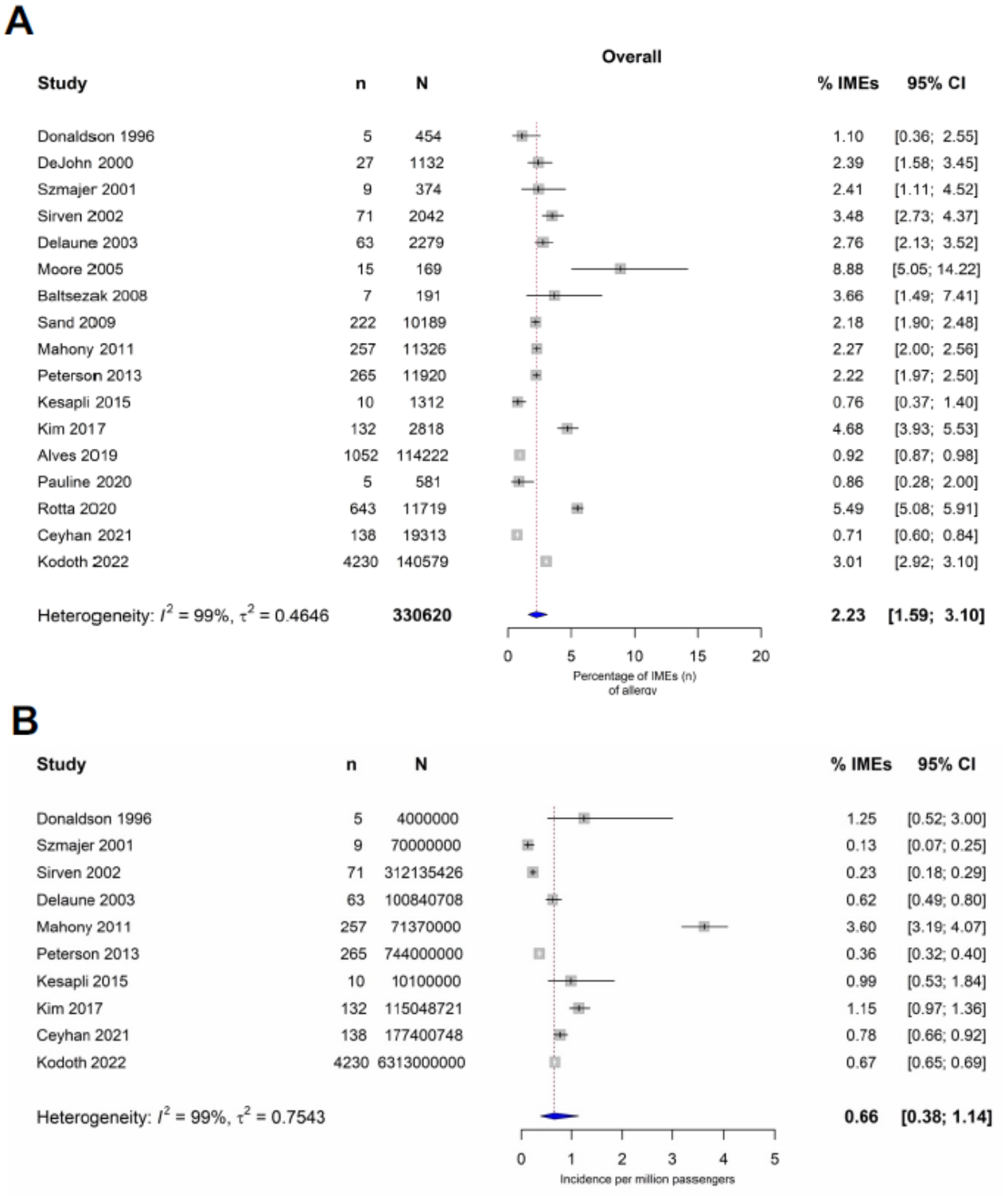


Figure 8: Forest plots for (**A**) the proportion of IMEs coded as being due to allergic reactions and (**B**) and incidence of IMEs due to allergic reaction per million passengers.

Finally, we assessed whether IMEs due to allergic reactions had changed over time. We found no evidence that either the absolute number or proportion of IMEs due to allergic reactions had increased over the past two decades, despite a documented increase in passenger numbers (Figure 9).

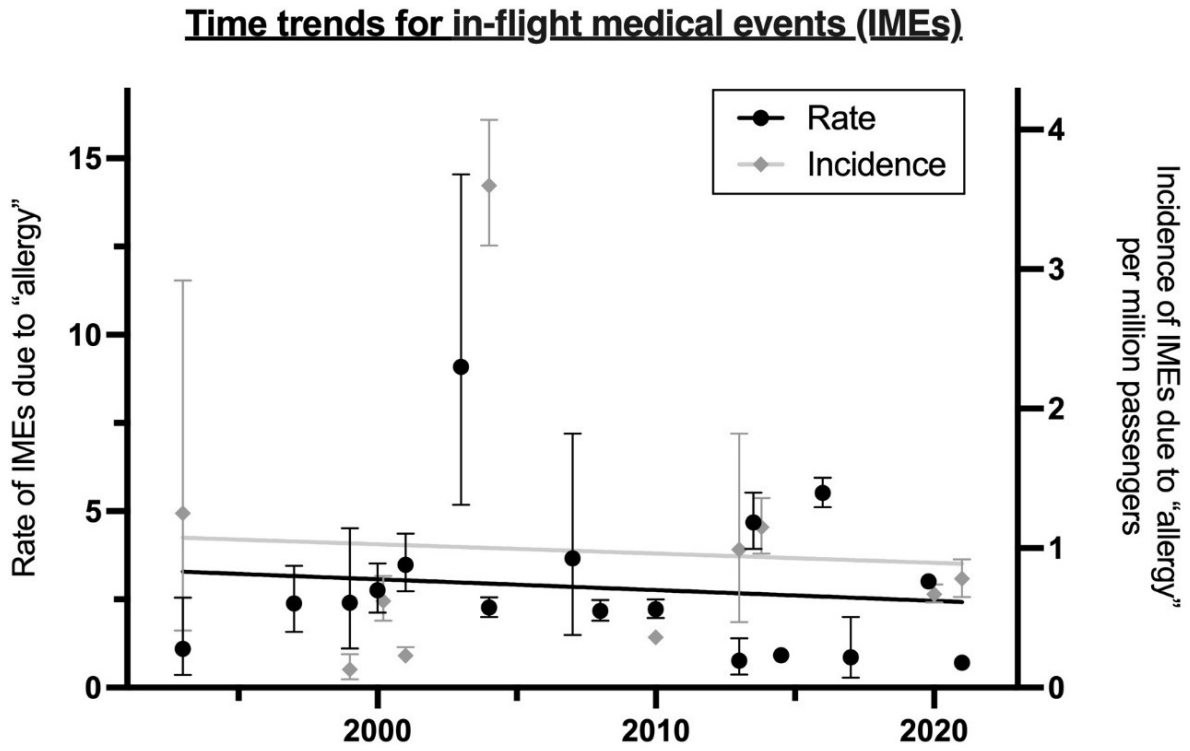


Figure 9: Time trends for in-flight medical events (IMEs) due to allergic causes over the last two decades, by study period.

3.1.2 Frequency of unintended allergic reactions during air travel reported by at-risk individuals

Eight studies reported the frequency of self-reported allergic reactions in food-allergic individuals while flying [37,58-64], three of which were published in the past 12 months [37,63,64]. All studies were assessed as being at moderate-high risk of bias, except that by Crealey and Byrne [64] which used prospective data collection in an unselected clinical cohort). This was due to the methodology typically used in these surveys (self-selected respondents, self-report with no adjudication of cases).

In general, less than 1 in 10 food-allergic individuals reported at least one incident while flying. Peanut was consistently the most common reported trigger for accidental reactions (Table 3). A high proportion (typically at least half) perceived their reaction as being due to exposure via a non-ingested route. Respiratory symptoms occurred in between 30-50% of reactions, but surveys did not distinguish between upper respiratory symptoms (similar to hay fever) and lower respiratory symptoms (anaphylaxis), although discordance between these two where reported indicated a clear predominance of upper respiratory symptoms. In general, only around one half of incidents were reported to the crew or ground staff.

Table 3: Studies describing passenger-reported allergic reactions to peanut and/or tree nuts during commercial flights

							Reported symptoms:					Treatment:			Communication:	
Study	**Risk of bias**	**Sample size**	**n**	**Age of cohort**	**Due to peanut**	**Due to non-ingestion**	**Anaphylaxis**	**Respiratory**	**Cardiovascular**	**Skin**	**Gastrointestinal**	**Adrenaline**	**Antihistamine**	**Had own medication**	**Notified Crew**	**Pre-notified Airline**
Sicherer 1999 [58]	High*	3704	42 (1%)	6m-50y	35 (83%)	21 (50%)	5 (12%)	11 (31%)	0	15 (43%)	2 (6%)	6 (14%)	28 (67%)	27 (64%)	14 (33%)	17 (40%)
Comstock 2007 [59]	High*	471	45 (10%)	2-50y	30 (71%)	30 (66%)	36 (88%)	N/A	N/A	N/A	N/A	4 (10%)	15 (37%)	12 (38%)	12 (29%)	N/A
Greenhawt 2009 [60]	Moderate - High	(150)	150	6m-60y	96 (64%)	125 (83%)	50 (33%)	42 (28%)	2 (1.4%)	84 (56%)	11 (7.5%)	15 (10%)	115 (77%)	115 (76%)	67 (44%)	96 (63%)
Greenhawt 2013 [61]	Moderate - High	3273	346 (11%)	3m-50y	239 (70%)	269 (78%)	N/A	287 (83%)	77 (22%)	290 (84%)	84 (24%)	46 (13%)	297 (86%)	309 (89%)	177 (51%)	193 (56%)
Beaumont 2015 [62]	Moderate - High	196	12 (6%)	4-47y	N/A	N/A	5 (42%)	5 (42%)	0	10 (83%)	2 (17%)	6 (50%)	7 (58%)	N/A	9 (75%)	6 (50%)
Martinez-Flores 2022 [63]	Moderate - High	13200	16 (0.1%)	4-80y	10 (63%)	7 (44%)	N/A	16 (100%)	6 (38%)	14 (88%)	13 (81%)	3 (19%)	10 (63%)	N/A	N/A	N/A
Crealey 2022 [64]	Low	498	3 (0.6%)	Children Median 7y	1 (33%)	0	1 (33%)	1 (33%)	N/A	N/A	N/A	1 (33%)	2 (67%)	N/A	0	N/A
Warren 2023 [37]	High*	4704	400 (8.5%)	All ages	46%	N/A		205 (51%)	67 (17%)	349 (87%)	119 (30%)	60 (15%)	243 (61%)	376 (94%)	238 (60%)	332 (83%)

3.1.3 Incidence of unintended allergic reactions during air travel in food-allergic individuals

Using the above analysis, we then determined how the incidence of IMEs due to allergic reactions compared to estimated incidences of food anaphylaxis incidents in food-allergic people in general, from a systematic review and meta-analysis [65]. Incidence of comparator risks using US and EU data were also included, as previously described [66]. In estimating the annual incidence of IMEs due to food allergy, we made the following assumptions:

- One flight per day per passenger.
- A population average of 4.2 flights per person per annum [67] and a rate of 52 flights per year for “frequent flyers”.
- Food-allergic passengers fly at the same frequency as those without food allergies.
- Food allergy related IMEs are only reported 50% of the time (as per Table 3), thus the true incidence of food-induced allergic reactions on board commercial aircraft is double that reported in the literature.

On this basis, we estimated that the annual incidence of a food-induced allergic reaction is 2.7 (95%CI 1.6-4.8) per 10,000 person-years, equivalent to one reaction per 3600 food-allergic passengers travelling in any one-year period (see Appendix 2). In food-allergic individuals who fly once per week, this increases to 34 (95%CI 20-59) per 10,000 person-years. This means that in a food-allergic person flying at a frequency equivalent to the population average, the incidence of an unintended allergic reaction due to food while on a commercial flight is around 100 times less than that for self-reported anaphylaxis “on the ground”, and 10 times less frequent than that for medically-coded anaphylaxis (Figure 10).

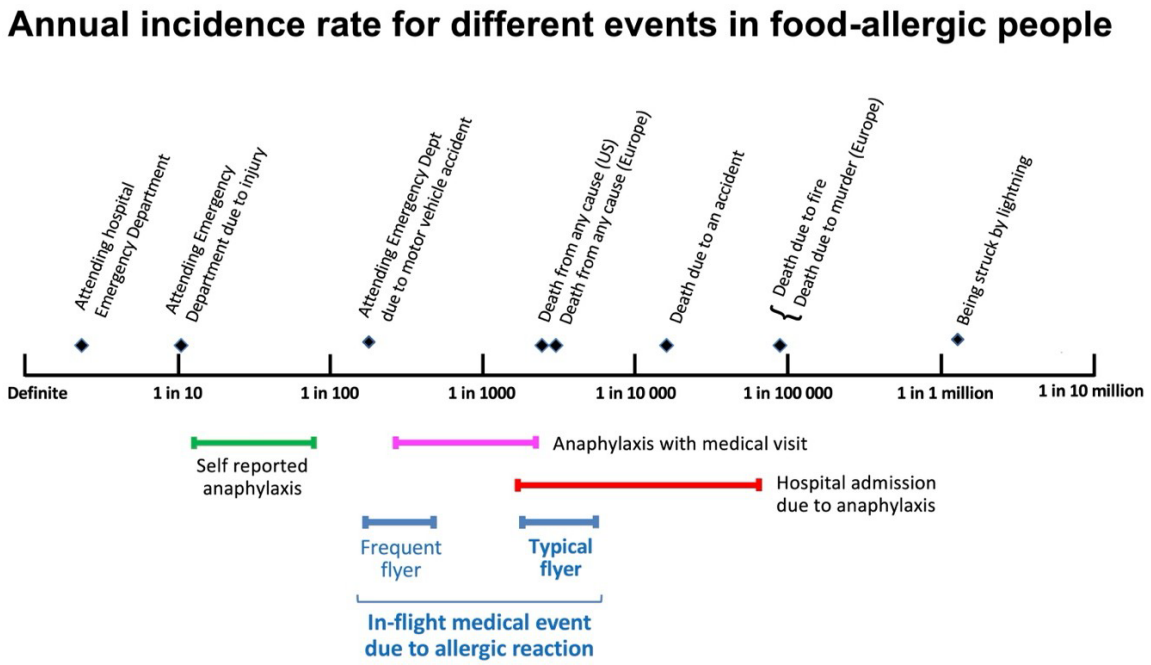


Figure 10: Estimated rates of food-induced allergic reactions in people with known food allergy during commercial flights, assuming a 2% prevalence of food allergy. Comparison is made to equivalent rates reported in food-allergic individual when not flying, together with reference risks (US population, unless otherwise stated). Data are shown as 95% confidence intervals for risk of food-induced allergic reaction, derived from the systematic review of Umasunthar et al [65].

3.1.4 Adrenaline use and anaphylaxis during IMEs due to allergic reactions

The majority of the above studies do not address the extent to which IMEs due to allergic reactions were treated with adrenaline and/or whether these reactions met established criteria for anaphylaxis.

The first line treatment of anaphylaxis is an intramuscular injection of adrenaline (epinephrine), but adrenaline is underused for anaphylaxis management, even in the healthcare settings [68]. At the same time, food-allergic individuals (or their carers) may use intramuscular adrenaline to treat more mild, non-anaphylaxis reactions – particularly if access to Emergency Medical Services is challenging. Evidence for this can be seen in Table 3, where there is a clear discordance in the proportion of reactions which were classified as anaphylaxis and the number treated with intramuscular adrenaline.

To address this evidence gap, Kodoth et al. undertook a retrospective study of a ground-based medical service (GBMS) database (MedAire) over a 3-year period (2017-2019) [57]. 4230 IMEs were identified as allergic events, with adrenaline administration recommended by the GBMS in 398 passengers (9.4% of IMEs reported), of which 328 received at least one adrenaline dose. Using data only from those airlines which consistently used GBMS to log IMEs, the incidence of allergic events was 0.91 cases per million passengers (not dissimilar to the estimate at meta-analysis reported in section 3.1.1). The incidence of allergic IME for which adrenaline administration was recommended was 0.08 (interquartile range 0.02-0.16) cases per million passengers. A limitation of the analysis was the use of adrenaline as a surrogate for anaphylaxis and/or severe allergic reaction; however, it is likely that not every reaction where adrenaline administration was recommended was anaphylaxis, nor is anaphylaxis synonymous with

a severe allergic reaction [69]. Furthermore, GBMS are probably cautious in their assessment of potential anaphylaxis, with a lower threshold for recommending adrenaline treatment given the absence of typical ground-based medical services. Therefore, it is likely that adrenaline use in the study by Kodoth et al. over-estimates the true rate of anaphylaxis.

The authors concluded that IMEs requiring adrenaline treatment are rare, with a rate of 1 event in 12.5 million passengers. Children aged 12 years and under had a lower rate of adrenaline use by logistic regression analysis (Odds ratio 0.36 (95% CI, 0.23-0.57); p<0.001). The causative food allergen for the IME was documented in 145 (44%) of the 328 cases where adrenaline was administered (Figure 11). Peanut and tree nuts were the most commonly reported triggers, making up two thirds of cases where a trigger was documented.

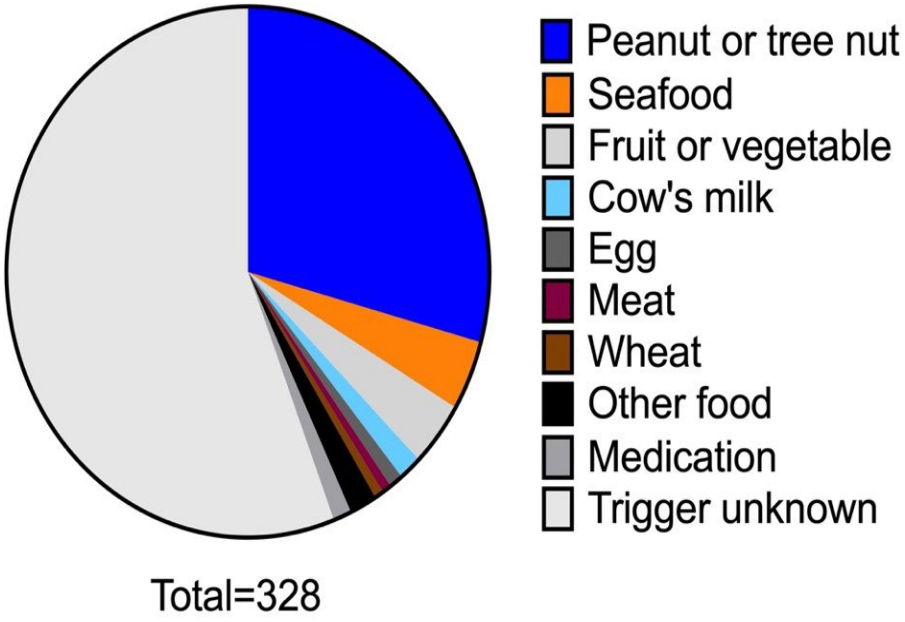


Figure 11: Reported food triggers for IMEs reported by Kodoth et al [57] and treated with intramuscular adrenaline. The trigger was documented in 145 (44%) cases.

3.2 Underlying allergen sources causing unintended allergic reactions in food-allergic individuals on commercial aircraft due to non-ingestion

3.2.1 Evidence for allergic reactions due to aerosolised food

While surveys of food-allergic individuals report a high rate of reaction due to allergen via non- ingestion (and in particular, by inhalation), these studies are confounded by selection bias and self- report without adjudication (see Section 3.1.2).

More objective evidence has been published in terms of the ability of allergic foods to induce reactions due to inhalation. The majority of these studies have focussed on peanut.

The first reported challenge study was that of Roberts et al, who undertook bronchial challenges in a confined space in nine children with a history of asthma symptoms following inhalational exposure to their trigger food allergen in a cooking environment; in seven cases, these challenges were blinded by including an exposure to a placebo food.

Five children developed objective wheeze and changes in lung function at bronchial challenge, to fish, chickpea and buckwheat [26]. No challenges were undertaken to peanut/tree nuts. While this demonstrates the proof-of-principle that some food- allergic individuals will react to inhalational exposure, it should be noted that the majority of patients included were tested to fish/seafood – which is far more likely as a cause of inhalational reactions than other food allergens, as discussed above [20,21] – and that the nine children were identified from a much larger clinical cohort of 750 food-allergic individuals, the vast majority of whom did not have a history of symptoms due to inhalational exposure.

Other investigators have explored whether less intensive exposure to peanut can induced symptoms in allergic individuals. Simonte et al. performed double-blind, placebo-controlled exposures to peanut butter due to both skin contact (0.2 mL pressed flat for 1 minute) and inhalation (peanut butter of a specified surface area held 12 inches from the face for 10 minutes) [70]. Placebo challenges were performed in a randomised order, using soy butter, with the scent masked using tuna, and mint. Thirty children participated (median age, 7.7 years); 13 had a history of previous reaction due to contact, and 11 due to inhalation. None of the 30 subjects had any reaction during inhalation challenge with peanut butter (although one patient reported transient oral itch during the inhalation challenge to placebo which resolved spontaneously). One third had mild local reactions limited to the skin with skin exposure, but no systemic symptoms. The authors concluded that “casual exposure to peanut butter is unlikely to elicit significant allergic reactions.”

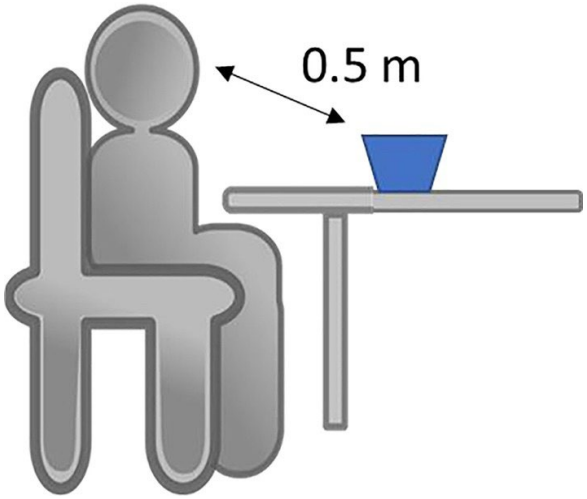


Figure 12: Inhalational challenge set-up used by Lovén Björkman et al [71]. Reprinted with permission.

Lovén Björkman et al. recruited 84 peanut-allergic children who underwent an unblinded airborne peanut challenge by being exposed to 300g of either roasted salted or dry-roasted peanuts placed in a bowl on a table, approximately 50 cm in front of the patient in a small room (Figure 11) [71]. 62 (74%) had previously reacted to (oral) peanut, but only three reported a previous reaction due to inhalation. A further five children without prior reaction due to ingestion also reported symptoms due to airborne peanut exposure. Only two children reported mild symptoms (mild rhinoconjunctivitis, oral itch) due to the airborne peanut challenge, neither required treatment.

3.2.2 Can peanut protein be detected in air samples during consumption of peanut?

An alternative approach taken by some research groups is to assess the extent to which peanut can be aerosolised. Two studies have shown that deshelling roasted peanut can result in very low level but detectable peanut allergen in the air directly above the peanuts, but only briefly during actual deshelling and not afterwards (Figure 12) – implying that the peanut dust is like to settle and not circulate in the air under normal conditions [72-74].

These data are consistent with those of Perry et al., who were unable to detect airborne peanut allergen in simulated real-life situations when participants consumed peanut butter, shelled peanuts, and unshelled peanuts, including in a confined space to simulate an aircraft cabin [75].

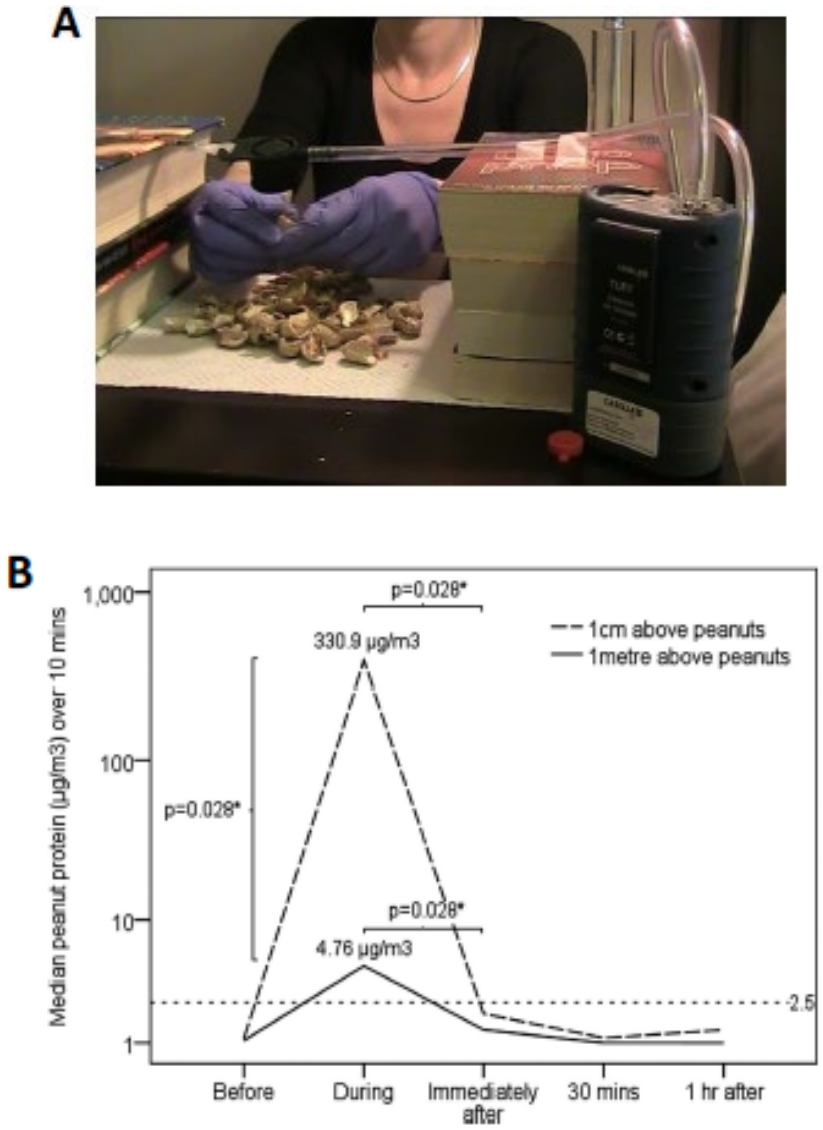


Figure 13: (**A**) Airborne peanut experiments with inhalable occupational medicine sampling head, 1cm above shelling peanuts. (**B**) Time course of airborne peanut during peanut deshelling. Air sampling was performed for 10 minutes before, during, immediately after, 30 and 60 minutes after deshelling peanuts at 1cm and 1m above the peanuts (n = 6). Reproduced from reference 74 under a Creative Commons CC-BY-NC-ND 4.0 International licence.

Lovén Björkman et al also undertook a simulation to evaluate for airborne peanut allergen [71]. The experimental set-up is shown in Figure 13. Peanut protein (up to 1mg/ml) was consistently detected directly above the peanut in the enclosed system, and at higher levels for dry-roasted rather than roasted peanut (perhaps because the roasted peanuts are wet-roasted in oil which might reduce spread). The amount of detectable peanut protein decreased dramatically with distance from the peanut (Figure 14). Only small amounts of peanut protein, able to interact with immune cells and cause an allergic reaction, could be detected in the air samples.

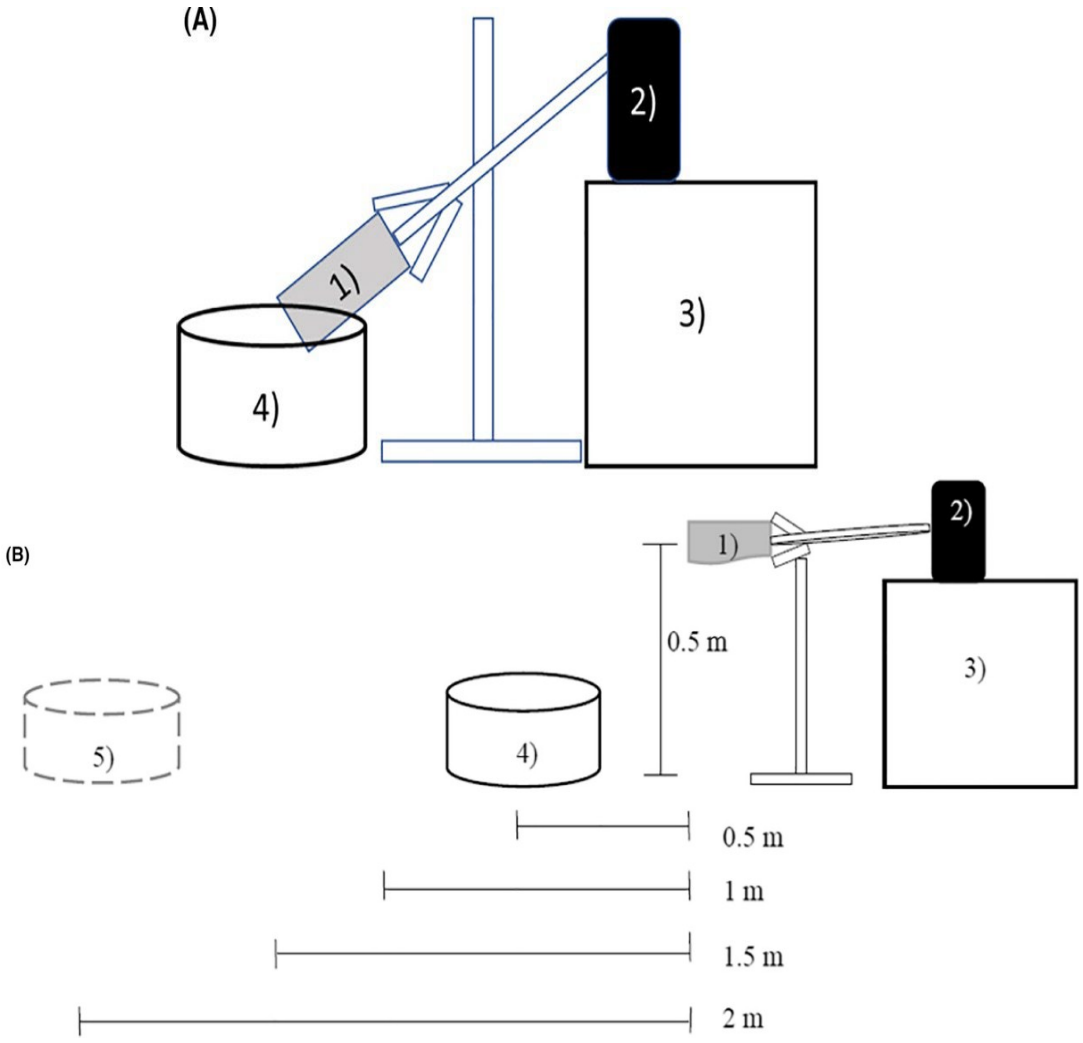


Figure 14: Experimental set-up used by Lovén Björkman et al [71], to measure airborne peanut at various times and distances after opening 200g of roasted or dry-roasted peanuts into a container and shaking them for 3 seconds, every 10 minutes. Air samples were collected either directly from the container with a lid in situ (**A**), or at 0.5 – 2 m distance away from the open container (**B**). Reprinted with permission.

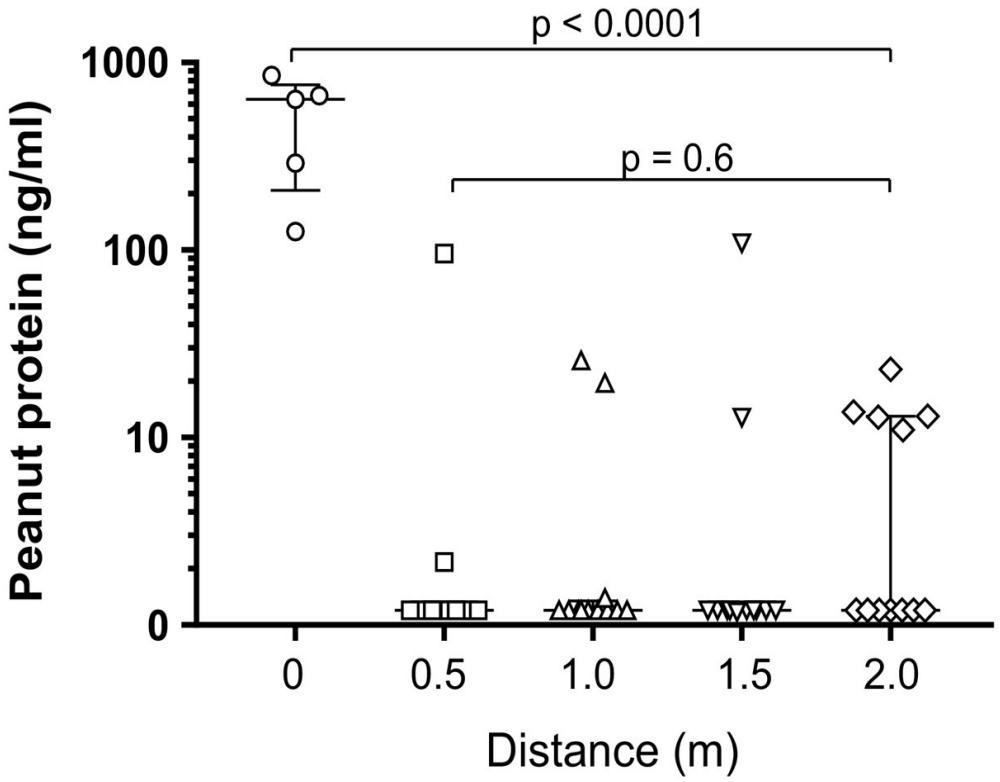


Figure 15: Peanut protein detected in airborne samples collected at different distances from the peanuts in the experiment by Lovén Björkman et al [71]. Reprinted with permission.

3.2.3 Food allergen distribution in ventilation systems of commercial aircraft

The above studies were performed in experimental simulations at ground level rather than in a controlled aircraft environment at altitude, where frequent air exchanges together with use of HEPA filtration might be expected to impact upon risk. Three studies were identified which have specifically evaluated the aircraft cabin environment for peanut allergen. Jones et al collected filter units from two commercial airliners at the time of their annual replacement after approximately 5000 flight hours. Unfortunately, it is not clear if these were HEPA units, since HEPA filtration was only introduced into commercial aircraft in the mid 1990s, which is when this study was done. Peanut allergen was detected in eluent from the filter, which the authors suggest is almost certainly going to be due to peanut consumption during flights [76]. Typical particle sizes for peanut dust range from 2-30 μm (micron) size range [77]. Thus, HEPA units which have a particle-removing efficiency of 99·97% at 0·3 microns would prevent recirculation of any peanut dust into the air cabin.

Paciencia et al analysed dust collected from the cabin carpet and seats on 10 short- and medium- haul commercial airplanes, as part of the aircraft cleaning routine [78]. Peanut protein (as the major peanut component, Ara h 3) was detected in all samples analysed, up to a maximum of 122mg/gram. Typical estimates for dust consumption per day are around 100mg dust. Ara h 3 constitutes around 20% of total peanut protein. It is theoretically possible that a typical exposure to dust over a 24 hour period at that level of Ara h 3 could result in an intake of around 60mg peanut protein. An exposure equivalent to 6 hours (typical of a medium-haul flight) could result in an exposure sufficient to trigger subjective symptoms in 30-50% and objective allergic symptoms in 10% of peanut-allergic individuals [79]. However, this assumes that a passenger would be “fully

exposed" to peanut residue in dust suspended in the cabin air – something which is very unlikely due to both the cabin ventilation system but also the use of high-efficiency filtration systems. Indeed, air sampling from simulations where peanut is consumed has failed to demonstrate peanut residue except when directly above the peanut source [71-74]. Nonetheless, this does provide a further explanation for the detection of peanut in cabin filter systems reported by Jones et al [76].

Jin et al. measured peanut present in surface swabs from airplane tray tables and seats and air samples, taken during a commercial flight in which deshelled roasted peanuts were eaten, and another flight when no peanuts were served [80]. Peanut protein was found in swabs taken from both the tray table and seat irrespective of whether peanut was served. The highest amounts were found in swabs taken shortly after eating peanut (see Table 4). No peanut was detected in air samples taken away from the site of peanut consumption; only one air sample, collected during active peanut consumption at the level of the tray table, had very low level peanut detected. The authors conclude that "any potential for accidental exposure to peanut protein in airplanes stems from surface contamination, not airborne exposure" – a conclusion consistent with data from other studies.

Table 4: Detection of peanut during active flights, as reported by Jin et al [80].

Surface sampled	Timing	Peanut served?	Estimated peanut protein (mg) per square foot
Seat & tray	During boarding (prior to peanuts being served)	Yes (after sampling)	21.5
Seat & tray	During boarding (prior to peanuts being served)	Yes (after sampling)	3.1
Seat & tray	Mid-flight (immediately after peanuts eaten)	Yes	441
Seat & tray	During boarding	No	1.2
Tray	Mid-flight	No	6.2, 16.1

3.3 Evidence relating to mitigation of unintended allergic reactions in food-allergic individuals on commercial aircraft

The above evidence suggests that the main source of potential allergen exposure, at least in terms of peanut and tree nuts, is not "airborne" but rather, due to the presence of these foods on surfaces such as seat coverings, tray tables and seat-back entertainment systems which nowadays almost universally include touch screen technology. Peanut and other "sticky" food proteins are thus transmitted to the hands and can be transferred either to the surface of food being consumed or directly to the individuals mouth/face resulting in the perception that reactions are due to airborne contamination. This would explain the discordance between the perception that "airborne peanut" commonly results in clinical reaction, and objective study data demonstrating an extremely low risk of reaction due to aerosolised peanut in challenge studies. On this basis, strategies to reduce allergen presence on surfaces would be expected to reduce inadvertent contact exposure and thus prevent such reactions from occurring.

A number of studies have looked at the efficiency of environmental measures in this regard. Perry et al. assessed the effectiveness of cleaning agents for peanut allergen removal from worktops, water fountains, and hands [75]. Standard washing of work

surfaces with detergent left detectable residue on 25% of surfaces, but this did not occur with commercial cleaning agents. In terms of handwashing, using water alone or alcohol-gel based hand sanitizer was not effective, but wet-wipes or handwashing with soap (liquid or bar soap) was.

Brough et al quantified environmental peanut protein levels in household dust, surfaces, bedding, and furnishings in the home environment, and the effectiveness of measures to reduce this [73,74]. Peanut protein was completely removed from granite worktops after cleaning with detergent, while levels were reduced (but still present) after cleaning wooden worktops with detergent and paper towel. Water alone was not effective (Figure 16). The authors also confirmed that peanut was easily transmitted around the home environment, both on hands and in saliva.

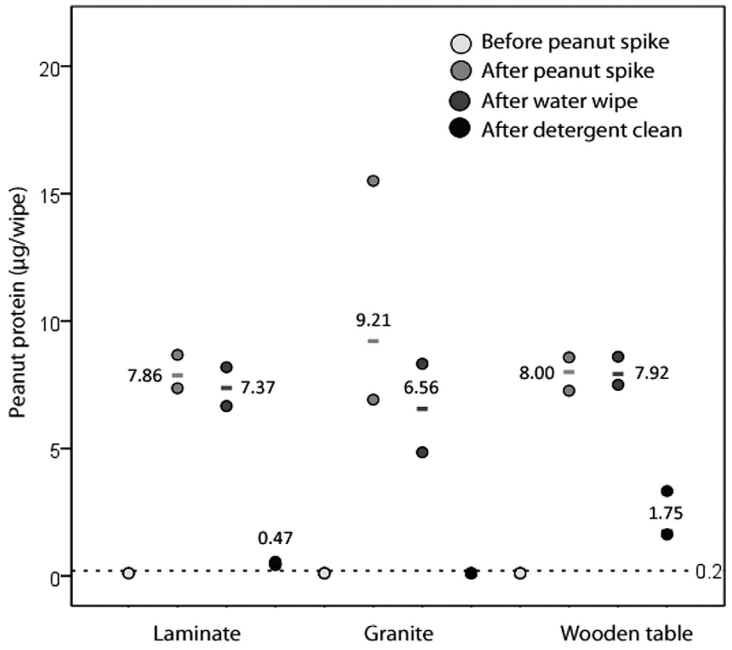


Figure 16: Peanut protein levels (micrograms per wipe) on three different table surfaces (granite, laminate, and wood) before and after a 0.5mL peanut butter spike, water wipe, and vigorous detergent cleaning (all data in triplicate) [73,74]. The lower limit of quantification (0.2µg per wipe) is shown as a dotted line. Reproduced from reference 74 under a Creative Commons CC-BY-NC-ND 4.0 licence.

These data support a recommendation that cleaning tray tables, seat surfaces and in-seat entertainment systems at the start of a flight using cleaning or sanitising wipes is likely to be an effective measure in reducing the risk posed by residual food proteins to food-allergic passengers.

Further evidence that local cleaning of the seat/table area can reduce risk of reaction can be found in a study by Greenhawt et al, who undertook a survey of 3,276 respondents from 11 countries to assess not only the reported frequency of IMEs due to food allergy but also included food-allergic respondents who had flown without incident [61]. The study was at medium-high risk of bias, due to the nature of the methodology (internet survey, self-report); however, the methodology did allow for a large enough sample that the authors could evaluate the potential impact of different measures which might mitigate against the risk of allergic reaction while in-flight (Table 5). Of note, the methods used could only identify measures associated with a reduce rate of passenger-reported incidents, rather than determine whether there was a causal relationship. For example, when passengers requested to sit in a “buffer zone” where immediately-adjacent

passengers were asked not to consume nuts, there was no information as to whether the request was made by the airline or whether other passengers complied; it is possible that food-allergic individuals who requested to sit in a "buffer zone" may have taken other precautions which resulted in a lower rate of reported reaction due to other actions. This hypothesis is supported by the finding that requesting any accommodation from the airline was associated with the second largest reduction in odds of a passenger-reported incident (Table 5).

Table 5: Strategies reported by Greenhawt et al which were found to associated with a reduced rate of passenger-reported, food allergy incidents [61].

Strategy	Odds Ratio (95% CI)
Requesting *any* accommodation from the airline	0.32 (0.19-0.54)
Requesting buffer zone	0.64 (0.44-0.94)
Requesting an announcement for other passengers not eat nuts	0.67 (0.46-0.96)
Requesting nut-free meal	0.43 (0.28-0.65)
Wiping tray table	0.61 (0.44-0.86)
Bringing own food	0.19 (0.13-0.27)
Avoiding use of airline-provided blanket/pillow	0.67 (0.48-0.94)

3.4 Evidence relating to the management of in-flight allergic reactions

The International Civil Aviation Organization (ICAO) provides recommendations on the contents of first-aid and onboard medical kits [33]. Current advice includes adrenaline (epinephrine) at a 1:1000 strength – that used for intramuscular injection to treat anaphylaxis – as well as an injectable antihistamine and inhaled bronchodilator. Oral antihistamines are not on the list, but "can be included in the first-aid kits where permitted by national regulations" [33]. The FAA requires both oral and injectable antihistamine to be carried; this change was made in 2001 due to "studies suggest[ing] the need for an oral treatment for allergic reactions" [34].

If adrenaline is needed to treat anaphylaxis in-flight, this must be drawn up via a needle and syringe, since the FAA and other regulators do not require carriage of adrenaline auto-injectors because "recent and former studies that the FAA has conducted on in-flight medical events did not reveal a need to make [adrenaline] auto-injectors available" [34]. The need to draw up the injection presents significant issues in terms of staff training, medical errors and delay [82]. As a result, some airlines choose to stock adrenaline autoinjectors, since these allow for more rapid administration of adrenaline, and can be done by untrained individuals where permitted by national regulations.

Intramuscular adrenaline injection is the first-line treatment of anaphylaxis according to all national and international guidelines. Furthermore, the Resuscitation Council UK Anaphylaxis Guideline – which is the main UK guideline on Anaphylaxis for healthcare

professionals – recently downgraded other medicines, such as antihistamines and steroids, such that they are no longer part of the management of anaphylaxis until the affected individual has been stabilized [3,83]. Priority must therefore be given to intramuscular adrenaline injection to treat potential anaphylaxis, rather than other medicines (although these can be useful to treat less severe, non-anaphylaxis reactions).

Allergic individuals at risk of anaphylaxis should be prescribed adrenaline auto-injectors (such as Epipen®, Jext® or Emerade®) to facilitate self-treatment in the event of a possible anaphylaxis reaction. In practice, in the UK only one third of food-allergic adults at risk of anaphylaxis are prescribed an adrenaline auto-injector; concerningly, over 40% of individuals with a previous anaphylaxis event to food do not have a prescription for adrenaline auto-injector on their national health record [84]. It is therefore not surprising that some surveys report rates of auto-injector carriage as low as 40% in those experiencing food-related allergic reactions during commercial flights [59].

Kodoth et al reported that around 50% of IMEs due to an allergic reaction occur on flights where adrenaline auto-injectors are included in the onboard medical kit [57]. The authors also found that carriage of auto-injector in the medical kit was associated with a higher frequency of usage, although the data did not identify whether the device used to treat the reaction was the passenger's own device or that in the medical kit [57]. Arguably, any intervention which increases the use of adrenaline to treat possible anaphylaxis should be encouraged.

Shaker and Greenhawt undertook an evaluation of the cost-effectiveness of adrenaline auto-injectors included as a "stock" item in the onboard medical kit on commercial aircraft [82]. They concluded that carriage of two devices was a cost-effective measure, with a supply cost of US$338 per two devices (estimated annual cost of $0.08 per at-risk passenger). The cost of supply in the UK setting is less than 50% of this amount, so including two adrenaline auto-injectors devices in the onboard medical kit would be potentially more cost-effective under this model.

4. Discussion

This systematic review of published literature has demonstrated that the rate of in-flight medical events due to food-induced allergic reactions is low, such that for the average passenger with food allergies, the risk of accidental reaction is around 10-100 times lower than that when not flying. Reassuringly, this risk seems to be stable over the past 20 years, despite an increase in passenger numbers and increasing prevalence of food allergy. However, this needs to be interpreted in the context of the vast majority of food-allergic individuals taking a number of significant precautions when travelling, ranging from avoiding flying in the first place, to wiping down their seat area and bringing their own food to eat during the flight. This is likely to impact upon actual risk.

For the vast majority of nut-allergic individuals, there is no evidence that peanut or tree nut allergens are aerosolised within the aircraft cabin and can subsequently cause allergic reactions. Any risk is further mitigated by the controlled cabin environment which includes filtration, often to a higher standard than that used in hospital environments. However, there is a common perception that reactions can occur due to inhalation of aerosolised peanut and tree nut proteins. Food-allergic passengers, and those caring for them, need to be informed that it is much more likely that the main risks posed to them are due to contaminated surfaces, where allergen is likely to be present and can be transferred either by touch on to food consumed during flight, or by direct hand-to-mouth/face inoculation. Simple strategies including wiping down the seat area, seat table

and in-flight entertainment system appear to be effective in reducing the risk. In this respect, allowing food-allergic passengers and their families early access to the cabin before boarding of other passengers may be helpful and provide reassurance. The USA Department of Transportation already requires airlines to allow passengers with peanut/tree nut allergies to preboard in order to wipe down their seating area, if this is requested by the passenger or caregiver [85].

Arguably, if peanuts/tree nuts were not provided during in-flight service, then there would be a lower risk posed to passengers with allergies to these foods. However, this may not be a valid assumption: at least one study has reported no difference in peanut in household dust between homes where peanut was completely avoided (due to allergic individuals in the household), and homes that did not restrict peanuts [81]. Furthermore, the rate of IMEs due to allergy has not significantly changed over time despite a significant drop in the number of airlines serving peanuts during in-flight service, although with the growth in low-cost short haul flights over this time, it is likely that nut-based snacks are purchased prior to flying and still consumed in-flight by many passengers. Ideally, the rate of IMEs would be normalised according to flight duration (and also whether flights were domestic or international), but most studies included in this analysis did not provide these data.

Given the lack of evidence that airborne transmission of peanut or tree nut allergens is likely, general “nut bans” on aircraft (for example, through announcements requesting passengers not to consume a specific food on a given flight) are not supported. Indeed, such requests can give a false sense of reassurance (as may be the case with “nut bans” in schools [86]), as well as increase the risk of confrontation amongst passengers and with cabin staff. While “food bans” are most widely applied to nuts, it is difficult to assert that “bans” to non-nut allergens (such as cow’s milk, wheat or fish) can be implemented if a passenger allergic to these foods is travelling. Food-allergic individuals may assert that peanut/tree nuts are of greater concern, but recent data has shown that amongst children in the UK, cow’s milk is now just as a common as a cause of severe and fatal anaphylaxis as peanut [87].

Rather, there needs to be a focus on reducing risk due to potential transmission through cross-contact. Policies should be in place to facilitate this, for example through preboarding of passengers with food allergies. Whether there is any benefit in terms of requesting a “buffer zone” – where passengers travelling in the immediate vicinity of a food-allergic passenger are asked not to consume the relevant allergen – is unclear. More research is needed to understand whether such strategies actually limit potential exposure and how dependent this is on the size of the exclusion zone; irrespective, it is likely that “buffer zones” provide important reassurance to food-allergic passengers, and avoid the scenario whereby a food-allergic passenger is sat next to another passenger consuming the allergen they are allergic to [38]. Implementing “buffer zones” also raises the question of which allergens can passengers be reasonably asked not to consume if sitting adjacent to an allergic individual. In this respect, non-nut allergens are probably less of an issue, since they do not persist on surfaces to the same extent as peanut/tree nuts (although cow’s milk is potentially more problematic since it is a high- protein food compared to many allergens and so small amounts of milk can pose issues to some milk-allergic individuals). Importantly, “buffer zones” must not cause a false sense of security, since their implementation would not affect risk due to other surfaces in the aircraft that food-allergic passengers may touch (for example, bathroom door handles).

One area not addressed in this report relates to reactions occurring due to unintended consumption of a food product containing an ingredient a person is allergic to. Surveys

report that many food- allergic passengers bring their own food to eat while flying; this food might be made at home, but is also commonly purchased at the airport. The prospective study undertaken by Crealey and Byrne identified five in-flight allergic reaction; three events were due to consumption of the trigger allergen in food purchased to boarding as a “safe” alternative, and one to a home-made sandwich [64]. This highlights the risk of human error in preparing for travel.

Food-allergic individuals at risk of anaphylaxis should be prescribed two adrenaline autoinjector devices which they should carry on their person at all times, including when on board aircraft. While national aviation authorities typically require adrenaline ampoules (at the relevant concentration to treat anaphylaxis) to be carried in the onboard medical kit as stock vials, given the need for additional training for their use, airlines should consider stocking a separate supply of adrenaline autoinjectors to be included in the on-board medical kit for cabin crew to use in an emergency. In the UK-setting, this is very likely to be a cost-effective measure.

Finally, a common observation from patient surveys is the difficulty reported by many food-allergic passengers, either in locating relevant airline policies or the consistency with which such policies are implemented by cabin crew [88,89]. It is helpful to provide this information in advance, so that cabin crews are not put in a difficult position where passengers make requests for which there may be little evidence and which run counter to the stated airline policy. Indeed, a lack of consistency in managing such situations, both between different airlines but also by cabin staff from different flights operated by the same airline, appears to be a major concern to food-allergic individuals when travelling. All airlines should have clear policies relating to food allergies which are easily available from their websites or on request. These policies should be applied consistently by both ground staff and cabin crew, in order to provide reassurance to food-allergic passengers and their caregivers.

5. Invited commentary from patient representative organisations

Food-allergic individuals (and their families) can be extraordinarily anxious about flying. The formality of going through airport security processes; the perception of being confined in a sealed cabin for hours with hundreds of strangers who may snack on something to which they are allergic; the possibility of an allergic reaction which could be life-threatening at 35,000 feet, without access to a full range of medical assistance, equipment and medications; the worry that if they do have a reaction, there may not be someone knowledgeable and sympathetic to help them – all these contribute to high levels of anxiety and concern when arranging travel.

In this context, whilst the evidence presented in this report is helpful in showing that the risk posed to food-allergic individuals when flying is no greater than when on the ground, it is not possible to dissect whether this is because of the significant steps food-allergic people (and accompanying companions) take when flying. More importantly, these data do little to help breach the gap between the perceived risk of an allergic reaction when flying and the actual risk according to the data. Food- allergic individuals therefore need to have confidence that their concerns are being acknowledged and taken seriously. In part, this can be addressed though airlines having a clear policy which is readily available (for example, on a website) and is implemented consistently by both ground and cabin crew.

A key take-home message from this report is the importance of passengers **cleaning their seat area**, including the tray table and the seat-back entertainment system. Airlines need to facilitate food- allergic passengers to prepare their seating area in this way: offering preboarding would be one way of doing so. An additional complication – the need for passengers to then wash their hands having cleaned their seat area – can be avoided by using disposable gloves when cleaning. Indeed, airlines may like to consider providing food-allergic passengers with a set of disposable gloves and suitable wipes. This would avoid the need for passengers to wash their hands during boarding of the cabin.

We expect the recommendation for airlines not to make pre-flight announcements will not be welcomed by some people with allergies. However, these are often limited to just peanut rather than all food allergens; food-allergic individuals tell us that these announcements are frequently ignored by other passengers. While more research is needed into the effectiveness of “buffer zones” in reducing actual risk of reaction, a targeted request, for example, asking adjacent passengers not to eat nuts in the immediate vicinity of a nut-allergic passenger would be reassuring and might reduce anxiety. This will require airlines to have a clear policy to assist cabin crew with such requests, particularly where another passenger refuses to comply with the request.

While commercial aircraft are required to carry injectable adrenaline in the emergency medical kit, the cabin crew may not be trained to administer it as it is usually suppled in vials. Therefore, all passengers at risk of anaphylaxis (or their parent/guardian) must take responsibility and carry their own adrenaline auto-injector devices with them when flying and know how to use them. We welcome the clear statement in this report that under UK legislation, medical authorisation is not needed to carry prescribed autoinjector devices through airport security and into the cabin, nor is permission required from airlines or government agencies. Notwithstanding, around 2% of anaphylaxis reactions need more than two doses to resolve, and we therefore support the recommendation that airlines

should consider stocking a separate supply of **"general use" adrenaline autoinjectors** to be included in the on-board medical kit for use in an emergency.

In summary, we ask airlines to acknowledge the concerns of food-allergic passengers and their families, respect reasonable requests which may be made, and approach such requests in a clear and consistent manner. This would be greatly facilitated if airline policies to assist food-allergic individuals were more consistent with one another, and made more easily accessible for passengers to help them prepare for their journey.

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APPENDIX 1:

Table S1: Risk of bias for included studies describing the incidence of in-flight medical events due to allergy, evaluated using the approach of Hoy et al [39]

Study	Study population	Sampling frame	Selection	Nonresponse bias	Data collection	Case definition	Evaluation	Consistent data collection	Recall bias	Numerator(s) / denominator(s)	OVERALL RISK OF BIAS
Donaldson 1996 [41]	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low
DeJohn 2000 [42]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Szmajer 2001 [43]	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low
Sirven 2002 [44]	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Moderate
Delaune 2003 [45]	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low
Moore 2005 [46]	Low	low	Unclear	Low	Low	Unclear	Low	Low	Low	Low	Moderate
Baltsezak 2008 [47]	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low	Low	Moderate
Sand 2009 [48]	Low	Low	Unclear	Moderate	Low	Unclear	Unclear	Unclear	Low	Low	Moderate
Mahony 2011 [49]	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low
Peterson 2013 [50]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Kesapli 2015 [51]	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Kim 2017 [52]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Alves 2019 [53]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Pauline 2020 [54]	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Moderate
Rotta 2020 [55]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Ceyhan 2021 [56]	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low
Kodoth 2022 [57]	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low

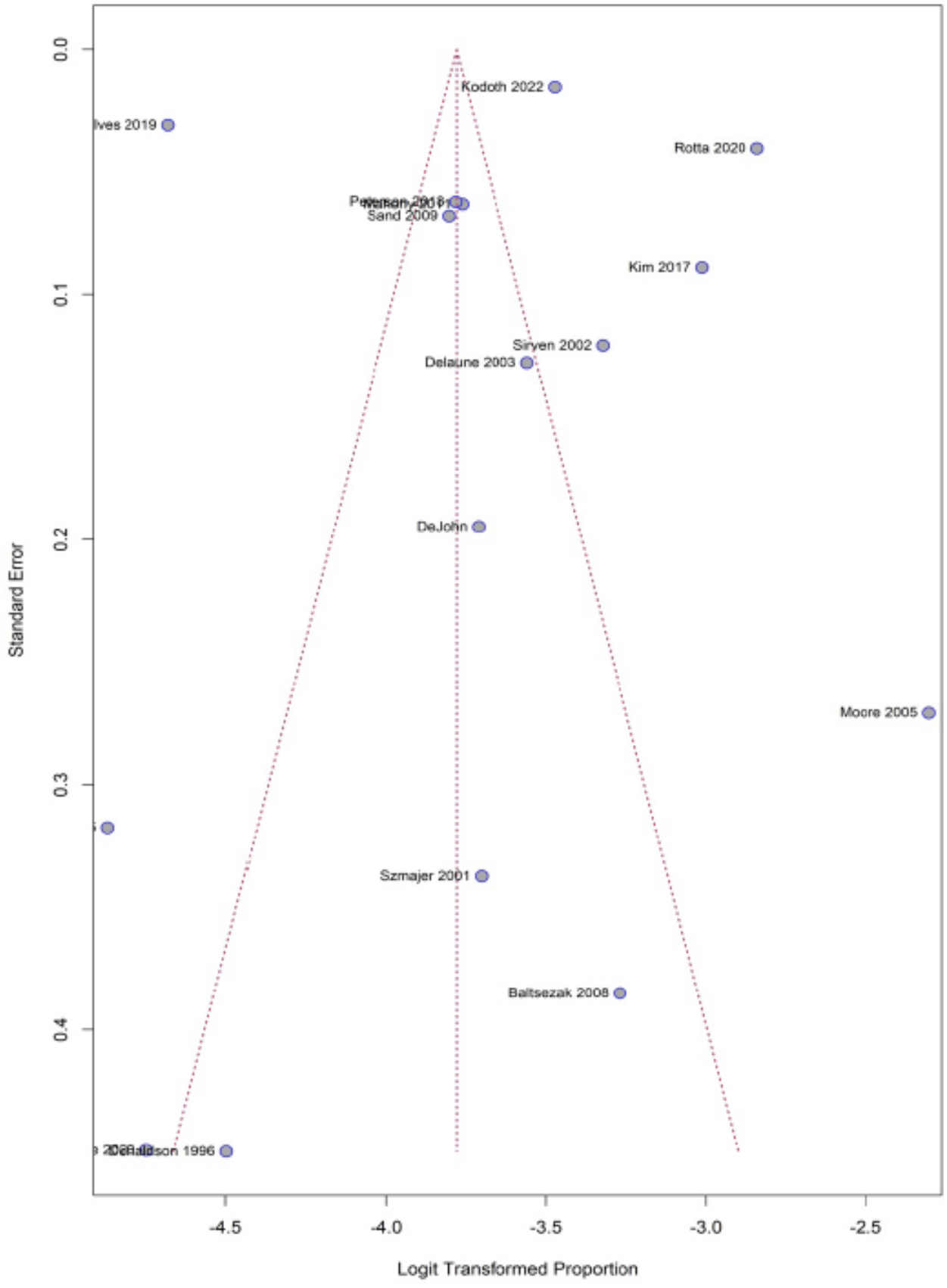

Figure S1: Funnel plot for studies describing the incidence of in-flight medical events due to allergy

Table S2: Risk of bias for included studies describing passenger-reported allergic reactions to peanut and/or tree nuts during commercial flights, evaluated using the approach of Hoy et al [39].

Study	Study population representative	Sampling frame	Selection	Nonresponse bias	Data collection	Case definition	Evaluation	Consistent data collection	Recall bias	Numerator(s) / denominator(s)	OVERALL RISK OF BIAS
Sicherer 1999 [58]	Unclear	Unclear	High	High	Low	Unclear	High	Low	Unclear	Low	High
Comstock 2007 [59]	Unclear	Unclear	High	Unclear	Low	Low	High	Low	High	Low	High
Greenhawt 2009 [60]	Unclear	Unclear	High	Low	Low	Low	High	Low	Unclear	Low	Moderate-High
Greenhawt 2013 [61]	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Low	Unclear	Unclear	Moderate-High
Beaumont 2015 [62]	Unclear	Low	Low	High	Low	Low	Moderate	Low	Moderate	Low	Moderate-High
Martinez-Flores 2022 [63]	Unclear	Unclear	Low	Unclear	Yes	Low	Low	Low	Unclear	Low	Moderate-High
Crealey 2022 [64]	Low	Low	Low	Unclear	Low	Low	Moderate	Low	Low	Low	Low
Warren 2023 [37]	Unclear	Unclear	High	Unclear	Low	Low	High	Low	Unclear	Low	High

Table S3: Risk of bias for included studies describing potential routes and mechanisms of allergen exposure relating to commercial flights, evaluated using ROBINS-E tool [40].

	Risk of confounding	Risk of bias arising from measuring exposure	Selection bias	Impact of any post-exposure interventions	Impact of missing data	Risk of bias due to outcome assessment	Risk of bias due to selective reporting	OVERALL RISK OF BIAS
Jones 1996 [76]	Some concerns	Low	Unclear	Low	Low	Unclear	Low	Some concerns
Roberts 2002 [26]	Some concerns	Low	Some concerns	Low	Some concerns	Low	Low	Some concerns
Simonte 2003 [70]	Low	Low	Moderate	Low	Low	Low	Unclear	Some concerns
Perry 2004 [75]	Low	Low	Low	Low	Low	Some concerns	Low	Low
Johnson 2013 [72]	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Some concerns
Brough 2013 [73]	Low	Low	Low	Low	Low	Low	Low	Low
Jin 2019 [80]	Some concerns	Low	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Paciencia 2020 [78]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Lovén Björkman 2021 [71]	Low	Low	Some concerns	Low	Low	Low	Low	Low

APPENDIX 2:

In estimating the annual incidence of IMEs due to food allergy, we made the following assumptions:

- One flight per day per passenger
- A population average of 4.2 flights per person per annum [67] and a rate of 52 flights per year for "frequent flyers".
- Food-allergic passengers are no more or less likely to fly at a different frequency to non-food- allergic individuals.
- Food allergy related IMEs are only reported 50% of the time (as per Table 3), thus the true incidence of food-induced allergic reactions on board commercial aircraft is double that reported in the literature.

	Average (mean)	Lower 95% CI	Upper 95% CI
Rates of IMEs per million passengers (irrespective of whether they have food allergy)	0.66	0.38	1.14
Assuming only half of IMEs due to food allergy are reported, rate of IMEs per million passengers (irrespective of whether they have food allergy)	1.32	0.76	2.28
Assuming a prevalence rate for food allergy of 2%, rate of IMEs per million Px with food allergy:	66	38	114
Assuming a rate of 4.2 flights per annum, the annual incidence of a food-induced allergic reaction in food-allergic passengers is: • per million person-years: • per 10,000 person-years:	 277 2.7	 160 1.6	 479 4.8
• This is equivalent to one food-induced allergic reaction during commercial air travel for every 3608 (95% CI 2089-6266) food-allergic passengers travelling, per annum			
For frequent flyers (taking one flight per week), the annual incidence of a food-induced allergic reaction in food-allergic passengers is: • per million person-years: • per 10,000 person-years:	 3432 34	 1976 20	 5928 59
• This is equivalent to one food-induced allergic reaction during commercial air travel for every 291 (95% CI 169-506) food-allergic passengers travelling, per annum			

CI, Confidence Interval.